



# Effective Health Care Program

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Comparative Effectiveness Review  
Number 51

## **Dietary Supplements in Adults Taking Cardiovascular Drugs**



Agency for Healthcare Research and Quality  
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## **Dietary Supplements in Adults Taking Cardiovascular Drugs**

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www.ahrq.gov

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**Prepared by:**

University of Ottawa Evidence-based Practice Center  
Ottawa, Ontario

**Investigators:**

Dugald Seely, N.D., M.Sc.  
Salmaan Kanji, Pharm.D.  
Fatemeh Yazdi, M.Sc.  
Jennifer Tetzlaff, M.Sc.  
Kavita Singh, M.P.H.  
Alexander Tsertsvadze, M.D., M.Sc.  
Margaret E. Sears, Ph.D.  
Andrea Tricco, Ph.D.  
T. C. Ooi, M.D.  
Michele Turek, M.D.  
Sophia Tsouros, B.Kin.  
Becky Skidmore, M.L.S.  
Raymond Daniel, B.A.  
Mohammed T. Ansari, M.B.B.S., M.Med.Sc., M.Phil.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

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We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Carolyn M. Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.  
Director, Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director  
Evidence-based Practice Program  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Elisabeth Kato, M.D., M.R.P.  
Task Order Officer  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

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## Key Informants

Brad Bradshaw  
Patient/Consumer  
Memphis, TN

Shiew-Mei Huang, Ph.D., FCP  
Office of Clinical Pharmacology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD

Alice Lichtenstein, D.Sc.  
Professor of Nutrition Science and Policy  
Tufts University  
Boston, MA

Katharine Lillie, M.D., A.B.F.P  
Medical Officer  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD

Edgar (Pete) Miller, M.D., Ph.D.  
Associate Professor  
Department of Medicine  
Johns Hopkins Medical University  
Baltimore, MD

Norman Stockbridge, Ph.D.  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD

Wendy Weber, N.D., Ph.D., M.P.H.  
Program Officer  
Division of Extramural Research  
National Center for Complementary and  
Alternative Medicine  
National Institutes of Health  
Bethesda, MD

## Technical Expert Panel

Joseph Betz, Ph.D.  
Director, Office of Dietary Supplements  
National Institutes of Health  
Bethesda, MD

Ryan Bradley, N.D., M.P.H.  
Affiliate Clinical Researcher  
Division of Cardiology  
University of Washington Medical School  
Seattle, WA

Charles Laporte, Pharm.D., Ph.D.  
Associate Scientist  
Ottawa Hospital Research Institute  
Ottawa, ON

Alice Lichtenstein, D.Sc.  
Professor of Nutrition Science and Policy  
Tufts University  
Boston, MA

Edgar (Pete) Miller, M.D., Ph.D.  
Associate Professor  
Department of Medicine  
Johns Hopkins Medical University  
Baltimore, MD

Gail Moreschi, M.D., M.P.H., F.A.C.P.  
Medical Officer  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville, MD

## **Peer Reviewers**

Mei Chung, Ph.D., M.P.H.  
Tufts University  
Boston, MA

Rebecca Costello, Ph.D.  
Office of Dietary Supplements  
National Institutes of Health  
Bethesda, MD

Arshad Jahangir, M.D.  
University of Wisconsin  
Milwaukee, WI

Norman Stockbridge, Ph.D.  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD

Wendy Weber, N.D., Ph.D., M.P.H.  
Program Officer  
Division of Extramural Research  
National Center for Complementary and  
Alternative Medicine  
National Institutes of Health  
Bethesda, MD

Donald Marcus, M.D.  
Baylor College of Medicine  
Houston, TX

Richard Nahin, Ph.D., M.P.H.  
Natuibak Center for Complementary and  
Alternative Medicine  
National Institutes of Health  
Bethesda, MD

# Dietary Supplements in Adults Taking Cardiovascular Drugs

## Structured Abstract

**Background.** A substantial proportion of patients with cardiovascular diseases use dietary supplements in anticipation of benefit. This also poses risks of adverse events from supplement-drug interactions and nonadherence associated with polypharmacy.

**Objectives.** For supplements commonly used by patients with cardiovascular disease, we examined benefits, harms, and effects on cardiovascular drug pharmacokinetics of coadministration of dietary supplements with cardiovascular drugs. We also sought evidence regarding variability among subgroups, and of statistical interactions between supplements and drugs.

**Data Sources.** We searched MEDLINE<sup>®</sup>, Embase, the Cochrane Library, International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED), as well as gray literature, from inception to September 2011.

**Study Selection.** Following a predefined protocol, two reviewers included experimental and observational studies comparing a supplement plus cardiovascular drug versus drug alone published in English or German; other languages were excluded due to concerns with study quality and applicability.

**Data Extraction.** One reviewer extracted data into a standardized electronic form, assessed study risk of bias, graded the strength of the body of evidence, and reported its applicability. Study risk of bias and strength of evidence regarding gradable outcomes were independently verified, as was a random 10 percent subset of all data.

**Data Synthesis.** Sixty-seven randomized controlled trials, two controlled clinical trials, and one observational study contributed evidence of limited validity in highly selected populations. Evidence was insufficient for all gradable clinical efficacy and harms outcomes (e.g., mortality, thrombotic events, serious adverse events) because there were few, small studies per supplement. One pragmatic trial in women showed no benefit from coadministering vitamin E with aspirin on a composite cardiovascular outcome. Evidence for most intermediate outcomes of efficacy was insufficient or of low strength and suggested no effect. Notable findings were incremental improvement of triglyceridemia with omega-3 fatty acid supplementation, stabilization of international normalized ratio with vitamin K added to warfarin therapy, and improved high-density lipoprotein cholesterol (HDL-C) with added garlic. Clinically nonsignificant or otherwise inconclusive changes were noted for pharmacokinetic outcomes.

**Limitations.** The evidence base principally consisted of underpowered short-term studies in selected populations, generally with moderate risk of bias.

**Conclusions.** Limitations of the evidence base precluded meaningful conclusions across most supplement-drug combinations. Low-strength evidence indicates benefits of omega-3 fatty acids, vitamin K, and garlic coadministration on specific intermediate outcomes. Evidence regarding harms was inconclusive. Care providers and researchers should query supplement use to improve care and to facilitate research regarding drug-supplement interactions.



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# Executive Summary

## Background

The American Heart Association estimates that more than 81 million American adults (one-third of all adults) have at least one form of cardiovascular disease (CVD).<sup>1</sup> CVD is broadly defined to include all the disorders of the arterial system, including the heart and coronary arteries, the arterial supply to the brain, and the peripheral arterial system. CVD manifests typically as hypertension, angina, myocardial infarction (MI), heart failure, stroke and transient ischemic attacks (TIAs), and intermittent claudication or blockage. While there has been progress in the control of CVD, it demands huge investments from the health care system, and represents great burdens and lost opportunities for individuals, families, and society overall.

In addition to lifestyle and dietary recommendations, frontline treatment for prevention and treatment of CVD is primarily pharmaceutical, with patients requiring, on average, 6.3 concomitant prescription drugs from, on average, 5.9 different drug classes for primary and secondary prophylaxis of the disease itself and management of associated comorbidities.<sup>2-4</sup>

Complementary and alternative medicine (CAM) refers to preventive and therapeutic modalities not generally considered to be part of conventional medicine,<sup>5</sup> including dietary supplements. CAM utilization has increased dramatically in North America over the past decades in both the general and CVD populations.<sup>6,7</sup>

The National Health Interview Survey indicated that Americans spent a total of \$34 billion out of pocket on CAM in 2007.<sup>8</sup> Estimates suggest that approximately one-third to two-thirds of people suffering from heart failure or other cardiovascular disease use dietary supplementation and are thus placed at risk for potential adverse events from interactions with other pharmacologically active agents and nonadherence associated with polypharmacy.<sup>7,9-13</sup> With compromised physiology due to aging, the elderly are most vulnerable to the adverse events of any drug interaction. On the other hand, addition of a dietary supplement to conventional cardiovascular drugs may confer benefit. Evidence of both benefits and harms of adding a supplement to cardiovascular drugs has been reported.<sup>6,14</sup>

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular medications and dietary supplements requires access to reliable drug-supplement information, as well as physicians' commitment to documenting patients' supplement use.<sup>15,16</sup> While a substantial amount of research and data is available describing drug–drug interactions in various populations, the evidence for drug-supplement interactions or simply add-on supplement effect is unclear, especially in the CVD populations.

## Objectives

The objective of this Comparative Effectiveness Review was to systematically synthesize and grade the strength of evidence of benefits and harms of adding a dietary supplement to cardiovascular drugs routinely prescribed in outpatient settings. A related objective included assessment of whether the altered outcomes of efficacy and/or effectiveness and harms are a result of a simple add-on effect of a dietary supplement or more complex interactions with the cardiovascular drug. Supplement–drug interactions were examined by investigating evidence of statistical and pharmacokinetic interactions.

These objectives were framed in the following Key Questions.

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared with cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on:

**Key Question 1.** Clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction and stroke)?

- (a) Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
- (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

**Key Question 2.** Intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

- (a) Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?
- (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

**Key Question 3.** Clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)?

- (a) Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
- (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

**Key Question 4.** Pharmacokinetic outcomes (e.g., half life [ $t_{1/2}$ ], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

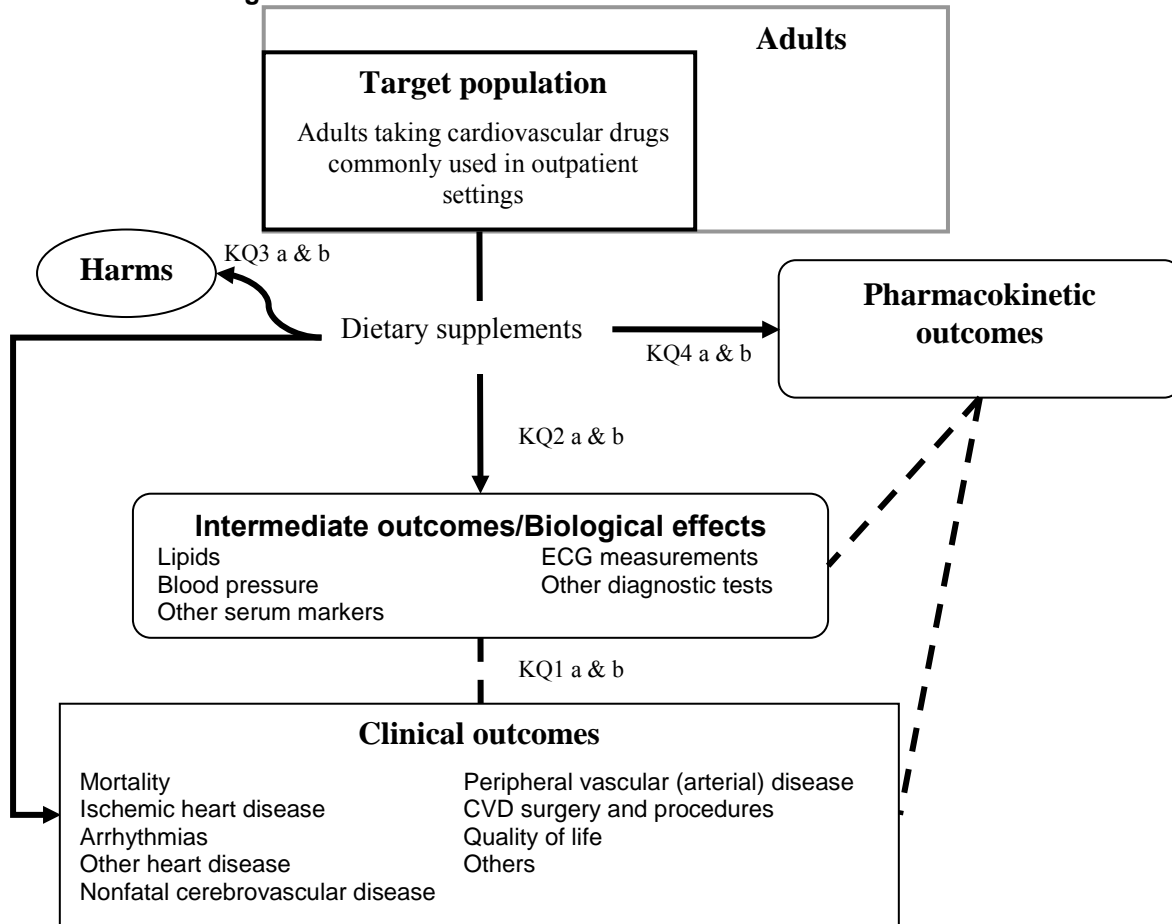
- (a) Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?
- (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

## Analytic Framework

The expectations behind using a dietary supplement with prescription cardiovascular drugs are improvement in the disease process (or its prevention) and reduction in harms related to cardiovascular drugs. These effects might come about through either an add-on effect of a supplement or its biological interaction with a cardiovascular drug. Benefits and harms are measured as outcomes that may be clinical outcomes, their proxy surrogates, or pharmacokinetic parameters. The analytic framework in Figure A depicts the causal pathways forming the basis of the Key Questions.



**Figure A. Analytic framework of dietary supplement coadministration with routinely prescribed cardiovascular drugs**



**Note:** CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

## Methods

### Input From Stakeholders

Preliminary broad searches identified the necessity to focus this review, so we formulated the population, intervention, comparator, and outcome (PICO) analytic framework and Key Questions in consultation with the Key Informants during a topic refinement stage. The range of dietary supplements was narrowed to include only those most commonly taken along with cardiovascular drugs and for which there was no recent review. A fifth Key Question, regarding P450 isozyme activity and cellular drug transport mechanisms, was dropped. The Key Informants included clinicians (cardiologists, naturopathic doctors, clinical pharmacology specialist, and nutritionist), a patient/consumer advocate, and systematic review research methodologists. The public were invited to provide comments on the Key Questions. During the review process, we followed an a priori research protocol developed with the clinical and methodological input of a Technical Expert Panel (TEP) of specialist clinicians and methodologists. The protocol followed the Effective Health Care Program's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>17</sup>

## Data Sources and Searches

We searched the following electronic databases from inception to September 1, 2011: MEDLINE<sup>®</sup>, Embase, the Cochrane Library (CENTRAL, CDSR, DARE, and HTA), International Bibliographic Information on Dietary Supplements (IBIDS), and Allied and Complementary Medicine Database (AMED). We developed peer-reviewed search strategies (shown in Appendix A of the full report) using a broad range of controlled vocabulary to address the various synonyms associated with this topic, as well as to cover any evolutionary gaps associated with the introduction of certain vocabulary terms. We also searched trial registries (e.g., ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts Conference Papers Index, and Scopus.

Results were refined using filters for systematic reviews, randomized controlled trials (RCTs), non-RCTs and observational studies, and safety. A more specific strategy related solely to herb-drug interactions was run in the same databases using only a systematic review filter.

We also contacted TEP members and the Scientific Resource Center at the Agency for Healthcare Research and Quality.

## Study Selection

Two reviewers screened titles, abstracts, and full-text reports, with conflicts resolved by consensus or third-party adjudication. A primary study was eligible if it:

- Was published in English or German.
- Examined a dietary supplement. A dietary supplement was defined as a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance, or a concentrate metabolite, constituent, or extract intended to increase the total dietary intake made for ingestion in pill, capsule, tablet, powder, or liquid form not represented for use as conventional food or as the sole item of a meal or diet).
- Compared the effect of adding a dietary supplement to cardiovascular medication(s) to the same cardiovascular medication(s) or to another dietary supplement (from the list above) added to the same cardiovascular medication(s).
- Evaluated use of a dietary supplement intended for ingestion as pill, capsule, tablet, powder, or liquid. The dietary supplements considered were coenzyme Q10, *Echinacea*, garlic, ginger, *Ginkgo biloba*, *Panax ginseng*, American ginseng, hawthorn, oral magnesium, niacin (no more than 250 mg/day), omega-3 fatty acids/fish oils, red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium, vitamin E, and vitamin K. This list was selected after extensive discussions with the TEP and reference to surveys of the general and cardiovascular populations in the United States.<sup>7,18-23</sup>
- Included cardiovascular drugs that were commonly used in outpatient settings (Table 1 of full report).
- Reported clinical or surrogate cardiovascular efficacy or harms, or pharmacokinetic outcomes, in any adult population.
- Was a randomized controlled trial, nonrandomized trial, or observational study with an independent concurrent or historical control group including at least five participants. For Key Question 4, studies employing participants as their own controls were also eligible. (This was a post hoc decision in light of the relevance of this design for study of pharmacokinetic interactions.)

Good-quality English language systematic reviews on the topic were also eligible. However, a systematic review could replace de novo synthesis of evidence only when the review was deemed to be current, obviating the need to update it.

Studies included after full-text screening were removed from data synthesis because of one or more of the following reasons:

- Cardiovascular drug(s) were not taken by at least 80 percent of participants in RCTs. Including such studies would have severely limited the applicability of evidence.
- The study reported effect estimates that did not reflect a comparison of supplement plus drug(s) versus drug(s) alone (or plus another supplement).
- No relevant outcome was reported in the study or the outcome data were not received from the authors of the studies. (Authors were contacted for data clarification and additional outcome data when data were recognized to have been recorded but not reported in the published study—for example, outcome data without a measure of dispersion.)
- The design of the study was lower in the hierarchy of evidence (i.e., nonrandomized experimental or observational study in the presence of higher quality RCT evidence) and did not meaningfully add to the evidence already included by being a longer term or pragmatic study reporting conclusive results.
- Studies included cardiovascular drugs not marketed in the United States.
- Administration dose and/or frequency of the dietary supplement was not quantified.

## **Data Extraction and Risk-of-Bias Assessment**

One reviewer extracted relevant data from each study and a second reviewer independently verified data for a 10 percent random sample of studies. Extraction items included general study characteristics (e.g., year of publication, study design); population characteristics (e.g., inclusion/exclusion criteria, age, race, level of activity, condition); intervention characteristics (e.g., dose, duration, details about comparators, level of care); and outcomes (i.e., clinical and surrogate outcomes of efficacy and harms, and pharmacokinetic outcomes) with their estimates. During the data extraction process, one reviewer with a clinical background rated study populations' 10-year coronary heart disease (CHD) risk according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines.<sup>24</sup>

We assessed study risk of bias according to outcome, using generic items for confounding and various types of bias (e.g., selection, performance, detection, and attrition bias) separately for each study design. Selected items from the McMaster Quality Assessment Scale of Harms were also incorporated into the risk-of-bias assessment for harm-related outcomes. Certain criteria were specific to particular study designs; for example, allocation generation and concealment applied only to RCTs.<sup>25</sup> For gradable outcomes, one reviewer rated the overall risk of bias for the study as low, moderate, or high risk, and a second reviewer independently verified the assessment. Outcomes were rated as high risk of bias if there was an apparent and major flaw in the study that would invalidate results. Appendix C in the full report provides the detailed individual study data and risk-of-bias ratings.

## Grading the Strength of the Body of Evidence and Applicability

In principle, a body of evidence originating in randomized trials starts with a presumed high strength of evidence and is downgraded across the domains when there is important overall risk of bias for contributing studies, inconsistency in the direction of the intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome rather than a clinical health outcome), or imprecision in effect estimates of an extent that neither important benefit nor harm can be ruled out. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence was graded based on the following four domains, per published guidance: overall risk of bias by outcome, consistency, directness, and precision.<sup>26</sup>

Gradable important outcomes for this review were identified a priori in consultation with the TEP (Table A). This was done because customarily only a subset of important outcomes that are more meaningful for decisionmaking concerning each specific Key Question are chosen.<sup>26</sup>

A methodologist and a content expert graded the strength of the body of evidence as “high,” “moderate,” “low,” or “insufficient.” From a larger list of outcomes of interest for each Key Question (see the Methods section of the full report).<sup>26,27</sup>

**Table A. A priori outcomes for grading the strength of evidence**

| Key Question | Outcomes   |
|--------------|--|
| 1            | Mortality (all-cause and vascular death); myocardial ischemic events (fatal myocardial infarction, nonfatal myocardial infarction, unspecified myocardial infarction, and acute coronary syndromes); cerebrovascular events (hemorrhagic/ischemic/unspecified stroke); quality of life; hospitalization; arrhythmia; and clinical outcomes of peripheral arterial disease  |
| 2            | Blood pressure (systolic and diastolic); lipid profile (low-density lipoprotein, high-density lipoprotein, and non-high-density lipoprotein cholesterol and triglycerides); international normalized ratio for coumarin derivatives; incidence of metabolic syndrome; and change in 10-year Framingham risk profile  |
| 3            | Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events); <sup>27</sup> withdrawal due to adverse events; clinical bleeding (intracranial, gastrointestinal, genitourinary, subretinal, etc.); renal dysfunction (e.g., proteinuria, elevated creatinine, need for transplant, glomerular filtration rate); hepatotoxicity (elevated enzymes or fulminant failure); and QT prolongation |
| 4            | Area under the plasma cardiovascular drug concentration-time curve (AUC), maximum drug concentration ( $C_{max}$ ), drug half-life ( $t_{1/2}$ ), and oral clearance   |

The strength of evidence was graded insufficient when there was no evidence for an outcome, when the direction of the estimates was inconsistent between studies without an identifiable cause, or when the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). When an effect estimate was associated with a confidence interval (CI) that was not only nonsignificant, but wide enough that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the effect as imprecise. This reflected our uncertainty regarding clinically important benefit or harm, or a clinically unimportant difference in effect estimates between the contrasting interventions.

Following published guidance, we summarized the determinants of applicability of the body of evidence for outcomes with conclusive results.<sup>28</sup> Studies that evaluated representative patient populations in usual or routine care conditions and lasting long enough to meaningfully measure health outcomes of both benefits and harms were considered pragmatic or effectiveness studies. In contrast, studies examining intermediate efficacy outcomes in highly selected patients were considered efficacy studies.<sup>29</sup>

## Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone or plus placebo or plus another dietary supplement. Meta-analyses were carried out when there was clinical and methodological homogeneity. For pharmacokinetic outcomes, we followed the U.S. Food and Drug Administration (FDA) guidance for analysis and interpretation of drug interaction studies—that is, the zone of bioequivalence is recommended to be between the lower and upper bound of the 90 percent geometric mean ratio (GMR), with a CI between 0.8 and 1.25.<sup>30</sup>

We did not pool experimental and observational studies, but did pool parallel studies with valid crossover randomized trials. We did not consider precrossover data for synthesis except when it was judged that the treatment given to participants in a given crossover trial was not appropriate for the condition under consideration.<sup>31,32</sup> Similarly, we did not pool crossover trials that had not employed a sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We did not meta-analyze observational studies because of the differences in adjustment for confounders and residual confounding.

Meta-analysis was considered when studies were randomized trials that included similar populations, compared the same type of dietary supplement versus comparator treatment, and reported the same outcome measures in the same statistical format (e.g., mean difference or GMR). Relative risk (RR) and post-treatment mean differences (MDs) were meta-analyzed using the DerSimonian and Laird random-effects model,<sup>33</sup> and Peto odds ratios were calculated when event rates were less than 1 percent.<sup>32</sup>

For studies with zero events in some arms or sparse data overall, we pooled using the fixed-effects Mantel-Haenszel method without continuity correction.<sup>34</sup> Studies with zero events in both arms were excluded from meta-analysis.<sup>32</sup> Where applicable, we examined statistical heterogeneity by calculating the synergy index (detailed in the Methods section of the full report).<sup>35</sup> The synergy index estimates the supplement-drug statistical interaction when the effect observed with the combination is of a magnitude that is greater than or less than would be anticipated in an additive model, knowing the independent effects of the supplement and drug. An S-index (ratio of effects measured to additive calculation) greater than 1 describes a positive interaction (synergism), and an S-index less than 1 indicates a negative interaction (antagonism). Statistical heterogeneity was assessed using Cochran's Q ( $\alpha = 0.10$ ) and the  $I^2$  statistic.

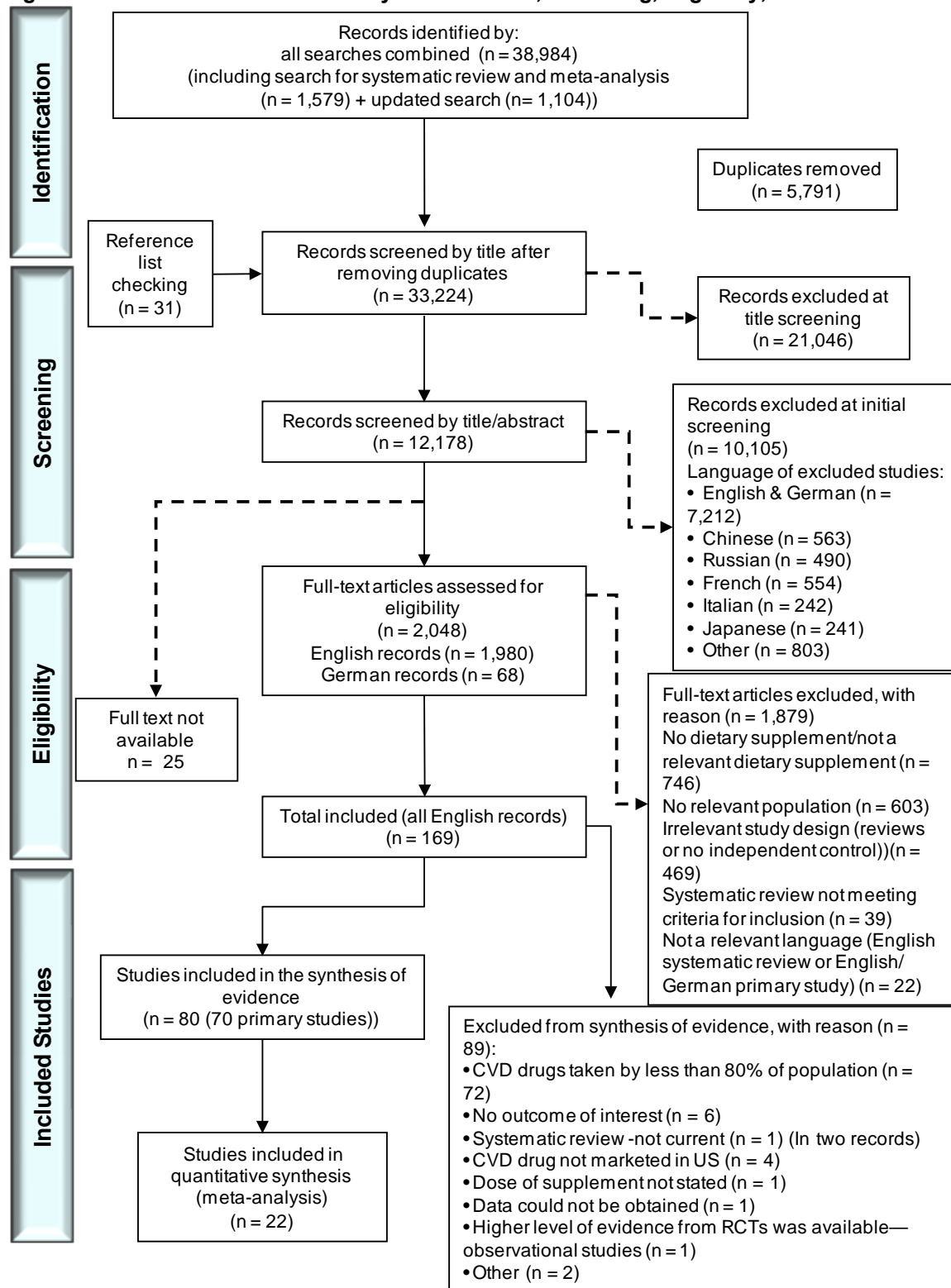
Outcome results were considered to be inconclusive when the pooled estimate or the single contributing study estimate had confidence intervals wide enough to incorporate both clinically important benefit and harm (i.e., type II error suggesting underpowered studies unable to precisely conclude benefit, harm, or no difference between treatments). Results were also considered to be inconclusive when studies could not be pooled—for example, when similar outcomes were reported in different statistical formats in studies or study results pointed in opposite directions. When inconclusive results were associated with a gradable outcome, strength of evidence was deemed insufficient.

## Results

### Overview

The PRISMA flow diagram summarizes the number of records screened and included (Figure B).

**Figure B. PRISMA flow chart of study identification, screening, eligibility, and inclusion**



**Note:** CVD = cardiovascular disease; RCT = randomized controlled trial.

In total, 38,984 records were identified by searches of databases (including gray literature, reference list checking, and search for systematic reviews and meta-analyses) and screened for eligibility. Seventy unique English-language studies (in 80 published articles), including one of observational design, contributed evidence. No systematic reviews were found to be eligible for evidence synthesis. Additionally, we found no relevant unique German publications. Twenty-two studies contributed to meta-analyses in this review.

Table B shows the most relevant risk-of-bias criteria for the randomized and controlled clinical trials included (n = 69).

**Table B. Risk-of-bias criteria and conflict of interest for all RCTs and CCTs**

| Item  | Percent of Total Studies (n = 69) |    |         |
|---|-----------------------------------|----|---------|
|   | Yes                               | No | Unclear |
| Adequate generation of allocation sequence      | 25                                | 3  | 72      |
| Allocation concealment                          | 9                                 | 0  | 92      |
| Comparability of groups                         | 25                                | 9  | 67      |
| Blinding of allocated intervention              | 22                                | 27 | 52      |
| Freedom from potential for conflict of interest | 29                                | 28 | 43      |

**Note:** Percents may not add to 100 due to rounding.

**Abbreviations:** CCT = controlled clinical trial; RCT = randomized controlled trial.

## Key Question 1. Clinical cardiovascular effectiveness/efficacy of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 1 is shown in Table C.

**Table C. Evidence for the clinical outcomes—Key Question 1**

| Outcome  | Supplement + Cardiovascular Drug(s)  |
|--|--|
| <b>Insufficient strength of evidence</b>   |  |
| <b>Conclusion: Inconclusive</b>  |  |
| <b>Single underpowered studies for each combination precluded meaningful conclusions</b> |  |
| All-cause mortality  | Coenzyme Q10 (33 mg TID) + ACE inhibitors<br><i>Ginkgo biloba</i> (40 mg QID) + Antiplatelet agents<br>Omega-3 fatty acids (4 g/day + Statins or aspirin or warfarin or fenofibrate<br>Vitamin K (150 µg/day) + Coumarin derivative <sup>a</sup> |
| Quality of life  | Coenzyme Q10 (100 mg/day) + ACE inhibitors   |
| Myocardial infarction  | Oral magnesium (365 mg/day) + Beta-blockers<br>Omega-3 fatty acids (1.8 g eicosapentaenoic acid +1.2 g docosahexaenoic acid) + Aspirin + Calcium channel antagonists<br>Vitamin K (100-150 µg/day) + Coumarin                                    |
| Arrhythmia   | Omega-3 fatty acids (4 g/day) + Statins  |
| Stroke   | Vitamin E (0.4 g/day) + Aspirin<br>Vitamin K (150 µg/day) + Coumarin <sup>b</sup>  |
| Ischemic stroke, hemorrhagic stroke, and TIA   | Vitamin E (600 IU/day) + ASA (aspirin)   |

<sup>a</sup>Small trial reported 1 death.

<sup>b</sup>Underpowered trial contributed evidence.

**Note:** Evidence was “insufficient” for all outcomes, so applicability is not presented.

**Abbreviations:** ACE = angiotensin-converting enzyme; QID = 4 times daily (every 6 hours); TIA = transient ischemic attack; TID = 3 times daily.

Twenty-one randomized controlled trials contributed evidence for Key Question 1.<sup>36-56</sup> No data were available from observational studies. Generally, across all combinations of dietary supplements and cardiovascular drugs, the strength of evidence of the gradable outcomes of comparative efficacy or effectiveness was graded insufficient. Type II error could not be excluded due to the low statistical power of mostly short-term efficacy trials. In addition, strict inclusion criteria excluded patients with uncontrolled comorbidities and acute ischemic events.

**Coenzyme Q10.** Insufficient evidence was found for the effect of coenzyme Q10 coadministered with angiotensin-converting enzyme (ACE) inhibitors on all-cause mortality and quality of life in 30 mostly male patients with left ventricular dysfunction over a 3-month period.<sup>54</sup> Adherence to simvastatin with or without supplement coadministration was 98 percent during a 12-week pilot study in 22 patients with previous statin-related myalgia.<sup>38</sup>

**Ginkgo biloba.** With no deaths observed, insufficient evidence for mortality was found for *G. biloba* coadministered with aspirin and/or pentoxifylline during a 4-week underpowered study in 33 South Asians with previous ischemic stroke.<sup>48</sup>

**Magnesium.** In a crossover trial of oral magnesium aspartate or placebo administered daily for 8 weeks to a selected group of 40 hypertensive patients with no comorbidities on therapeutic doses of beta-blockers, a single event of myocardial infarction was noted.<sup>42</sup>

**Omega-3 fatty acids.** Insufficient evidence from underpowered efficacy studies addressed the outcomes of mortality (in 50 healthy men)<sup>36</sup> and arrhythmia (in 122 highly selected dyslipidemic patients)<sup>40</sup> when omega-3 fatty acids were coadministered with statins. In three short-term efficacy trials of omega-3 fatty acid and statin coadministration, statin adherence as judged by pill count was found to be greater than 95 percent in both treatment groups.<sup>37,44,53</sup>

Insufficient evidence from single efficacy trials did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were aspirin (291 high-risk patients followed for 1 year with 9 deaths), warfarin (319 high-risk patients followed for 1 year with 5 deaths), and fenofibrate (unclear 10-year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths).<sup>47,56</sup>

Insufficient evidence addressed the outcome of acute myocardial infarction in a 6-month efficacy study of omega-3 fatty acids in addition to therapeutic doses of aspirin plus calcium channel antagonist following successful coronary angioplasty in 58 participants.<sup>51</sup>

**Vitamin E.** Insufficient evidence with sparse events of stroke and transient ischemic attack was provided by an efficacy trial of vitamin E plus aspirin versus aspirin alone in 100 highly selected patients with previous neurologic deficit.<sup>49</sup>

**Vitamin K.** Insufficient evidence was found for mortality and stroke. In one 6-month efficacy trial in 70 selected groups of patients with unstable international normalized ratios (INRs) anticoagulated with warfarin with coadministered vitamin K, no stroke and 1 death were observed.<sup>41</sup>

**Other supplement-cardiovascular drug combinations and outcomes.** Three notable trials reported outcomes that were not a priori gradable outcomes.



One pragmatic trial in 19,934 women randomized to vitamin E plus aspirin versus aspirin alone for 10 years noted no significant differences for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR, 0.95; 95 percent CI, 0.79 to 1.13).<sup>39</sup> Although components of the composite outcome were gradable, it was not possible to discern if shifts in the incidence of stroke and heart attack might have been obscured in this composite outcome.

Inconsistent evidence on rates of restenosis following successful coronary angioplasty, best explained by differences in study population, design, and treatment, was found with omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists.<sup>51,52</sup> When 82 highly selected male patients took omega-3 fatty acids daily along with therapeutic doses of aspirin, dipyridamole, and calcium channel antagonists, significantly lower rates of restenosis (at least 50 percent reduction in diameter) were observed compared with the cardiovascular drugs alone (RR, 0.40; 95 percent CI, 0.20 to 0.82); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups.<sup>52</sup> No differences were noted in rates of restenosis when a similar but lower quality trial was conducted in 107 South Asians in India who were not taking dipyridamole.<sup>51</sup>

Underpowered studies addressed other outcomes that were not graded per the a priori protocol. These included exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks for various dietary supplement and cardiovascular drug combinations. Most studies were short-term efficacy trials.

No data were identified for hospitalization or peripheral arterial disease for any supplement-cardiovascular drug(s) combination.

No evidence on outcomes of clinical efficacy/effectiveness was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, supplemental doses of niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, or vitamin D (with or without calcium) supplementation coadministered with a cardiovascular drug.

### **Key Question 1a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?**

A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of preidentified subgroups or documentation of any dose-response effect.

### **Key Question 1b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?**

No study analyzed statistical interactions between a supplement and a cardiovascular drug in terms of clinical outcomes.

### **Key Question 2. Intermediate cardiovascular efficacy outcomes of cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement**

Evidence for Key Question 2 is shown in Table D.

**Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2**

| Outcome Measure                 | Dietary Supplement + CV Drug (s)  | Conclusion, Effect Estimate   | Applicability  |
|---------------------------------|---|---|--|
| <b>Low strength of evidence</b> |   |   |  |
| Lipid profile                   | Co-Q10 (200 mg/day) + Fenofibrates  | No difference for HDL-C (1 study)<br>MD, 1.55 mg/dL (95% CI, -6.78 to 3.68)   | Mean age: 53 years<br>Mixed gender<br>High CHD risk<br>12 weeks treatment                      |
| Lipid profile                   | Garlic (4 g/day) + Nitrates   | In favor of combination for HDL-C (1 study)<br>MD, 8.40 mg/dL (95% CI, 1.91 to 14.89)   | Unknown age, gender<br>High CHD risk<br>12 weeks treatment                                     |
| Lipid profile                   | Garlic (4 g/day) + Warfarin   | In favor of combination for HDL-C (1 study)<br>MD, 4.50 mg/dL (95% CI, 0.19 to 8.81)  | Mean age: 56 years<br>Mixed gender<br>High CHD risk<br>12 weeks treatment                      |
| Lipid profile                   | Omega-3 fatty acids (3.6 g/day omega-3 to 9.2 g/day fish oil) + Statins             | In favor of combination:<br>TG (2 studies pooled)<br>MD, -74.95 mg/dL (95% CI, -95.80 to -54.10)<br>No difference for:<br>HDL-C (7 studies pooled)<br>MD, 1.70 mg/dL (95% CI, -1.52 to 4.92)<br>LDL-C (6 studies pooled)<br>MD, -1.06 mg/dL (95% CI, -5.28 to 3.16)<br>Achieving LDL-C and HDL-C targets (1 study)<br>RR, 0.93 (95% CI, 0.84 to 1.03) and 1.00 (95% CI, 0.90 to 1.10), respectively | Mean age: 45-63 years<br>Mixed or unclear CHD risk<br>Mixed gender<br>Up to 25 weeks treatment |
| Lipid profile                   | Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin                | In favor of combination for TG (2 studies not pooled)<br>-81.00 mg/dL (95% CI, -125.30 to -36.70) and -54.00 mg/dL (95% CI, -94.1 to -13.90)  | Mean age: 57 years<br>85% males<br>High CHD risk<br>4-6 weeks treatment                        |
| Lipid profile                   | Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole | In favor of CV drug alone for LDL-C (1 study)<br>21.00 mg/dL (95% CI, 3.30 to 38.70)<br>In favor of combination for TG (1 study)<br>-81.0 mg/dL (95% CI, -125.30 to -36.70)   | Mean age: 56 years<br>100% males<br>High CHD risk<br>Up to 12 weeks treatment                  |

**Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2 (continued)**

| Outcome Measure                             | Dietary Supplement + CV Drug (s)                 | Conclusion, Effect Estimate  | Applicability   |
|---|--|--|---|
| <b>Low strength of evidence (continued)</b> |  |  |   |
| Lipid profile                               | Vitamin E (900 mg/day) + Nifedipine              | In favor of combination for LDL-C (1 study) MD, -39.83 mg/dL (95% CI, -71.29 to -8.37)<br>In favor of combination for TG (1 study) MD, -23.91 mg/dL (95% CI, -35.89 to -11.93) | Elderly<br>Mixed gender<br>High CHD risk<br>12 weeks treatment                            |
| Blood pressure                              | Omega-3 fatty acids (2 g/day) + Statins          | In favor of combination for SBP (1 study) MD, -8.50 mmHg (95% CI, -16.33 to -0.66)<br>No difference for DBP (1 study) MD, 0.20 mmHg (95% CI, -4.76 to 5.16)                    | Mean age among groups: 44-53 years<br>Mixed gender<br>Mixed CHD risk<br>5 weeks treatment |
| Blood pressure                              | Omega-3 fatty acids (4 g/day fish oil) + Statins | Median reductions from baseline in SBP (1 study) (-5.00 vs. 0.30 mmHg, p = 0.008) and DBP (-3.30 vs. -1.80 mmHg, p = 0.045)  | Mean age: 58 years<br>Mixed gender<br>Unclear CHD risk<br>6 weeks treatment               |
| Blood pressure                              | Omega-3 fatty acids (3-5 g/day) + ACE inhibitors | No difference between groups for SBP (2 studies pooled): MD, -0.51 mm/Hg (95% CI, -10.59 to 9.57) or for DBP: MD, -1.75 mm/Hg (95% CI, -5.98 to 2.48)                          | Mean age: 40-55 years<br>Mixed gender<br>Unclear CHD risk<br>6-25 weeks treatment         |
| INR   | Vitamin K (150 µg /day) + Anticoagulants         | In favor of combination (1 study) RR for % of time in therapeutic range, 9.0% (95% CI, 1.42 to 16.57)<br>RR for n achieving stable INR, 2.56 (95% CI, 1.24 to 5.28)            | Elderly (age range 58-85 years)<br>Mixed gender<br>Unclear CHD risk<br>25 weeks treatment |

**Table D. Evidence for the gradable intermediate efficacy outcomes—Key Question 2 (continued)**

| Outcome  | Dietary supplement + CV Drug (s)  |
|--|---|
| <b>Insufficient strength of evidence</b>   |   |
| <b>Conclusion: Inconclusive (type II error or inconsistent direction of estimates)</b> |   |
| Lipid profile  | <p><b>All lipid(s):</b><br/>           Coenzyme Q10 (100 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate;<br/>           Garlic (4 g/day) + Warfarin; Garlic (4 mL/day) + Statins/Aspirin<br/> <i>Ginkgo biloba</i> (120 mg/day) + Antiplatelets<br/>           Magnesium (365 mg/day) + Hydrochlorothiazide<br/>           Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 g/day) + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Niacin/Aspirin; Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids + Statins<br/>           Vitamin E (0.6g/day) + Gemfibrozil; Vitamin E (100 mg/day, 100 IU/day) + Statins</p> <p><b>Only specific lipid(s):</b><br/> <b>TG:</b> Niacin (250 mg/day) + Propranolol<br/>           Garlic (4 g/day) + Nitrates<br/>           Omega-3 fatty acids + ACE inhibitors<br/>           Magnesium (4.5 g/day) + Hydrochlorothiazide<br/>           Vitamin E (900 mg/day) + Antiplatelet agents<br/> <b>LDL-C:</b> Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin<br/> <b>HDL-C:</b> Vitamin E (900 mg/day) + Nifedipine<br/>           Omega-3 fatty acids (1.8 g/day) + Calcium channel blockers + Aspirin; Omega-3 fatty acids (3.2 g/day) + Calcium channel blockers + Aspirin + Dipyridamole</p> |
| Blood pressure   | <p>Coenzyme Q10 (200 mg/day) + Fenofibrates (systolic blood pressure)<br/> <i>Echinacea</i> (5 g/day) + Warfarin<br/>           Garlic (4 g/day) + Warfarin<br/> <i>Ginkgo biloba</i> (120 mg/day) + Aspirin; <i>G. biloba</i> (300 mg/day) + Antiplatelet thienopyridines;<br/> <i>G. biloba</i> (120 mg/day) + Cilostazol<br/>           Magnesium (4.5 g/day) + Hydrochlorothiazide; Magnesium (3.65 g/day) + Beta-adrenergic antagonists<br/>           Omega-3 fatty acids (10 g/day) + Aspirin; Omega-3 fatty acids (4 g/day) + Beta-blockers<br/>           Vitamin E (600 mg/day) + Furosemide; Vitamin E (900 mg/day) + Nifedipine; Vitamin E (600 mg/d) + Gemfibrozil</p>   |
| INR  | <p><i>Echinacea</i> (5 g/day) + Warfarin<br/>           Garlic (4 g/day) + Warfarin<br/>           Ginger (3.6 g/day) + Warfarin<br/> <i>Ginkgo biloba</i> (2 g/day) + Warfarin<br/>           Ginseng (1.5-2 g/day) + Warfarin<br/>           Omega-3 fatty acids (4 g/day) + Warfarin</p>   |
| QT prolongation  | Vitamin E (400 IU/day) + Statins  |

**Note:** CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein-cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein-cholesterol; MD = mean difference; RR = relative risk; SBP = systolic blood pressure; TG = triglycerides.

Fifty-seven RCTs and two non-RCTs were included for this Key Question. No relevant observational study was identified. Study participants in most studies had mixed (low and/or moderate) or unclear CHD risk (27.1 percent and 37.3 percent, respectively). Study quality was variable. In the majority of RCTs, the generation of allocation sequence (78 percent) and allocation concealment (93 percent) were unclear. In about 20 percent of studies, participants, health care providers, or outcome assessors were blinded to treatment allocation. This information was not clear for 56 percent of the studies.

The majority of evidence on intermediate outcomes was contributed by small underpowered RCTs whose statistically nonsignificant results with wide confidence intervals could rule out neither important benefits nor harms. Due to this imprecision, the strength of evidence for several gradable outcomes was rated insufficient (inconclusive results). When a significant effect was observed, we graded the strength of evidence to be low because of limitations in the internal validity of studies, surrogacy of outcomes, and generally poor to absent reproducibility among

studies in the direction of effect estimates (Table D). None of the studies reported outcomes evaluating incidence of metabolic syndrome, incidence of hypotension, carotid-intima media thickness, or change in 10-year Framingham risk profile.

**Coenzyme Q10.** Evidence was available from four RCTs with unclear CHD risk (49 Asians with hypercholesterolemia<sup>57</sup>), mixed CHD risk (44 participants with statin-induced myalgia<sup>38</sup>), and high CHD risk (40 participants with diabetes and dyslipidemia<sup>58</sup> and 30 participants with ischemic or idiopathic dilated cardiomyopathy<sup>54</sup>). Overall, no significant differences (grade: insufficient; results inconclusive) were seen between the combination of coenzyme Q10 plus a cardiovascular drug versus drug alone in post-treatment levels of:

- C-reactive protein (statins).
- High-density lipoprotein-cholesterol (HDL-C) (statins or fenofibrate).
- Non-HDL-C (fenofibrate).
- Total cholesterol (statins or fenofibrate).
- Triglycerides (statins or fenofibrate).
- Ejection fraction (ACE inhibitors).
- Systolic blood pressure (SBP) (fenofibrates).

Lowgrade evidence was available from one trial indicating no significant difference in high density lipoprotein-cholesterol (HDL-C) for the combination of coenzyme Q10 plus fenofibrate versus fenofibrates alone.

**Echinacea.** In one small study in 12 healthy male participants (low CHD risk),<sup>59</sup> post-treatment levels of INR and platelet aggregation were not significantly different in the combination of Echinacea plus warfarin than with warfarin alone. The results were inconclusive.

**Garlic.** Four studies examined the effects of garlic in combination with warfarin (48 participants with unclear CHD risk<sup>60</sup> and 16 males with low CHD risk<sup>61</sup>), nitrates (60 participants with high CHD risk<sup>62</sup>), and statins plus aspirin (19 participants with high CHD risk<sup>63</sup>).

The effect of garlic plus warfarin versus warfarin alone on post-treatment lipid profile, blood pressure, INR, platelet aggregability, and platelet count was not significant (inconclusive; grade: insufficient)<sup>60,61</sup> except for significant improvement of HDL-C levels for garlic plus warfarin versus warfarin alone (grade: low).<sup>60</sup>

In participants with coronary artery disease (high CHD risk), the combination of garlic plus nitrates<sup>62</sup> significantly improved total cholesterol (MD, -28.20 mg/dL [95 percent CI, -48.30 to -8.10]) and HDL-C levels, but not triglyceride levels (MD, -10.30 mg/dL [95 percent CI, -27.60 to 7.00]).

The effects of garlic combined with statins plus aspirin<sup>63</sup> on lipid profile, C-reactive protein, platelet count, and Agaston calcium score were not significantly different from those of statins plus aspirin in participants with coronary artery disease (Framingham risk >20 percent).

**Ginger.** In one trial of 12 healthy male participants there was no significant difference in post-treatment INR (inconclusive; grade: insufficient) or platelet aggregability between participants taking the combination of ginger plus warfarin versus warfarin alone.<sup>64</sup>

**Ginkgo biloba.** Five RCTs investigated this supplement in combination with antiplatelet agents (acetylsalicylic acid,<sup>65,66</sup> clopidogrel,<sup>67</sup> or ticlopidine<sup>68</sup>), an anticoagulant (warfarin<sup>64</sup>), or a

vasodilator (cilostazol<sup>67</sup>). For *G. biloba* plus antiplatelet agents (104 participants in total, mixed CHD risk),<sup>65,66</sup> the differences in clotting time, partial thromboplastin time, platelet count, lipid parameters, and blood pressure were not significant (results for lipids and blood pressure inconclusive; grade: insufficient).

The pooled results of two trials (24 participants with mixed CHD risk,<sup>68</sup> 10 participants with low CHD risk<sup>67</sup>) indicated no significant differences in platelet aggregation and bleeding time between the *G. biloba* plus antiplatelet combination versus antiplatelet-only groups. Similarly, *G. biloba* (200 mg of *G. biloba* leaf, 9.6 mg of ginkgo flavonglycosides, 2.4 mg of ginkgolides and bilobalide three times/day) plus warfarin did not result in significantly different post-treatment levels of platelet aggregability or INR (result for INR inconclusive; grade: insufficient) in 12 healthy males.<sup>64</sup> In one trial, however,<sup>67</sup> platelet aggregability (MD, 18.00 percent [95 percent CI, 1.92 to 34.08]) and bleeding time (MD, 1.02 minutes [95 percent CI, 0.10 to 1.94]) were significantly better in the *G. biloba* plus cilostazol combination group than the cilostazol-only group.

**Ginseng.** Three RCTs investigated various ginseng products in combination with warfarin.<sup>69-71</sup> The results from these studies for INR were conflicting (inconclusive; grade: insufficient). Two trials showed no significant difference (25 participants with high CHD risk,<sup>69</sup> 12 males with low CHD risk<sup>71</sup>). One trial (20 participants with low CHD risk<sup>70</sup>) showed a significant difference, with lower peak INR and AUC of INR in the combination versus control group (MD, -0.19 [95 percent CI, -0.36 to -0.07] for peak INR and -0.43 [95 percent CI -1.00 to -0.09] for AUC of INR). The differences in prothrombin time,<sup>69</sup> platelet count,<sup>69</sup> or platelet aggregability<sup>71</sup> between the ginseng-warfarin combination and warfarin-only groups were not significant (results were inconclusive).

**Hawthorn.** One small trial<sup>72</sup> found no significant difference in an ECG measure (PR interval, which is measured from the beginning of the P wave to the beginning of the QRS complex) between participants receiving hawthorn plus digoxin and those receiving digoxin alone (results inconclusive) in 11 adults at low risk for CHD.

**Magnesium.** Three RCTs investigated oral magnesium in combination with hydrochlorothiazide<sup>73,74</sup> or beta-adrenergic antagonists<sup>42</sup> in participants with hypertension. In two trials, SBP and DBP (diastolic blood pressure) did not differ significantly between the magnesium hydrochlorothiazide combination versus hydrochlorothiazide-alone groups in the study with 18 participants with unclear CHD risk<sup>73</sup> or the study with 21 participants with low/moderate CHD risk<sup>74</sup> (inconclusive; grade: insufficient). Similarly, in another study,<sup>42</sup> neither SBP nor DBP was significantly different in 39 participants receiving the combination of magnesium plus beta-adrenergic antagonists versus those receiving beta-adrenergic antagonists alone. In one trial,<sup>73</sup> post-treatment total cholesterol and triglyceride levels were not significantly different between the magnesium-hydrochlorothiazide combination versus hydrochlorothiazide-alone groups (inconclusive; grade: insufficient).

**Niacin (no more than 250 mg/day).** One RCT in 28 participants with hyperlipoproteinemia (unclear CHD risk)<sup>75</sup> investigated niacin in combination with propranolol. Post-treatment levels of triglycerides and total cholesterol were not significantly different between the group receiving niacin plus propranolol and the groups receiving propranolol alone (inconclusive; grade:

insufficient). This study was judged to be at high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg).

**Omega-3 fatty acids.** Twenty-four RCTs investigated the use of omega-3 fatty acids plus cardiovascular drugs (statins, ACE inhibitors, calcium channel blockers alone or with other cardiovascular drugs, fenofibrates, niacin plus aspirin, aspirin, beta-blockers, or an anticoagulation agent) versus cardiovascular drugs alone.

The effect on post-treatment triglyceride (TG) levels of adding the supplement to statins was modified according to baseline levels of triglycerides. Specifically, in participants with higher mean baseline levels of TG (greater than 200 mg/dL) there was a statistically significant pooled mean reduction in post-treatment TG levels in the combination arm (two trials, grade: low).<sup>40,76</sup> In contrast, the meta-analysis of four studies with participants with lower levels of TG at baseline (under 200 mg/dL) showed no significant difference between the groups (grade: insufficient). Pooled analyses for levels of HDL-C (seven trials), LDL-C (six trials), and total cholesterol (six trials) showed no significant differences (grade: low) in participants with mixed or unclear CHD risk. The mean SBP was significantly lowered in the supplement-statin combination group (grade: low) in 22 participants with hyperlipemia. Evidence was inconclusive for the outcomes of total cholesterol/HDL-C ratio, non-HDL-C, lipoprotein A, diastolic blood pressure, and bleeding time. Additionally, for nongradable outcomes such as C-reactive protein and blood coagulation parameters (prothrombin time (PT), activated partial thromboplastin time [aPTT], platelet aggregation), there were no significant differences between combination and control groups.

Trials of 43 elderly males undergoing angioplasty using omega-3 fatty acids-statins combinations reported post-treatment levels of non-HDL-C, total cholesterol/HDL-C ratio, and platelet count that were conflicting (opposite direction of effect estimates) and thus inconclusive (grade: insufficient).

In trials using omega-3 fatty acids-ACE inhibitors combination treatment, there were no changes in blood pressure (no difference; grade: low), but significantly more participants experienced at least 50 percent reduction in proteinuria in favor of the combination treatment (RR, 4.00 [95 percent CI, 1.40 to 11.30]).<sup>77</sup>

In one trial using omega-3 fatty acids-fenofibrate combination treatment in participants with high triglyceride levels,<sup>56</sup> the incidence of hypertension was not significantly different in the combination versus control group (RR, 0.98 [95 percent CI, 0.14 to 6.85]).

In one trial<sup>50</sup> using omega-3 fatty acids-calcium channel blockers combinations, there was no significant difference between the combination and control groups in post-treatment lipid profile (inconclusive; grade: insufficient). Two other trials using aspirin in addition to calcium channel blockers found significant differences in triglycerides (grade: low) in favor of the combination treatment.<sup>51,52</sup> These trials were not pooled because dipyridamole was an additional drug in one trial and not in another.

In one underpowered trial (14 participants with atherogenic dyslipidemia, unclear CHD risk<sup>78</sup>), post-treatment lipid profile did not differ significantly between the combination of omega-3 fatty acids plus niacin and aspirin versus niacin and aspirin (inconclusive; grade: insufficient). In one trial (11 participants with unclear CHD risk), treatment with 3 or 6 g/day omega-3 fatty acids plus warfarin versus warfarin resulted in no significant difference in post-treatment INR values between groups (no numeric data provided).

**Vitamin E.** Ten RCTs and one controlled clinical trial<sup>79</sup> examined the use of vitamin E with antiplatelet agents (aspirin or ticlopidine),<sup>80</sup> aspirin,<sup>49</sup> furosemide,<sup>81</sup> gemfibrozil,<sup>79</sup> nifedipine,<sup>82</sup> or statins.<sup>46,83-87</sup>

In one trial,<sup>80</sup> post-treatment total cholesterol and triglyceride levels were not significantly different between the groups receiving vitamin E-antiplatelet agent (aspirin or ticlopidine) combination versus aspirin or ticlopidine alone in 16 participants with carotid atherosclerosis (inconclusive; grade: insufficient). Platelet aggregation was significantly decreased with vitamin E supplementation plus aspirin compared with aspirin alone (MD, -1.70 per cm<sup>2</sup> [95 percent CI, -2.06 to -1.34]).<sup>49</sup>

The effect of vitamin E-furosemide combination on blood pressure was not significantly different from that of furosemide alone in 24 participants with essential hypertension (inconclusive; grade: insufficient).<sup>81</sup> The vitamin E-nifedipine combination significantly lowered total cholesterol (MD, -35.96 mg/dL [95 percent CI, -46.96 to -24.96]), LDL-C (grade: low), and triglycerides (grade: low), but not HDL-C (inconclusive, grade: insufficient) or SBP (inconclusive, grade: insufficient) in 30 elderly subjects at high risk of CHD.<sup>82</sup>

There was no significant difference in lipid profile across trials using vitamin E-gemfibrozil or vitamin E-statins combinations when compared with the cardiovascular drug alone (inconclusive; grade: insufficient). (See pooled analyses for HDL-C, LDL-C, total cholesterol, and triglycerides.) Likewise, there was no significant difference in blood pressure (inconclusive; grade: insufficient) for vitamin E-gemfibrozil combination, and no significant difference in C-reactive protein, prothrombin time, and platelet count for vitamin E-statins combinations compared with cardiovascular drug(s) alone.

**Vitamin K.** In one trial,<sup>41</sup> percentage of time INR was in therapeutic range was improved in the group receiving vitamin K-coumarin derivative (warfarin) combination compared with warfarin alone. In addition, number of participants achieving stable INR was higher in combination than with warfarin alone.

Overall evidence indicates that supplementation with vitamin K may improve the stability of anticoagulant therapy (grade: low).

**Other supplements.** No evidence was identified for effects of red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on intermediate outcomes.

**Key Question 2a.** Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

**Key Question 2b.** Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular efficacy outcomes?

Two studies contributed to the evidence regarding statistical interaction between cardiovascular drugs and dietary supplements for this section.<sup>44,78</sup> One study assessed statistical interaction using general linear modeling.<sup>44</sup> No significant interactions were observed between the combination of omega-3 fatty acids and statins with regard to changes in lipid profile (HDL-



C, LDL-C, total cholesterol, triglycerides, non-HDL-C) in 52 obese men with dyslipidemia and insulin resistance (moderate/moderately high risk for CHD).<sup>44</sup> Authors of another trial<sup>78</sup> conducted a formal assessment of statistical interaction using ANOVA (analysis of variance) and found that the decrease in triglyceride levels resulting from the combination of omega-3 fatty acids plus niacin was more than twice the additive effect of either therapy alone in 29 participants with atherogenic dyslipidemia (unclear CHD risk).

### Key Question 3. Clinical or intermediate harms with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement

Evidence for Key Question 3 is shown in Table E.

**Table E. Evidence for the gradable harms outcomes—Key Question 3**

| Outcome Measure   | Dietary Supplement + CV Drug(s)   |
|---|---|
| <b>Insufficient strength of evidence</b>  |   |
| <b>Conclusion: Inconclusive (type II error or inconsistent direction of estimates)</b>                    |   |
| Serious adverse events  | Coenzyme Q10 (100-200 mg/day) + Statins<br><i>Ginkgo biloba</i> (300 mg/day) + ASA; <i>G. biloba</i> + Warfarin<br>Magnesium (365 mg/day) + Beta-adrenergic antagonists<br>Omega-3 fatty acids (3-4 g/day) + Statins or fenofibrate   |
| Withdrawal due to adverse events  | Coenzyme Q10 (3-4 g/day) + Statins or fenofibrate<br><i>Echinacea</i> (5 g/day) + Warfarin<br><i>Ginkgo biloba</i> (40 mg/day) + ASA and/or pentoxifylline; <i>G. biloba</i> (2 g/day) + Warfarin; <i>G. biloba</i> (240 mg/day) + Digoxin<br>Ginseng (3 g/day) + Warfarin<br>Magnesium (365 mg/day) + Hydrochlorothiazide; Magnesium (365 mg/day) + Beta-adrenergic antagonists<br>Niacin (250 mg/day) + Beta-adrenergic antagonists<br>Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan;<br>Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (4 g/day) + Fenofibrate; Omega-3 fatty acids (3 or 6 g/day) + Warfarin<br>Vitamin E (400 IU/day) + ASA; Vitamin E (1350 IU/day) + Nifedipine |
| Bleeding (major, minor, and undefined)  | Garlic (10 mL/day) + Warfarin<br><i>Ginkgo biloba</i> (300 mg/day) + ASA<br>Ginseng (3 g/day) + Warfarin<br>Omega-3 fatty acids (4 g/day) + ASA; Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (3 g/day) + Ramipril and/or irbesartan;<br>Omega-3 fatty acids (4 g/day) + ASA + Dipyridamole + Calcium channel blockers; Omega-3 fatty acids (mean 3 g/day) + ASA + Clopidogrel;<br>Omega-3 fatty acids (3 or 6 g/day) + Warfarin<br>Vitamin E (400 IU/day) + ASA<br>Vitamin K (5 mg/day) + Warfarin   |
| Renal dysfunction (abnormal glomerular filtration rate, creatinine, blood urea nitrogen, serum potassium) | Coenzyme Q10 (100-200 mg/day) + ACE inhibitors; Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (200 mg/day) + Fenofibrate<br><i>Ginkgo biloba</i> (300 mg/day) + ASA; <i>G. biloba</i> (80 mg/day) + Ticlopidine<br>Magnesium (365 mg/day) + Hydrochlorothiazide<br>Omega-3 fatty acids (4-9 g/day) + Statins; Omega-3 fatty acids (4 g/day) + Fenofibrate<br>Vitamin E (400 IU/day) + Statins; Vitamin E (1350 IU/day) + Nifedipine   |
| Hepatotoxicity (abnormal liver enzymes)   | Coenzyme Q10 (100-200 mg/day) + Statins; Coenzyme Q10 (100-200 mg/day) + ACE inhibitors<br>Omega-3 fatty acids (4-9 g/day) + Statins<br>Vitamin E (400 IU/day) + Statins  |
| Corrected QT interval   | Vitamin E (400 IU/day) + Statins  |

**Note:** ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid (aspirin); CV = cardiovascular.

A total of 58 studies contributed evidence for Key Question 3. One included study was a retrospective cohort study examining omega-3 fatty acids and antiplatelet agents; it had important limitations in design and reporting, as it was unclear regarding participant selection, confounding, and blinding of outcome assessors.<sup>88</sup> The rest of the studies were RCTs, mostly of moderate risk of bias for the gradable outcomes of harms (serious adverse events, withdrawal due to adverse events, renal dysfunction, hepatotoxicity, QT interval, and bleeding). Most of these studies recruited a small number of participants and were underpowered for the outcomes of harm.

Meta-analyses were possible for some omega-3 fatty acids studies. Other evidence could not be pooled because either there was a single study per outcome or zero events in both treatment arms.

For all combinations of dietary supplement and cardiovascular drug, the strength of evidence for all gradable outcomes was insufficient due to inconsistent effect estimates across studies suggesting conflicting findings with no obvious explanation or statistically nonsignificant estimates with wide confidence intervals (Table E). Most crossover trials incorporated an adequate washout period, so carryover effect was not a major concern.

**Coenzyme Q10.** Five short-term (up to 12 weeks duration) small RCTs that included participants with mixed (moderate and high risk)/unclear<sup>38,57,89</sup> or high<sup>54,58</sup> CHD risk examined coenzyme Q10 plus statins, fenofibrate, ACE inhibitors, or, in one study, vitamin E added to statins. No statistically significant differences were observed for total adverse events,<sup>54,57</sup> abnormalities in fasting blood glucose,<sup>57,58</sup> myoglobin,<sup>57</sup> creatine phosphokinase (CPK),<sup>57,58,89</sup> electrocardiogram (ECG),<sup>58</sup> or retinopathy.<sup>58</sup> However, the studies were underpowered to detect differences in these harms.

One RCT of 32 participants with statin-induced myopathic symptoms<sup>89</sup> found a significantly greater number of subjects with reduced myopathic pain (RR, 4.18 [95 percent CI, 1.50 to 11.46]) and lower pain severity scores on the Brief Pain Inventory (MD, -1.76 [95 percent CI, -2.93 to -0.58]) and pain interference score (MD, -1.43 [95 percent CI, -2.76 to -0.10]) in the combination group (coenzyme Q10 100 mg/day plus statins) versus vitamin E (400 IU/day) plus statin group. A small pilot RCT of 44 participants with self-reported myalgia unable to take adequate doses of statins<sup>38</sup> did not find a significant difference in myalgia, using a visual analog scale, or in number of participants tolerating simvastatin (RR, 1.23 [95 percent CI, 0.80 to 1.90]) in participants taking coenzyme Q10 plus statins versus statin-alone groups.

**Echinacea.** One small RCT of 12 healthy volunteers examined Echinacea plus a single dose of warfarin versus warfarin alone. No withdrawals due to adverse events or other adverse events were observed.<sup>59</sup>

**Garlic.** Four small short-term RCTs examined garlic in combination with warfarin, nitrates, or statins plus aspirin in healthy males<sup>61</sup> or those with cardiovascular conditions.<sup>60,62,63</sup> No significant between-group differences were observed across gradable and nongradable outcomes such as fasting blood glucose,<sup>60,62,63</sup> anemia,<sup>60</sup> and leukopenia.<sup>63</sup> Wide confidence intervals for differences in bleeding and fasting blood glucose precluded drawing any meaningful conclusions.

**Ginkgo biloba.** Seven small RCTs examined G. biloba plus warfarin, digoxin, aspirin, aspirin and/or pentoxifylline, nitrates, cilostazol or clopidogrel, or ticlopidine.<sup>48,64-68,90</sup> The subjects either were healthy volunteers,<sup>64,65,67,68,90</sup> had experienced acute ischemic stroke,<sup>48</sup> or had peripheral arterial disease.<sup>66</sup> Two of these studies included only a single dose of cilostazol/clopidogrel<sup>67</sup> or ticlopidine,<sup>68</sup> so their results should be interpreted with caution. Across all cardiovascular medications, nonsignificant results were observed for gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, hepatotoxicity, and serious adverse events). Nonsignificant results were also found for all other harms, such as total adverse events,<sup>66,67,90</sup> upset stomach,<sup>66</sup> anemia,<sup>65,66</sup> abnormal white blood cell count,<sup>65</sup> gastrointestinal events,<sup>48,90</sup> diarrhea,<sup>64</sup> constipation,<sup>64</sup> hypoglycemia,<sup>66</sup> hyperglycemia,<sup>66</sup> leukopenia,<sup>66</sup> thrombocytopenia,<sup>66</sup> and abnormal ECG.<sup>66</sup> These studies were underpowered to detect any differences in harms outcomes.

**Ginseng.** Three RCTs examined the effects of Panax ginseng,<sup>69,71</sup> American ginseng,<sup>70</sup> and Korean ginseng<sup>71</sup> plus warfarin versus warfarin alone. No statistically significant effects were observed in gradable outcomes (i.e., withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity) or nongradable outcomes such as prothrombin time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, constipation, hematocrit, and anemia.<sup>69</sup> These trials were all small and underpowered.

**Hawthorn.** One RCT examined hawthorn plus digoxin versus digoxin alone in eight healthy volunteers.<sup>72</sup> No statistically significant differences were observed in incidence of flatulence, nausea, insomnia, headache, and dizziness.

**Magnesium.** Two small RCTs in hypertensive subjects examined the effects of magnesium plus hydrochlorothiazide or beta-adrenergic antagonists.<sup>42,73</sup> No statistically significant differences were observed for withdrawal due to adverse events,<sup>42,73</sup> renal dysfunction,<sup>42,73</sup> serious adverse events,<sup>42</sup> diarrhea,<sup>73</sup> vomiting,<sup>73</sup> nausea,<sup>73</sup> adverse events,<sup>73</sup> hypercalcemia,<sup>73</sup> abnormal fasting blood glucose,<sup>73</sup> or abnormal ECG.<sup>73</sup>

**Niacin (not more than 250 mg/day).** One RCT of 20 subjects with hyperlipoproteinemia investigated the effects of niacin plus propranolol versus propranolol alone.<sup>75</sup> No statistically significant differences were found in nausea and flushing or in hypotension. This study was at high risk of bias because groups received different dosages of propranolol (20 mg in combination group and 60 mg in monotherapy group).

**Omega-3 fatty acids.** Twenty-two studies (21 RCTs and 1 retrospective cohort study) examined omega-3 fatty acids plus statins,<sup>36,37,40,53,91-97</sup> aspirin,<sup>47,52,78,98,99,99</sup> aspirin and clopidogrel,<sup>88</sup> aspirin in combination with dipyridamole and calcium channel blockers,<sup>52</sup> warfarin,<sup>47,55</sup> ramipril and/or irbesartan,<sup>77</sup> or fenofibrate.<sup>56</sup> These studies were generally small and underpowered. They recruited healthy subjects, or subjects with CHD or risk factors for CHD.

For omega-3 fatty acids plus statins versus statins alone, meta-analyses yielded nonsignificant estimates for serious adverse events, withdrawal due to adverse events, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total adverse events, dyspepsia, headache, constipation, upper respiratory infection, and elevated creatine kinase (CK)/creatinine phosphokinase (CPK). However, a significantly elevated fasting blood glucose in

the omega-3 fatty acids plus statin group was observed in one RCT.<sup>40</sup> For omega-3 fatty acids in combination with other cardiovascular drugs, no significant differences were found in harms outcomes.

**Vitamin E.** Ten RCTs examined vitamin E plus aspirin,<sup>39,49,100</sup> nifedipine,<sup>82</sup> furosemide,<sup>81</sup> or statins.<sup>46,83,84,86,87</sup> No statistically significant differences were observed for total adverse events,<sup>100</sup> incidence of headache,<sup>100</sup> gastrointestinal discomfort,<sup>100</sup> incidence of cancer,<sup>39</sup> abnormalities in fasting blood glucose,<sup>81,82</sup> glycosylated hemoglobin,<sup>87</sup> leukopenia,<sup>46</sup> or anemia.<sup>46</sup> These studies recruited subjects who were healthy, or who had CHD or risk factors for CHD. Sample sizes were generally small, except for one study that recruited over 9,000 women.<sup>39</sup>

**Vitamin K.** One RCT of 6 months duration examined the effects of vitamin K plus warfarin versus warfarin alone.<sup>41</sup> No significant differences were found for bleeding<sup>41</sup> or withdrawal due to adverse events.<sup>41</sup> This study recruited 70 participants with indications for anticoagulant therapy.

**Other supplements.** No evidence on clinical harms was identified for the effects of ginger, red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs.

**Key Question 3a. Do the effect estimates of clinical or intermediate harms vary by age, ethnicity, gender, or health status?**

Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

**Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?**

One RCT presented data that would allow examination of the interaction between vitamin E supplements and the cardiovascular medication aspirin. This RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events) among treatment regimes.<sup>100</sup>

**Key Question 4. Pharmacokinetic outcomes with cardiovascular drug(s) plus supplement versus drug(s) plus placebo, no supplement, or another supplement**

Evidence for Key Question 4 is shown in Table F.

**Table F. Strength of evidence for the gradable pharmacokinetic outcomes—Key Question 4**

| Outcome Measure  | Dietary Supplement + CV Drug(s)   | Conclusion                             | Applicability of Evidence  |
|--|---|--|--|
| <b>Low strength of evidence</b>  |   |  |  |
| AUC <sub>∞</sub> , C <sub>max</sub> , half-life, and clearance (S- and R-warfarin)                   | <i>Echinacea</i> (5 g/day) + Warfarin<br>Ginger (3.6 g/day) + Warfarin<br><i>Ginkgo biloba</i> (25 mg single dose) + Warfarin | No clinically significant interactions | Healthy volunteer pharmacokinetic studies using single dose of 25 mg warfarin  |
| AUC <sub>∞</sub> , half-life, and clearance (S- and R-warfarin)                                      | Garlic (4 g/day) + Warfarin   | No clinically significant interactions | Healthy volunteer pharmacokinetic study using single dose of 25 mg warfarin  |
| AUC <sub>∞</sub> , half-life, and C <sub>max</sub> (ticlopidine)                                     | <i>Ginkgo biloba</i> (80-240 mg/day) + Ticlopidine  | No clinically significant interactions | Healthy Korean males given single dose of 250 mg of ticlopidine  |
| C <sub>max</sub> , half-life, and clearance (S- and R-warfarin)                                      | Ginseng (25 mg single dose) + Warfarin  | No clinically significant interactions | Healthy volunteer pharmacokinetic study of American and Korean ginseng and either 3 doses of 5 mg warfarin over 3 days of week 1 and week 4 or a single dose of 25 mg warfarin |
| AUC <sub>ss</sub> , C <sub>max</sub> (statin)  | Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin  | No clinically significant interactions | Healthy volunteer studies based on therapeutic doses of statins for 14 days  |
| <b>Outcome Measure</b>   |   | <b>Dietary Supplement + CV Drug</b>    |  |
| <b>Insufficient strength of evidence</b>   |   |  |  |
| <b>Conclusion: Inconclusive (potential for type II error or inconsistent direction of estimates)</b> |   |  |  |
| C <sub>max</sub> (S- and R-warfarin)   | Garlic (4 g/day) + Warfarin   |  |  |
| AUC <sub>∞</sub> , C <sub>max</sub> , half-life, and clearance (digoxin)                             | <i>Ginkgo biloba</i> (80-240 mg/day) + Digoxin  |  |  |
| AUC <sub>∞</sub> (warfarin)  | Ginseng (3 g/day) + Warfarin  |  |  |
| Half-life and clearance (rosuvastatin and atorvastatin and/or metabolites)                           | Omega-3 fatty acids (4 g/day) + Rosuvastatin or atorvastatin  |  |  |
| AUC <sub>ss</sub> , C <sub>max</sub> , half-life, and clearance (beta-hydroxysimvastatin)            | Omega-3 fatty acids (4 g/day)/ + Simvastatin;<br>Garlic (3600µg of allicin twice daily) + Statins                             |  |  |
| AUC <sub>∞</sub> , C <sub>max</sub> , half-life, and clearance (digoxin)                             | Hawthorn (900 mg/day) + Digoxin   |  |  |

**Note:** AUC<sub>∞</sub> = area under the curve to infinity; AUC<sub>ss</sub> = area under the curve at steady-state; C<sub>max</sub> = maximum concentration; CV = cardiovascular.

Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes.<sup>36,59,61,64,68,70-72,90,93,95,101</sup> No data were available from observational studies. Generally, these studies were open-label crossover RCTs of moderate risk of bias for the gradable outcomes, including between 8 and 50 healthy volunteers. Six studies investigated cardiovascular drug kinetics following a single dose.<sup>59,61,64,68,71,90</sup> The clinical significance of the interaction was evaluated using the FDA guidance.<sup>30</sup> According to this guidance, the statistical significance of interactions alone cannot determine the clinical significance of interactions. Interactions are deemed significant when the 90 percent confidence intervals of the geometric mean ratio (GMR) fall clearly outside of the default no-effect range of 0.80 to 1.25.

It must be noted that the evidence of pharmacokinetic interactions may not translate into altered clinical effectiveness or harms. Also, evidence originating in healthy young adults may

not be applicable to older CVD patients taking cardiovascular drugs due to possible differences in abilities to absorb, metabolize, and excrete drugs.

**Echinacea.** Evidence of low strength demonstrated no clinically significant interactions between a mixture of 600 mg of *Echinacea angustifolia* root plus 675 mg of *E. purpurea* root given four times a day for a period of 2 weeks and a single dose of 25 mg warfarin. The 90 percent upper and lower bound of GMR for the individual warfarin pharmacokinetic parameters were within the 0.80 to 1.25 boundaries of bioequivalence (Table F).<sup>59</sup>

**Garlic.** Interactions of 7.4 mg/day of allicin pretreatment for 2 weeks with a single dose of 25 mg warfarin are unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.<sup>61</sup> Evidence from one garlic-statin trial demonstrated insufficient evidence for pharmacokinetic interactions between the supplement (3600 µg of allicin twice daily) and 20 mg single doses of both simvastatin and pravastatin.<sup>101</sup> Interactions and bioequivalence could not be clearly established.

**Ginger.** Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with ginger and a single 25 mg dose of warfarin.<sup>64</sup>

**Ginkgo biloba.** Evidence of low strength demonstrated no clinically significant interactions between 7-day pretreatment with *G. biloba* and a single 25 mg dose of warfarin.<sup>64</sup> Low-strength evidence revealed no clinically significant interactions between single doses of *G. biloba* and ticlopidine.<sup>68</sup> Insufficient evidence addressed interactions between 7-day pretreatment with *G. biloba* and single doses of digoxin. While pharmacokinetic outcomes showed statistically nonsignificant changes, data were not reported as GMRs, so meaningful conclusions could not be drawn.<sup>90</sup>

**Ginseng.** *Panax ginseng* (Korean ginseng) coadministered with warfarin demonstrated no clinically significant interactions based on evidence of low strength.<sup>71</sup> In contrast, interactions of American ginseng (*P. quinquefolius* 2 g/day from weeks 2 to 4) with warfarin were unclear. Low-strength evidence suggested no clinically relevant interactions for some pharmacokinetic outcomes, while for other important outcomes the strength of evidence was graded as insufficient.<sup>70</sup>

**Hawthorn.** In a trial of hawthorne (84.3 mg/day of oligomeric procyanidines) added to digoxin for 21 days versus digoxin alone for 10 days, no significant differences in pharmacokinetic outcomes were observed between groups. As analyses evaluated mean differences instead of GMRs, we could not exclude type II error and graded the strength of evidence as insufficient for clinically significant interactions.<sup>72</sup>

**Omega-3 fatty acids.** Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between omega-3 fatty acids and various statins.<sup>36,93,95</sup> Each study compared a statin (rosuvastatin, atorvastatin, or simvastatin) coadministered with 4 g/day of omega-3 fatty acids versus statin alone over a 14-day period. Insufficient evidence for interactions with simvastatin precluded meaningful conclusions about interactions because

pharmacokinetic outcomes were analyzed as differences in arithmetic means, yielding nonsignificant results with potential for type II error.<sup>95</sup> Interactions with rosuvastatin or atorvastatin were unclear because for some of the pharmacokinetic outcomes there was low-strength evidence suggesting no clinically relevant interactions, while for other important pharmacokinetic outcomes the strength of evidence was graded as insufficient.<sup>36,93</sup>

**Other supplements.** No studies were found examining pharmacokinetic interactions between a cardiovascular drug and coenzyme Q10, magnesium, niacin (no more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K.

#### Key Question 4a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

A paucity of evidence for supplement-drug combinations precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender.

#### Key Question 4b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

Statistical interaction data were not reported in any pharmacokinetic study.

## Discussion

Patients with cardiovascular disease commonly take dietary supplements along with prescription drugs, but this review uncovered a paucity of high-quality research into benefits and interactions of drugs coadministered with some of the most common supplements. No trials were identified for most potential combinations, while those that were found were generally underpowered efficacy trials of short duration in highly selected populations.

Clinical outcomes were reported in a sparse collection of inconclusive trials; therefore, evidence on important gradable clinical outcomes was rated insufficient. Findings of note include inconsistent evidence of decrease in rates of coronary artery restenosis following successful angioplasty with coadministration of omega-3 fatty acids in two trials with aspirin and other cardiovascular drugs. Also, evidence from a well-powered pragmatic trial in women showed no benefit of adding vitamin E to daily aspirin on the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death; evidence on individual vascular events was not available.

For most intermediate outcomes of efficacy, such as lipid profile, blood pressure, and INR, we found either insufficient evidence or evidence of low strength demonstrating no effect; however, evidence indicated that omega-3 fatty acids (2 to 4 g/day) likely do not interfere with the efficacy of statin therapy or calcium channel blockers in the presence of antiplatelet agents, but may provide independent benefit in resolving hypertriglyceridemia. There is evidence of low strength that supplemental vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin. Also, garlic (4 to 10 g/day) may not interact negatively with nitrates and warfarin, and may confer independent benefit in improving HDL-C and total cholesterol. However, our confidence in the validity and reproducibility of these benefits on intermediate outcomes is low.

Safety of intake of dietary supplements concomitant with prescription cardiovascular medications is largely unclear due to insufficient evidence. Evidence regarding benefit of

coenzyme Q10 in reducing myalgia in participants with statin-induced myopathic pain is based on two small RCTs and is inconclusive. One study found benefit of supplementation of coenzyme Q10 versus vitamin E added to statins, while another pilot study reported no significant differences between groups using simvastatin with or without coenzyme Q10 in myalgia and tolerance for statin therapy.

Evidence of low strength demonstrated no clinically significant pharmacokinetic interactions when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin or when *G. biloba* was coadministered with ticlopidine. Insufficient or conflicting evidence addressed most other supplement-drug pharmacokinetic interactions.

Without an adequate evidence base from the literature, variability in effects across clinically important subgroups (e.g., age, ethnicity, gender, and health status) could not be assessed.

Limitations of our systematic review process include our restriction of the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Up to 30 percent of included studies were assessed to have potential for financial conflict of interest, and approximately 45 percent did not report funding information. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in the presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.<sup>102,103</sup> In fact, a recent recommendation is that tests for funnel plot asymmetry should be used only in a minority of meta-analyses that include at least 10 studies of unequal sizes per analysis without substantial heterogeneity in their effect sizes.<sup>104</sup> We did not adopt other means of evaluating publication bias and selective outcome reporting, such as comparing publications with study protocol, because of time and resource limitations. Seemingly, another limitation could be the exclusion of indirect evidence of drug interactions derived from surrogate measures, such as alterations in probe drug metabolism, that highlight effects on enzymes involved in drug metabolism. As such evidence traditionally originates in healthy volunteers, the applicability of such evidence would have been as much of a concern as for the pharmacokinetic outcomes we examined, whose applicability was restricted to healthy volunteers with uncompromised drug metabolism. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs. For example, a given combination of multivitamins coadministered with a cardiovascular drug or drugs would be limited both in causal inference of supplement–drug(s) interactions and in applicability to the specific doses and combinations of vitamins employed as intervention in the study. Finally, we considered potential benefits, harm, or bioequivalence independently for pharmacokinetic outcomes, according to the FDA guidance.<sup>30</sup> In the absence of guidance regarding intermediate outcomes, we did not draw conclusions on the two sides of clinical decisionmaking, such as “unknown benefit but harm is unlikely” and “unknown harm but benefit is unlikely.”

Available evidence poorly addresses the safety and effectiveness of coadministration of dietary supplements with cardiovascular drugs. Given the steady increase in the use of dietary supplements for self-care and the identified gaps in research, we make the following recommendations for future research.

1. First and foremost, future research with dietary supplements should involve substances for which the identity of the agents can be clearly ascertained and the chemical composition well characterized and, ideally, standardized. If the active ingredients or biologic activity of these substances is not known, then studies to characterize these variables, identify mechanisms of action, and describe safety should precede clinical



efficacy studies. According to the 2011-15 strategic plan of the National Center for Complementary and Alternative Medicine (NCCAM), clinical trials of dietary supplements will not be supported without documentation of biology and mechanism of action.<sup>105</sup>

2. As extant literature is largely based on few small-size efficacy studies of limited internal validity examining intermediate outcomes, future supplement-cardiovascular drug interaction trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical effectiveness and harms outcomes.
3. Most studies were conducted in specialty settings, excluded patients with comorbidities or uncontrolled comorbidities, and did not include ethnic and racial minorities; prospective trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also collect data and undertake subgroup analysis for age, gender, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme.
4. A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes according to FDA guidance for bioequivalence studies.<sup>30</sup> Future experiments of drug interactions must evaluate pharmacokinetic outcomes as geometric mean ratios with predefined margins of bioequivalence. Future studies of drug interactions must report pharmacokinetic outcomes as geometric mean ratios. This would allow statistically significant as well as nonsignificant outcomes to be interpreted in terms of clinical significance, using predefined margins of bioequivalence.
5. Given the dearth of studies examining interactions between specific supplements and cardiovascular drugs, future clinical trials and observational studies that explore the effect of cardiovascular drugs should additionally assess the use of dietary supplements and include this in the reporting of results. One way to facilitate this would be to consider inclusion of inquiry about dietary supplement use and other CAM care in reporting guidelines such as CONSORT (CONsolidated Standards of Reporting Trials).
6. Phase I trials of cardiovascular drugs should include older populations and, if possible, a pharmacokinetic assessment that includes dietary supplement usage.
7. As subgroups were underrepresented in existing studies, future studies investigating supplement-drug interactions should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities.
8. When possible, comparative effectiveness studies should include a statistical analysis for supplement–drug interactions, and the trials should be powered accordingly.
9. Until well-powered experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Observational studies compliant with STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) guidelines should be powered appropriately to address predefined endpoints of both efficacy and safety in a naturalistic setting, where the population sampled is reflective of the population for which these data would be meaningful.<sup>106</sup>
10. Given the difficulty and resource-intensive nature of clinical trials, other sources of data should be considered to derive information regarding drug-dietary supplement interactions. Possibilities include synthesis of reports of adverse events made to both

FDA and the Pharmacovigilance program at Health Canada. In addition, electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the sparse evidence on supplement–cardiovascular drug interaction that currently exists.

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# Introduction

Vascular disease is a preventable condition that is the leading contributor to mortality in the United States<sup>107</sup>, and second place in Canada after cancer.<sup>108</sup> Vascular disease includes peripheral vascular disease evident in hypertension; cardiovascular disease such as angina pectoris, myocardial infarction and heart failure; and cerebrovascular disease such as transient ischemic attack (TIA) and stroke.

The American Heart Association estimates that more than 81 million American adults (one-third of all American adults) have at least one form of cardiovascular disease (CVD), broadly defined to include all vascular disease.<sup>1</sup> While there has been progress in the control of CVD, it demands huge investments from the health care system and represents great burdens and lost opportunities for individuals, families and society overall.

In addition to lifestyle and dietary recommendations, front line treatment for prevention and treatment of cardiovascular disease is primarily pharmaceutical, with patients requiring on average 6.3 concomitant prescription drugs, from on average 5.9 different drug classes, for primary and secondary prevention of the disease itself and management of associated comorbidities.<sup>2-4</sup> The prescription drugs considered in this review are summarized in Table 1.

**Table 1. Cardiovascular drugs of interest**

| Cardiovascular Drug Category                     | Drug Class  | Drugs of Interest |              |
|--|---|-------------------|--------------|
| Beta adrenergic antagonists                      |   | acebutalol        | nadolol      |
|  |   | betaxolol         | nebivolol    |
|  |   | bisoprolol        | pindolol     |
|  |   | carvedilol        | propranolol  |
|  |   | labetalol         | sotalol      |
|  |   | metoprolol        | timolol      |
| Calcium channel antagonists                      | Dihydropyridine   | amlodipine        | nifedipine   |
|  |   | felodipine        | nimodipine   |
| isradipine                                       |   | nisoldipine       |              |
| nicardipine                                      |   |                   |              |
|  | Non-Dihydropyridine                                       | diltiazem         | verapamil    |
| Renin-angiotensin-aldosterone system antagonists | Angiotensin-converting enzyme inhibitors (ACE inhibitors) | benazepril        | moexipril    |
|  |   | captopril         | perindopril  |
|  |   | enalapril         | quinapril    |
|  |   | fosinopril        | ramipril     |
|  |   | lisinopril        | trandolapril |
|  | Angiotensin II receptor blockers (ARBs)                   | candesartan       | olmesartan   |
|  |   | eprosartan        | telmisartan  |
|  |   | irbesartan        | valsartan    |
|  |   | losartan          |              |
|  | Renin inhibitors  | aliskiren         |              |
| Aldosterone receptor antagonist                  | epplerenone   | spironolactone    |              |

**Table 1. Cardiovascular drugs of interest (continued)**

| Cardiovascular Drug Category | Drug Class                       | Drugs of Interest   |  |
|------------------------------|----------------------------------|---|--|
| Vasodilators                 | Central vasodilators             | clonidine<br>guanabenz                                    | guanfacine<br>methyldopa                   |
|                              | Direct vasodilators              | diazoxide<br>hydralazine                                  | minoxidil                                  |
|                              | Nitrates                         | isosorbide<br>dinitrate<br>nitroglycerin                  |  |
|                              | Phosphodiesterase inhibitors     | sildenafil<br>tadalafil                                   | varafenafil<br>cilostazol                  |
|                              | Prostacycline                    | alprostadil<br>epoprostenol                               | iloprost<br>treprostinil                   |
|                              | Endothelin antagonist            | bosentan  | ambrisentan                                |
|                              | Miscellaneous vasodilators       | papaverine<br>isoxsuprine                                 | rauwolfia alkaloids                        |
|                              | Alpha adrenergic blockers        |   | doxazosin<br>prazosin                      |
| Antiarrhythmic drugs         | Class 1a                         | disopyramide<br>procainamide                              | quinidine                                  |
|                              | Class 1b                         | mexilitine  |  |
|                              | Class 1c                         | encainide<br>flecainide                                   | propafenone                                |
|                              | Class III                        | amiodarone<br>dofetilide                                  | dronedarone                                |
| Inotropic agents             |                                  | digoxin   |  |
| Antilipemic agents           | Bile acid sequestrants           | colestipol<br>colesevelam                                 | cholestyramine<br>resin                    |
|                              | Cholesterol absorption inhibitor | ezetimibe   |  |
|                              | Fibric acid Derivatives          | fenofibrate   | gemfibrozil                                |
|                              | HMG-CoA reductase Inhibitors     | atorvastatin<br>fluvastatin<br>lovastatin                 | pravastatin<br>rosuvastatin<br>simvastatin |
|                              | Miscellaneous                    | niacin >250 mg/day*                                       |  |
|                              | Anticoagulants                   | Coumarin derivatives                                      | warfarin                                   |
| Heparins                     |                                  | dalteparin<br>enoxaparin                                  | heparin<br>tinzaparin                      |
| Antiplatelet agents          |                                  | acetylsalicylic acid (ASA)                                | clopidogrel<br>ticlopidine                 |
| Diuretics                    | Loop diuretics                   | bumetanide<br>ethacrynic acid                             | furosemide<br>torsemide                    |
|                              | potassium-sparing (K-sparing)    | amilioride  | triamterene                                |
|                              | Thiazide                         | chlorothiazide<br>hydrochlorothiazide<br>methyclothiazide | bendroflumethazide<br>polythiazide         |
|                              | Thiazide-like                    | chlorthalidone<br>indapamide                              | metolazone                                 |

**Note:** \* Niacin at not more than 250 mg/day doses was considered to be a dietary supplement.

Complementary and alternative medicine (CAM) refers to preventive and therapeutic modalities not generally considered to be part of conventional medicine,<sup>5</sup> including dietary supplements. CAM utilization has increased dramatically in North America over the past decades in both the general and cardiovascular disease populations.<sup>6,7</sup> The National Health

Interview Survey (NHIS) indicated that a total of \$34 billion in annual out-of-pocket expenditures was spent on CAM in 2007.<sup>8</sup> Of this amount, 44 percent was spent on non-vitamin, non-mineral supplements.<sup>8</sup> Estimates suggest that approximately one-third to nearly two-thirds of people suffering from heart failure or other cardiovascular disease use some form of dietary supplements, and are thus placed at risk for potential adverse events from interactions among pharmacologically active agents.<sup>7,9-11</sup> To further complicate the issue, dietary supplements in the US are not regulated in the same manner as drugs. According to the Dietary Supplement Health and Education Act of 1994, manufacturers of supplements are not held to the same standards as manufacturers of prescription and over-the-counter drugs with respect to providing evidence of efficacy and safety prior to marketing.<sup>109</sup> Furthermore, dietary supplements are not required to obtain United States Food and Drug Administration (FDA) approval, nor are there any FDA regulations that require evidence of purity, quality or composition prior to marketing. These products are available in pharmacies, grocery stores, health food stores, and via the internet, and are often consumed by patients without the knowledge of their care providers under the mistaken impression that supplements are safe, or without adverse effects. The purported benefits of dietary supplements are widespread and largely unsubstantiated. Many supplements have been suggested to be beneficial in various forms of cardiovascular disease (i.e., coenzyme Q10, omega-3 fatty acids and vitamin E for cardioprotection, garlic for hypercholesterolemia, hawthorn for congestive heart failure) with varying levels of evidence supporting these claims.<sup>110</sup> The dietary supplements considered in this review, and the proposed mechanisms of action for selected supplements with purported cardiovascular benefits, are summarized in Table 2.

**Table 2. Dietary supplements considered in this review**

| <b>Supplement category</b> | <b>Supplement</b>                      | <b>Proposed Mechanism of Action</b>  | <b>Purported Outcome Effect (<i>italics – evidence unclear</i>)</b>                |
|----------------------------|--|--|--|
| Vitamins and minerals      | Niacin ( $\leq 250$ mg/day)*           | Vasodilator, antioxidant, increases degradation and reduces synthesis of cholesterol | At higher doses<br>Lipid lowering<br>Anti-atherogenic                              |
|                            | Vitamin A (beta carotene) <sup>†</sup> | Lipid soluble antioxidant  | <i>Anti-atherogenic<br/>Cardioprotective</i>                                       |
|                            | Vitamin D <sup>†</sup>                 | Blood mineral homeostasis  | Replete levels provide anti-hypertension, cardioprotective effect                  |
|                            | Vitamin E                              | Lipid soluble antioxidant  | <i>Anti-atherogenic<br/>Cardioprotective<br/>With high doses, bleeding risk</i>    |
|                            | Vitamin K                              | Involved in the endogenous production of clotting factors                            | Reversal of warfarin associated bleeding<br>Stabilize warfarin dosing/titration    |
|                            | Magnesium                              | Essential cofactor in the Na-K-ATPase enzyme system, coronary vasodilator            | Anti-arrhythmic<br>Cardioprotective (thrombolytic)<br><i>Controls hypertension</i> |

**Table 2. Dietary supplements considered in this review (continued)**

| Supplement category   | Supplement  | Proposed Mechanism of Action   | Purported Outcome Effect ( <i>italics – evidence unclear</i> )   |
|---|---|--|--|
| Herbs or other botanicals   | Ginseng (American - <i>Panax quinquefolius</i> ; Asian - <i>Panax ginseng</i> ) | Largely unknown but proposed to have adaptogenic immunomodulatory and neuroprotective properties                           | “Tonic” improving exercise and mental capacity<br>Anti-carcinogenic, stress reducing, and neuroprotective                                    |
|   | <i>Echinacea</i> ( <i>E. purpurea</i> , <i>E. angustifolia</i> )                | Immunostimulant  | Symptom control for mild upper respiratory tract infections  |
|   | Garlic supplements ( <i>Allium sativum</i> )                                    | Inhibitor of HMG-CoA reductase, antioxidant, inhibitor of platelet aggregation   | Lipid lowering<br>Anti-atherogenic<br>Antithrombotic<br>Lowers blood pressure<br><i>Possible bleeding risk</i>                               |
|   | Ginger supplements ( <i>Zingiber officinale</i> )                               | Anti-inflammatory effect, inhibitor of platelet aggregation  | Anti-emetic<br><i>Anti-atherogenic Cardioprotective Antithrombotic</i>   |
|   | Ginkgo ( <i>Ginkgo biloba</i> )   | Antioxidant<br>Neuroprotectant<br>Circulatory stimulant  | Memory enhancement associated with dementia, Alzheimers<br><i>Possible bleeding risk</i>   |
|   | Omega-3 fatty acids   | Anti-inflammatory<br>Modulates VLDL and chylomicron metabolism   | Lower triglycerides and CHD risk<br>Anti-atherogenic<br>High dose risks in CHD of bleeding, altered blood sugar, increased LDL-C, arrhythmia |
| Refined dietary substances, to increase the total dietary intake (e.g., enzymes or tissues from organs or glands) | Coenzyme Q10  | Cofactor in oxidative respiration<br>Fat soluble antioxidant (Endogenous production decreases with age)                    | Antiatherogenic<br>Used in cardiovascular conditions for deficiency (natural or statin-induced)  |
|   | Red yeast rice extract  | Inhibitor of HMG-CoA reductase   | Lipid lowering   |
|   | Resveratrol   | Antioxidant<br>Anti-inflammatory   | Anti-cancer<br>Cardioprotective  |
|   | Hawthorn  | Enhances intracellular calcium sensitivity in cardiomyocytes<br>Increases degradation and reduces synthesis of cholesterol | Symptom control in CHF<br>Lipid lowering<br>Anti-atherogenic<br>Inotropic for arrhythmias  |

**Notes:** The primary source for this table is the Natural Standard database of Foods, Herbs and Supplements (<http://naturalstandard.com/databases/herbssupplements/all/>)

\* Niacin at higher doses was considered to be a cardiovascular drug.

† The following vitamin analog forms are considered pharmaceutical drugs and were therefore excluded:

Analogs of vitamin A [bexarotene, fenretinide; 13-cis-retinoic acid (isotretinoin, Accutane); 9-cis retinoic acid (Alitretinoin); and all trans retinoic acid (ATRA) (tretinoin)]; and

Analogues of vitamin D [Calcitriol; dihydrotachysterol (DHT); alfacalcidol (1 $\alpha$ -(OH)D<sub>3</sub>); calcipotriol; tacalcitol; 19-nor-1,25(OH)<sub>2</sub>D<sub>2</sub> (19-norD<sub>2</sub>), oxacalcitriol (OCT), 22-oxa-1,25(OH)<sub>2</sub>D<sub>3</sub>; paricalcitol; doxercalciferol; 1 $\alpha$ -hydroxyvitamin D<sub>2</sub> (1 $\alpha$ -(OH)D<sub>2</sub>); falecalcitriol]

**Abbreviations:** CHD = coronary heart disease; CHF = congestive heart failure; HMG-CoA = 3-hydroxy-3-methyl-glutaryl coenzyme A; LDL-C = low density lipoprotein cholesterol.

People at risk of or suffering from cardiovascular disease often take dietary supplements alongside prescribed drugs. The use of supplements may complement standard care, or may have a detrimental effect on the pharmacodynamics or pharmacokinetics of standard care. Given the uncertainty, and potential for harm, we need to understand better the risks and benefits, or lack thereof, associated with concomitant usage.

An example whereby the addition of a dietary supplement may confer benefit would be combining coenzyme Q10 with statin therapy. Amongst other actions, coenzyme Q10 has been

shown to lower cholesterol, specifically low-density lipoprotein cholesterol,<sup>6</sup> and while not proven, it is plausible that coenzyme Q10 reduces myalgia associated with statin therapy.<sup>111,112</sup>

Alternatively, the concomitant use of dietary supplements and cardiovascular drugs may lead to detrimental outcomes directly (i.e., either clinical or surrogate outcomes) or indirectly. For example, key factors within coagulation pathways are directly affected by garlic, fish oil, fenugreek, saw palmetto, *Ginkgo biloba* and danshen, which all have been shown to inhibit blood coagulation.<sup>10,113-115</sup> However, increased bleeding is a serious potential risk when these dietary supplements are coupled with common anticoagulants like aspirin, warfarin, or ticlopidine. Conversely other supplements, even a seemingly innocuous one like green tea extract, that contains vitamin K, may counteract the anticoagulant effects of certain drugs and thus limit their effectiveness.<sup>116</sup> Similarly, drug-dietary supplement interactions can negatively impact surrogate outcomes, as illustrated by metabolic enzyme induction. St. John's wort for example, taken often for the treatment of depression, is a potent inducer of the CYP3A4 enzyme.<sup>117</sup> This enzyme is involved in the oxidative metabolism of many synthetic drugs,<sup>114,115,118-121</sup> including cardiac glycosides, beta-adrenergic blockers, calcium channel blockers, statins, angiotensin receptor antagonists, and anticoagulants.<sup>10,114,116</sup> Increasing the metabolism of any of these drugs with use of this popular herbal product could reduce their effectiveness and potentially result in serious clinical consequences. Conversely, if prescription medication dosage is adjusted in the context of regular ingestion of a CYP3A4 enzyme inhibitor, then supplement cessation may result in excessive drug levels with other serious clinical consequences.

Concomitant use of dietary supplements and cardiovascular drugs may also affect clinically relevant outcomes indirectly. Risks for both non-adherence and interactions inevitably increase with the number of medications and supplements taken, and this is of greatest concern in the elderly.<sup>12,13</sup> In addition to concerns of polypharmacy, the elderly also experience physiological changes that make them more susceptible to interactions, as a consequence of alterations in metabolism and excretion, affecting both pharmacodynamics and pharmacokinetics.<sup>122,123</sup> The increasing morbidity that occurs within older populations suffering from CVD, in conjunction with greater potential for drug interactions, makes this subgroup particularly important to explore.

Thus, understanding the potential for drug-supplement interactions and consequences of such interactions is essential for clinicians and patients when prescribing medications, or advising or deciding to add dietary supplements to current medication and supplement regimes.

Incorporation in clinical practice of knowledge regarding the impact of concomitant use of cardiovascular disease medications and dietary supplements requires access to reliable drug-supplement information, as well as a commitment to documentation by clinicians.<sup>15,16</sup>

As a consequence of U.S. drug regulatory policy, much more research and data are available describing drug-drug interactions than drug-supplement interactions. Comprehensive systematic review of interactions between dietary supplements and drugs specifically in patients taking prescription medications for cardiovascular disease is clearly needed. Recently published systematic reviews addressing aspects related to this topic are not comprehensive, or focus on different populations of interest.<sup>115,119,121</sup> This synthesis evaluates literature that addresses meaningful clinical outcomes, as well as important surrogate or intermediate outcomes, in the context of patients concurrently taking prescription drugs and dietary supplements for prevention and treatment of CVD.

The Key Questions examined in this review are as follows:

In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on:

1. clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] and stroke)?
  - (a) Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
  - (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?
2. intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?
  - (a) Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?
  - (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?
3. clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)?
  - (a) Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
  - (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?
4. pharmacokinetic outcomes (e.g., T<sub>1/2</sub>, area under the concentration curve [AUC]) of cardiovascular drugs of interest?
  - (a) Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?
  - (b) Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

## Methods

The methods for this Comparative Effectiveness Review follow the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by the Agency for Healthcare Research and Quality (AHRQ).<sup>17</sup> Unless stated otherwise, all methods and analyses were determined a priori and documented in a research protocol that was publicly posted by AHRQ for comments. Screening of literature and inclusion/exclusion of studies were tracked and presented according to the PRISMA methodology.<sup>124</sup>

## Topic Development and Refinement

This evidence report addresses several Key Questions regarding the effects of concomitant use of specific dietary supplements and cardiovascular drugs compared with cardiovascular drugs alone or with different dietary supplements. The original topic nomination was for a comparative effectiveness review (CER) of the risks and benefits for elderly patients taking cardiovascular medication concomitantly with herbal supplements. Discussions were held with Key Informants representing the FDA, the National Center for Complementary and Alternative Medicine (NCCAM), and several other institutions on scope of the topic, research questions to be asked, and methodology of evidence synthesis to be adopted. The panel included clinicians (e.g., cardiologists, naturopathic doctors, a clinical pharmacology specialist, and a nutritionist), a patient (consumer), and systematic review research methodologists.

As preliminary searching indicated scarce data in the elderly subgroup, it was decided with the Key Informants to broaden the review topic to the benefits and risks of dietary supplement use in adults taking drugs for prevention and treatment of cardiovascular disease (CVD). Subgroups of interest were added to a preliminary list of demographic and clinical categories that included those with renal dysfunction and genetic polymorphisms in CYP2D6, 2C9, and 2C19. Drug-functional food and drug-conventional food interactions were considered but it was decided that should be evaluated as a separate research project due to the size of such an undertaking. Five research Key Questions were finalized in the topic refinement process regarding the comparative efficacy, effectiveness, harms and pharmacokinetics of a dietary supplement coadministered with a cardiovascular drug. Subquestions sought to investigate subgroup effects and evidence of specific drug-supplement statistical interaction. An indirect question enquired about evidence based on human studies that some of the most commonly used dietary supplements cause alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.

All dietary supplements, according to the Dietary Supplement Health and Education Act of 1994 (DSHEA) definition, were of investigational interest. The dietary supplement was defined as one of the following substances:

- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands); or
- a concentrate, metabolite, constituent or extract.

Furthermore, it must also conform to the following criterion:

- intended for ingestion in pill, capsule, tablet, powder or liquid form not represented for use as a conventional food or as the sole item of a meal or diet.

AHRQ's Effective Health Care Program posted the proposed Key Questions for public comment on their Web site from August 16 through September 13, 2010. In response, the following five general comments were received: (1) the review scope should be restricted to the most common dietary supplements and cardiovascular drugs; (2) the review should focus on patient-oriented outcomes; (3) the review should examine issues related to quality, dose and purity of the dietary supplements of interest; (4) the review should distinguish between regular and occasional users of dietary supplements; (5) the review should distinguish between nutrient and non-nutrient supplements. The Evidence-based Practice Center (EPC), with input from Key Informants and the Technical Expert Panel (TEP), reviewed and refined the Key Questions to ensure that the questions were specific and explicit about what information was being reviewed.

## Protocol and Project Scope Amendment

The review according to the approved topic refinement document was proven to require resources beyond those allocated to the EPC center. The search of included data bases yielded more than 32,000 records; beyond expectations founded on targeted search during topic refinement. A random 10 percent title, abstract and full text screening was conducted to estimate the final size of the review and the projected number of included studies was beyond review resources. Several telephone and e-mail discussions were held with the TEP members and the Task Order Officer. Finally, three modifications were made as an amendment to the original research protocol based on the topic refinement document:

- Restrict to dietary supplements commonly used in adults and elderly taking cardiovascular medication for which current evidence on possible drug-supplement interaction is lacking. With input from the TEP, and surveys of the general and cardiovascular populations in the United States reported in literature,<sup>7,18-23</sup> the revised list of dietary supplements was arrived at as follows:
  - A. dietary supplements commonly perceived to provide cardiovascular benefit, with a high probability of being used simultaneously with cardiovascular drugs: coenzyme Q10; garlic; ginger; *Ginkgo biloba*; ginseng; multivitamins; vitamin A or beta carotene; vitamin D; vitamin E; omega-3 fatty acids or fish oils; niacin; and magnesium.
  - B. other dietary supplements commonly used by the population using cardiovascular drugs, for which there is some reason to believe there may be an interaction with cardiovascular drugs: *Echinacea*; St. John's wort; red yeast rice; resveratrol; hawthorn; and vitamin K.
  - C. supplements falling into categories A or B may be omitted from the list if there is already well understood interaction and a review would be redundant. On this basis, it was proposed that these be excluded: St. John's wort; therapeutic doses of niacin (greater than 250 mg/day); and magnesium as infusion or injection.
- Eliminate the indirect question enquiring about alterations in cytochrome P450 isozyme activity and in cellular drug transport mechanisms.
- Restrict foreign-language report inclusion to German only.



Language restriction was based on the fact that during the screening of the 10 percent random sample of a total of 32, 000 records, most commonly identified foreign languages were German (24 percent), Russian (16 percent), and Chinese (44 percent), comprising 84 percent of reports in language other than English. Other languages included Norwegian (4 percent), and Italian, Polish, Swedish, Dutch, and French (2 percent each). Because of uncertain applicability of Russian and Chinese language studies to the United States population and settings, the only foreign language considered to be eligible was German.

The list of relevant dietary supplements, rationale for the above-mentioned project scope amendments, and other details, are presented in the Table 3 below.

**Table 3. Protocol amendments**

| Item  | Amendment   | Section of the Protocol Report Affected  |
|---|---|--|
| Revision to the list of dietary supplements | Include only:<br>Coenzyme Q10<br><i>Echinacea</i><br>Garlic<br>Ginger<br><i>Ginkgo biloba</i><br>Ginseng<br>Hawthorn<br>Magnesium (oral)<br>Niacin ( $\leq 250$ mg/day)<br>Omega-3 fatty acids<br>Red yeast rice extract<br>Resveratrol<br>Vitamin A<br>Vitamin D $\pm$ calcium<br>Vitamins E and K | Definition of intervention<br>Method: Table 1 (intervention Key Questions1- 4)                         |
| Language of publication                     | Restriction to English and German for experimental and observational studies  | Methods: criteria for inclusion;<br>Table 1: report characteristics                                    |
| Restriction of Key Questions                | Elimination of Key Question 5   | Key Question 5<br>Analytic framework<br>Methods: criteria for inclusion, Table 1: grading the evidence |

**Abbreviation:** mg = milligrams.

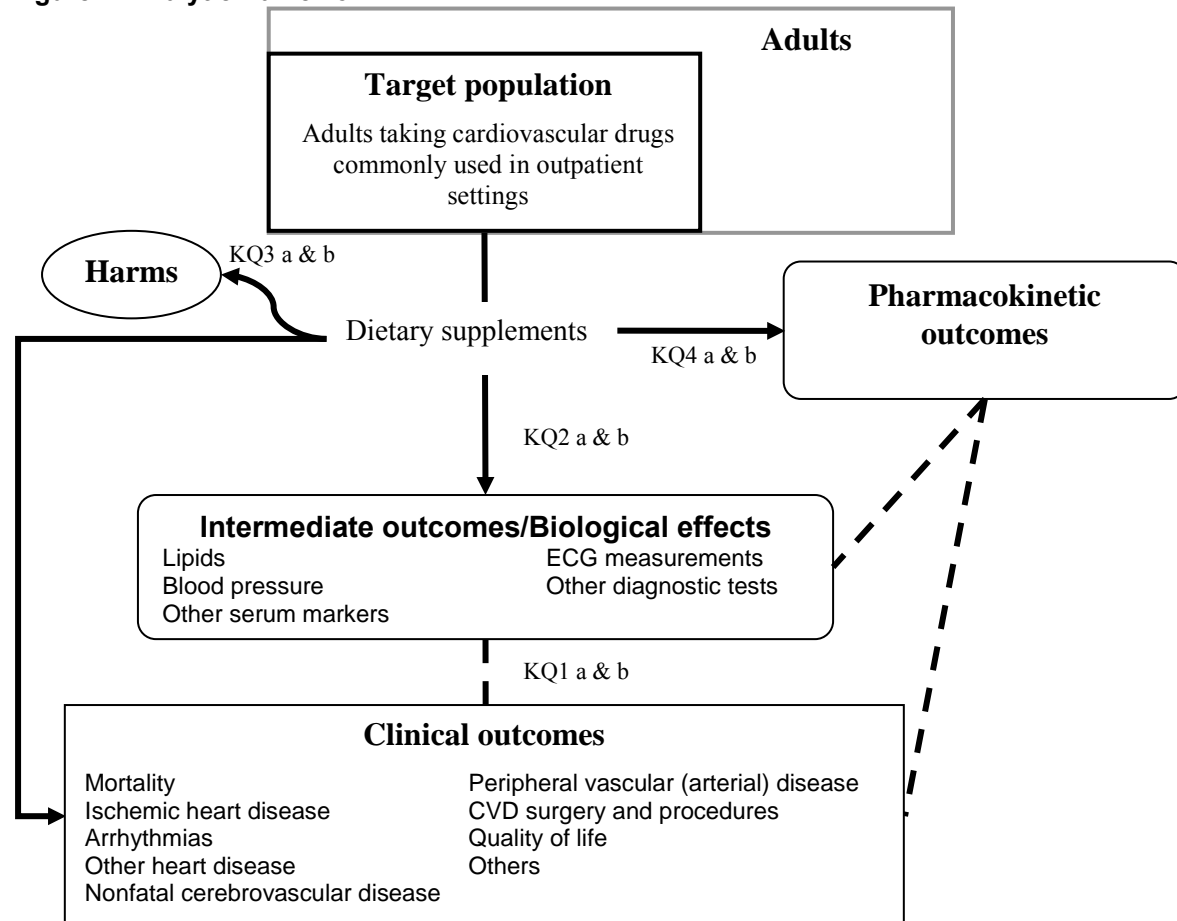
## Development of the Analytic Framework

The analytic framework depicts the causal pathways forming the basis of the Key Questions (Figure 1). The framework outlines the conceptual basis or expectations for adding a dietary supplement to prescribed cardiovascular drugs. Expectations include improvement in efficacy and reduction in harms related to cardiovascular drugs. Outcomes that represent these changes may be clinical, surrogate (proxy for clinical), or pharmacokinetic. Altered outcomes may be a result of an add-on effect of the dietary supplement and/or supplement-drug interaction. Drug interactions may be seen as biologic (i.e., pharmacodynamic or pharmacokinetic interactions reflected in altered clinical and surrogate outcomes of benefit and harms) or statistical.<sup>125</sup> Statistical interactions measure biologic interactions in terms of a product term added to a linear model. The Key Questions posed therefore examine whether outcomes of benefit and harms change with the addition of a dietary supplement. In addition, they examine pharmacokinetic and statistical interactions.

In the context of the population of interest, the Key Questions are indicated along the corresponding arrows connecting treatment and outcomes of interest. The framework includes

seven sections. The first section represents the adult population, within which the target population is included. The remaining six sections are: (1) target population (adults taking cardiovascular drugs commonly used in the outpatient setting); (2) treatment (dietary supplements); (3) intermediate outcomes/biological effects (lipid levels, blood pressure, electrocardiogram measurements, other serum markers, and diagnostic tests); (4) clinical outcomes (mortality, ischemic heart disease, arrhythmias, cerebrovascular disease, peripheral arterial disease, cardiovascular disease surgery and procedures, and quality of life); (5) harms (allergic reactions, significant bleeding, and neurological and gastrointestinal adverse events); and (6) pharmacokinetic outcomes (measures of drug absorption, distribution, metabolism, and excretion).

**Figure 1. Analytic framework**



**Abbreviations:** CVD = cardiovascular disease; ECG = electrocardiography; KQ = Key Question.

## Literature Search Strategy

An experienced medical information specialist developed and tested the electronic search strategies by using a combination of controlled vocabulary and free text, in consultation with the team. An independent information specialist peer-reviewed the search strategies according to the PRESS checklist.<sup>126</sup>

To identify primary study reports (see Appendix A), we searched the following electronic databases: Ovid MEDLINE<sup>®</sup> In-Process and other Non-Indexed Citations, and Ovid MEDLINE<sup>®</sup> (1950 to Sept 1, 2011); Embase (1980 to Sept 1, 2011); Cochrane Library via the Wiley interface

(Sept 1 2011) including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment Database and Cochrane Central Register of Controlled Trials; International Bibliographic Information on Dietary Supplements (IBIDS) on October 26, 2010; and Allied and Complementary Medicine Database (AMED) 1985 to September 1, 2011. We used controlled vocabulary (e.g., “Dietary Supplements,” “Drugs, Chinese Herbal,” “Phytotherapy”) and keywords (e.g., nutritional supplements, garlic, ginger) in combination with controlled vocabulary and keywords related to cardiovascular agents. A broad range of controlled vocabulary was used to address the various synonyms associated with this topic, as well as to cover any evolutionary gaps associated with the introduction of certain vocabulary terms. Results were refined using filters for systematic reviews, RCTs, non-RCTs and observational studies, and safety. A more specific strategy related solely to herb–drug interactions was run in the same databases using only a systematic review filter.

To identify systematic reviews addressing research questions similar to the Key Questions outlined for this review, we used a slightly modified strategy from that indicated above, by including a systematic review filter (for MEDLINE and Embase) and limiting the search of the Cochrane Library to the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database (see Appendix Y). The identification of relevant systematic reviews addressing any one of the Key Questions would serve the purpose of replacing a de novo process involving primary synthesis with existing systematic reviews.

We restricted our searches to human studies without imposing any language or date restrictions. We attempted to identify unpublished literature (including abstracts and conference proceedings) through searches of trial registries (e.g., ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, World Health Organization Clinical Trials), the Cambridge Scientific Abstracts (CSA) Conference Papers Index, and Scopus. Additional references were identified by scanning bibliographies of relevant systematic reviews and clinical trials. We also contacted Technical Expert Panel (TEP) members.

Through the Scientific Resource Center, we contacted the industry (see Appendix B for list of drug manufacturers contacted) for scientific information packets (SIPs) on drug-supplement interaction and requested:

- a current product label;
- randomized controlled trials, published or unpublished; and
- observational studies, published or unpublished.

All identified citations were downloaded into a Reference Manager 12<sup>127</sup> database for duplicate removal and early analysis. The unique references were then uploaded into DistillerSR,<sup>128</sup> a review management Web application.

## **Study Selection**

### **Process Description**

The reviewers involved in initial screening attended a screening training session and pilot tested the screening forms. Titles were screened by one reviewer; all exclusions were independently screened by a second reviewer. A similar process of screening was followed to screen abstracts of studies that passed the title screen. Two reviewers independently screened the full text of all included records. Discrepancies were resolved by consensus.

## Eligibility Criteria for Systematic Reviews

When available, topically relevant reviews were to be included to answer one or more of the Key Questions. As per the Cochrane Collaboration definition,<sup>129</sup> a systematic review includes: a specific research question; a search strategy (e.g., sources such as electronic databases, period covered by the search); and methods used to assess the risk of bias of studies included in the review. Narrative reviews were excluded. We limited our review to those systematic reviews judged to be of “Good” quality (see below for how quality of a review was assessed). Reasons for exclusion were noted. We planned to replace de novo evidence synthesis with good quality systematic review evidence only when it was deemed current, obviating the need to update.

## Eligibility Criteria for Primary Studies

We aimed to include hypothesis-testing as opposed to hypothesis generating studies (case-reports and series). We thus included experimental and observational comparative studies (i.e., those with independent controls) evaluating the benefits or harms of concomitant dietary supplement use in adults taking cardiovascular medications versus no dietary supplement (or other dietary supplement). In a post hoc decision, we expanded the study design criteria to allow inclusion of single arm controlled before-after pharmacokinetic studies in which posttreatment values were compared with baseline values. This was because we considered such evidence as a reasonable comparison between drug-supplement and drug alone for pharmacokinetic outcomes when an adequate washout period was employed. This review was limited to human studies with specific eligibility criteria presented in Table 4.

**Table 4. Study inclusion criteria**

| Population     |   |   |
|----------------|---|---|
| <b>KQs 1–4</b> | Adult participants (the majority of participants $\geq 16$ years of age or with subgroup data presented for adults) taking at least one specific cardiovascular drug or one specific class of cardiovascular drugs such as $\alpha$ -adrenergic antagonists, antiarrhythmic drugs, anticoagulants, antilipemic agents, antiplatelet agents, $\beta$ -adrenergic antagonists, calcium channel antagonists, diuretics, inotropic agents, renin-angiotensin-aldosterone system antagonists, and other vasodilators (e.g., centrally acting, phosphodiesterase inhibitors, prostacyclin derivatives, endothelin antagonists, etc) | The drugs were restricted to those commonly used in U.S. outpatient settings for treatment and prevention of cardiovascular disorders.                      |
| Intervention   |   |   |
| <b>KQs 1–4</b> | Coenzyme Q10<br><i>Echinacea</i><br>Garlic<br>Ginger<br><i>Ginkgo biloba</i><br>Ginseng<br>Hawthorn<br>Magnesium (oral)   | Niacin ( $\leq 250$ mg/d)<br>Omega-3 fatty acids<br>Red yeast rice extract<br>Resveratrol<br>Vitamin A<br>Vitamin D $\pm$ calcium<br>Vitamin E<br>Vitamin K |
| Comparator     |   |   |
| <b>KQs 1–4</b> | No dietary supplement (placebo, no treatment) or another dietary supplement.  |   |

**Table 4. Study inclusion criteria (continued)**

| <b>Outcomes</b>  |  |  |
|--|--|--|
| <p><b>KQ 1</b><br/>Clinical outcomes</p>                                       | <p>Mortality</p> <ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Vascular death</li> <li>• Specific vascular death (e.g., fatal MI, fatal stroke)</li> </ul> <p>Ischemic Heart Disease (Coronary Artery Disease)</p> <ul style="list-style-type: none"> <li>• All myocardial infarction (MI, acute MI)</li> <li>• Nonfatal MI (MI, acute MI)</li> <li>• Unstable angina</li> <li>• Acute coronary syndrome</li> <li>• Coronary artery disease composite outcomes (combination)</li> <li>• Coronary (re)stenosis/graft occlusion/vasospasm (<i>post hoc</i>)</li> </ul> <p>Arrhythmias</p> <ul style="list-style-type: none"> <li>• Sudden death</li> <li>• Ventricular fibrillation</li> <li>• Ventricular tachycardia</li> <li>• Atrial fibrillation</li> <li>• Heart block</li> </ul> <p>Other heart disease</p> <ul style="list-style-type: none"> <li>• Congestive heart failure</li> <li>• Valvular disease</li> </ul> <p>Adherence to prescribed cardiovascular drug or regimen</p> <p>Hospitalization</p> | <p>Cerebrovascular disease</p> <ul style="list-style-type: none"> <li>• All stroke</li> <li>• Hemorrhagic stroke</li> <li>• Thrombotic stroke</li> <li>• Transient ischemia attack (TIA)</li> <li>• Carotid artery disease (not measured by IMT or Doppler)</li> <li>• Other</li> </ul> <p>Peripheral arterial disease (PAD)</p> <ul style="list-style-type: none"> <li>• Limb thrombosis/leg ischemia</li> <li>• Claudication (pain walking)</li> <li>• Mesenteric ischemia</li> <li>• Abdominal aortic aneurysm</li> <li>• Ankle-brachial index</li> <li>• Other reported clinical PAD</li> </ul> <p>CVD surgery and procedures</p> <ul style="list-style-type: none"> <li>• Coronary artery revascularization (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], stent)</li> <li>• Valve replacement</li> <li>• Carotid revascularization (<math>\pm</math> stent)</li> <li>• Peripheral revascularization (<math>\pm</math> stent)</li> <li>• Amputation</li> </ul> <p>Syncope</p> <p>Quality of life</p> <p>Renal replacement therapy</p> |
| <p><b>KQ 2</b><br/>Intermediate outcomes (limited to established outcomes)</p> | <p>Lipids</p> <ul style="list-style-type: none"> <li>• Total cholesterol</li> <li>• Low-density lipoprotein cholesterol (LDL-C)</li> <li>• High-density lipoprotein cholesterol (HDL-C)</li> <li>• Triglycerides</li> <li>• Lipoprotein a (LP(a))</li> <li>• Non-HDL-C</li> </ul> <p>Other serum markers</p> <ul style="list-style-type: none"> <li>• C-reactive protein (CRP)</li> </ul> <p>Blood pressure</p> <ul style="list-style-type: none"> <li>• Systolic (SBP)</li> <li>• Diastolic (DBP)</li> <li>• Hypertension (HTN), new or worsening (e.g., need for change in therapy)</li> <li>• Hypotension</li> </ul>  | <p>Electrocardiographic (ECG) measurements (<math>\geq 24</math> h Holter monitor, PR interval) other than established arrhythmias (based on context, this might be evaluated as a harms outcome rather than efficacy)</p> <p>Other diagnostic tests</p> <ul style="list-style-type: none"> <li>• Carotid intima-media thickness (IMT), as measured by Doppler ultrasound</li> <li>• Coronary/cerebral arterial calcification</li> </ul> <p>Platelet aggregability</p> <p>Bleeding and coagulation times</p> <p>Ejection fraction</p> <p>Incidence of metabolic syndrome and change in 10-year Framingham risk profile</p>   |

**Table 4. Study inclusion criteria (continued)**

|   |   |   |
|---|---|---|
| <b>KQ 3</b><br>Harms  | Clinical adverse events <ul style="list-style-type: none"> <li>• Serious adverse events (composite outcome)<sup>c</sup></li> <li>• Neurologic adverse events (e.g., neuropathy, seizure)</li> <li>• Allergic reactions (e.g., anaphylaxis, skin, transient acute airway disease)</li> <li>• Gastrointestinal adverse events (e.g., diarrhea, constipation, nausea/vomiting)</li> <li>• Clinically significant bleeding (e.g., intracerebral/intraventricular, gastrointestinal, hematuria)</li> <li>• Withdrawal due to adverse events</li> <li>• Other reported important clinical adverse events</li> </ul> | Organ toxicity <ul style="list-style-type: none"> <li>• Liver (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], or hepatitis)</li> <li>• Renal (blood urea nitrogen [BUN], creatinine, glomerular filtration rate [GFR])</li> <li>• Bone marrow (e.g., leukopenia, anemia, neutropenia, thrombocytopenia)</li> </ul> Fasting blood glucose<br>Hemoglobin A <sub>1c</sub><br>QT interval<br>Other harms |
| <b>KQ 4</b><br>Pharmacokinetic and pharmacodynamic outcomes | Absorption <ul style="list-style-type: none"> <li>• Bioavailability (F), maximum drug concentration (C<sub>max</sub>) and time to C<sub>max</sub> (t<sub>max</sub>) (latter two were added post hoc)</li> </ul> Area under the concentration curve (AUC)  | Distribution <ul style="list-style-type: none"> <li>• Volume of distribution (V<sub>d</sub>; e.g., in L/kg)</li> </ul> Metabolism/Excretion <ul style="list-style-type: none"> <li>• Clearance, elimination constant (K<sub>el</sub>), half life (t<sub>1/2</sub>)</li> </ul>   |
| <b>Timing</b>   |   |   |
| <b>KQs 1–4</b>  | No restrictions have been prespecified based on the timing of an intervention and/or duration of length of followup of the studies.   | This will be considered as a dose (or exposure) response modifier in the assessment of heterogeneity and applicability.   |
| <b>Setting</b>  |   |   |
| <b>KQs 1–4</b>  | No restrictions have been prespecified based on the setting of the studies.   | This will be considered in the assessment of heterogeneity and applicability.   |
| <b>Study Design</b>   |   |   |
| <b>KQs 1–4</b>  | Experimental (randomized or nonrandomized controlled trial) and observational (cohort, case-control, cross-sectional) comparative studies with independent (concurrent or historical) control group including at least five participants.   | For KQ 4, studies employing participants as their own control were also eligible ( <i>post hoc</i> decision).   |
| <b>Report Characteristics</b>                               |   |   |
| <b>KQs 1–4</b>  | No limits on publication year or status<br>Publication language:<br>Systematic reviews: limited to English  | Primary studies: limited to the English language or German  |

**Abbreviations:** CVD = cardiovascular disease; KQ = Key Question.

## Data Extraction and Data Management

Prior to data abstraction, we iteratively developed and pilot tested a standardized data extraction form. One reviewer extracted relevant data from each study and a second reviewer independently verified data from a 10 percent random sample of studies. In contrast with data pertaining to other Key Questions, where errors were few and sporadic (less than 0.5 percent), we noted some missed harms outcomes; therefore a second reviewer verified that all reported outcomes data of interest were extracted. Before this harms data verification was carried out, we clarified understanding of the reporting of harms. For example, we decided that when authors reported regular laboratory harms surveillance by testing for liver enzymes, glomerular filtration

rate, blood urea nitrogen and serum creatinine, and then disclosed that no adverse events were identified, zero patients with events of raised levels of these enzymes should be extracted. Likewise a statement that no thrombotic event was identified was extracted as zero patients with stroke, angina and myocardial infarction. We could not generate extractable harms data from reports stating for example, “no significant adverse events were observed,” “no adverse effects of clinical importance occurred,” or “all remaining adverse events were mild in severity.” We extracted all harms data, not merely those thought to be drug related. Discrepancies in data extractions were resolved through discussions or with a help of third reviewer. Data extractors were not blinded to study information. If a study was reported in multiple publications, we extracted data from the latest and/or most complete publication and supplemented it with data from companion publications, as appropriate. We sought additional information from authors, when necessary. Data were input into DistillerSR.<sup>128</sup> During the data extraction process, one reviewer with clinical background rated study populations’ 10-year CHD risk as per Table 5 below, according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP, ATP III) guidelines.<sup>24</sup> When all participants were healthy non-smokers, study level 10-year CHD risk was categorized as low.

**Table 5. Ten-year coronary heart disease risk strata used to categorize study participants**

| Category  | Details   |
|---|---|
| High risk<br>(10-year risk >20%)  | A Participants with established coronary heart disease, i.e., anyone or more of the following: <i>coronary death, acute coronary syndromes, myocardial infarction, angina, heart failure, and coronary artery procedures (angioplasty or bypass surgery)</i>  |
|   | B Participants with noncoronary form of atherosclerotic disease, i.e., anyone or more of the following: <i>peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or &gt; 50% obstruction of a carotid artery)</i>  |
|   | C Those diagnosed with diabetes or those reported in the paper as high risk according to NCEP ATP III criteria  |
| Moderate to moderately high risk<br>(10-year risk <10% to maximum of 20%) | Two or more of the following risk factors in >80% of participants: <i>cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low HDL-C (&lt;40 mg/dL), family history of premature CHD (CHD in male first-degree relative &lt;55 years; CHD in female first-degree relative &lt;65 years), age (men ≥45 years; women ≥55 years)</i> |
| Low risk (0-1 risk factors)   | Zero or just one of the above risk factors  |
| Mixed risk  | Participants clearly in more than one of the above categories   |
| Unclear risk  | Participants could be in one or a mix of the above categories   |

**Abbreviations:** BP = blood pressure; CHD = coronary heart disease; HDL-C = high density lipoprotein-cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

There was some additional attrition after studies were included during screening. Of the included studies, we extracted data when the following additional criteria were met:

- The dietary supplement was added to one or more cardiovascular drug(s) that were all taken by 100 percent or the majority (at least 80 percent) of participants in randomized controlled trials;
- Nonrandomized controlled trials, or observational studies reported effect estimates reflective of a supplement plus drug(s) versus drug(s) alone comparison (or with another supplement);

- Studies reported, or data could be obtained from authors, for at least one relevant outcome;
- The design of the study was lower in the hierarchy of evidence (i.e., nonrandomized experimental or observational study in presence of higher RCT evidence), and did not meaningfully add (by not being a longer-term or pragmatic study reporting conclusive results) to the already included evidence from a higher study design category;
- Studies were on a cardiovascular drug not marketed in the U.S.A.;
- Dosing of the dietary supplement was specified.

Remaining studies were transparently eliminated from data synthesis with reasons.

## Extracted Data Elements

The following elements were extracted:

- Study and report characteristics (first author, study design, study setting, duration of followup, year and language of publication, funding source, treatment sequence generation, treatment allocation concealment, use of blinding)
- Population characteristics (inclusion/exclusion criteria, number of enrolled and analyzed participants, age, gender, ethnicity/race, health status, comorbidities, baseline nutrient exposures and/or background diet, methods used to assess baseline nutrient exposures, specific cardiovascular drugs and drug classes, drug doses, dose regimens, duration of treatment, potential confounders such as blood pressure, concomitant medication, smoking, lipid levels, number and reasons for withdrawals or drop-outs)
- Intervention characteristics (name, brand, and country of manufacturer of a dietary supplement or extract, license/registration of the product in the country of manufacture, source from which a dietary supplement or extract was manufactured, method of authentication, dosage regimen and quantitative description, dose form, qualitative testing for authenticity of herbal species, purity assessment for contamination/substitution, standardization, storage conditions and length, methods and instruments for assessing nutrient-intake exposures including validation by using nutrient biomarkers)
- Control (comparator) intervention characteristics
  - Placebo - description/definition in placebo-controlled trials, duration of treatment, similarity of treatments)
  - Other dietary supplement - same data as above
- Outcomes
  - Continuous measures (mean baseline and final values, within-treatment arm mean change, between-treatment arm mean difference, standard deviation, if reported means – the corresponding variance, standard error, 95 percent confidence interval)
  - Binary outcomes (number of participants with an event, risk of an event, odds of an event, risk ratio, odds ratio, hazard ratio, variance, standard error, 95 percent confidence interval, crude or adjusted measures of effect)
  - Definitions
  - Measurement method(s)
  - Timing of measurement
  - Data analysis details
  - Statistical test used



- Regression models (model type, covariates)

For systematic reviews, we planned to extract data on the research question, search strategy, design of individual studies included in a review, risk of bias assessment methods, population characteristics (inclusion and exclusion criteria, type of cardiovascular drug intake), and treatment characteristics (name and type of dietary of supplement).

## **Assessment of Study Risk of Bias and Quality of Systematic Reviews**

Risk of bias of individual studies was assessed according to outcomes. One reviewer assessed risk of bias of all individual primary studies (randomized trials, nonrandomized controlled trials, cohort, and case-control studies). The risk of bias for gradable outcomes was verified by two reviewers, while a random ten percent of risk of bias assessment was verified for other outcomes. Disagreements were resolved by discussions with a third team member.

We used generic criteria to assess study risk of bias (Table 6). These criteria estimate risk of bias across five domains (selection bias, performance bias, attrition bias, detection bias, and other bias). The domains were tailored according to study design. For example, specific subdomains such as randomization sequence generation were assessed only for randomized trials (parallel arm and crossover). Crossover randomized trials were assessed with the following additional criteria: appropriateness of crossover design; washout period (the length of time had to be at least 3 times the half life of drug elimination); and the report of appropriate data analysis (i.e., based on within-subject differences). The subdomain of blinding (within the Performance Bias domain) of participants, healthcare providers, and outcome assessors to treatment allocation was assessed only for experimental designs (i.e., randomized and non-randomized trials). We assessed the completeness of outcome data (i.e., attrition bias due to loss to followup or withdrawals) by comparing the number of participants who entered the study with the number of participants reported in outcome table(s). We then assessed whether there was complete followup of all participants, small lost to followup (less than 20 percent) or differential lost to followup.

Other forms of bias assessed included potential financial conflict of interest and selected criteria from the McMaster Quality Assessment Scale of Harms (McHarm).<sup>25</sup> All domains had response options of “Yes,” “No,” or “Unclear” with allowance for justifications of such judgments. For each gradable outcome in a study we provided an overall risk of bias rating designated as high, moderate, or low (Table 7). In order to be classified as high risk of bias, a study must have demonstrated some apparent and major flaw (within that study design category) that would invalidate results.

**Table 6. Criteria for risk of bias assessment**

| Criteria  | Experimental<br>Controlled Trials (RCT<br>and non-RCT) | Observational<br>Controlled<br>Studies | Uncontrolled<br>Experimental<br>Studies |
|---|--|--|---|
| <b>Selection Bias</b>   |  |  |   |
| Appropriateness of participant selection*   |  | X                                      | X                                       |
| Randomization sequence generation†  | X  |  |   |
| Allocation concealment  | X  |  |   |
| Control for important baseline/prognostic factors‡: restriction, similarity of groups at baseline, matching, and/or adjustment in the analysis  | X  | X                                      |   |
| <b>Performance Bias</b>   |  |  |   |
| Purity/standardization of dietary supplement§   | X  | X                                      | X                                       |
| Blinding of subjects and providers to treatment allocation  | X  |  |   |
| <b>Attrition Bias</b>   |  |  |   |
| Completeness of outcome data (attrition and exclusions) with focus on differential loss to followup or overall high loss to followup and potential for associated confounding‡              | X  | X                                      | X                                       |
| <b>Detection Bias</b>   |  |  |   |
| Blinding of outcome assessors to treatment or exposure status in experimental or cohort studies or blinding of exposure assessors to case/control status in case-control studies.           | X  | X                                      | X                                       |
| Extent to which valid outcomes were described¶  | X  | X                                      | X                                       |
| <b>Other</b>  |  |  |   |
| Financial conflict of interest  | X  | X                                      | X                                       |
| Criteria for assessment of harms (from the McHarm checklist <sup>130</sup> ): prespecified and valid definition of harms, mode of harms collection (e.g., active or passive, standard tool) | X  | X                                      | X                                       |

**Notes:** \* Appropriateness of participant selection included whether participants from each arm were from the same or different populations, the use of adequate definitions and measurements of exposed/nonexposed or case/control status and demonstration that outcomes were not present at beginning of prospective studies.

† For RCTs only.

‡ Important baseline/prognostic factors evaluated: age, gender, race, baseline diet/nutrient exposures for dietary substance of interest, smoking, concomitant medications/supplements, and health status, including comorbidities and LDL-C and blood pressure if these measures were not included as study outcomes.

§ Description of the source, methods of extraction, and constituents of the dietary supplement (e.g., quantification or quality assurance/standardization of dose/purity, stability and length of storage).

¶ Definition and methods used to assess outcome including timing, and comparability of assessment across study arms.

**Abbreviation:** RCT = randomized controlled trial.

**Table 7. Overall risk of bias ratings**

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|  |
|--|
| <b>Low risk of bias.</b> These studies have the least bias and results are considered valid. Examples of characteristics of these studies include the following: a formal randomized controlled design; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; low dropout rate; and clear reporting of dropouts. |
| <b>Moderate risk of bias.</b> These studies are susceptible to some bias, but it is not sufficient to invalidate the results. They do not meet all the criteria required for a rating of low risk of bias because they have some deficiencies, but no flaw is likely to cause major bias. Study deficiency may be missing information, making it difficult to assess limitations and potential problems.   |
| <b>High risk of bias.</b> These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.  |

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Methodological quality of included systematic reviews was assessed using the AMSTAR tool,<sup>131</sup> which rates each systematic review with a “Yes,” “No,” “Cannot answer,” or “Not applicable” across the 11 domains. The overall assessment of quality for each systematic review was based on a reviewer’s overall judgment given their responses to the individual AMSTAR items, and had three overall ratings: “Good,” “Fair,” or “Poor.” In general, “Good” quality systematic reviews were defined as those having few or no methodological/reporting shortcomings (low risk of bias). “Fair” quality systematic reviews were defined as those having some methodological flaws although not sufficient to seriously bias or invalidate the review results. “Poor” quality systematic reviews were defined as those having serious flaws sufficient to seriously bias or invalidate the review results, and were not eligible for inclusion in the evidence synthesis. An independent reviewer helped to resolve any discrepancies regarding the AMSTAR tool assessment between the reviewers.

## Grading the Strength of the Body of Evidence

In principle, a body of evidence originating in randomized trials starts with a presumed high strength of evidence, and is downgraded across the domains when there is important overall risk of bias of contributing studies, inconsistency in direction of intervention effect, indirectness of the outcome of interest (e.g., a surrogate outcome, rather than a clinical health outcome) and imprecision in effect estimates of an extent that neither important benefit nor harm can be ruled out. For nonrandomized studies, the body of evidence starts with a presumed low strength of evidence but may be upgraded across certain domains. The strength of a body of evidence was graded based on the following four domains, per previously published guidance: overall risk of bias by outcome, consistency, directness, and precision.<sup>26</sup> A methodologist and a content expert graded the strength of the body of evidence as “High,” “Moderate,” “Low,” or “Insufficient” (Table 8). A third methodologist with clinical background adjudicated to resolve disagreements. Given the results we found, optional domains such as dose-response association and existence of confounders were not applicable in this comparative effectiveness review. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.<sup>102,103</sup>

The strength of evidence was graded insufficient when there was no evidence for an outcome, when direction of estimates were inconsistent between studies without an identifiable cause, or when the body of evidence from the contributing study/studies was underpowered for the outcome of interest (imprecise estimate). That is, when the effect estimate associated with

confidence intervals was not only nonsignificant, but wide enough such that the clinical action would differ if the upper versus the lower boundary of the CI represented the truth, we rated the estimate as imprecise, reflecting our uncertainty about clinically important benefits, harms or clinically unimportant differences in effect estimates between the contrasting interventions.

Customarily only a subset of important outcomes are chosen to grade the strength of evidence—outcomes that are most meaningful for decision making given a specific Key Question.<sup>26</sup> In consultation with the Technical Expert Panel (TEP), the review team chose the following outcomes for grading the strength of the body of evidence:

Key Question 1. Mortality (all-cause and vascular death), myocardial ischemic events (fatal myocardial infarction, nonfatal myocardial infarction, unspecified myocardial infarction, and acute coronary syndromes), cerebrovascular events (hemorrhagic/ischemic/unspecified stroke), quality of life, hospitalization, arrhythmia, and clinical outcomes of peripheral arterial disease

Key Question 2. Blood pressure (systolic and diastolic), lipid profile (low density lipoprotein, high density lipoprotein, and non-high density lipoprotein cholesterol; and triglycerides), international normalised ratio for coumarin derivatives, incidence of metabolic syndrome, and change in 10-year Framingham risk profile.

Key Question 3. Serious adverse events (composite outcome according to the Food and Drug Administration definition of serious adverse events),<sup>27</sup> withdrawal due to adverse events, clinical bleeding (intracranial, gastrointestinal, genitourinary, subretinal, etc.), renal dysfunction (e.g., proteinuria, elevated creatinine, need for transplant, glomerular filtration rate), hepatotoxicity (elevated enzymes or fulminant failure), and QT prolongation

Key Question 4. Area under the plasma cardiovascular drug concentration-time curve (AUC), maximum drug concentration ( $C_{max}$ ), drug half-life( $t_{1/2}$ ), and oral clearance.

**Table 8. Strength of evidence grade and definition<sup>26</sup>**

| Grade        | Definition   |
|--------------|--|
| High         | High confidence that the evidence reflects the true effect.<br>Further research is very unlikely to change our confidence in the estimate of effect.                               |
| Moderate     | Moderate confidence that the evidence reflects the true effect.<br>Further research may change our confidence in the estimate of effect, and may change the estimate.              |
| Low          | Low confidence that the evidence reflects the true effect.<br>Further research is likely to change our confidence in the estimate of effect, and is likely to change the estimate. |
| Insufficient | Evidence is either unavailable or does not permit a conclusion.  |

## Applicability

We followed previously published guidance, and summarized the population, intervention, comparator, outcome, timing and setting (PICOTS) to assess the applicability of the body of evidence for outcomes or categories of similar outcomes.<sup>28</sup> We considered age, race/ethnicity and gender representation; strictness of exclusion criteria; 10-year CHD risk; study setting; whether or not the cardiovascular drug(s) was administered in therapeutic doses; frequency of monitoring of adherence; surrogacy of outcomes; and short versus long-term treatment duration as important aspects determining applicability. Applicability is reported for all conclusive results. When direction of effect was indeterminate either because of lack of evidence or under powered evidence (with imprecise and nonsignificant data), applicability of evidence was not reported. Studies that evaluated representative patient populations in usual or routine care conditions lasting long enough to meaningfully measure health outcomes of both benefit and harm while comparing the intervention with standard of care were considered pragmatic or

effectiveness studies as opposed to efficacy studies examining intermediate efficacy outcomes in highly selected patients less likely to experience harms.<sup>29</sup>

## Data Synthesis and Analysis

All analyses compared the combination of dietary supplement plus cardiovascular drug with cardiovascular drug alone (or plus placebo or another dietary supplement). The decision to meta-analyze or qualitatively synthesize outcome specific evidence from primary studies depended upon the presence or absence of homogeneity in clinical and methodological characteristics across studies, and the statistical format of outcome reporting. For pharmacokinetic outcomes in Key Question 4, we followed the FDA guidance for analysis and interpretation of drug interaction studies.<sup>30</sup> Because data are usually skewed, the guidance recommends that the pharmacokinetic outcomes in drug interaction studies be reported, after log transformation, as geometric mean ratios (GMR) with their 90 percent confidence intervals (CI) based on a procedure termed the ‘two one-sided test procedure.’ A conservative margin of bioequivalence for most drug interactions is recommended to be between the lower and upper bound 90 percent GMR CI of 0.8 and 1.25. We refer to this as the zone of clinical nonsignificance.

Meta-analysis was considered, or studies were considered suitable for pooling if they were randomized trials that included similar populations in terms of demographics, morbidity, and intake of cardiovascular drug(s) or classes of drugs (e.g., participants aged 65 years or younger, healthy or with diabetes or history of myocardial infarction, use of warfarin or nitrates), compared the same type of dietary supplement (e.g., niacin, oral magnesium, fish oil) versus comparator treatment (e.g., other dietary supplement, no treatment, placebo), and reported the same outcome measures in the same statistical format (e.g., mean difference or geometric mean ratios [GMR]). Where risk of bias differed across studies, this was explored by sensitivity analyses. We did not plan to meta-analyze observational and experimental studies; however, we pooled parallel with crossover randomized studies.<sup>32</sup> We did not consider pre-crossover data for synthesis except when it was judged that the treatment given to participants in a given crossover trial was not appropriate for the condition under consideration.<sup>31,32</sup> Similarly, we did not pool crossover trials that had not employed sufficient washout period between the two treatment periods because of bias arising from carryover treatment effects. We planned not to meta-analyze observational studies because of the differences in adjustment for confounders and residual confounding.

We used a DerSimonian and Laird random-effects model to generate pooled estimates of relative risk (RR) if an outcome was measured on a dichotomous scale, and weighted between-group mean difference (for end points and within group changes), if an outcome was measured on a continuous scale.<sup>33</sup> The measure of variability of the pooled estimates was a 95 percent confidence interval. Statistical heterogeneity was assessed using Cochran’s Q ( $\alpha=0.10$ ) and the  $I^2$  statistic. All analyses were performed using *Comprehensive Meta Analysis* version 2.2.057 (New Jersey, USA); StatsDirect Ltd. *StatsDirect* statistical software,<sup>132</sup> and *R: A Language and Environment for Statistical Computing*, Foundation for Statistical Computing.<sup>133</sup>

When studies failed to report summary statistics (e.g., mean score, standard deviation, standard error), we calculated the needed parameters if individual participant data were provided. If a study reported only a standard error of the mean response, we converted it into a standard deviation. Trials were not meta-analyzed if the mean and standard deviation could not be ascertained. Trials with obvious between-group baseline imbalance in a continuous outcome

were not pooled unless the mean change from baseline and corresponding standard deviation for the compared study groups were reported.

We used the Peto odds ratio method when event rates were less than 1 percent.<sup>32</sup> For studies with zero events in some arms or sparse data overall, we pooled using the fixed effects Mantel-Haenszel method without continuity correction.<sup>34</sup> Studies with zero events in both arms were excluded from meta-analysis.<sup>32</sup>

Outcome results were considered inconclusive when the pooled estimate or the single contributing study estimate had confidence intervals wide enough to incorporate both important benefit and harm (i.e., type II error suggesting underpowered studies unable to precisely conclude benefit, harm or no difference between treatments). When studies could not be pooled, for example when similar outcomes were reported in different statistical formats, or study results pointed in opposite directions, results were also labelled as inconclusive. When inconclusive results were associated with a gradable outcome, strength of evidence was deemed insufficient.

Exploration of heterogeneity was planned to examine clinical and methodological diversity, to answer subquestion (a) of the four Key Questions by carrying out subgroup and sensitivity analyses, and/or meta-regression if there was a sufficient number of studies (4 studies for each categorical subgroup variable, and 6 to 10 for a continuous subgroup variable).<sup>32</sup> This was not carried out because of a paucity of studies for each outcome.

Prespecified clinical subgroups included: gender (male, female), ethnicity (including Hispanic, Asian, African American, and Native American), age (those age 65 years and above, and 80 years and above), baseline health status (healthy volunteers, participants according to coronary heart disease risk category, participants at risk for cardiovascular disease, participants with known cardiovascular disease, participants with diabetes, participants with hepatic or renal dysfunction or end-stage renal disease, participants taking a cardiovascular drug for an indication other than cardiovascular disease), and genotypic polymorphisms (e.g., in CYP2D6, 2C9, 2C19).

Sensitivity analyses were to be conducted to explore whether the effect estimates of dietary supplement treatment were influenced by methodological variables such as overall study risk of bias, adequacy of participant selection, important confounding, blinding of outcome assessors, purity/dose/stability of a dietary supplement, or duration of treatment or followup.

Statistical interaction was to be investigated for all four Key Questions. To determine measureable interactions between cardiovascular drugs and dietary supplements, we followed the procedures described below:

- If a study explicitly examined interaction between cardiovascular drug and dietary supplement, then we extracted the study's findings along with the method for assessing interaction.
- When studies did not investigate statistical interaction between the dietary supplement plus cardiovascular drug group and the cardiovascular drug alone group, we carried out test for interactions when data for at least four groups were reported. These groups had to be supplement plus cardiovascular drug group, supplement alone group, cardiovascular drug alone group, and a common comparator placebo or no treatment group. For studies that presented dichotomous data we calculated the synergy index (S).<sup>35</sup>

$$\text{Synergy Index (S)} = \frac{1 - RR_{11}}{1 - RR_{01}RR_{10}}$$

Where  $RR_{11}$  is the relative risk for subjects exposed to cardiovascular drug and dietary supplement, and  $RR_{01}$  and  $RR_{10}$  are the relative risks for subjects exposed to cardiovascular drug

alone and dietary supplement alone respectively. An S-index greater than 1 describes a positive interaction (synergism) and an S-index less than 1 indicates a negative interaction (antagonism). For continuous outcomes, individual patient data were needed to have been modeled in a linear regression with an interaction term.

## Definitions

Pharmacokinetic Measurements: Absorption, Distribution, Metabolism, and Excretion. Adapted from Rowland and Tozer 1995<sup>134</sup>

## Pharmacokinetics

The study of the mechanisms of absorption, distribution, metabolism and elimination of an administered drug in the living organism

### Absorption

Absorption can refer to any route of administration except intravenous administration (i.e., enteral, subcutaneous, transdermal).

1. Fractional bioavailability (F): the fraction of a non-intravenously administered dose of a drug that reaches the systemic circulation (unit: percent)
2. Time to maximum concentration ( $t_{max}$ ): the time at which the maximum plasma concentration of a drug occurs following administration of an extravascular dose (unit: minute or hour)
3. Maximum concentration ( $C_{max}$ ): the highest drug concentration in plasma after an extravascular dose (unit:  $\mu\text{g mL}^{-1}$ )
4. The area under the plasma drug concentration-time curve ( $AUC_{0-t}$ ): the measure of an exposure of plasma to a drug over a given time period. It is calculated as the area under the serum concentration-time curve which is based on multiple drug concentration measurements at various time points (unit:  $\mu\text{g mL}^{-1}\text{hour}$ )

### Distribution

Volume of distribution (Vd) is the apparent volume into which a drug distributes in the body at equilibrium. Alternatively, it is the volume of plasma at the drug concentration required to account for the entire drug in the body (unit: L/kg) Volume is not limited to plasma. For example, volume of distribution will exceed plasma volume or total body water volume for highly lipophilic drugs.

### Metabolism/Excretion

1. Clearance: the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion (unit: mL/hour)
2. The elimination half-life ( $t_{1/2}$ ): the time required to reduce the plasma concentration of a drug or the total amount of drug in the body to one half of its initial value (unit: hour)

# Results

## Screening and Inclusion of Records

Overall, 33,224 records were identified by searches of databases after removing all duplicates. The PRISMA diagram in Figure 2 depicts the flow of retrieved records through the phases of screening and inclusion.

A total of 169 English publication studies were included after title/abstract, and full text screening. None of the 68 German publications screened at full text level met the eligibility criteria. Eighty-nine studies were subsequently excluded from the data synthesis for the following reasons:

- Proportion of population taking cardiovascular drugs was less than 80 percent, preventing accurate analysis of interaction of supplement and cardiovascular drug (n=72);
- No outcome of interest was reported (n=6)<sup>135-140</sup>
- Cardiovascular drug was not used in U.S.A. (n=4)<sup>141-144</sup>
- Dose of supplement was not reported (n=1)<sup>145</sup>
- Outcome data were reported only for the first period crossover (n=1)<sup>146</sup>
- A sequential study was not included in synthesis of evidence because higher quality randomized controlled trial (RCT) evidence was available for the same pharmacokinetic outcome, for the same drug-supplement combination (n=1)<sup>147</sup>
- No response was received to a data request made to authors (n=1)<sup>148</sup>
- High quality systematic review was of limited utility because it was out of date. Inclusion would have necessitated a de novo process for the included studies; (n=1)<sup>149</sup> (In two separate records).
- Observational study reported outcomes where higher level of evidence was available from RCT for the same outcomes (n=1)<sup>150</sup>

As a result, 80 reports were included in the evidence synthesis of this review and entered the quality assessment and data extraction. Among these, seven studies were reported in more than one publication, amounting to 18 records (Table 9). We identified one of these records as the primary report of the study and other(s) as a companion; however, relevant data from all related reports were used in the evidence syntheses. With this approach, 70 primary studies were included and are referenced accordingly in this review (Table 9). One of the included studies was observational,<sup>88</sup> two were controlled clinical trials,<sup>62,79</sup> and the remaining 66 studies were RCTs.

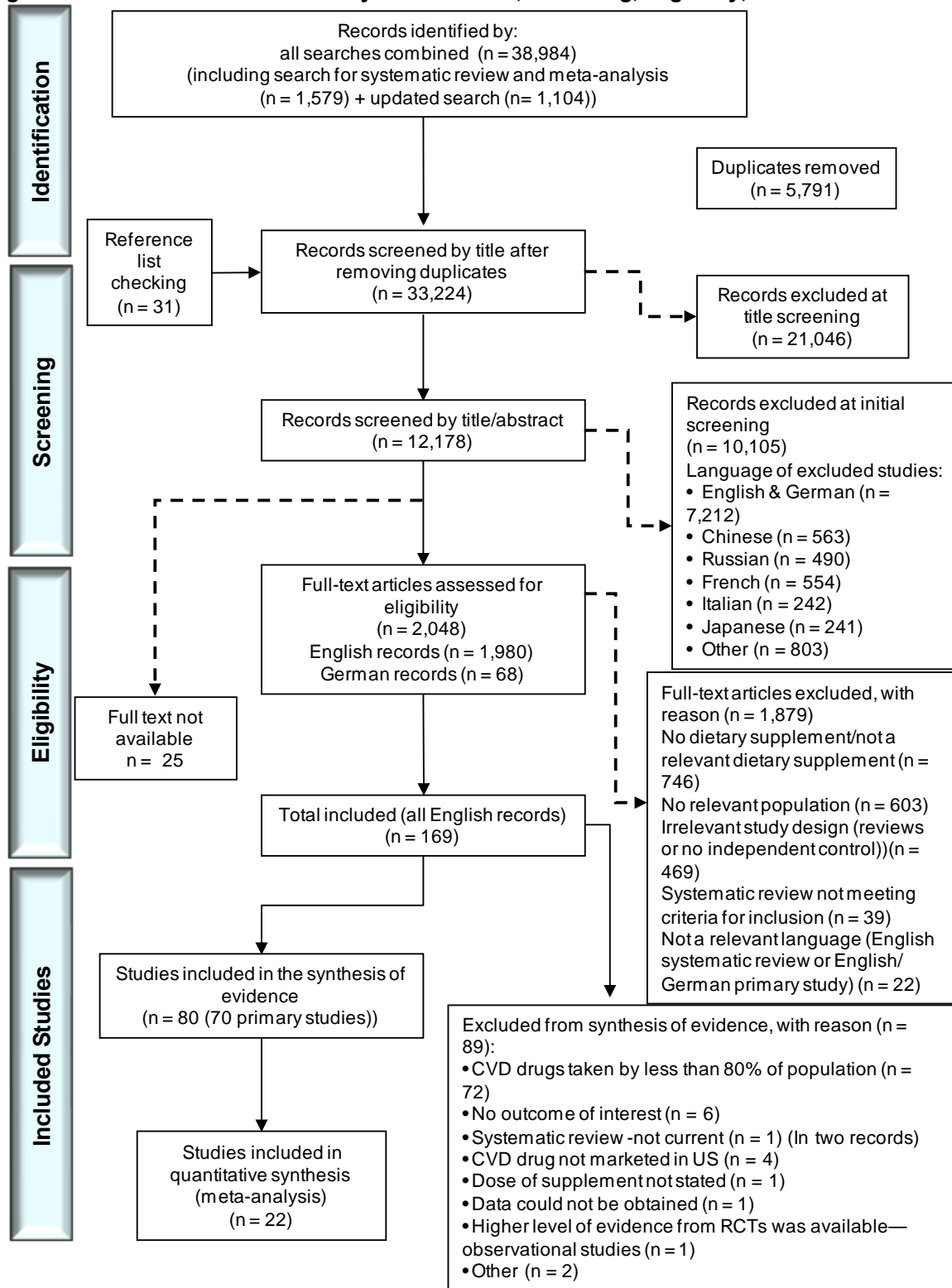
Twenty two RCT studies contributed to meta-analyses and the remaining were included in the qualitative syntheses of evidence.<sup>36,37,40,44,53,67,68,73,74,76,77,83-86,91,93-96,151,152</sup>

We contacted authors of two records requesting additional data or seeking data clarification.<sup>39,148</sup> One of the authors,<sup>39</sup> responded to our query and provided additional data which was incorporated in the evidence syntheses.

Comprehensive individual study data and quality assessment are presented in Appendix C.



Figure 2. PRISMA flow chart of study identification, screening, eligibility, and inclusion



**Table 9. Primary and companion records for studies with multiple reports**

| Primary Record              | Companion Record(s)   |
|-----------------------------|---|
| Budoff 2004 <sup>63</sup>   | Budoff 2006 <sup>153</sup>  |
| Chan 2002 <sup>44</sup>     | Chan 2006, Chan 2003, Chan 2002, Chan 2010, Chan 2002, Chan 2002 <sup>138,154-158</sup> |
| Davidson 2007 <sup>40</sup> | Maki 2010 <sup>159</sup>  |
| Gardner 2007 <sup>66</sup>  | Chan 2002 <sup>157</sup>  |
| Nordøy 1998 <sup>160</sup>  | Nordøy 2000 <sup>16</sup>   |
| Nordøy 2003 <sup>92</sup>   | Nordøy 2001 <sup>161</sup>  |
| Roth 2009 <sup>56</sup>     | Bays 2009 <sup>162</sup>  |

Key Question 1. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on clinical cardiovascular effectiveness/efficacy outcomes (e.g., mortality and specific cardiovascular or cerebrovascular conditions such as myocardial infarction [MI] and stroke)?

- a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?
- b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

## Overview

Twenty-one RCTs addressed Key Question 1.<sup>36-56</sup> No relevant data were available from observational studies. No evidence on clinical outcomes was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D with or without calcium supplementation (Table 10). There was insufficient evidence for the gradable outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations, due to lack of data. A paucity of studies for each supplement-drug combination of interest precluded exploration of heterogeneity in terms of pre-identified subgroups (Key Question 1a). No study examined any statistical interaction between supplement and drug on clinical outcomes (Key Question 1b). Table 11 summarizes characteristics of included studies and Table 12 summarizes their risks of bias. Below we report results separately for each supplement and cardiovascular drug combination, by outcomes for which evidence was available. We then grade the evidence for the pre-stated gradable outcomes, and summarize the PICOTS determinants of applicability for conclusive results across all outcomes—that is, when results were not impacted by the possibility of type II error. In all analyses, the intervention was administration of a dietary supplement along with one or more cardiovascular drug or class of drugs, while the comparator was administration of the drug or its class alone. Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

**Table 10. Overview of availability of evidence for clinical outcomes—Key Question 1**

| Supplement and Cardiovascular Drug(s)                                   | Outcome   | Number of Studies |
|---|---|-------------------|
| <b>Coenzyme Q10</b>   |   |                   |
| Statins ( <i>Dm</i> )   | Adherence   | 1                 |
| ACE inhibitor with other CV drugs ( <i>Dm</i> )                         | Mortality   | 1*                |
| ACE inhibitor with other CV drugs ( <i>Cs</i> )                         | Quality of life   | 1*                |
| <b>Ginkgo biloba</b>  |   |                   |
| Aspirin ( <i>Dm</i> )   | Mortality   | 1                 |
| Aspirin ( <i>Cs</i> )   | Other clinical outcomes                                 | 1 (NRS)           |
| <b>Magnesium (oral)</b>   |   |                   |
| Beta-blocker ( <i>Dm</i> )  | Myocardial infarction                                   | 1*                |
| <b>Omega-3 fatty acids/fish oils</b>                                    |   |                   |
| Statins ( <i>Dm</i> )   | Adherence   | 3*                |
|   | Mortality   | 1*                |
|   | Arrhythmia  | 1                 |
|   | Other clinical outcomes (exacerbation of CHF)           | 1                 |
| Calcium channel antagonist plus aspirin ( <i>Dm</i> )                   | Myocardial infarction                                   | 1                 |
|   | Procedures (CABG and PCI)                               | 1                 |
|   | Other clinical outcomes (Restenosis)                    | 1                 |
| Aspirin plus dipyridamole plus calcium channel antagonist ( <i>Dm</i> ) | Other clinical outcomes (Restenosis)                    | 1                 |
| Aspirin plus dipyridamole plus calcium channel antagonist ( <i>Cs</i> ) | Other clinical outcomes (Restenosis)                    | 1                 |
| Aspirin ( <i>Dm</i> )   | Other clinical outcomes (Graft occlusion <sup>†</sup> ) | 1                 |
| Warfarin ( <i>Dm</i> )  | Other clinical outcomes (Graft occlusion)               | 1                 |
| Calcium channel antagonist ( <i>Cs</i> )                                | Other clinical outcomes (induced coronary vasospasm)    | 1                 |
| Fibrates ( <i>Dm</i> )  | Mortality   | 1                 |
| <b>Vitamin E</b>  |   |                   |
| Aspirin ( <i>Dm</i> )   | Composite outcome                                       | 1                 |
|   | Stroke  | 1                 |
|   | TIA   | 1                 |
| Statin ( <i>Dm</i> )  | Adherence   | 1                 |
| Calcium channel antagonist ( <i>Cs</i> )                                | Unstable angina   | 2                 |
| <b>Vitamin K</b>  |   |                   |
| W ( <i>Dm</i> )   | Adherence   | 1                 |
|   | Mortality   | 1                 |
|   | Stroke  | 1                 |

**Notes:** \*At least one crossover RCT; <sup>†</sup> omega-3 fatty acids supplement also contained  $\alpha$ -tocopherol

**Abbreviations:** ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; CHF = congestive heart failure; *Cs* = outcomes data were continuous; *Dm* = outcomes data were dichotomous; NRS = neurologic recovery score; PCI = percutaneous coronary intervention; QoL = quality of life; RCT = randomized controlled trial; TIA = transient ischemic attack; UA = unstable angina.

**Table 11. Summary of study characteristics for studies addressing clinical outcomes**

| Study Characteristic | Distribution   |
|----------------------|--|
| Sample CHD risk      | Low 4.8%<br>Moderate to moderately high 4.8%<br>High 43%<br>Mixed 14%<br>Unclear 33%   |
| Geographical region  | North America 33%<br>Europe 24%<br>Australia/New Zealand 10%<br>East Asia 14%<br>Rest of Asia 10%<br>NR 9%   |
| Setting              | Primary care/community 38%<br>Specialty care 24%<br>NR 38%   |
| Duration             | Mean 41 weeks (SD 112), range 2 weeks to 10 years  |
| Total N randomized   | Mean 1043(SD 4330), range 11 to 19,934, total across studies = 21895   |
| Age                  | Mean age 56 years (SD 9)   |
| Gender               | Two trials exclusively in males, <sup>44,52</sup> and one in females. <sup>39</sup> Of the mixed gender studies, 60% included females representing less than 40% of study sample.      |
| Race/Ethnicity       | Eight studies reported race/ethnicity distribution. Most included a majority of Caucasian participants. One study included all Asians and another majority Hispanics. <sup>50,55</sup> |

**Abbreviations:** CHD = cardiovascular heart disease; SD = standard deviation.

**Table 12. Risk of bias and potential for conflict of interest for studies addressing clinical outcomes**

| Items  | % of Total RCTs |    |         |
|--|-----------------|----|---------|
|  | Yes             | No | Unclear |
| <b>All RCTs (N=21)</b>                                       |                 |    |         |
| Adequate generation of allocation sequence                   | 38              | 0  | 62      |
| Allocation concealment                                       | 5               | 0  | 95      |
| Comparability of groups                                      | 19              | 19 | 62      |
| Purity of supplement   | 71              | 19 | 10      |
| Blinding of allocated intervention                           | 43              | 5  | 52      |
| Adequately addressed missing data                            | 52              | 0  | 48      |
| Freedom from potential conflict of interest                  | 24              | 33 | 43      |
| <b>Crossover RCTs (N=4)</b>                                  |                 |    |         |
| Suitability of crossover design for the study condition      | 100             | 0  | 0       |
| Freedom from carryover effect                                | 50              | 25 | 25      |
| Appropriateness of statistical analysis for crossover design | 0               | 50 | 50      |
| Comparability of groups between periods 1 and 2              | 25              | 0  | 75      |
| Freedom from bias introduced by dropouts                     | 100             | 0  | 0       |

**Abbreviations:** N = total number; RCTs = randomized controlled trials.

## Coenzyme Q10

### Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone

**All-cause mortality and quality of life.** These outcomes were reported in one crossover randomized placebo-controlled trial with a duration of 3 months, in 30, mostly male patients with left ventricular dysfunction, at a specialty center. Coenzyme Q10 (33 mg three times daily) plus maximally tolerated doses of angiotensin-converting enzyme (ACE) inhibitors was compared with ACE inhibitors alone. The majority of patients (i.e., greater than 80 percent) were also taking digoxin, furosemide, hydralazine and/or nitrates. A single death in the placebo group was noted.<sup>54</sup> No significant differences were noted in quality of life scores using the Minnesota “Living with Heart Failure” questionnaire (mean sum of all scores posttreatment 26.7±17.9 versus 26.5±18.7). It is not clear whether the statistical analysis incorporated within patient differences in order to fully utilize the robustness of this crossover design. The strength of evidence is summarized in Table 13.

**Table 13. Strength of evidence for ACE inhibitors with or without coenzyme Q10—Clinical outcomes**

| Risk of Bias               | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|----------------------------|-------------|------------|-----------|----------------------|---|
| <b>All-cause mortality</b> |             |            |           |                      |   |
| Moderate                   | NA          | Direct     | Imprecise | Insufficient         | The study was grossly underpowered for this outcome                         |
| <b>Quality of life</b>     |             |            |           |                      |   |
| Moderate                   | NA          | Direct     | Imprecise | Insufficient         | No significant differences were noted. Type II error could not be excluded. |

**Abbreviations:** ACE = angiotensin converting enzyme; NA = not applicable.

### Coenzyme Q10 Plus Statins Versus Statins Alone

**Adherence.** A 12-week pilot study of limited internal validity (unclear adequacy of sequence generation, allocation concealment and blinding) assessed adherence to statins. A select group of patients with moderate to high 10 year coronary heart disease (CHD) risk and self reported statin associated myalgia were included. The trial did not demonstrate any difference in rates of adherence to simvastatin (10 mg/day to 40 mg/day) between add-on coenzyme Q10 (200 mg/day) and statin alone in patients with previous statin related myalgia. Adherence to simvastatin was 98 percent in both groups, but it is not clear how adherence was assessed.<sup>38</sup>

## Ginkgo Biloba

### Ginkgo Biloba Plus Antiplatelets Versus Antiplatelets Alone

**All-cause mortality and neurologic recovery score.** These outcomes with *G.biloba* extract (40 mg every six hours) were investigated over 4 weeks in 62 South Asian patients with previous ischemic stroke, who were on regular aspirin and/or pentoxphylline.<sup>48</sup> Trial limitations included

unclear allocation concealment, attrition bias, and potential imbalance between groups in terms of the nature of neurologic deficits. The trial was clearly underpowered and of too short duration to detect differences in all-cause mortality and neurologic improvement in the modified Mathew’s scale. There were no deaths and no significant differences in neurologic recovery score after one month of treatment. The mean relative change from baseline in linear transformed Mathew’s scale averaged approximately 20 in both groups, and showed improvement over time (mean difference (MD)) 0.81 [95 percent confidence interval (CI) -9.12, 10.74].<sup>48</sup> Strength of evidence is summarized in Table 14.

**Table 14. Strength of evidence for aspirin and/or pentoxophylline with or without *Ginkgo biloba*—Clinical outcomes**

| Outcome             | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|---------------------|--------------|-------------|------------|-----------|----------------------|---|
| All-cause mortality | Moderate     | NA          | Direct     | Imprecise | Insufficient         | The study was grossly underpowered for this outcome |

**Abbreviation:** NA = not applicable.

## Oral Magnesium

### Magnesium Plus Beta-Blockers Versus Beta-Blockers Alone

**Myocardial infarction.** A single event of myocardial infarction was observed in a randomized crossover controlled trial of oral magnesium aspartate (365 mg daily) or placebo administered daily for 8 weeks to a selected group of 40 hypertensive patients with no comorbidities, on therapeutic doses of beta-blockers. The trial was underpowered to detect differences in clinical outcomes and lacked a clear description of several risk of bias items.<sup>42</sup> Strength of evidence is summarized in Table 15.

**Table 15. Strength of evidence for beta-blockers with or without magnesium—Clinical outcomes**

| Outcome               | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|-----------------------|--------------|-------------|------------|-----------|----------------------|---|
| Myocardial Infarction | Moderate     | NA          | Direct     | Imprecise | Insufficient         | The study was grossly underpowered for this outcome |

**Abbreviations:** NA = not applicable.

## Omega-3 Fatty Acids/Fish Oils

### Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone

**Mortality, arrhythmia, and adherence to medication.** These outcomes were assessed in five trials.

Zero mortality in one randomized crossover pharmacokinetic study of omega-3 fatty acids (4 g/day) with atorvastatin (80 mg/day) versus atorvastatin monotherapy, over 14 days in 50 healthy nonsmoking adults provided insufficient evidence.<sup>36</sup>

In another study, a single case of supraventricular tachycardia (in the add-on 4 g/day omega-3 fatty acid group) in an 8-week efficacy trial in 256 highly selected dyslipidemic patients on statin therapy constituted insufficient evidence for the arrhythmia outcome.<sup>40</sup> There was also one case of exacerbation of congestive heart failure in the add-on omega-3 fatty acid group.<sup>40</sup>

Rates of adherence to statin therapy were reported in three efficacy trials of 6 to 12 weeks duration in highly selected patient populations with dyslipidemia with or without add-on 4 to 9 g/day of omega-3 fatty acids. All studies had unclear risk of bias for adequacy of sequence generation and allocation concealment. Adherence to statin therapy was judged by pill count. No differences in statin adherence rates were noted between both groups – across all three studies, adherence rates in the two groups were equal to or greater than 95 percent.<sup>37,44,53</sup> Strength of evidence is summarized in Table 16.

## Omega-3 Fatty Acids/Fish Oils Plus Cardiovascular Drugs Versus Cardiovascular Drugs Alone

**Mortality, myocardial infarction, cardiovascular procedures, restenosis, coronary vasospasm, and graft occlusion.** These outcomes were assessed with various cardiovascular drugs. Insufficient evidence from single efficacy trials with sparse events did not demonstrate a difference in the outcome of all-cause mortality when study cardiovascular drugs were either aspirin (291 high risk patients followed for 1 year, with nine deaths), warfarin (319 high risk patients followed for 1 year with 5 deaths), or fenofibrate (unclear 10 year CHD risk in 167 participants with hypertriglyceridemia followed for 8 weeks with no deaths) (Table 16).<sup>47,56</sup>

In a 6 month efficacy study of omega-3 fatty acids daily (1.8 g eicosapentaenoic acid plus 1.2 g docosahexaenoic acid) in addition to therapeutic doses of aspirin plus calcium channel antagonist versus the latter two drugs alone, six cases of acute myocardial infarction were identified among 58 patients who had undergone successful coronary angioplasty (relative risk [RR] 1.70 [95 percent CI 0.32, 8.84]) (Table 16).<sup>51</sup> The same study reported non-significant differences among 26 patients requiring subsequent angioplasty (RR 1.35 [95 percent CI 0.68, 2.70]) and four who underwent coronary artery bypass graft (RR 0.84 [95 percent CI 0.12, 5.78]).<sup>51</sup>

**Table 16. Strength of evidence for cardiovascular drug(s)\* with or without omega-3 fatty acids/fish oils—Clinical outcomes**

|   | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|---|--------------|-------------|------------|-----------|----------------------|---|
| <b>Statins</b>                          |              |             |            |           |                      |   |
| All-cause mortality and arrhythmia      | Moderate     | NA          | Direct     | Imprecise | Insufficient         | Studies were grossly underpowered for both outcomes   |
| <b>Aspirin, warfarin or fenofibrate</b> |              |             |            |           |                      |   |
| All-cause mortality                     | Moderate     | NA          | Direct     | Imprecise | Insufficient         | Studies were grossly underpowered. Aspirin+omega-3 fatty acids RR 1.29 (95% CI 0.35, 4.72) Warfarin+omega-3 fatty acids RR 1.25 (95% CI 0.21, 7.38) Fenofibrate+omega-3 fatty acids RR was not estimable because of zero deaths |

**Table 16. Strength of evidence for cardiovascular drug(s)\* with or without omega-3 fatty acids/fish oils—Clinical outcomes (continued)**

|   | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions                                    |
|---|--------------|-------------|------------|-----------|----------------------|--|
| <b>Aspirin and calcium channel antagonist</b> |              |             |            |           |                      |  |
| <b>Acute myocardial infarction</b>            | Moderate     | NA          | Direct     | Imprecise | Insufficient         | Single study, underpowered for clinical events |

\*Cardiovascular drugs were aspirin, warfarin, or fenofibrate

**Abbreviations:** CI = confidence interval; NA = not applicable; RR = relative risk

**Coronary artery restenosis.** Rates of restenosis were investigated with coronary angiography three to four months following successful angioplasty, in 82 highly selected male patients. Although it was not an a priori outcome for this review, we are reporting restenosis because of its clinical relevance.<sup>52</sup> Restenosis was defined as 50 percent narrowing of the luminal diameter. Outcome assessors were blinded to treatment allocation. In this randomized trial, patients were treated either with a daily dose of 3.2 grams of eicosapentaenoic acid added to therapeutic doses of the combination of aspirin, dipyridamole, and calcium channel antagonists, or the latter three drugs in combination. Significantly lower rates of restenosis were observed in the treatment group (RR 0.40 [95 percent CI 0.20, 0.82]); however, the mean percentage reduction in luminal diameter was not significantly different between the two groups. These results conflict with a similar trial conducted in India in 107 patients, that found no significant difference in rates of early restenosis (RR 1.33 [95 percent CI, 0.76, 2.30]).<sup>51</sup> Restenosis rates were not significantly influenced by gender or age (*p* greater than 0.05 for interaction).<sup>51</sup> Possible explanations for these differing trial results, besides differences in patient populations, include that in the Indian trial patients were not treated with dipyridamole, and in the same trial followup angiography was only conducted in those with angina symptoms or a positive exercise test (unlike the previously discussed trial that undertook followup angiography in all patients), thereby potentially biasing the results by excluding healthier individuals.

Coronary vasospasm induced by intracoronary acetylcholine was studied in 22 Japanese patients with variant angina randomized to 4 months treatment with therapeutic doses of diltiazem plus eicosapentaenoic acid (1.8 g/day), or diltiazem alone. Patients served as their own controls. Acetylcholine induced vasoconstriction, measured as percentage change in post nitrate coronary artery diameter compared to the baseline response, was significantly improved in those receiving omega-3 fatty acids but not in the control group.<sup>50</sup> The report was unclear as to how the randomization sequence was generated, allocation was concealed, and outcome assessors were blinded. Based on the reported data, our comparative analysis of posttreatment percentage change in coronary artery diameter following intracoronary acetylcholine injection showed nonsignificant differences between supplement plus diltiazem and diltiazem alone groups (percentage mean difference in spastic segment was -1.3 [95 percent CI -10.34, 7.74]) and in nonspastic segments was 0.9 [95 percent CI -4.56, 6.36])

Coronary bypass graft occlusion rates were evaluated after one year, in 610 participants on either aspirin (300 mg/day) or warfarin (target prothrombin International Normalized Ratio [INR] 2.5-4.2), in conjunction with placebo or omega-3 fatty acids (4 g/day) plus  $\alpha$ -tocopherol (15 mg/day) as an anti-oxidant.<sup>47</sup> Graft occlusion was predefined as visualization of the lack of contrast flow on followup angiography. An important limitation of this randomized trial was its lack of clear reporting of adequate allocation concealment. No significant differences in graft occlusion rates were noted, but studies were underpowered to detect a difference (Table 17).



**Table 17. Graft occlusion rates with omega-3 fatty acids/fish oils and  $\alpha$ -tocopherol—Clinical outcomes**

| Occlusion Subtype                               | Drugs and Supplements                               | RR (95% CI)       |
|---|---|-------------------|
| <b>Internal mammary artery graft occlusion</b>  |   |                   |
|   | Warfarin+ omega-3 fatty acids+ $\alpha$ -tocopherol | 1.25 (0.70, 2.23) |
|   | Aspirin+ omega-3 fatty acids+ $\alpha$ -tocopherol  | 1.03 (0.50, 2.14) |
| <b>Vein graft occlusion, distal anastomosis</b> |   |                   |
|   | Warfarin+ omega-3 fatty acids+ $\alpha$ -tocopherol | 0.84 (0.66, 1.07) |
|   | Aspirin+ omega-3 fatty acids+ $\alpha$ -tocopherol  | 0.83 (0.65, 1.06) |
| <b>Patients with &gt; 1 occluded vein graft</b> |   |                   |
|   | Warfarin+ omega-3 fatty acids+ $\alpha$ -tocopherol | 0.79 (0.62, 1.01) |
|   | Aspirin+ omega-3 fatty acids+ $\alpha$ -tocopherol  | 0.89 (0.69, 1.15) |

**Abbreviations:** CI = confidence interval; RR = relative risk.

## Vitamin E ( $\alpha$ -Tocopherol)

### Vitamin E Plus Cardiovascular Drug Versus Cardiovascular Drug Alone

**Stroke, transient ischemic attacks, adherence, angina, myocardial infarction, and vascular death.** These outcomes were assessed in five trials.

In an efficacy trial, 100 highly selected patients with previous reversible or irreversible ischemic neurologic deficit and good performance status presenting to a university hospital were randomized to vitamin E (0.4 g/day) plus aspirin (325 mg/day) versus aspirin alone for a period of two years. Nine patients experienced outcomes of stroke (seven ischemic, two hemorrhagic), and three experienced recurrent transient ischemic attack, precluding definitive conclusions (Table 18).<sup>49</sup>

**Table 18. Strength of evidence for aspirin with or without vitamin E—Clinical outcomes**

|  | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|--|--------------|-------------|------------|-----------|----------------------|---|
| <b>Aspirin</b>   |              |             |            |           |                      |   |
| All stroke, ischemic stroke, hemorrhagic stroke and transient ischemic attacks | Moderate     | NA          | Direct     | Imprecise | Insufficient         | Small efficacy trial clearly underpowered for clinical events |

**Abbreviation:** NA = not applicable

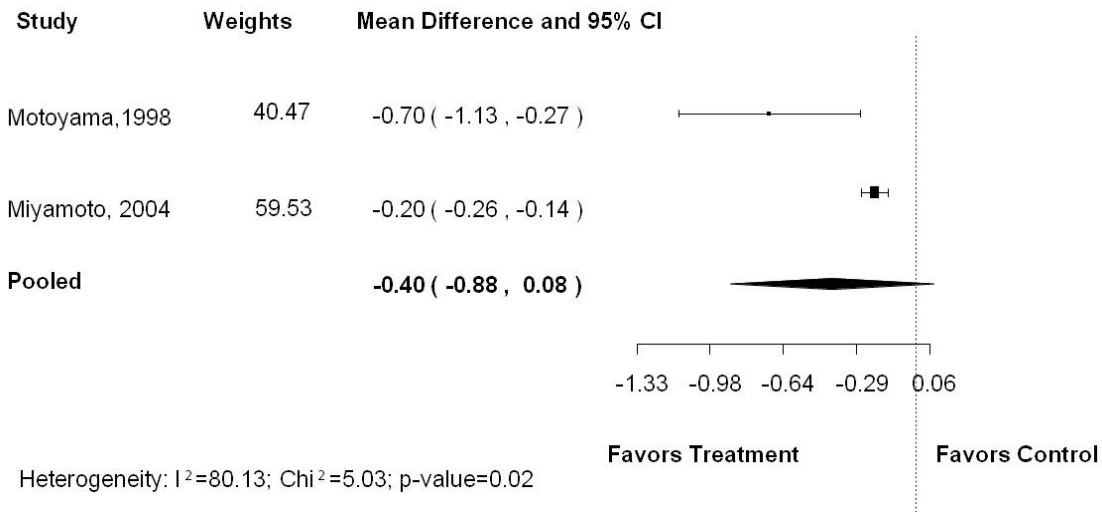
Adherence to a statin was reported in one trial that randomized a highly selected group of 220 hypercholesterolemic patients with normal triglycerides on a standardized diet of 100 mg/day of vitamin E plus 20 to 40 mg/day of pravastatin versus pravastatin alone.<sup>46</sup> Ninety-eight percent of all patients were compliant with their treatment.

In one pragmatic trial in 19,934 women randomized to vitamin E (600 IU/day) plus aspirin (100 mg/day) versus aspirin alone for 10 years, no significant differences were noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent CI 0.79, 1.13]).<sup>39</sup> Data regarding the total number of participants randomized

into the two groups were obtained from the authors. Although components of the composite outcome were gradable, it was not possible to discern if shifts in incidence of stroke and heart attack might have been obscured in this composite outcome.

Two trials, each of one month duration, in a total of 60 highly selected Japanese patients with variant angina, were inconclusive for the mean number of angina attacks per patient following addition of vitamin E (400 mg/day) to therapeutic doses of diltiazem (MD -0.40 [95 percent CI -0.88, 0.08]) (Figure 3).<sup>43,45</sup>

**Figure 3. Forest plot of the mean number of angina attacks for participants administered aspirin with or without vitamin E**



## Vitamin K

### Vitamin K Plus Warfarin Versus Warfarin Alone

**Mortality, stroke, and adherence to cardiovascular medication.** Insufficient evidence was found for mortality and stroke. One 6 month efficacy trial in 70 selected patients with unstable INRs, anticoagulated with warfarin, reported no stroke and one death.<sup>41</sup> During the 6 month study period, two of 35 patients failed to take their warfarin and the supplement on a single occasion.<sup>41</sup> Strength of evidence is summarized in Table 19.

**Table 19. Strength of evidence for warfarin with or without vitamin K—Clinical outcomes**

| Cardiovascular drug / Outcome  | Risk of Bias | Consistency | Directness | Precision | Strength of Evidence | Conclusions   |
|--------------------------------|--------------|-------------|------------|-----------|----------------------|---|
| All-cause mortality and stroke | Moderate     | NA          | Direct     | Imprecise | Insufficient         | Two small trials clearly underpowered for clinical events |

**Abbreviation:** NA = not applicable

**Key Question 1a. Do the effect estimates of clinical cardiovascular outcomes vary by age, ethnicity, gender, or health status?**

A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of pre-identified subgroups.

## Key Question 1b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for clinical cardiovascular outcomes?

No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.

### Main Points for Key Question 1: Clinical Outcomes

For Key Question 1, we compared dietary supplement(s) coadministered with cardiovascular drug(s), with the cardiovascular drug(s) alone, to investigate comparative clinical efficacy/effectiveness, subgroup effects and statistical interactions.

- Twenty-one randomized controlled trials contributed evidence.
- For all predetermined gradable clinical outcomes for which evidence was found, the strength of evidence of comparative efficacy or effectiveness was graded insufficient because type II error could not be excluded due to the low power of studies. When compared with the specific cardiovascular drug alone, insufficient evidence was found for an effect of coenzyme Q10 coadministered with ACE inhibitors on all-cause mortality and quality of life; *Ginkgo biloba* plus aspirin and/or pentoxifylline on all-cause mortality; oral magnesium and beta-blockers on myocardial infarction; omega-3 fatty acids plus statins on all-cause mortality and arrhythmia; omega-3 fatty acids plus aspirin, warfarin or fenofibrate on all-cause mortality; omega-3 fatty acids plus aspirin and calcium channel antagonist on acute myocardial infarction; vitamin E plus aspirin on stroke and transient ischemic attacks; and vitamin K plus warfarin derivative on all-cause mortality and stroke.
- No differences in adherence to statins were noted with coadministration of coenzyme Q10, omega-3 fatty acids, and vitamin E, with adherence rates greater than 90 percent in both drug plus supplement and drug alone groups. Evidence supporting benefit of omega-3 fatty acids added to conventional antiplatelet therapy and calcium channel antagonists on rates of restenosis following successful coronary angioplasty is conflicting. Underpowered studies addressed all other outcomes such as exacerbation of congestive heart failure, number of patients undergoing cardiac procedures, graft occlusion, neurologic recovery score, coronary vasospasm, and number of angina attacks in patients with variant angina for various dietary supplement and cardiovascular drug combinations
- Most studies were short-term efficacy trials, except for one pragmatic trial on 19,934 women randomized to vitamin E (600 IU/day) plus aspirin (100 mg/day) versus aspirin alone for 10 years. In this trial, no significant difference was noted for the composite outcome of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95, 95 percent CI, 0.79, 1.13).
- With no data, there was insufficient evidence for the outcomes of hospitalization and those related to peripheral arterial disease across all supplement-cardiovascular drug(s) combinations.
- No evidence on clinical outcomes was found for *Echinacea*, garlic, ginger, ginseng, hawthorn, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, and vitamin D (with or without calcium supplementation) coadministered with a cardiovascular drug(s)

- A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of pre-identified subgroups, or documentation of any dose-response effect.
- No study analyzed statistical interaction between a supplement and a cardiovascular drug on clinical outcomes.

**Key Question 2.** In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on intermediate cardiovascular efficacy outcomes (e.g., lipids, blood pressure, electrocardiographic measurements, serum markers, bleeding, and coagulation times)?

a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

## Overview

Fifty-eight RCTs and one controlled clinical trial addressed Key Question 2. The availability of evidence is summarized in Table 20. The dietary supplements used in the studies were the following: coenzyme Q10 (five studies),<sup>38,54,57,58,89</sup> *Echinacea* (one study),<sup>59</sup> garlic (four studies),<sup>60-63</sup> ginger (one study),<sup>64</sup> *Ginkgo biloba* (five studies),<sup>64-68</sup> ginseng (three studies),<sup>69-71</sup> hawthorn (one study),<sup>72</sup> magnesium (three studies),<sup>42,73,74</sup> niacin (one study),<sup>75</sup> omega-3 fatty acids (24 studies),<sup>37,40,44,50-53,55,56,76-78,91,92,94-99,151,152,163,164</sup> vitamin E (11 studies),<sup>46,49,79-87</sup> and vitamin K (one study)<sup>41</sup>. No evidence was identified for effects of red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on intermediate outcomes. No study addressed the following outcomes: incidence of metabolic syndrome; incidence of hypotension; carotid-intima media thickness; or change in 10-year Framingham risk profile. Two studies examined statistical interaction.<sup>44,78</sup> One study used general linear modeling to assess interaction between fish/marine oils and atorvastatin on lipid parameters.<sup>44</sup> The other study used ANOVA to assess interaction between omega-3 fatty acids and niacin plus aspirin on triglyceride levels.<sup>78</sup> No relevant data were available from observational studies. One systematic review reporting the effectiveness of concomitant administration of omega-3 fatty acids plus statins compared with statins alone on lipid profiles in participants requiring lipid lowering therapy<sup>149</sup> was not included for synthesis because it was determined to be out of date. Details of individual study characteristics, risk of bias and outcomes data are reported in Appendix C.

**Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2**

| Supplement and Cardiovascular Drug(s) | Outcome                   | Number of Studies |
|---------------------------------------|---------------------------|-------------------|
| <b>Coenzyme Q10</b>                   |                           |                   |
| ACE inhibitors*                       | Ejection Fraction         | 1                 |
| Fenofibrate                           | Lipid Profile             | 1                 |
|                                       | Blood Pressure – Systolic |                   |
| Statins                               | Lipid Profile             | 3                 |

**Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2 (continued)**

| Supplement and Cardiovascular Drug(s)   | Outcome  | Number of Studies |
|---|--|-------------------|
| <b>Echinacea</b>                        |  |                   |
| Warfarin                                | INR<br>Platelet Aggregation  | 1                 |
| <b>Garlic</b>                           |  |                   |
| Nitrates                                | Lipid Profile  | 1                 |
| Statins + Aspirin                       | Lipid Profile<br>CRP<br>Platelet Count<br>Coronary Artery Calcification  | 1                 |
| Warfarin                                | Lipid Profile<br>Blood Pressure – Systolic and Diastolic<br>Platelet Count<br>Platelet Aggregation                         | 1                 |
|   | INR  | 2                 |
| <b>Ginger</b>                           |  |                   |
| Warfarin                                | INR<br>Platelet Aggregation  | 1                 |
| <b>Ginkgo biloba</b>                    |  |                   |
| Aspirin                                 | Lipid Profile<br>Blood Pressure – Systolic and Diastolic<br>Clotting Time<br>Platelet Count<br>Partial Thromboplastin Time | 1                 |
|   | Platelet Aggregation   | 2                 |
| Antiplatelet drugs –<br>thienopyridines | Blood Pressure – Systolic<br>Clotting Time<br>Platelet Count   | 1                 |
|   | Platelet Aggregation<br>Bleeding Time  | 2                 |
| Cilostazol                              | Blood Pressure – Systolic<br>Platelet Aggregation<br>Clotting Time<br>Platelet Count                                       | 1                 |
| Warfarin                                | INR<br>Platelet Aggregation  | 1                 |
| <b>Ginseng</b>                          |  |                   |
| Warfarin                                | INR  | 3                 |
|   | Prothrombin Time<br>Platelet Count<br>Platelet Aggregation   | 1                 |
| <b>Hawthorn</b>                         |  |                   |
| Digoxin                                 | PR Interval  | 1                 |
| <b>Magnesium</b>                        |  |                   |
| Beta-Adrenergic Antagonists             | Blood Pressure – Systolic and Diastolic  | 1                 |
| Hydrochlorothiazide                     | Lipid Profile  | 1                 |
|   | Blood Pressure – Systolic and Diastolic  | 2                 |
| <b>Niacin ≤ 250 mg</b>                  |  |                   |
| Propranolol                             | Lipid Profile  | 1                 |

**Table 20. Overview of availability of evidence for intermediate outcomes—Key Question 2 (continued)**

| Supplement and Cardiovascular Drug(s)   | Outcome   | Number of Studies |
|---|---|-------------------|
| <b>Omega-3 fatty acids/fish oils</b>  |   |                   |
| ACE inhibitors  | Lipid Profile   | 2                 |
|   | Blood Pressure – Systolic and Diastolic                   |                   |
|   | Urinary Protein Excretion<br>Reduction in Proteinuria     | 1                 |
| Aspirin   | Lipid Profile   | 2                 |
|   | Platelet Count  |                   |
|   | Blood Pressure – Systolic and Diastolic                   | 1                 |
| Beta-Adrenergic Antagonists   | Blood Pressure – Systolic and Diastolic                   | 1                 |
| Calcium Channel Blockers  | Lipid Profile   | 1                 |
| Calcium Channel Blockers<br>with + Aspirin<br>(with or without<br>dipyridamole) | Lipid Profile   | 2                 |
|   | Platelet Count  | 1                 |
| Fenofibrate   | Lipid Profile   | 1                 |
|   | Incidence of Hypertension                                 |                   |
| Niacin + Aspirin  | Lipid Profile   | 1                 |
| Statins   | Lipid Profile   | 11                |
|   | Blood Pressure – Systolic and Diastolic<br>Platelet Count | 3                 |
|   | CRP<br>Blood Coagulation                                  | 1                 |
| Warfarin  | INR   | 1                 |
| <b>Vitamin E</b>  |   |                   |
| Antiplatelets   | Lipid Profile   | 1                 |
|   | Platelet Aggregation                                      |                   |
| Furosemide  | Blood Pressure – Systolic and Diastolic                   | 1                 |
| Gemfibrozil   | Lipid Profile   | 1                 |
|   | Blood Pressure – Systolic and Diastolic                   |                   |
| Nifedipine  | Lipid Profile   | 1                 |
|   | Blood Pressure – Systolic and Diastolic                   |                   |
| Statins   | Lipid Profile   | 6                 |
|   | CRP   | 1                 |
|   | Prothrombin Time<br>Platelet Count                        |                   |
| <b>Vitamin K</b>  |   |                   |
| Anticoagulants  | INR   | 2                 |

**Note:** \*Subjects were also taking digoxin, furosemide, hydralazine, or nitrates.

**Abbreviations:** ACE = angiotensin converting enzyme; CRP = C-reactive protein; INR = international normalized ratio

Participant and study characteristics are summarized in Table 21.

**Table 21. Summary of study characteristics for studies addressing intermediate outcomes—Key Question 2**

| Characteristic      | Distribution  |
|---------------------|---|
| Sample CHD risk     | <ul style="list-style-type: none"> <li>• Low 8.0%</li> <li>• Moderate to moderately high 2.3%</li> <li>• High 20.3%</li> <li>• Mixed 33.2%</li> <li>• Unclear 36.2%</li> </ul>  |
| Geographical region | <ul style="list-style-type: none"> <li>• North America 15.3%</li> <li>• Europe 28.8%</li> <li>• Australia/New Zealand 10.2%</li> <li>• East Asia 6.8%</li> <li>• Rest of Asia 3.4%</li> <li>• NR 10.2%</li> </ul>                                     |
| Setting             | <ul style="list-style-type: none"> <li>• Primary care/community 34.0%</li> <li>• Specialty care 21.7%</li> <li>• NR 44.3%</li> </ul>  |
| Duration            | Mean 10 weeks (SD 14.7)<br>Range 1 week to 2 years  |
| Total N randomized  | Mean 50.6(SD 51.7), range 10 to 332, total across studies = 3,201   |
| Age                 | Mean age 48.8 years (SD 14.4)   |
| Gender              | Ten all-male trials. <sup>44,52,59,61,64,65,67,68,71,98</sup><br>In 28.0% of the mixed gender studies, females were less than 40% of the study sample   |
| Race/Ethnicity      | Eighteen (31.0%) studies reported race/ethnicity distribution.<br>Five studies included a majority of Caucasian participants.<br>Three studies included all Asians <sup>50,57,68</sup><br>Two studies included majority of Hispanics <sup>55,95</sup> |

**Abbreviations:** CHD = coronary heart disease; N = total number in trial; NR = not reported; SD = standard deviation.

Assessment of risks of bias is summarized in Table 22. Among all RCTs the purity of supplement was the item most frequently reported, while underreporting of generation and concealment of allocation represented the greatest potential for bias. In all crossover trials the study design was deemed to be suitable for the studied condition and a majority were judged to be free of carryover effect.

**Table 22. Risk of bias and potential for conflict of interest—Key Question 2**

| Items   | Yes                              | No | Unclear |
|---|----------------------------------|----|---------|
| <b>All RCTs</b>                                 | <b>% of total studies (N=58)</b> |    |         |
| Adequate generation of allocation sequence      | 20                               | 2  | 78      |
| Allocation concealment                          | 9                                | 0  | 91      |
| Comparability of groups                         | 9                                | 46 | 46      |
| Purity of supplement                            | 81                               | 12 | 7       |
| Blinding of allocated intervention              | 22                               | 24 | 53      |
| Adequately addressed missing data               | 63                               | 3  | 34      |
| Freedom from potential for conflict of interest | 24                               | 31 | 47      |

**Table 22. Risk of bias and potential for conflict of interest—Key Question 2 (continued)**

| Items  | Yes  | No   | Unclear |
|--|--|------|---------|
| <b>Crossover RCTs</b>  | <b>% of total crossover studies (N=19)</b> |      |         |
| Suitability of crossover design for the study condition      | 100  | 0    | 0       |
| Free of carryover effect                                     | 26.3                                       | 63.2 | 10.5    |
| Appropriateness of statistical analysis for crossover design | 21.1                                       | 21.1 | 57.9    |
| Comparability of groups between periods 1 and 2              | 10.5                                       | 0.0  | 89.5    |
| Freedom from bias introduced by dropouts                     | 5.3  | 78.9 | 15.8    |

**Abbreviations:** N = total number; RCTs = randomized controlled trials.

## Coenzyme Q10

Five RCTs, including four parallel-arm trials,<sup>38,57,58,89</sup> and one crossover trial<sup>54</sup> examined cardiovascular drugs with and without coenzyme Q10. The trials were conducted in Australia,<sup>38,54,58</sup> North America,<sup>89</sup> and East Asia.<sup>57</sup> The number of included participants across these trials ranged from 30<sup>54</sup> to 49,<sup>57</sup> and they received statins (atorvastatin, simvastatin),<sup>38,57</sup> fenofibrate,<sup>58</sup> ACE inhibitors (specific agents not stated), or vitamin E<sup>89</sup> in addition to other cardiovascular drugs (digoxin, furosemide, hydralazine, nitrates, or statins).<sup>54</sup> According to the National Cholesterol Education Program, Adult Treatment Panel III,<sup>165</sup> the study participants were categorized as having a high,<sup>54,58</sup> unclear,<sup>57,89</sup> or mixed (moderate and high)<sup>38</sup> risk for CHD. The duration of treatment across the studies ranged from 4<sup>89</sup> to 12 weeks.<sup>38,54,57,58</sup> Generally, these studies were reported to be double-blind and had moderate risk of bias across the outcomes of interest. The washout period in the one crossover trial was adequate to minimize or avoid a carryover treatment effect.<sup>54</sup> Further details on study, participant, and treatment characteristics are presented in Appendix C.

Summary of findings and strength of evidence data are presented in Table 23. No meta-analysis was possible for coenzyme Q10 studies because when more than one study reported a particular outcome,<sup>38,57,89</sup> the treatment effect was either not reported,<sup>89</sup> or it was reported as a median (interquartile range) change,<sup>38</sup> so the study results were in a format that is unsuitable for statistical pooling.

## Coenzyme Q10 Plus Statins Versus Statins Alone

**C-reactive protein (CRP).** One placebo-controlled parallel-arm RCT examined CRP changes in participants with unclear CHD risk.<sup>57</sup> The 12-week mean CRP levels were not different between groups with add-on dietary supplement treatment (100 mg/day) versus the statin-only (10 mg/day) group.

**High density lipoprotein-cholesterol.** Two placebo-controlled parallel-arm randomized trials examined HDL-C changes in participants with unclear or mixed CHD risk.<sup>38,57</sup> In one trial, mean HDL-C levels after 12 weeks of treatment were not significantly different for those receiving coenzyme Q10 (100 mg/day) plus statins (10 mg/day) versus those receiving only statins.<sup>57</sup> Similarly, in the second trial (200 mg/day coenzyme Q10; 10-40 mg/day statins), there was no significant between-group difference for the median change in HDL-C.<sup>38</sup>



**Low density lipoprotein-cholesterol, total cholesterol and triglycerides.** Two trials in participants with mixed<sup>38</sup> or unclear CHD risk investigated changes in LDL-C.<sup>57</sup> Levels were not significantly different following treatment with coenzyme Q10 plus statins compared with plus statins alone after 12 weeks.<sup>38,57</sup> Mean differences<sup>57</sup> and between-group difference for the median change<sup>38</sup> were not significant for LDL-C, total cholesterol, or triglycerides.

### **Coenzyme Q10 Plus Statins Versus Vitamin E Plus Statins**

**Lipid profile, low density lipoprotein-cholesterol, total cholesterol and triglycerides.** In one trial of 32 participants with unclear CHD risk, changes of LDL-C, TC, and TG levels were studied.<sup>89</sup> Results from this RCT indicated no differences in lipid profile (total cholesterol, LDL-C, triglycerides) after 30 days of treatment with coenzyme Q10 (100 mg/day) plus statins or vitamin E (400 IU/day) plus statin groups in participants with statin induced myopathic pain (numeric data were not provided).<sup>89</sup>

### **Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone**

Participants were also taking digoxin, furosemide, hydralazine, and nitrates.

**Ejection fraction.** One randomized crossover trial reported ejection fraction in participants with heart failure (high CHD risk).<sup>54</sup> The 12 week posttreatment ejection fraction in the treatment (coenzyme Q10 [100 mg/day] plus ACE inhibitors) and control (ACE inhibitors alone) groups were not significantly different.

### **Coenzyme Q10 Plus Fenofibrate Versus Fenofibrate Alone**

**Lipid profiles and systolic blood pressure.** One parallel arm randomized trial in participants with type II diabetes and high CHD risk reported changes in systolic blood pressure.<sup>58</sup> The 12 week posttreatment mean levels in the treatment (200 mg/day coenzyme Q10 plus 200 mg/day fenofibrate) and control (fenofibrate alone) groups did not significantly differ for any of the outcomes assessed (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C, and systolic blood pressure).

**Applicability.** Low grade evidence of no effect on HDL-C was found in a primarily (70 percent) male population, of mean age 53 years, with high risk for cardiovascular disease. Treatment was over 12 weeks, with fenofibrate and with or without coenzyme Q10.

**Table 23. Strength of evidence for cardiovascular drugs with and without coenzyme Q10—Intermediate outcomes**

| Cardiovascular drug(s)/ Outcome     | Risk of bias | Consistency | Directness | Precision | Grade        | Treatment effect and conclusion* MD (95% CI)   |
|-------------------------------------|--------------|-------------|------------|-----------|--------------|--|
| <b>Statins</b>                      |              |             |            |           |              |  |
| CRP <sup>57</sup>                   | -            | -           | -          | -         | -            | No difference<br>0.02 mg/L (-0.64, 0.68)   |
| HDL-C (mg/dL) <sup>38,57</sup>      | Moderate     | Consistent  | Indirect   | Imprecise | Insufficient | Inconclusive<br>5.02 mg/dL (-3.73, 13.77) <sup>57</sup><br>Arm-specific median change 0.39 versus -0.77, p=0.65 <sup>38†</sup>   |
| LDL-C (mg/dL) <sup>38,57</sup>      | Moderate     | Consistent  | Indirect   | Imprecise | Insufficient | Inconclusive<br>8.12 mg/dL (-3.79, 20.03) <sup>57</sup><br>Arm-specific median change -65.73 versus -50.27, p=0.53 <sup>38</sup> |
| TC (mg/dL) <sup>38,57</sup>         | -            | -           | -          | -         | -            | Inconclusive<br>11.9 (-3.55, 27.53) <sup>57</sup><br>Arm-specific median change -58.00 versus -61.87, p=0.57 <sup>38</sup>       |
| TG (mg/dL) <sup>38,57</sup>         | Moderate     | Consistent  | Indirect   | Imprecise | Insufficient | Inconclusive<br>-21.26 (-48.88, 6.36) <sup>57</sup><br>Arm-specific median change -35.43 versus -26.57, p=0.90 <sup>38</sup>     |
| <b>ACE inhibitors</b>               |              |             |            |           |              |  |
| Ejection fraction (%) <sup>54</sup> | -            | -           | -          | -         | -            | No difference<br>0 (-4.75, 4.75)   |
| <b>Fenofibrate</b>                  |              |             |            |           |              |  |
| HDL-C (mg/dL) <sup>58</sup>         | Moderate     | NA          | Indirect   | Precise   | Low          | No difference<br>-1.55 (-6.78, 3.68)   |
| LDL-C (mg/dL) <sup>58</sup>         | Moderate     | NA          | Indirect   | Imprecise | Insufficient | Inconclusive<br>3.87 (-19.30, 27.04)   |
| TC (mg/dL) <sup>58</sup>            | -            | -           | -          | -         | -            | Inconclusive<br>0 (-23.17, 23.17)  |
| TG (mg/dL) <sup>58</sup>            | Moderate     | NA          | Indirect   | Imprecise | Insufficient | Inconclusive<br>8.85 (-52.49, 70.19)   |
| Non-HDL-C (mg/dL) <sup>58</sup>     | Moderate     | NA          | Indirect   | Imprecise | Insufficient | Inconclusive<br>0.87 (-22.30, 24.04)   |
| SBP (mmHg) <sup>58</sup>            | Moderate     | NA          | Indirect   | Imprecise | Insufficient | Inconclusive<br>-3.40 (-15.56, 8.76)   |

**Notes:** \* Mean difference and 95 percent confidence interval; range for mean difference given only when evidence consists of multiple studies that were not pooled; (-) is indicated where non-gradable outcomes are reported (for example TC, or CRP)

† Arm-specific median change (from baseline) was not used to assess the domain of precision

**Abbreviations:** ACE = angiotensin-converting enzyme; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NA = not applicable; NR = not reported; TC = total cholesterol; TG = triglycerides; RCT = randomized controlled trial; SBP = systolic blood pressure; wk(s) = week(s); yr(s) = year(s).

## Echinacea

### Echinacea Plus Warfarin Versus Warfarin Alone

One crossover RCT in 12 healthy male volunteers examined the effect of two weeks pre-treatment with *Echinacea* (600 mg of *E. angustifolia* root plus 675 mg of *E. purpurea* root daily) and a single dose of warfarin (25 mg) versus warfarin alone.<sup>59</sup>

There was no effect on blood pressure, maximum International Normalized Ratio (INR<sub>max</sub>), geometric mean ratio [GMR] 1.04 [90 percent CI 0.95, 1.13], AUC of INR (MD 2.50 [95 percent CI -17.72, 22.72] and GMR 1.09 [95 percent CI 0.91, 1.31]), or measures of platelet aggregation (using three different platelet agonists: adenosine diphosphate, arachidonic acid and collagen; data not shown). Strength of evidence is summarized in Table 24.

**Table 24. Strength of evidence for warfarin with and without *Echinacea*—Intermediate outcomes**

| Cardio-vascular Drug(s)/ Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Treatment Effect and Conclusion MD (95% CI)  |
|----------------------------------|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Warfarin</b>                  |              |             |                      |           |              |  |
| Blood pressure                   | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | No difference<br>Systolic blood pressure: 2.20 mm Hg (-8.98, 13.38)<br>Diastolic blood pressure: -0.80 mm Hg (-8.21, 6.61) |
| INR <sub>max</sub>               | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | No difference<br>INR <sub>max</sub> 0.10 (-0.20, 0.40)   |

**Abbreviations:** CI = confidence interval; MD = mean difference; mm Hg = millimetres of mercury.

## Garlic

Four RCTs, including three parallel-arm trials,<sup>60,62,63</sup> and one crossover trial<sup>61</sup> examined cardiovascular drugs with and without garlic. The trials were conducted in Australia,<sup>61</sup> North America,<sup>60,63</sup> and Europe.<sup>62</sup> The number of included participants across these trials ranged from 12<sup>61</sup> to 60,<sup>62</sup> and they received statins plus aspirin,<sup>63</sup> warfarin,<sup>60,61</sup> or nitrates.<sup>62</sup> According to the National Cholesterol Education Program, Adult Treatment Panel III,<sup>165</sup> the study participants were categorized as having a high,<sup>62,63</sup> unclear,<sup>60</sup> or low<sup>61</sup> CHD risk. The duration of treatment across the studies ranged from one day<sup>61</sup> to 12 months.<sup>63</sup> The washout period in the one crossover trial was adequate to minimize or avoid a carryover treatment effect. Further details on study, participant, and treatment characteristics are presented in Appendix C. Strength of evidence is summarized in Table 25.

### Garlic Plus Warfarin Versus Warfarin Alone

Two small RCTs, one parallel-group<sup>60</sup> and one crossover<sup>61</sup> trial, examined the effect of treating patients on warfarin with garlic extracts. Both studies concluded that supplementation with garlic in patients taking warfarin does not further affect INR, based on various measures including INR,<sup>60</sup> or INR<sub>max</sub>, AUC of INR, or the number of participants with an INR greater than 4 (no events in either arm).<sup>61</sup>

One study<sup>60</sup> in 48 participants with prosthetic heart valves, or diagnosed with deep vein thrombosis, valvular heart disease, or atrial fibrillation assessed the effects of aged garlic extract

(AGE) (10 mL/day) plus warfarin. No significant effects were seen for total cholesterol, LDL-C, or triglycerides. However, there was a statistically significant increase in HDL-C in the combination group. Neither blood pressure, nor platelet count (data not shown) were significantly affected.

One crossover study<sup>61</sup> found no significant effect of pretreatment with garlic (4 g single dose) plus a single dose of warfarin (25 mg) on platelet aggregation (using four different agents: adenosine diphosphate, arachidonic acid, collagen and ristocetin; data not presented). Participants in this trial were 16 healthy male adults of known CYP2C9 and VKORC1 genotype.

All results for major review outcomes, aside from HDL-C, were considered to have insufficient strength of evidence (Table 25). The strength of evidence for HDL-C was initially rated as insufficient by one reviewer because the lower bound confidence interval of 0.19 mg/dL is not clinically meaningful. A second reviewer provided a rating of low because the estimate is statistically significant. Adjudication by a third reviewer led to a final rating of low.

### **Garlic Plus Nitrates Versus Nitrates Alone**

One controlled clinical trial<sup>62</sup> recruited 60 participants with coronary artery disease to receive either garlic oil (4 g/day) or placebo in addition to their prescribed nitrates (specific drugs and doses were not reported). Compared with placebo, administration of garlic was found to significantly decrease total serum cholesterol, and increase serum HDL-C.<sup>62</sup> Serum triglycerides were also reduced but the comparison was not statistically significant. These results were considered to provide insufficient strength of evidence for triglycerides and low strength of evidence for HDL-C in favor of combination treatment (Table 25).

### **Garlic Plus Statins and Aspirin Versus Statins and Aspirin Alone**

One small parallel group trial<sup>63</sup> randomly allocated 23 participants with, or at high risk for coronary artery disease to receive AGE (4 mL, 305 g/L of extracted solids/day) or placebo in addition to their prescribed statins (10-40 mg/day) and aspirin (dose not specified) over a period of one year. Compared with placebo, administration of AGE was not found to have a significant effect on lipid parameters (total cholesterol (TC), TC/HDL-C, HDL-C, LDL-C, triglycerides), CRP, or platelet count.

This study also examined two measures of coronary artery calcification: volume calcium score (using isotropic interpolation method) and Agatston calcium score (multiplying the lesion area by a coefficient based on the peak density within plaque). The first measure was found to be lowered significantly by supplementation with garlic compared with placebo (change in volume calcium score:  $-83.80 \text{ mm}^3$  [95 percent CI  $-164.22, -3.38$ ]; percent change in volume calcium score per year:  $-14.7 \text{ mm}^3$  [95 percent CI  $-28.93, -0.47$ ]). No differences were found in the second measure.

Strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table 25).

**Table 25. Strength of evidence for cardiovascular drugs with and without garlic—Intermediate outcomes**

| Cardio-vascular Drug(s)/ Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect MD (95% CI)   |
|----------------------------------|--------------|-------------|----------------------|-----------|--------------|---|
| <b>Warfarin</b>                  |              |             |                      |           |              |   |
| Blood pressure (mmHg)            | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>Systolic:<br>2.20 (-8.98, 13.38)<br>Diastolic:<br>-0.80 (-8.21, 6.61)   |
| LDL-C (mg/dL)                    | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>4.20 mg/dL (-12.01, 20.41)  |
| HDL-C (mg/dL)                    | Moderate     | NA          | Indirect (surrogate) | Precise   | Low          | <b>In favor of combination treatment</b><br>4.50 mg/dL (0.19, 8.81)   |
| Total cholesterol (mg/dL)        | -            | -           | -                    | -         | -            | <b>No difference</b><br>12.50 (-3.74, 28.74)  |
| Triglycerides (mg/dL)            | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>31.90 (-23.66, 87.46)   |
| INR                              | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>INR: -0.20 (-0.83, 0.43)<br>INR <sub>max</sub> : -0.10 (95% CI -0.63, 0.43)<br>AUC of INR :<br>4.30 (-35.90, 44.50)<br>INR > 4<br>No events in either arm |
| <b>Nitrates</b>                  |              |             |                      |           |              |   |
| HDL-C (mg/dL)                    | High         | NA          | Indirect (surrogate) | Precise   | Low          | <b>In favor of combination treatment</b><br>8.40 (1.91, 14.89)  |
| Total cholesterol (mg/dL)        | -            | -           | -                    | -         | -            | <b>In favor of combination treatment</b><br>-28.20 (-48.30, -8.10)  |
| Triglycerides (mg/dL)            | High         | NA          | Indirect(surrogate)  | Imprecise | Insufficient | <b>No difference</b><br>-10.30 (-27.60, 7.00)   |

**Table 25. Strength of evidence for cardiovascular drugs with and without garlic—Intermediate outcomes (continued)**

| Cardio-vascular Drug(s)/ Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect MD (95% CI)        |
|----------------------------------|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Statins + Aspirin</b>         |              |             |                      |           |              |  |
| LDL-C (mg/dL)                    | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>-25.10 (-54.69, 4.49)  |
| HDL-C (mg/dL)                    | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>4.30 (-7.55, 16.15)    |
| Triglycerides (mg/dL)            | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>No difference</b><br>-21.20 (-93.42, 51.02) |

**Abbreviations:** AUC = area under the curve; CI = confidence interval; HDL-C = high density lipoprotein-cholesterol; INR = international normalized ratio; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; (-) is indicated where non-gradable outcomes (total cholesterol) are reported

**Applicability.** Garlic in addition to nitrates for 3 months was found to significantly improve total cholesterol and HDL-C compared with nitrates alone, in subjects with healed myocardial infarction with or without angina.<sup>62</sup> Garlic in addition to statins plus aspirin for 12 months significantly lowered a measure of coronary artery calcification in subjects with known coronary artery disease.<sup>63</sup>

## Ginger

One crossover RCT compared a single dose of warfarin following seven days pre-treatment with ginger (3.6 g/day) with warfarin alone in 12 healthy male subjects (Table 26).<sup>64</sup> The study also included a warfarin plus *G. biloba* group (data for the comparison between warfarin plus ginger and warfarin plus *Ginkgo* is in the *G. biloba* section).

The same study reported AUC of INR for the combination of ginger plus warfarin versus warfarin alone.<sup>64</sup> One of the two analyses of the data suggests a possible effect of unknown clinical significance. The mean difference in platelet aggregation was not statistically significant (MD 0.6 [95 percent CI -0.42, 1.62]) but the geometric mean ratio was statistically significant. Given the inconsistency in findings, strength of evidence was graded as insufficient for INR (Table 26).

**Table 26. Strength of evidence for warfarin with or without ginger—Intermediate outcomes**

| Cardio-vascular Drug(s) / Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect   |
|-----------------------------------|--------------|-------------|----------------------|-----------|--------------|---|
| AUC of INR <sup>64</sup>          | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>MD 1.00 (95% CI -43.68, 45.68)<br>GMR 1.01 (90% CI 0.93, 1.15) |

**Abbreviations:** AUC of INR = area under the curve of the international normalized ratio; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference.

## Ginkgo Biloba

Five RCTs investigated *G. biloba* with cardiovascular drugs (Table 27).<sup>64-68</sup> Four studies included subjects taking antiplatelet agents (aspirin,<sup>65,66</sup> clopidogrel,<sup>67</sup> or ticlopidine<sup>68</sup>). One study included subjects taking an anticoagulant (warfarin<sup>64</sup>) and one study included subjects taking a vasodilator (cilostazol<sup>67</sup>).

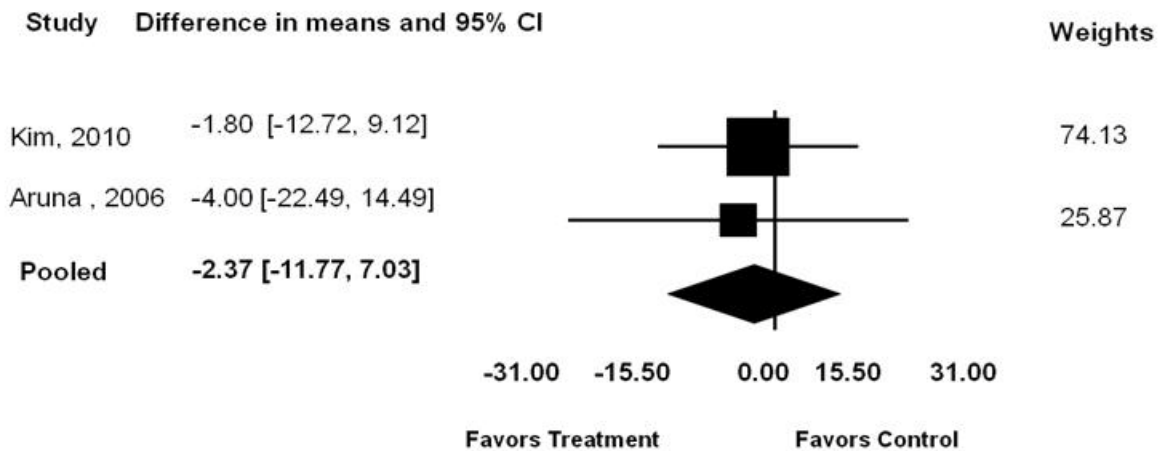
### G. Biloba Plus Antiplatelet Agents Versus Antiplatelet Agents Alone

Aspirin was administered with *G. biloba* in two studies, of young healthy males (240 mg/day *G. biloba*)<sup>65</sup> or elderly subjects with peripheral arterial disease or risk factors for cardiovascular disease (300 mg/day *G. biloba*).<sup>66</sup> Although platelet aggregation was reported in both studies, meta-analysis could not be performed because different posttreatment effect estimates were reported (mean<sup>65</sup> and mean change from baseline<sup>66</sup>). Both studies reported nonsignificant differences in platelet aggregation. Nonsignificant differences were also reported in clotting time,<sup>66</sup> bleeding time,<sup>65</sup> partial thromboplastin time,<sup>65</sup> and platelet count.<sup>65</sup> No changes were found in lipid parameters and blood pressure (reported qualitatively only).<sup>65</sup>

In two studies, single doses of a thienopyridine antiplatelet drug (clopidogrel<sup>67</sup> or ticlopidine<sup>68</sup>) were administered with or without single doses of *G. biloba*(80 mg/day). The pooled estimates for platelet aggregation were statistically nonsignificant (Figures 4 and 5), as was the pooled estimate for bleeding time (Figure 6). There were no significant changes in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).<sup>67</sup>

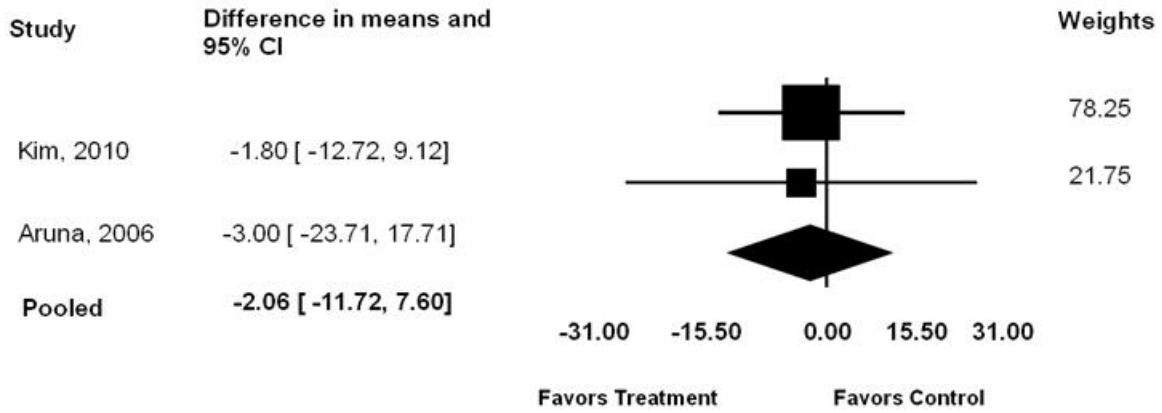
Strength of evidence was insufficient for blood pressure and lipid profile (Table 27).

**Figure 4. Forest plot of posttreatment mean difference of platelet aggregation for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5  $\mu$ L of 10  $\mu$ M ADP or 2.5  $\mu$ L of 10  $\mu$ M ADP)-(percent)**



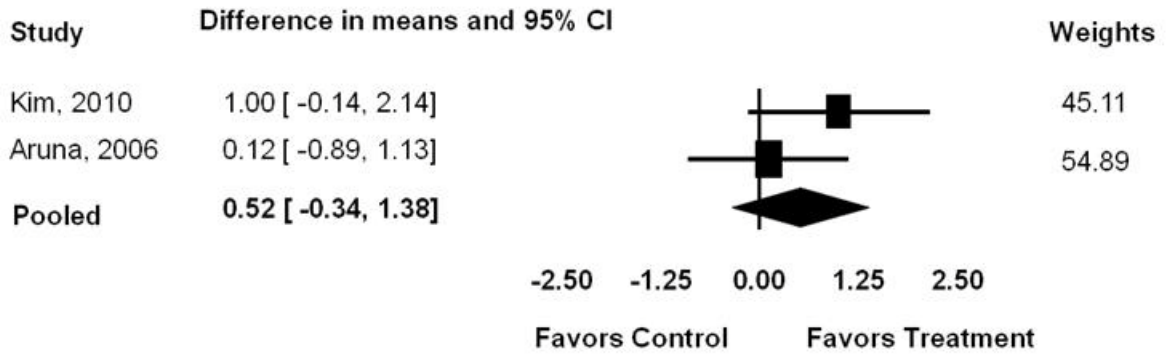
Heterogeneity:  $I^2 = 0.0\%$ ,  $\text{Chi}^2 = 0.04$ ,  $p\text{-value} = 0.84$

**Figure 5. Forest plot of posttreatment mean of platelet aggregation for clopidogrel/ticlopidine with or without *G. biloba* (induced by 5  $\mu$ L of 10  $\mu$ M ADP or 2.5  $\mu$ L of 5  $\mu$ M ADP)-(percent)**



Heterogeneity:  $I^2 = 0.0\%$ ,  $\text{Chi}^2 = 0.01$ ,  $p\text{-value} = 0.92$

**Figure 6. Forest plot of bleeding time for clopidogrel/ticlopidine with or without *G. biloba*-(minutes)**



Heterogeneity:  $I^2 = 21.8\%$ ,  $\text{Chi}^2 = 1.28$ ,  $p\text{-value} = 0.26$



## G. Biloba Plus Warfarin Versus Warfarin Alone

One crossover RCT examined single dose warfarin (25 mg/day) following either no pretreatment or seven days pretreatment with *G. biloba* (12 g/day) or ginger (3.6 g/day) in healthy subjects.<sup>64</sup> Compared with warfarin alone, there was a statistically significant increase in platelet aggregation (GMR 1.14 [90 percent CI 1.08, 1.20]). However, the difference in AUC of INR was not statistically significant. Compared with warfarin plus ginger, there were no statistically significant differences in platelet aggregation or AUC of INR.

Strength of evidence comparing *G. biloba* plus warfarin with warfarin alone or warfarin plus ginger was insufficient for INR (Table 27).

## G. Biloba Plus Cilostazol Versus Cilostazol Alone

One crossover RCT examined single dose cilostazol (100 mg) with or without single dose *G. biloba* (120 mg) in healthy South Asian males.<sup>67</sup> Bleeding time was slightly prolonged in the *G. biloba* plus cilostazol group. One measure of platelet aggregation was statistically significant (MD 18.00 percent [95 percent CI 1.92, 34.08]). There was no significant change in clotting time, systolic blood pressure, or platelet count (reported qualitatively only).

Strength of evidence for systolic blood pressure was insufficient (Table 27).

**Table 27. Summary and strength of evidence for cardiovascular drugs with or without *G. biloba*—Intermediate outcomes**

| Cardio-vascular Drug/ Outcome                  | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Antiplatelet drugs</b>                      |              |             |                      |           |              |  |
| Bleeding Time (min) <sup>67,68</sup>           | Moderate     | -           | -                    | -         | -            | <b>Inconclusive</b><br>Pooled 0.52 (95% CI -0.34, 1.38)                                |
| Blood Pressure – Systolic and Diastolic        | Moderate     | NA          | Indirect (surrogate) | NA        | Insufficient | <b>Inconclusive</b>  |
| Lipid Profile (LDL-C, HDL-C, TG) <sup>65</sup> | Moderate     | NA          | Indirect (surrogate) | NA        | Insufficient | <b>Inconclusive</b>  |
| <b>Warfarin</b>                                |              |             |                      |           |              |  |
| AUC of INR (versus warfarin alone)             | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>MD -3.00 (95% CI -62.00, 56.00)<br>GMR 0.93 (90% CI 0.81, 1.05) |
| AUC of INR (versus warfarin plus ginger)       | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>MD -4.00 (95% CI -62.84, 54.84)                                 |
| <b>Cilostazol</b>                              |              |             |                      |           |              |  |
| Bleeding Time (min) <sup>67</sup>              | Moderate     | -           | -                    | -         | -            | <b>Inconclusive</b><br>MD 1.02 (95% CI 0.10, 1.94)                                     |
| Blood pressure - Systolic                      | Moderate     | NA          | Indirect (surrogate) | NA        | Insufficient | <b>Inconclusive</b>  |

**Abbreviations:** AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; NA = not applicable; TG = triglycerides.

## Ginseng

Three RCTs compared ginseng plus warfarin with warfarin alone (Table 28).<sup>69-71</sup>

### Ginseng Plus Warfarin Versus Warfarin Alone

Reported outcomes included INR,<sup>69-71</sup> prothrombin time,<sup>69</sup> platelet aggregation,<sup>71</sup> and platelet count.<sup>69</sup>

Meta-analyses were not possible because of differences in patient populations (e.g., healthy versus postischemic stroke) and incompatible effect estimates (e.g., differences in means and differences in medians). One small study using *Panax ginseng* (1.5 g/day) in subjects with ischemic stroke reported no statistically significant differences in peak and AUC of INR, peak and AUC of prothrombin time, and platelet count.<sup>69</sup> A study in young, healthy subjects, however, reported significantly lower peak INR and AUC of INR in the American ginseng (2 g/day) plus warfarin group.<sup>70</sup> Another small study using single doses of warfarin in 12 healthy males found no differences in AUC of INR and platelet aggregation after seven days pretreatment with ginseng (*Panax ginseng*, 3 g/day).<sup>71</sup>

Strength of evidence was graded as insufficient for peak INR and AUC of INR (Table 28).

**Table 28. Strength of evidence for warfarin with or without ginseng—Intermediate outcomes**

| Cardio-vascular Drugs(s) / Outcome | Risk of Bias | Consistency  | Directness           | Precision | Grade        | Conclusion Treatment Effect*  |
|------------------------------------|--------------|--------------|----------------------|-----------|--------------|---|
| <b>Warfarin</b>                    |              |              |                      |           |              |   |
| INR <sub>peak</sub>                | Moderate     | Inconsistent | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>MD range 0.01-0.11 (95% CI -0.20 to -0.06, 0.08 to 0.42]<br><br>MedD-0.19 ( 95% CI -0.36, -0.07]   |
| AUC of INR MD                      | Moderate     | Inconsistent | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>MD range 0.03-0.49 (95% CI -39.10 to -0.28, 0.34 to 39.30]<br><br>MedD-0.43 ( 95% CI -1.00, -0.09] |

**Note:** \* Range is provided when more than one study is being summarized.

**Abbreviations:** AUC of INR = area under the curve of the International Normalized Ratio; CI = confidence interval; GMR = geometric mean ratio; MD = mean difference; MedD = difference of the medians; NA = not applicable; TG = triglycerides.

## Hawthorn

In a randomized crossover trial, subjects were administered digoxin 0.25 mg/day for 10 days or digoxin 0.25 mg/day plus hawthorn 450 mg twice daily for 3 weeks.<sup>72</sup> Subjects were tested with a standard 12-lead electrocardiogram for PR interval measurements. The difference between groups was statistically nonsignificant.

## Magnesium

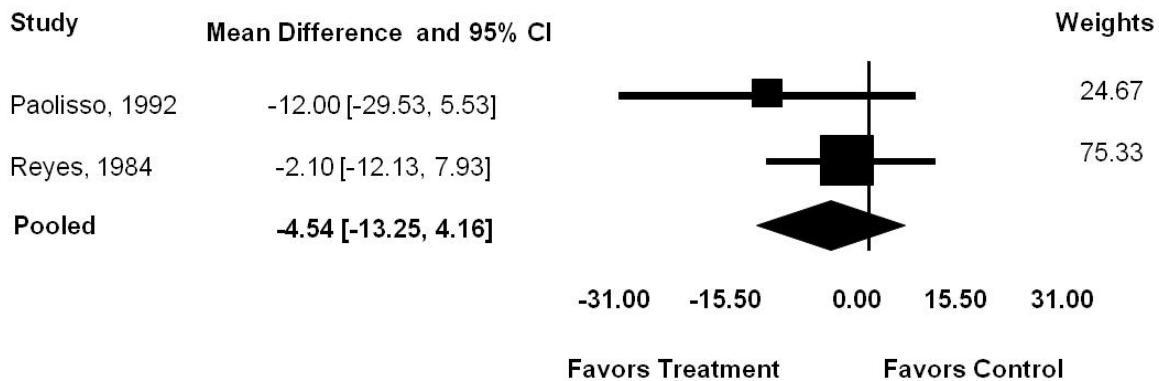
Three RCTs investigated the use of oral magnesium with cardiovascular drugs: magnesium plus hydrochlorothiazide<sup>73,74</sup> and magnesium plus beta-adrenergic antagonists.<sup>42</sup> Reported outcomes included total cholesterol, triglycerides, and systolic and diastolic blood pressure.

## Magnesium Plus Hydrochlorothiazide Versus Hydrochlorothiazide Alone

In an eight week trial of 18 elderly subjects with benign essential hypertension taking magnesium (365 mg/day), nonsignificant differences were found in total cholesterol, triglycerides, and supine systolic and diastolic blood pressure.<sup>73</sup> Nonsignificant differences for systolic and diastolic blood pressure (supine and standing) were also reported in a seven week trial using magnesium (365 mg/day) in 21 subjects with mild to severe uncomplicated essential hypertension.<sup>74</sup> These two studies were meta-analyzed for supine systolic and diastolic blood pressure and the pooled estimates were statistically nonsignificant (Figures 7 and 8).<sup>73,74</sup>

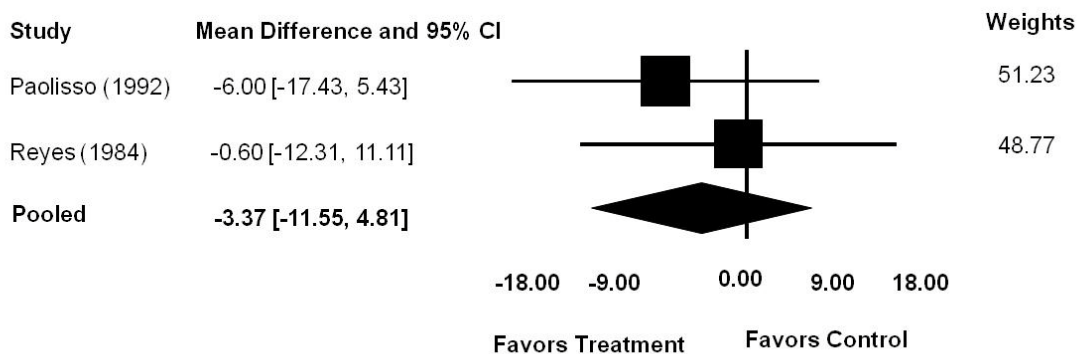
Strength of evidence was graded as insufficient for systolic and diastolic blood pressure and triglyceride level (Table 29).

**Figure 7. Forest plot of supine systolic blood pressure for hydrochlorothiazide with or without magnesium (mmHg)**



Heterogeneity:  $I^2 = 0.0\%$ ,  $\text{Chi}^2 = 0.92$ ,  $p\text{-value} = 0.34$

**Figure 8. Forest plot of supine diastolic blood pressure for hydrochlorothiazide with or without magnesium (mmHg)**



Heterogeneity:  $I^2 = 0.0\%$ ,  $\text{Chi}^2 = 0.42$ ,  $p\text{-value} = 0.52$

## Magnesium Plus Beta-Adrenergic Antagonists Versus Beta-Adrenergic Antagonists Alone

In a crossover RCT, 39 subjects with essential hypertension on atenolol, metoprolol, pindolol, or propranolol were randomized to receive magnesium (365 mg/day) or placebo for eight weeks. Effect estimates for supine and standing systolic and diastolic blood pressures were statistically nonsignificant.<sup>42</sup>

Strength of evidence was graded as insufficient for systolic and diastolic blood pressure (Table 29).

**Table 29. Strength of evidence for cardiovascular drugs with or without magnesium—Intermediate outcomes**

| Cardio-vascular Drug(s)/ Outcome   | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect* MD (95% CI)   |
|------------------------------------|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Hydrochlorothiazide</b>         |              |             |                      |           |              |  |
| Blood pressure (mm Hg)             | Moderate     | Consistent  | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br><i>Systolic</i><br>Supine: Pooled<br>-4.54 (-13.25, 4.16)<br>Standing:<br>0 (-5.94, 5.94)<br><i>Diastolic</i><br>Supine: Pooled<br>-3.37 (-11.55, 4.81)<br>Standing:<br>1.00 (-8.84, 10.84) |
| Triglycerides (mg/dL)              | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>1.77 (-103.19, 106.73)  |
| <b>Beta-adrenergic antagonists</b> |              |             |                      |           |              |  |
| Blood pressure (mm Hg)             | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br><i>Systolic</i><br>Supine:<br>-4.26 (-12.56, 4.04)<br>Standing:<br>-4.34 (-13.90, 5.22)<br><i>Diastolic</i><br>Supine:<br>-2.65 (-6.85, 1.55)<br>Standing:<br>-1.65 (-6.18, 2.88)           |

**Note:** \* Range is provided when more than one study is being summarized; pooled data is from meta-analysis of more than one study.

**Abbreviations:** CI = confidence interval; MD = mean difference; mm Hg = millimetres of mercury; NA = not applicable.

## Niacin (Not More Than 250 mg)

One parallel-arm RCT described the use of niacin with propranolol in 16 subjects with Type II or Type IV hyperlipoproteinemia (Table 30).<sup>75</sup> This study was rated as high risk of bias because groups were administered different dosages of propranolol (20 mg and 60 mg). Effect estimates for total cholesterol and triglycerides were statistically nonsignificant.

Strength of evidence was insufficient for triglycerides (Table 30).

**Table 30. Strength of evidence for propranolol with or without niacin—Intermediate outcomes**

| Cardio-vascular Drug(s) / Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect MD (95% CI)  |
|-----------------------------------|--------------|-------------|----------------------|-----------|--------------|--|
| Triglycerides (mg/dL)             | High         | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>In Type II hyperlipoproteinemia :<br>8.40 (-114.22, 97.42)<br><br>In Type IV hyperlipoproteinemia :<br>-49.83 (-523.94, 424.28) |

**Abbreviations:** CI = confidence interval; MD: mean difference; NA: not applicable

## Omega-3 Fatty Acids/Fish Oil

Twenty-four RCTs, including 18 parallel-arm trials,<sup>40,44,50-53,55,56,76-78,91,92,94,98,151,152,163</sup> and six crossover trials<sup>37,95-97,99,164</sup> contributed evidence. The trials were conducted in North America,<sup>37,40,52,55,56,78,94,95,99,163</sup> Australia,<sup>44,151,152,164</sup> Europe,<sup>53,76,77,91,92,96-98</sup> and Asia.<sup>50,51</sup> The number of included participants in these trials ranged from 11<sup>55</sup> to 658.<sup>91</sup> The participants across studies received the following cardiovascular drugs: statins (atorvastatin, simvastatin, lovastatin),<sup>37,40,44,53,76,91,92,94-97,151,163</sup> calcium channel blockers,<sup>50-52</sup> niacin plus aspirin,<sup>78</sup> ACE inhibitors,<sup>77,152</sup> aspirin,<sup>98,99</sup> beta-blockers,<sup>164</sup> anticoagulation agents,<sup>55</sup> and fenofibrates.<sup>56</sup> In two trials, calcium channel blockers were used concomitantly with either aspirin,<sup>51</sup> or aspirin plus dipyridamole.<sup>52</sup> In most of the trials, participants were categorized as having unclear or mixed (different combinations of low, moderate/moderately high, and high) risk of coronary heart disease.<sup>165</sup> The duration of treatment ranged from 2 weeks<sup>95,98</sup> to 25 weeks.<sup>151,152</sup> Further details on study, participants and treatment characteristics are presented in Appendix C.

Generally, most of these studies were reported to be double blind and had a moderate risk of bias across the outcomes of interest. In crossover trials, the adequacy of washout period was not clear for one trial,<sup>37</sup> there was a potential of carryover in one trial (i.e., the treatment effect depended on the order of drug randomization),<sup>99</sup> and no washout period was employed for another trial.<sup>164</sup> The washout period length reported for three other trials was deemed to be adequate.<sup>95-97</sup>

Summary of findings and strength of evidence data are presented in Table 31. Meta-analyses were performed for the following outcome measures: HDL-C, LDL-C, total cholesterol, and triglycerides (Figures 9 to 14).

## Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone

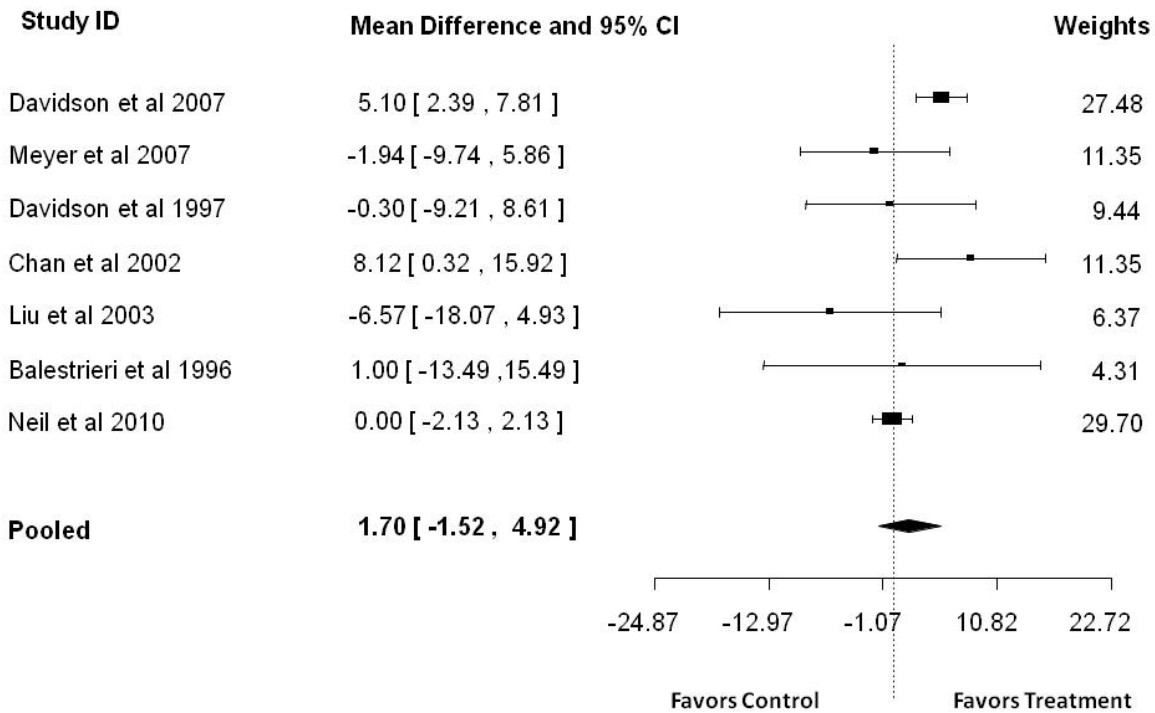
**C-Reactive protein (CRP)** was assessed in one placebo-controlled parallel arm randomized trial in participants at mixed CHD risk.<sup>44</sup> The six week posttreatment geometric mean CRP levels were not different between the omega-3 fatty acids (4 g/day) plus atorvastatin and control (atorvastatin alone) groups.

**High density lipoprotein-cholesterol.** Posttreatment HDL-C was reported in 11 randomized trials.<sup>37,40,44,53,91,92,94,96,97,151,163</sup> In five studies,<sup>44,53,96,151,163</sup> the mean endpoint differences in HDL-

C levels for participants with unclear or mixed CHD risk were not significantly different between the omega-3 fatty acids (2 to 10 g/day) combination and statins alone group. In one trial of participants at moderate CHD risk,<sup>40</sup> the eight week posttreatment mean HDL-C level was significantly greater in the dietary supplement versus control group (MD 5.10 [95 percent CI 2.36, 7.83]). A meta-analysis based on the results from seven studies (participants with unclear or mixed CHD risk),<sup>40,44,53,91,96,151,163</sup> indicated that the mean HDL-C levels did not differ between the omega-3 fatty acids (2.0 to 10.0 g/day) combination and statins alone group (Figure 9). Results from the remaining four trials reporting mean change,<sup>92</sup> percent change,<sup>97</sup> or percent median change<sup>37,94</sup> were not consistent. Specifically, one trial of participants with mixed CHD risk reported a significant difference in the five week posttreatment mean change in favor of the omega-3 fatty acids (2 g/day) combination (difference in mean change 2.32 [95 percent CI 0.18, 4.45]).<sup>92</sup> Similarly, two other trials of participants with unclear<sup>94</sup> and mixed<sup>37</sup> CHD risk reported significantly greater (i.e., improved) posttreatment percent increase in median HDL-C levels at 6 weeks (difference 7.2 percent, p 0.001),<sup>37</sup> at eight weeks (difference of 2.4 percent, p less than 0.001)<sup>94</sup> or at 16 weeks (difference of 6.3 percent, p less than 0.001)<sup>94</sup> in favor of the dietary supplement intervention (4 g/day). In contrast, the percent change in HDL-C (from baseline) in one crossover trial of participants with mixed CHD risk was not significantly different between the dietary supplement (4 g/day) and control group at six weeks after the baseline (6.0 percent versus 14.0 percent).<sup>97</sup>

Overall, results indicated no difference in posttreatment HDL-C levels between the dietary supplement and control interventions (Table 31).

**Figure 9. Posttreatment HDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)**



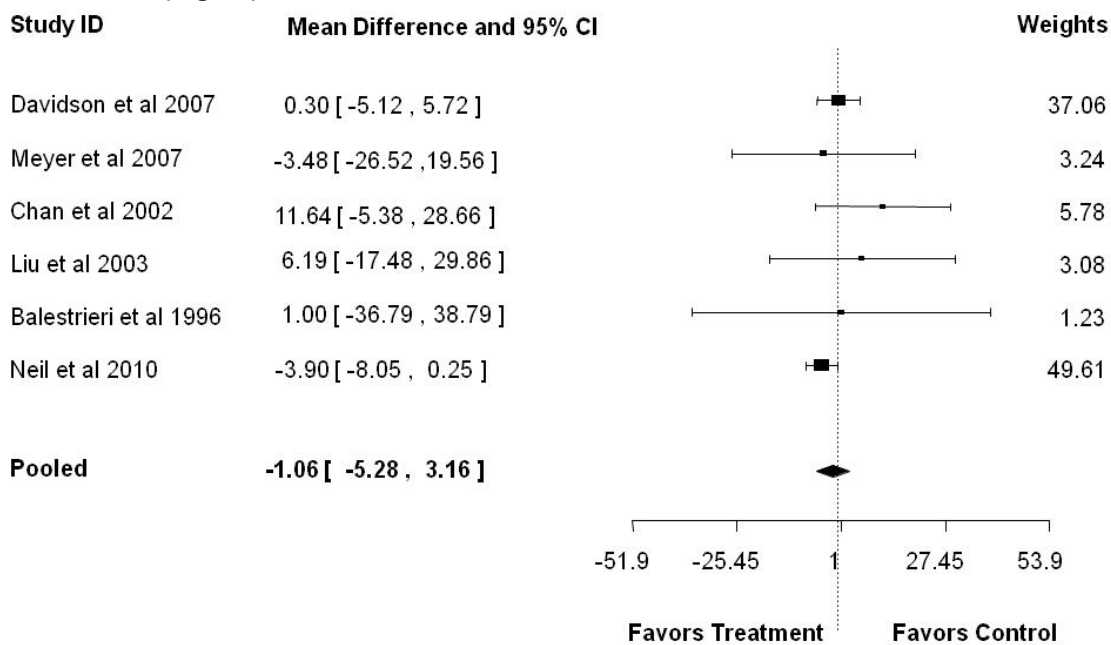
Heterogeneity:  $I^2=55.92\%$ ;  $Chi^2=14.13$ ;  $p\text{-value}=0.03$

**Low density lipoprotein-C.** Posttreatment levels of levels of LDL-C were reported in 10 randomized trials.<sup>37,40,44,53,91,92,94,96,97,151</sup> In six trials,<sup>40,44,53,91,96,151</sup> the mean endpoint differences in LDL-C levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement (2.0 to 9.2 g/day) and the control groups. Likewise, one trial found no significant difference in the mean change between the dietary supplement (2 g/day) and control groups (difference in mean change -5.84 mg/dL [95 percent CI -16.88, 5.20]).<sup>92</sup>

Our meta-analysis based on the results from 6 studies (participants with unclear or mixed CHD risk),<sup>40,44,53,91,96,151</sup> indicated that the mean LDL-C levels did not differ between the intervention (2.0 to 9.2 g/day) and control groups (Figure 10).

Two other trials of participants with unclear<sup>94</sup> and mixed<sup>37</sup> CHD risk reported that there was no significant difference in either posttreatment percent change in least squares mean (difference of 1.30 percent, p 0.43)<sup>37</sup> or percent change in median (difference at 8 weeks 2.2 percent, p 0.24; at 16 weeks 0.3 percent, p 0.64)<sup>94</sup> in LDL-C levels for the supplement(4 g/day) versus control groups. The percent change in LDL-C (from baseline) in one crossover trial of participants at low CHD risk was not significantly different between the dietary supplement (6 g/day) and control group at six weeks (-39.0 percent versus -37.0 percent, p greater than 0.05).<sup>97</sup>

**Figure 10. Posttreatment LDL-C levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)**



Heterogeneity: I<sup>2</sup>=16.86%; Chi<sup>2</sup>=4.43; p-value=0.49

**Total cholesterol.** Posttreatment levels of TC were reported for 11 trials.<sup>37,40,44,53,76,91,92,94,96,97,151</sup> The pooled results based on our meta-analysis of six trials in participants with unclear or mixed CHD risk<sup>40,44,53,91,96,151</sup> showed that the mean total cholesterol levels did not differ significantly between the intervention (2 to 9 g/day) and control groups (Figure 11; pooled mean difference: -3.86 [95 percent CI -10.69, 2.97])

In two other trials,<sup>76,92</sup> the mean endpoint/mean change differences in total cholesterol levels for participants with unclear or mixed CHD risk were not significantly different between the dietary supplement and the control groups.

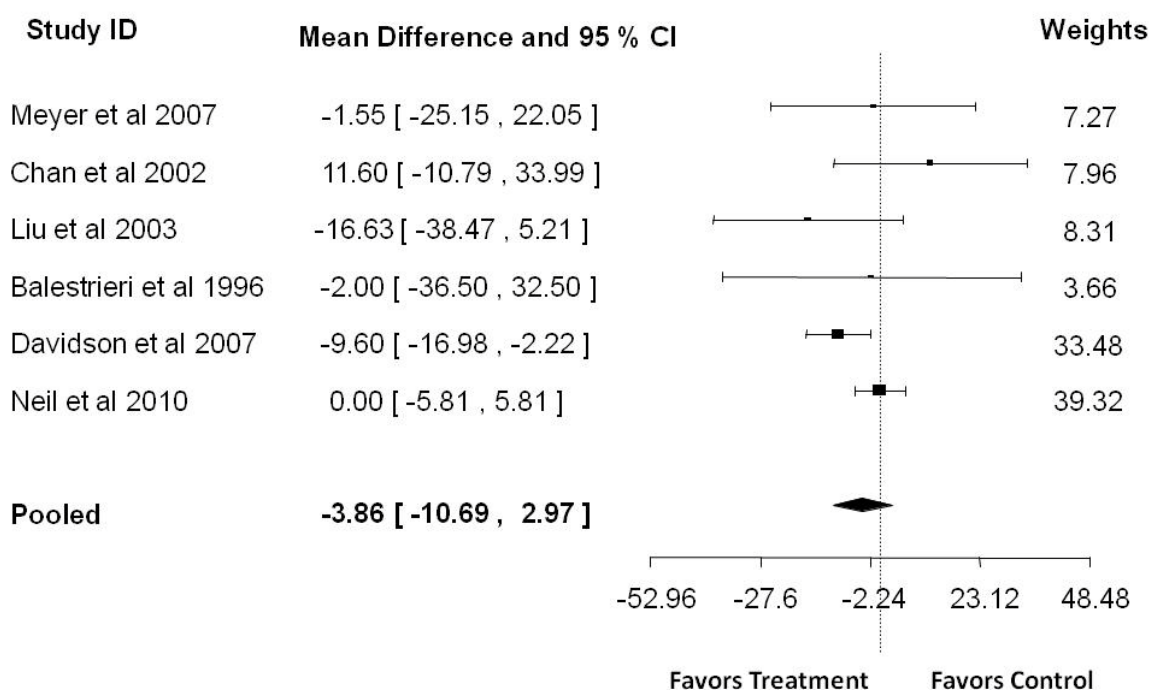
Similarly, one crossover trial<sup>97</sup> using 6 g/day omega-3 fatty acids did not find a significant difference for mixed CHD risk participants in the posttreatment total cholesterol percent change from baseline between the two treatment groups (-31.0 versus -27.0, p greater than 0.05).

In one trial of participants with unclear CHD risk,<sup>40</sup> the 8 week posttreatment mean total cholesterol level was significantly improved in the dietary supplement (4 g/day) versus control group (mean difference: -9.60 [95 percent CI -17.05, -2.14]). Two other trials reported significantly greater reductions in median total cholesterol percent change from baseline in the dietary supplement versus control groups for participants with mixed and unclear CHD risk (median percent change -2.7, p 0.006<sup>37</sup> and -5.8, p value less than 0.001<sup>94</sup>).

One trial in participants with mixed CHD risk did not report numerical data.<sup>76</sup>

The wide confidence intervals around the pooled estimate rendered the results regarding posttreatment total cholesterol levels as inconclusive (Table 31).

**Figure 1. Posttreatment total cholesterol levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)**



Heterogeneity:  $I^2=35.42\%$ ;  $\text{Chi}^2=7.19$ ;  $p\text{-value}=0.21$

**Triglycerides.** Posttreatment levels of TG were reported for 12 trials which included participants with unclear or mixed CHD risk.<sup>37,40,44,53,76,91,92,94,96,97,151,163</sup>

Initial pooling of six trials reporting posttreatment mean triglyceride levels revealed some degree of statistical heterogeneity ( $I^2$  63.53 percent; Chi-squared statistic 15.95; p 0.01).<sup>40,44,53,76,96,151</sup> After careful examination of the study factors that could potentially explain this heterogeneity, we found that in two studies<sup>40,76</sup> which were conducted in specialty clinics,

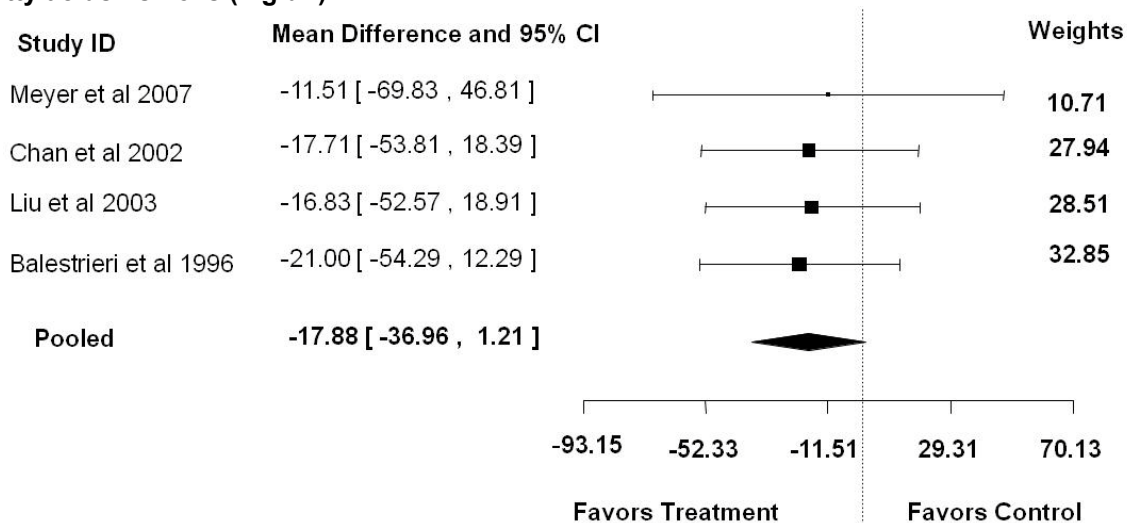


the participants' baseline triglycerides levels were on average higher than those in other studies, thereby resulting in a greater magnitude of the observed mean differences in favor of the dietary supplement intervention (-73.50 mg/dL<sup>40</sup> and -91.23 mg/dL<sup>76</sup>). The meta-analysis of the two studies in participants with higher baseline levels of TG (greater than 200 mg/dL) resulted in a significant pooled estimate of mean difference in favor of adding the supplement to statins (I<sup>2</sup> 0 percent, Chi-squared statistic 0.21) (Table 31). The meta-analysis based the remaining four studies in participants with lower baseline levels of TG (less than 200 mg/dL) showed a non-significant pooled mean difference (Figure 12) with no significant heterogeneity (I<sup>2</sup> 0 percent; Chi-squared statistic 0.08; p 0.99).<sup>44,53,96,151</sup> Omega-3 fatty acid supplements ranged from 4 to 9.2 g/day, and participants were at mixed (moderate/moderately high<sup>44</sup>, or low/moderate/high<sup>96</sup>) or unclear CHD risk. Information on clinical settings for these studies was not reported.

Three trials reporting median<sup>37,94</sup> or mean<sup>97</sup> percent change from baseline in triglyceride levels showed significantly reduced (i.e., improved) levels for the dietary supplement versus control groups of participants with mixed (low/moderate/high) CHD risk, using omega-3 fatty acids (4 to 6 g/day)<sup>37,97</sup> or unclear CHD risk, using omega-3 fatty acids (4 g/day).<sup>94</sup> In contrast 4 month posttreatment median triglyceride levels were numerically similar between omega-3 fatty acids (2 g/day) plus statins versus statin alone group in participants with type II diabetes (97.4 mg/dL versus 106.2 mg/dL, p value was not reported) in one trial.<sup>91</sup>

The wide confidence intervals around the pooled estimate rendered the results with regards to posttreatment triglyceride levels between the dietary supplement and control interventions as inconclusive (Table 31).

**Figure 12. Posttreatment triglyceride levels in subjects taking statins with or without omega-3 fatty acids/fish oils (mg/dL)**



Heterogeneity: I<sup>2</sup>=0.0%; Chi<sup>2</sup>=0.08; p-value=0.99

**Non-HDL-C.** Posttreatment levels of non-HDL-C were reported for five trials, in which participants had mixed or unclear CHD risk.<sup>37,40,44,94,163</sup> Dose of supplements used were 4 g/day in three trials,<sup>37,40,44,94</sup> and 7.2 g/day in one trial.<sup>163</sup> Of three trials reporting mean non-HDL-C levels,<sup>40,44,163</sup> one trial in 254 participants with unclear CHD risk<sup>40</sup> indicated significantly lower (i.e., improved) posttreatment mean non-HDL-C in the dietary supplement group compared with the control group, whereas the remaining two trials (44 participants in both trials) showed no

significant between-group mean difference.<sup>44,163</sup> The pooling of results from the three trials<sup>40,44,163</sup> revealed statistical heterogeneity across the effect estimates ( $I^2$  58.86 percent; Chi-squared statistic 4.96;  $p$  0.08). There was no obvious explanation for this heterogeneity; the participants across these trials were of either unclear or mixed CHD risk. These studies were not pooled.

Trials reporting median percent change from baseline in non-HDL-C levels showed significantly greater (i.e., improved) reduction in non-HDL-C favoring the dietary supplement groups over the control groups in participants with unclear CHD risk<sup>94</sup> and mixed CHD risk.<sup>37</sup>

The overall results regarding posttreatment non-HDL-C levels between the treatment groups were determined to be inconclusive (Table 31).

**TC/HDL-C ratio.** Posttreatment levels of the TC/HDL-C ratio were reported for four trials.<sup>37,40,94,163</sup> Doses of supplement in these trials ranged from 4 to 7.2 g/day. Two trials in participants with unclear CHD risk<sup>40,163</sup> reporting posttreatment mean TC/HDL ratio levels yielded discrepant results, one in favor of the dietary supplement group,<sup>40</sup> and the other in favor of neither group.<sup>163</sup> This discrepancy in the results for TC/HDL-C ratio may have been due to differences between participants' CHD risk across the studies. Based on the differences in CHD risk and the different directions of the effect estimates, it was decided not to pool these studies.

Two other trials in participants with mixed<sup>37</sup> or unclear CHD risk<sup>94</sup> reported significant differences in posttreatment percent change in least squares mean<sup>37</sup> or percent change in median at eight weeks<sup>94</sup> in the TC/HDL-C ratio, favoring the dietary supplement over the control intervention.

The overall results regarding differences in posttreatment TC/HDL-C ratio levels between the treatment groups were inconclusive (Table 31).

**Predefined thresholds of LDL-C and non-HDL-C.** The proportion of participants reaching these thresholds was reported for one 16 week, parallel arm trial in participants with unclear CHD risk.<sup>94</sup> At the end of the treatment, there was no difference in the proportion of participants reaching pre-defined targets of either LDL-C (below 160, 130, or 100 mg/dL, or HDL-C (below 190, 160, or 130 mg/dL) between the supplement intervention (omega-3 fatty acids 4 g/day) and control groups (Table 31).

**Lipoprotein A.** Posttreatment levels of lipoprotein A were reported for one trial.<sup>96</sup> In this crossover randomized trial, participants with familial hypercholesterolemia (mixed CHD risk) were treated over 4 weeks, for each treatment period. The difference in the 4 week posttreatment mean lipoprotein A levels between the omega-3 fatty acids (5.1 g/day) and control groups was not significant (Table 31).

**Blood pressure.** Systolic and diastolic blood pressure levels posttreatment were reported for four trials; three parallel arm<sup>91,92,151</sup> and one crossover<sup>37</sup> trial. In the first parallel arm trial<sup>92</sup> participants with mixed CHD risk receiving omega-3 fatty acids (2 g/day) combined with statins (10 mg/day) for five weeks experienced significantly greater reductions in mean systolic blood pressure but not in diastolic blood pressure, compared with participants receiving statins alone. In two parallel arm trials with a treatment period of 16<sup>91</sup> and 25 weeks<sup>151</sup> in participants with unclear CHD risk there was no significant difference in the blood pressure between the omega-3

fatty acids (2 g/day in one trial, and 4 or 8 g/day in the other trial) in combination with statins versus statins alone. Statistical test results for the comparison were not provided.

In one crossover trial,<sup>37</sup> participants with mixed CHD risk receiving omega-3 fatty acids (4 g/day) and statins (20 mg/day) experienced significantly greater median reductions from baseline in systolic and diastolic blood pressure compared with those receiving the control intervention.

We were unable to perform a meta-analysis given the lack of data<sup>151</sup> and the differences in effect measures, reported as reductions in median<sup>37</sup> and mean levels.<sup>92</sup>

The overall results showed lower posttreatment systolic blood pressure levels for the combination of omega-3 fatty acids and statins versus statins alone group (Table 31).

**Blood coagulation.** This outcome was reported for a crossover randomized trial in healthy participants.<sup>95</sup> After 2 weeks of treatment, there was no difference between the groups of omega-3 fatty acids (4 g/day) in combination with statins (80 mg/day) versus statins alone in the following blood coagulation parameters: prothrombin time, activated partial thromboplastin time, platelet aggregation with adenosine diphosphate, or platelet aggregation with collagen.

**Platelet count.** Posttreatment platelet count was reported for three trials; one parallel arm<sup>76</sup> and two crossover trials.<sup>95,97</sup> Study participants in these trials had mixed CHD risk (healthy volunteers, and participants with combined or familial hyperlipidemia). The differences between posttreatment mean change<sup>76,95</sup> or percent change<sup>97</sup> in platelet counts between baseline and two to six weeks between the omega-3 fatty acids (4 to 6 g/day) and control groups was not significant. Two trials<sup>76,95</sup> reporting posttreatment mean change in platelet count were not pooled because standard deviations were not reported for one study.<sup>95</sup>

**Bleeding time.** Posttreatment bleeding time was reported for a crossover randomized trial that included participants with mixed CHD risk (familial hyperlipidemia).<sup>97</sup> There was no difference in percent change for bleeding time between the omega-3 fatty acids (6 g/day) and the control groups following 6 weeks of treatment.

## **Omega-3 Fatty Acids/Fish Oils Plus ACE Inhibitors Versus ACE Inhibitors Alone**

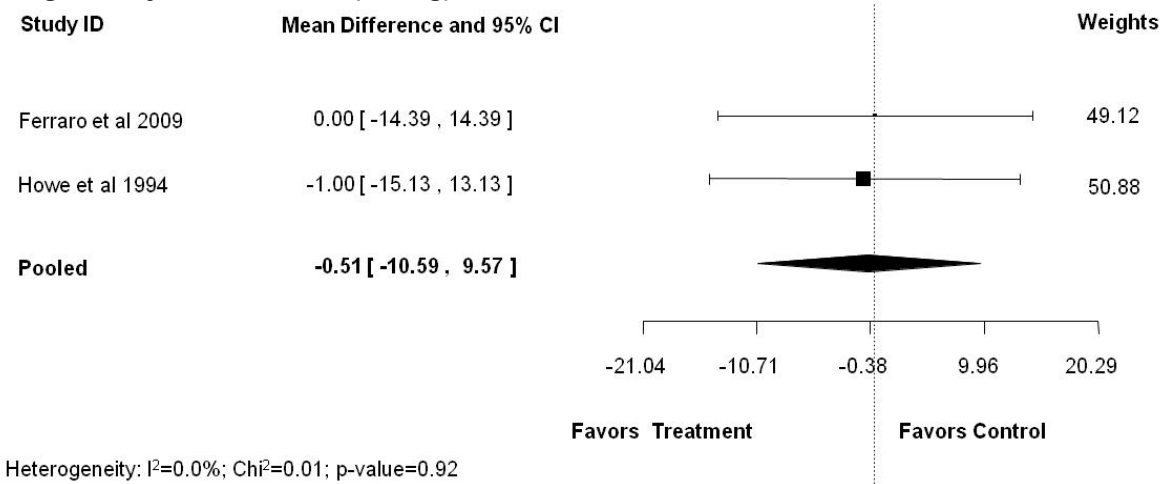
**Triglycerides.** Posttreatment levels were reported for two parallel arm trials in participants with unclear CHD risk (Table 31).<sup>77,152</sup> In a 25 week trial<sup>77</sup> the difference in mean triglyceride levels between the omega-3 fatty acids (5 g/day) and control groups was not significant. In contrast, in a 6 week trial<sup>152</sup> the mean triglyceride reduction significantly favored the supplement (3 g/day) over the control group.<sup>152</sup> These trials were not pooled due to differences in the reported effect measures.

The overall results regarding posttreatment triglyceride levels between the treatment groups were inconclusive.

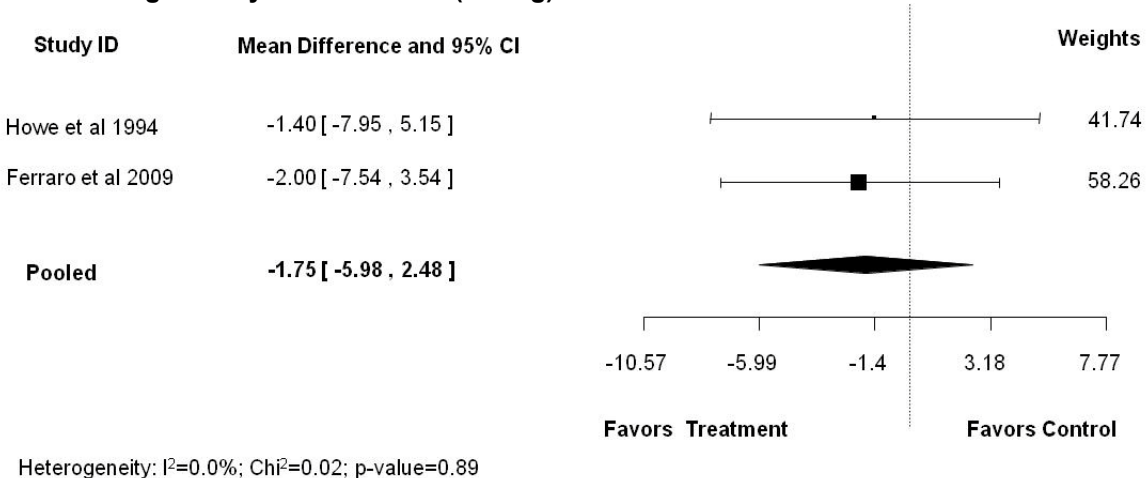
**Blood Pressure.** Systolic and diastolic blood pressure levels posttreatment were reported for two parallel arm trials in participants with unclear CHD risk, with supplementation with omega-3 fatty acids (3 to 5 g/day)<sup>77,152</sup> There was no significant between-group difference in either systolic blood pressure (mean difference 0 mm Hg<sup>77</sup> and -1.00 mm Hg<sup>152</sup>) or diastolic blood pressure (-1.40 mm Hg<sup>77</sup> and -2.00 mm Hg<sup>152</sup>).

The pooled analysis of these trials<sup>77,152</sup> indicated that there was no difference in either systolic (Figure 13) or diastolic (Figure 14) blood pressure between the intervention and control groups.

**Figure 13. Posttreatment systolic blood pressure in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils (mmHg)**



**Figure 14. Posttreatment diastolic blood pressure in subjects taking ACE inhibitors with or without omega-3 fatty acids/fish oils (mmHg)**



**Urinary protein.** Posttreatment data (protein excretion, and at least 50 percent reduction in proteinuria) was reported for one 25 week parallel arm trial in participants with unclear CHD risk.<sup>77</sup> The participants in the omega-3 fatty acids (3 g/day) plus ACE inhibitors (10 mg/day ramipril plus 300 mg/day irbersartan) combination group had significantly reduced (i.e., improved) mean urinary protein excretion compared with participants in the ACE inhibitor alone (367 mg/day versus 1353 mg/day). Similarly, the proportion of participants who achieved at least 50 percent reduction in proteinuria was significantly greater (i.e., improved) in the supplement versus control group (80 percent versus 20 percent).

## **Omega-3 Fatty Acids/Fish Oils Plus Fenofibrate Versus Fenofibrate Alone**

One study<sup>56</sup> contributed evidence (Table 31). This was a parallel arm double blind placebo-controlled trial in 167 participants in whom the treatment allocation concealment was unclear (moderate risk of bias). Participants had unclear CHD risk and received treatment for eight weeks (4 g/day omega-3 fatty acids plus 130 mg/day fenofibrate versus 4 g/day placebo plus 130 mg/day fenofibrate). The percent change from baseline to week 8 was not significantly different between participants in the dietary supplement and control groups for HDL-C, total cholesterol/HDL-C ratio, total cholesterol, non-HDL-C, or triglycerides. In contrast, the percent change (i.e., reduction) from baseline in LDL-C levels was significantly greater in the dietary supplement versus control group. The incidence of hypertension was not significantly different between the two groups.

The overall results of this study on levels of LDL-C, HDL-C, TC/HDL-C ratio, total cholesterol, and non-HDL-C (reported as median percent change) were inconclusive.

## **Omega-3 Fatty Acids/Fish Oils Plus Calcium Channel Blockers Versus Calcium Channel Blockers Alone**

One study<sup>50</sup> contributed evidence (Table 31). This 16 week parallel arm open label active treatment controlled trial was in 22 participants at high CHD risk (variant angina). The supplement treatment (1.8 g/day omega-3 fatty acids plus 90 to 120 mg/day diltiazem versus diltiazem) allocation concealment was unclear (moderate risk of bias). The posttreatment mean difference in total cholesterol, LDL-C, HDL-C, and triglycerides were not significantly different between participants in the dietary supplement and control groups. Due to wide confidence intervals, these results were inconclusive.

## **Omega-3 Fatty Acids/Fish Oils Plus Aspirin and Calcium Channel Blockers Versus Aspirin and Calcium Channel Blockers Alone**

One study<sup>51</sup> contributed evidence (Table 31). This parallel arm single-blind (only assessors were blinded) active treatment (calcium channel blockers plus aspirin) controlled trial was in 107 participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). Participants in this trial were at high CHD risk (pre-coronary angioplasty) and received their treatment for 6 weeks (3 g/day omega-3 plus calcium channel blockers and 150 mg/day aspirin versus calcium channel blockers and aspirin). The posttreatment mean triglycerides was significantly lower (i.e., improved) in the participants receiving the dietary supplement versus controls. The mean differences in total cholesterol, HDL-C, and LDL-C were not significantly different between the dietary supplement and control groups. The wide confidence intervals around these estimates rendered these results inconclusive (grade: insufficient).

## **Omega-3 Fatty Acids/Fish Oils Plus Calcium Channel Blockers, Aspirin, and Dipyridamole Versus Calcium Channel Blockers, Aspirin, and Dipyridamole**

One study<sup>52</sup> contributed evidence (Table 31). This parallel arm single-blind controlled trial was in 82 male participants for whom the randomization sequence was computer-generated and treatment allocation concealment was unclear (moderate risk of bias). All men in this trial were

at high CHD risk (postcoronary angioplasty) and received their treatment for 12 weeks (3.2 g/day omega-3 plus calcium channel blockers, 325 mg/day aspirin and 225 mg/day dipyridamole versus calcium channel blockers, aspirin and dipyridamole). Although the posttreatment mean LDL-C was significantly greater (i.e., worsened) in the participants receiving the dietary supplement versus controls, the mean triglyceride levels were significantly lower (i.e., improved) in the dietary supplement versus the control group. HDL-C, total cholesterol, and platelet count were not significantly different. The wide confidence intervals around these estimates rendered these results inconclusive (grade: insufficient).

### **Omega-3 Fatty Acids/Fish Oils Plus Niacin (More Than 250 mg), and Aspirin Versus Niacin (More Than 250 mg), and Aspirin**

One study<sup>78</sup> contributed evidence (Table 31). This parallel arm placebo controlled active treatment (niacin plus aspirin) trial was in 14 participants for whom the randomization sequence and treatment allocation concealment were unclear (moderate risk of bias). The participants in this trial had unclear CHD risk (atherogenic dyslipidemia) and received their treatment for 12 weeks (4 g/day omega-3 plus 500 to 3000 mg/day niacin plus 325 mg/day aspirin versus niacin and aspirin).

The posttreatment mean differences in total cholesterol, HDL-C, LDL-C and triglycerides were not significantly different between the dietary supplement and control groups.

### **Omega-3 Fatty Acids/Fish Oils Plus Aspirin Versus Aspirin Alone**

In two trials in healthy participants with low or mixed CHD risk, a single dose of aspirin (325 mg<sup>99</sup> or 100 mg<sup>98</sup>) was administered following two to three weeks of omega-3 fatty acids (8 to 10 g/day) or placebo pre-treatment.

### **Omega-3 Fatty Acids/Fish Oils Plus Beta-Adrenergic Antagonists Versus Beta-Adrenergic Antagonists**

**Blood Pressure.** Systolic and diastolic blood pressure change posttreatment was reported for one trial.<sup>164</sup> This double-blind crossover trial was in 25 participants with unclear CHD risk, on beta-blocker monotherapy who were randomized to receive omega-3 fatty acids (4 g/day) or placebo for 6 weeks. No washout period was reported for this trial. The data for this study were not reported clearly, which precluded meaningful synthesis of the evidence.

### **Omega-3 Fatty Acids/Fish Oils Plus Warfarin Versus Warfarin Alone**

One 4 week study<sup>55</sup> contributed evidence. This was a parallel double blind (blinding status of participants, care providers, or study assessors was unclear), placebo-controlled trial in 11 participants with unclear CHD risk, for whom the randomization sequence and treatment allocation concealment were unclear (high risk of bias – there was a baseline between-group imbalance in gender and age). Treatment was 3 g/day or 6 g/day omega-3 fatty acids plus warfarin versus placebo plus warfarin. There was no significant difference in posttreatment INR values between the dietary supplement and control groups (p 0.41; no additional numerical data were provided).

**Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes**

| Cardio-vascular Drug(s)/ Outcome                            | Risk of Bias | Consistency  | Directness | Precision | Grade        | Conclusion Treatment Effect*   |
|---|--------------|--------------|------------|-----------|--------------|--|
| <b>Statins</b>  |              |              |            |           |              |  |
| CRP <sup>44,158</sup><br>(mg/L)                             | -            | -            | -          | -         | -            | <b>No difference</b><br>Geometric mean difference:<br>1.14<br>(95% CI 0.6, 2.4) versus<br>1.80 mg/L<br>(95% CI 1.3, 3.2)   |
| HDL-C <sup>37,40,44,53,92,94,96,97,151,163</sup><br>(mg/dL) | Moderate     | Inconsistent | Indirect   | Precise   | Low          | <b>No difference</b><br>Pooled mean difference:<br>2.26(95% CI -1.82, 6.34)<br><small>40,44,53,96,151,163</small>  |
| LDL-C <sup>37,40,44,53,92,94,96,97,151</sup><br>(mg/dL)     | Moderate     | Inconsistent | Indirect   | Precise   | Low          | <b>No difference</b><br>Pooled mean difference:<br>1.33 mg/dL (95% CI -3.56,<br>6.22) <sup>40,44,53,96,151</sup>   |
| TC <sup>37,40,44,53,76,92,94,96,97,151</sup><br>(mg/dL)     | Moderate     | Inconsistent | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>Pooled mean difference:<br>-7.06 mg/dL (95% CI -14.50,<br>0.37) <sup>40,44,53,96,151</sup>  |
| TG <sup>40,76</sup>   | Moderate     | Consistent   | Indirect   | Precise   | Low          | <b>In favour of combination</b><br>Pooled mean difference:<br>-74.95 mg/dL (95% CI -<br>95.80, -54.10) <sup>40,76</sup>  |
| TG <sup>37,40,44,53,76,92,94,96,97,151,163</sup><br>(mg/dL) | Moderate     | Consistent   | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>Pooled mean difference:<br>-17.88 mg/dL<br>(95% CI -36.96, 1.21)<br><small>44,53,96,151</small>   |
| Non-HDL-C <sup>37,40,44,94,163</sup><br>(mg/dL)             | Moderate     | Inconsistent | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>-14.70 (95% CI -21.77, -<br>7.62) <sup>40</sup><br>5.42 (95%CI -15.75, 26.59)<br><small>44</small><br>5.60 (95% CI -34.06, 45.26)<br><small>163</small><br>Median changes<br>-40.2% vs -33.7%, p<br><0.001 <sup>94</sup><br>-40.0% vs -34.3%, p<<br>0.001 <sup>37</sup> |
| TC/HDL-C<br>ratio <sup>37,40,94,163</sup>                   | -            | -            | -          | -         | -            | <b>Inconclusive</b><br>-0.60 (95% CI -0.83, -0.36) <sup>40</sup><br>0.29 (95% CI -0.90, 1.48)<br><small>163</small><br>% change least squares<br>means<br>-6.5%, p<0.001 <sup>37</sup><br>Median change<br>-38.3% vs -34.5%, p less<br>than 0.001  |

**Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)**

| Cardio-vascular Drug(s)/ Outcome                                      | Risk of Bias | Consistency  | Directness | Precision | Grade        | Conclusion Treatment Effect*   |
|---|--------------|--------------|------------|-----------|--------------|--|
| LDL-C (<160/130/100 mg/dL) <sup>94</sup>                              | Moderate     | NA           | Indirect   | Precise   | Low          | <b>No difference</b><br>RR 0.93 (95% CI 0.84, 1.03)  |
| HDL-C (<190/160/130 mg/dL) <sup>94</sup>                              | Moderate     | NA           | Indirect   | Precise   | Low          | <b>No difference</b><br>RR 1.00 (95% CI 0.91, 1.11)  |
| Lipoprotein A <sup>96</sup> (mg/dL)                                   | -            | -            | -          | -         | -            | <b>Inconclusive</b><br>2.00 (95% CI -34.40, 38.40)   |
| Systolic Blood Pressure <sup>37,92,151</sup>                          | Moderate     | Inconsistent | Indirect   | Precise   | Low          | <b>In favor of supplement-CV drug combination</b><br>-8.50 mm Hg (95% CI -16.33, -0.66) <sup>92</sup><br>Median change from baseline -5.0 vs. +0.3 mmHg <sup>37</sup><br><br>No difference (data not given) <sup>151</sup>             |
| Diastolic Blood Pressure <sup>37,92,151</sup> (mm Hg)                 | Moderate     | Inconsistent | Indirect   | Precise   | Low          | <b>No difference</b><br>0.20 (95% CI -4.76, 5.16) <sup>92</sup><br>No difference (data not given) <sup>151</sup><br><b>In favor of supplement-CV drug combination</b><br>Median change from baseline -23.3 vs. -1.8 mmHg <sup>37</sup> |
| Blood Coagulation <sup>95</sup><br>PT<br>aPTT<br>PA/AD<br>PA/Collagen | -            | -            | -          | -         | -            | <b>No difference</b><br>-0.10 sec (95% CI -0.28, 0.08)<br>0.10 sec (95% CI -0.62, 0.82)<br>1.10 % (95% CI -5.05, 7.25)<br>0.90 % (95% CI -5.70, 7.50)  |
| Platelet Count <sup>76,95,97</sup>                                    | -            | -            | -          | -         | -            | <b>Inconclusive</b><br>-9.82 10 <sup>3</sup> /μL (95% CI -42.79, 23.15) <sup>95</sup><br>6.00 10 <sup>3</sup> /μL (95% CI 1.74, 10.25) <sup>76</sup><br>17.0% vs 20.0% change, p>0.05 <sup>97</sup>                                    |
| Bleeding Time <sup>97</sup>   | -            | -            | -          | -         | -            | <b>No difference</b><br>1.0% (95% CI -0.59, 2.59)  |
| <b>ACE inhibitors</b>   |              |              |            |           |              |  |
| TG <sup>77,152</sup> mg/dL  | Moderate     | Inconsistent | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>-38.6 (95% CI -160.62, 83.42) <sup>77</sup><br>-24.35 mg/dL (95% CI -45.31, -3.38) <sup>152</sup>   |



**Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)**

| <b>Cardio-vascular Drug(s)/ Outcome</b>             | <b>Risk of Bias</b> | <b>Consistency</b> | <b>Directness</b> | <b>Precision</b> | <b>Grade</b> | <b>Conclusion Treatment Effect*</b>  |
|---|---------------------|--------------------|-------------------|------------------|--------------|--|
| Systolic Blood Pressure <sup>77,152</sup><br>mm Hg  | Moderate            | Consistent         | Indirect          | Precise          | Low          | <b>No difference</b><br>Pooled mean difference:<br>-0.51 (95% CI -10.59, 9.57)                     |
| Diastolic Blood Pressure <sup>77,152</sup><br>mm Hg | Moderate            | Consistent         | Indirect          | Precise          | Low          | <b>No difference</b><br>Pooled mean difference:<br>-1.75 (95% CI -5.98, 2.48)                      |
| Urinary Protein excretion <sup>77</sup><br>mg/d     | -                   | -                  | -                 | -                | -            | <b>In favor of supplement-CV drug combination</b><br>-986.00 (95% CI -1763.43,-208.56)             |
| ≥50% Reduction in Proteinuria <sup>77</sup>         | -                   | -                  | -                 | -                | -            | <b>In favor of supplement-CV drug combination</b><br>RR 4.00 % of participants (95%CI 1.40, 11.30) |
| <b>Fenofibrate</b>                                  |                     |                    |                   |                  |              |  |
| LDL-C <sup>56</sup>                                 | Moderate            | NA                 | Indirect          | Unclear          | Insufficient | <b>In favor of supplement-CV drug combination</b><br>48.20% vs 39.00% change, p=0.03               |
| HDL-C <sup>56</sup>                                 | Moderate            | NA                 | Indirect          | Unclear          | Insufficient | <b>Inconclusive</b><br>-1.90% vs 1.30% change, p>0.05  |
| TC <sup>56</sup>                                    | Moderate            | NA                 | Indirect          | Unclear          | Insufficient | <b>Inconclusive</b><br>-8.00% vs -5.10% change, p>0.05   |
| TC/HDL-C <sup>56</sup>                              | -                   | -                  | -                 | -                | -            | <b>Inconclusive</b><br>-4.80% vs -8.30% change, p>0.05   |
| TG <sup>56</sup>                                    | Moderate            | NA                 | Indirect          | Unclear          | Insufficient | <b>Inconclusive</b><br>-60.80% vs -53.80% change, p=0.059  |
| Non-HDL-C <sup>56</sup>                             | Moderate            | NA                 | Indirect          | Unclear          | Insufficient | <b>Inconclusive</b><br>-8.20% vs -7.10% change, p>0.05   |
| Incidence of hypertension (% of participants)       | -                   | -                  | -                 | -                | -            | <b>Inconclusive</b><br>RR 0.98 (95% CI 0.14, 6.85)   |
| <b>Calcium Channel Blockers</b>                     |                     |                    |                   |                  |              |  |
| LDL-C <sup>50</sup> (mg/dL)                         | Moderate            | NA                 | Indirect          | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 (95% CI -94.30, 94.30)  |
| HDL-C <sup>50</sup> (mg/dL)                         | Moderate            | NA                 | Indirect          | Imprecise        | Insufficient | <b>Inconclusive</b><br>-2.00 (95% CI -32.7, 28.70)   |
| TC <sup>50</sup> (mg/dL)                            | Moderate            | NA                 | Indirect          | Imprecise        | Insufficient | <b>Inconclusive</b><br>5.00 (95% CI -91.30, 101.30)  |
| TG <sup>50</sup> mg/dL                              | Moderate            | NA                 | Indirect          | Imprecise        | Insufficient | <b>Inconclusive</b><br>-32.00 (95% CI -112.60, 176.60)   |

**Table 31. Strength of evidence for cardiovascular drug(s) with and without omega-3 fatty acids—Intermediate outcomes (continued)**

| Cardio-vascular Drug(s)/ Outcome                         | Risk of Bias | Consistency | Directness | Precision | Grade        | Conclusion Treatment Effect*  |
|--|--------------|-------------|------------|-----------|--------------|---|
| <b>Calcium Channel Blockers + Aspirin</b>                |              |             |            |           |              |   |
| LDL-C <sup>51</sup> mg/dL                                | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>1.00 (95% CI -10.90, 12.90)                                  |
| HDL-C <sup>51</sup> mg/dL                                | Moderate     | NA          | Indirect   | Precise   | Insufficient | <b>Inconclusive</b><br>-2.00 (95% CI -32.70, 28.70)                                 |
| TC <sup>51</sup> mg/dL                                   | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>9.00 (95% CI -6.40, 24.40)                                   |
| TG <sup>51</sup> mg/dL                                   | Moderate     | NA          | Indirect   | Precise   | Low          | <b>In favor of supplement-CV drug combination</b><br>-54.00 (95% CI -94.1, -13.90)  |
| <b>Calcium Channel Blockers + Aspirin + Dipyridamole</b> |              |             |            |           |              |   |
| LDL-C <sup>52</sup> (mg/dL)                              | Moderate     | NA          | Indirect   | Precise   | Low          | <b>In favor of CV drug alone</b><br>21.00 (95% CI 3.30, 38.70)                      |
| HDL-C <sup>52</sup> (mg/dL)                              | Moderate     | NA          | Indirect   | Precise   | Insufficient | <b>Inconclusive</b><br>0 (95% CI -4.00, 4.00)                                       |
| TC <sup>52</sup> (mg/dL)                                 | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>19.00 (95% CI -1.70, 39.70)                                  |
| TG <sup>52</sup> (mg/dL)                                 | Moderate     | NA          | Indirect   | Precise   | Low          | <b>In favor of supplement-CV drug combination</b><br>-81.0 (95% CI -125.30, -36.70) |
| Platelet count <sup>52</sup> (10 <sup>3</sup> /μL)       | -            | -           | -          | -         | -            | <b>Inconclusive</b><br>-2.80 (95% CI -56.20, 0.20)                                  |
| <b>Niacin + Aspirin</b>                                  |              |             |            |           |              |   |
| LDL-C (mg/dL)  | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>17.00 (95% CI -6.60, 40.60)                                  |
| HDL-C (mg/dL)  | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>1.00 (95% CI -13.20, 15.20)                                  |
| TC (mg/dL)   | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>9.00 (95% CI -19.10, 37.10)                                  |
| TG (mg/dL)   | Moderate     | NA          | Indirect   | Imprecise | Insufficient | <b>Inconclusive</b><br>-94.00 (95% CI -196.80, 8.80)                                |
| <b>Warfarin</b>  |              |             |            |           |              |   |
| INR  | High         | -           | Indirect   | -         | -            | No numeric data provided  |

**Note:** \* Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.

**Abbreviations:** ACE = angiotensin-converting enzyme; aPPT = activated partial prothrombin time; CHD = coronary heart disease; CRP = C-reactive protein; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NA = not applicable; NR = not reported; PA/AD = platelet aggregation/adenosine diphosphate PT = prothrombin time; RCT = randomized controlled trial; RR=relative risk; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; vs = versus; wk(s) = week(s); yr(s) = year(s).

**Applicability.** Statin combinations were examined in populations with 22 to 100 percent males, with unclear to mixed CHD risk, and mean age ranging from 30 years to 63 years. ACE inhibitors were examined in populations with 40 to 85 percent males, with unclear or high CHD

risk, and mean age 40 years to 60 years. Calcium channel blockers plus aspirin plus dipyridamole were examined in a male population, with high CHD risk, and mean age 56 years. Trial duration ranged from 4 to 25 weeks.

## **Vitamin E**

Ten RCTs and one controlled clinical trial examined the use of Vitamin E with cardiovascular drugs. Subjects were concomitantly taking antiplatelet agents (aspirin or ticlopidine)<sup>49,80</sup>, furosemide<sup>81</sup>, gemfibrozil<sup>79</sup>, nifedipine<sup>82</sup>, or statins.<sup>46,83-87</sup>

### **Vitamin E Plus Antiplatelet Agents Versus Antiplatelet Agents Alone**

Two parallel-arm RCTs examined the effect of concomitant use of vitamin E and antiplatelet agents.<sup>49,80</sup> In comparison with no treatment, 6 weeks of treatment with vitamin E (400 to 450 IU/day) was not found to effect total cholesterol in atherosclerotic plaque in 16 participants with high CHD risk taking aspirin or ticlopidine<sup>80</sup>. No changes in serum total cholesterol and triglyceride levels at followup were noted (reported qualitatively only). These results were potentially impacted by Type II error due to small sample size.

Platelet aggregation was assessed in a trial comparing vitamin E (400 IU/day) plus aspirin with aspirin alone in elderly, primarily white, subjects with transient ischemic attack, minor stroke, or residual neurologic deficits (unclear CHD risk).<sup>49</sup> Treatment was administered for 2 years. Platelet adhesion to collagen III was significantly decreased by vitamin E supplementation.

Strength of evidence was insufficient for triglycerides (Table 32).

### **Vitamin E Plus Furosemide Versus Furosemide Alone**

One small parallel-arm RCT of 24 participants examined the concomitant use of Vitamin E and furosemide.<sup>81</sup> Participants were randomized to receive either Vitamin E (600 mg/day) and furosemide (25 mg/day) or furosemide (25 mg/day) with placebo for 4 weeks. No significant differences were found in systolic and diastolic blood pressure. Strength of evidence for blood pressure was insufficient (Table 32).

### **Vitamin E Plus Nifedipine Versus Nifedipine Alone**

One small crossover RCT in 30 participants at high CHD risk examined vitamin E (900 mg/day) plus nifedipine versus placebo plus nifedipine.<sup>82</sup> Nifedipine long-acting formulation (average dose 88 plus/minus 11 mg/day) and Vitamin E were administered for four months.

Supplementation with Vitamin E was found to significantly lower total serum cholesterol, LDL-C, and triglycerides. HDL-C was slightly raised by administration of vitamin E, but the estimate was not statistically significant. There were no statistically significant differences in systolic and diastolic blood pressure.

The strength of evidence was insufficient for systolic and diastolic blood pressure, and HDL-C. Strength of evidence for improvement in LDL-C and triglyceride levels with combination treatment was low (Table 32).

**Applicability.** This study recruited elderly (mean age 73.8 plus/minus 2.1 years), moderately obese subjects with stable effort angina and high CHD risk.

## Vitamin E Plus Gemfibrozil Versus Gemfibrozil Alone

The combination of vitamin E (600 mg/day) and gemfibrozil was assessed in one controlled clinical trial in 67 participants.<sup>79</sup> Subjects were hyperlipidemic and were divided into young (mean age 29.5 plus/minus 4.9 years) and elderly (mean age 71.5 plus/minus 3.6 years) groups. No statistically significant effects were observed in lipid parameters or blood pressure. Effect estimates had very wide 95 percent confidence intervals, so this study was underpowered to detect statistically significant results. Strength of evidence for blood pressure and lipid parameters was insufficient (Table 32).

## Vitamin E Plus Statins Versus Statins Alone

Six RCTs addressed combined use of vitamin E (400 to 1000 U/day) and statins, including atorvastatin<sup>87</sup>, simvastatin<sup>83-86</sup>, and pravastatin<sup>46</sup>. All studies included subjects with hypercholesterolemia. In some studies, subjects also had additional conditions, such as diabetes<sup>87</sup> and vascular disease.<sup>86</sup>

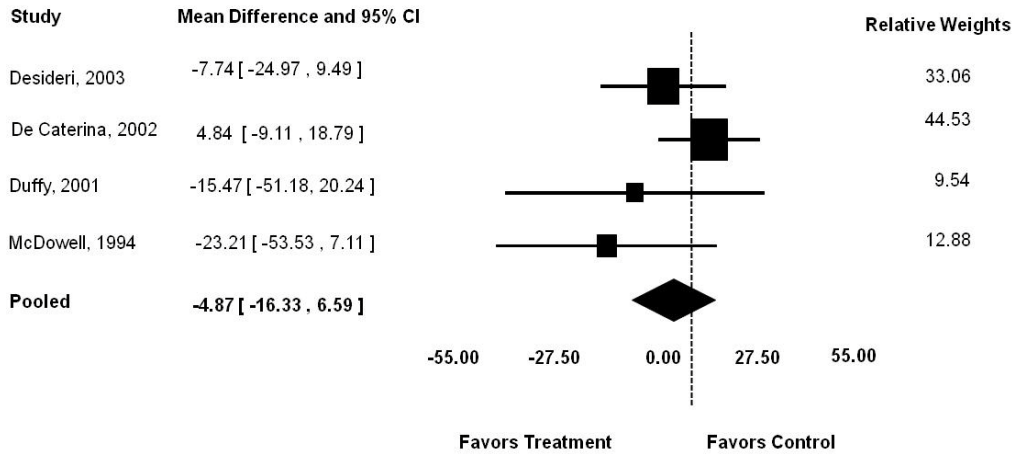
Lipid parameters were reported in all studies. Meta-analyses of total cholesterol, LDL-C, HDL-C, and triglycerides were undertaken for four trials.<sup>83-86</sup> Two trials could not be meta-analyzed because different effect estimates were reported (i.e., one trial reported serum lipid parameters in a qualitative manner only<sup>87</sup> and one trial reported lipid parameters as percent change from baseline<sup>46</sup>).

One study reported nonsignificant differences in cholesterol and triglyceride levels in non-HDL subfraction for combination vitamin E plus atorvastatin.<sup>87</sup> Another study reported nonsignificant differences for percent change in baseline for total cholesterol, LDL-C, HDL-C, and triglycerides for combination vitamin E plus pravastatin.<sup>46</sup>

The four trials that were pooled involved administration of vitamin E with simvastatin (total sample size 106).<sup>83-86</sup> Dosages of vitamin E and simvastatin ranged from 400 to 1000 U/day and 10 to 40 mg/day respectively. The pooled effect estimates for total cholesterol, LDL-C, HDL-C, and triglycerides were all statistically nonsignificant (Figures 15–18). Heterogeneity was minimal for all pooled estimates except for LDL-C ( $I^2$  64.6 percent, p-value 0.04). The observed heterogeneity could not be explained by variation of doses of supplement or cardiovascular drug. The strength of evidence was insufficient for LDL-C, HDL-C, and triglycerides (Table 32).

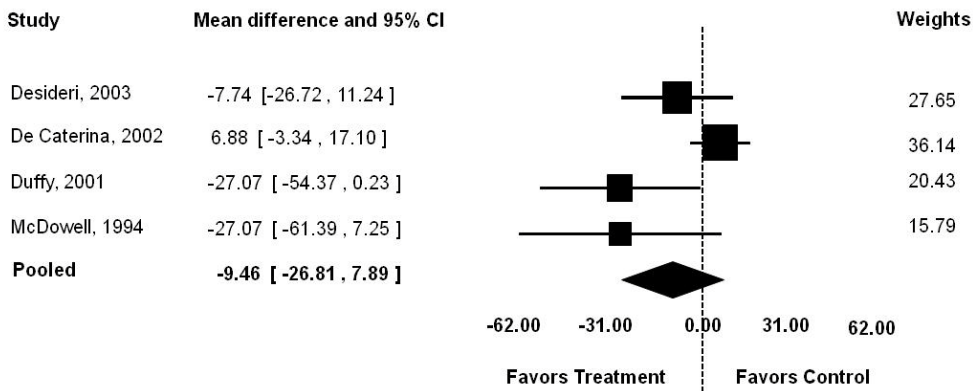
Other reported outcomes included C-reactive protein, prothrombin time, and platelet count. In a study of middle aged hypercholesterolemic subjects at low CHD risk, a statistically significant difference for C-reactive protein in favor of Vitamin E plus simvastatin was found (MD -0.40 mg/L (95 percent CI -0.66, -0.14)).<sup>85</sup> In another study of hypercholesterolemic subjects, no differences were found in prothrombin time and platelet count between Vitamin E plus pravastatin and pravastatin alone (reported qualitatively only).

**Figure 15. Forest plot of total cholesterol for statins with or without vitamin E (mg/dL)**



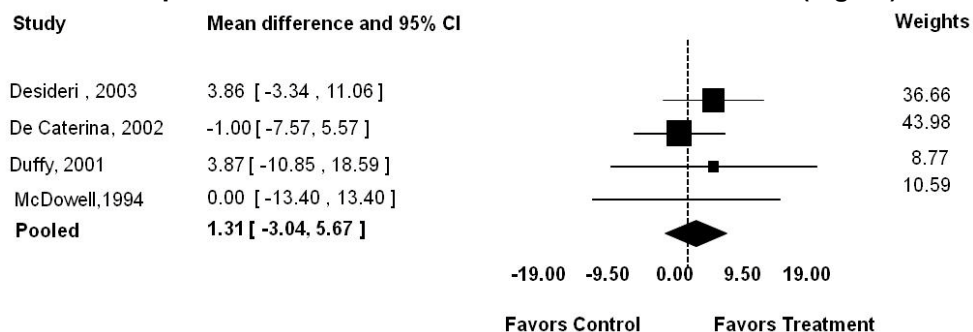
Heterogeneity:  $I^2 = 18.0\%$ ,  $Chi^2 = 3.66$  p-value = 0.30

**Figure 2. Forest plot of LDL-C for statins with or without vitamin E (mg/dL)**



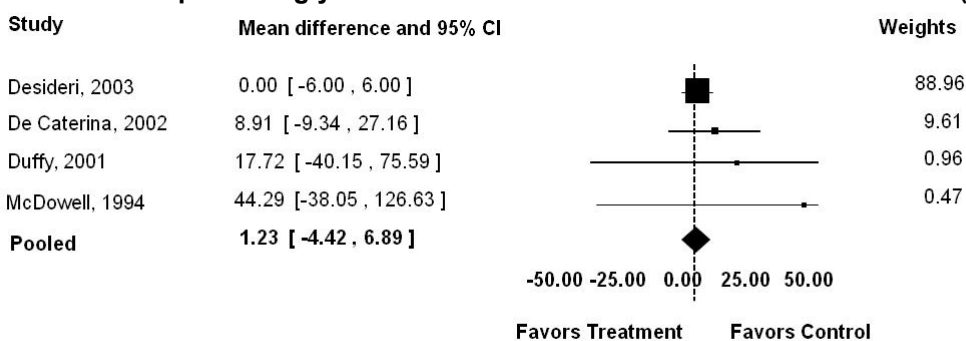
Heterogeneity:  $I^2 = 64.6\%$ ,  $Chi^2 = 8.49$ , p-value = 0.04

**Figure 17. Forest plot of HDL-C for statins with or without vitamin E (mg/dL)**



Heterogeneity:  $I^2 = 0.0\%$ ,  $Chi^2 = 1.11$ ,  $p\text{-value} = 0.78$

**Figure 18. Forest plot of triglyceride levels for statins with or without vitamin E (mg/dL)**



Heterogeneity:  $I^2 = 0.0\%$ ,  $Chi^2 = 2.20$ ,  $p\text{-value} = 0.53$

**Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E—Intermediate outcomes**

| Cardiovascular Drugs(s) / Outcome                                       | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect* MD (95% CI)   |
|---|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Antiplatelet Agents</b>  |              |             |                      |           |              |  |
| Triglycerides   | Moderate     | NA          | Indirect (surrogate) | NA        | Insufficient | <b>Inconclusive</b><br>No changes observed at end of follow-up (reported qualitatively only) |
| Platelet adhesion to collagen III (/cm <sup>2</sup> x 10 <sup>5</sup> ) | -            | -           | Indirect (surrogate) | -         | -            | <b>In favor of combination treatment</b><br>MD -1.70 (-2.06, -1.34)].                        |

**Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E— Intermediate outcomes (continued)**

| Cardiovascular Drugs(s) / Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade        | Conclusion Treatment Effect* MD (95% CI)   |
|-----------------------------------|--------------|-------------|----------------------|-----------|--------------|--|
| <b>Furosemide</b>                 |              |             |                      |           |              |  |
| Blood pressure                    | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Systolic<br>-3.00 mmHg<br>(-7.69, 1.69)<br>Diastolic<br>-2.00 mmHg<br>(-6.36, 2.36)   |
| <b>Nifedipine</b>                 |              |             |                      |           |              |  |
| Blood pressure                    | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Systolic<br>-2.00 mmHg<br>(-19.55, 15.55)<br>Diastolic<br>-1.00 mmHg<br>(-3.79, 1.79)   |
| LDL-C                             | Moderate     | NA          | Indirect (surrogate) | Precise   | Low          | <b>In favor of combination treatment</b><br>-39.83 mg/dL<br>(-71.29, -8.37)  |
| HDL-C                             | Moderate     | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>4.26 mg/dL<br>(-2.02, 10.54)  |
| Triglycerides                     | Moderate     | NA          | Indirect (surrogate) | Precise   | Low          | <b>In favor of combination treatment</b><br>-23.91 mg/dL<br>(-35.89, -11.93)   |
| Total cholesterol(TC) (mg/dL)     | -            | -           | Indirect (surrogate) | -         | -            | <b>In favor of combination treatment</b><br>MD-35.96 (-46.96, -24.96),   |
| <b>Gemfibrozil</b>                |              |             |                      |           |              |  |
| Blood Pressure                    | High         | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Systolic<br>7.00 mmHg (-14.07, 28.07) (elderly)<br>-3.00 mmHg (-22.46, 16.46) (young)<br>Diastolic<br>4.00 mmHg (-11.29, 19.29) (elderly)<br>-1.00 mmHg (-13.00, 11.00) (young) |
| LDL-C                             | High         | NA          | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>6.96 (-132.08, 146.00) (elderly)<br>-4.25 (-16.85, 8.35) (young)  |

**Table 32. Strength of evidence for cardiovascular drug(s) with and without vitamin E—Intermediate outcomes (continued)**

| Cardiovascular Drugs(s) / Outcome | Risk of Bias | Consistency  | Directness           | Precision | Grade        | Conclusion Treatment Effect* MD (95% CI)   |
|-----------------------------------|--------------|--------------|----------------------|-----------|--------------|--|
| HDL-C                             | High         | NA           | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>0 (-4.42, 4.42) (elderly)<br>6.19 (-1.28, 13.66) (young)            |
| Triglycerides                     | High         | NA           | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>-23.91 (-336.44, 288.62) (elderly)<br>-7.97 (-45.23, 29.29) (young) |
| <b>Statins</b>                    |              |              |                      |           |              |  |
| HDL-C                             | Moderate     | Inconsistent | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Pooled MD 1.31 mg/dL (-3.04, 5.67)                                  |
| LDL-C                             | Moderate     | Consistent   | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Pooled MD -9.46 mg/dL (-26.81, 7.89)                                |
| Triglycerides                     | Moderate     | Consistent   | Indirect (surrogate) | Imprecise | Insufficient | <b>Inconclusive</b><br>Pooled MD 1.23 mg/dL (-4.42, 6.89)                                  |

**Note:** \* Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.

**Abbreviations:** CI = confidence interval; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; MD = mean difference; NA = not applicable.

## Vitamin K

### Vitamin K Plus Coumarin Derivatives Versus Coumarin Derivatives Alone

One parallel-group RCT examined the effect of concomitant use of Vitamin K (5 mL volume per dose with concentration of 30 µg/mL vitamin K) and warfarin.<sup>41</sup> One cohort study was also identified that assessed whether vitamin K intake in subjects taking anticoagulants is associated with subtherapeutic INR.<sup>150</sup> The results of this study have not been included in the evidence synthesis as it added no further insights to the existing randomized trial.

The percentage of time that INR remained in the therapeutic range was reported (defined as INR within 0.5 of 2.0 to 3.0). Patients receiving Vitamin K stayed in the INR therapeutic range for a statistically significant longer percentage of time than patients who received warfarin alone.

INR control was also examined in terms of the standard deviation of the INR<sup>41</sup> and the number of participants achieving improved INR control compared with six months prior to study.<sup>41</sup> Vitamin K was found to increase stability of anticoagulation treatment (Table 33). Furthermore, the number of participants achieving stable INR was higher in combination with warfarin (RR 2.56 [95 percent CI 1.24, 5.28]).<sup>41</sup>

Strength of evidence for the statistically significant INR measures was low (Table 33).



**Applicability.** Participants with atrial fibrillation being anticoagulated with warfarin for thromboembolic prophylaxis, but with unstable INR control.<sup>41</sup> The trial was of 6 months duration.

**Table 33. Strength of evidence for coumarin derivatives with and without vitamin K—Intermediate outcomes**

| Cardiovascular Drugs(s) / Outcome | Risk of Bias | Consistency | Directness           | Precision | Grade | Conclusion Treatment Effect* (95% CI)   |
|-----------------------------------|--------------|-------------|----------------------|-----------|-------|---|
| % time in INR therapeutic range   | Moderate     | Consistent  | Indirect (surrogate) | Precise   | Low   | <b>In favor of combination treatment</b><br>MD 9% (1.42, 16.57)                             |
| SD of INR                         | Moderate     | NA          | Indirect (surrogate) | Precise   | Low   | <b>In favor of combination treatment</b><br>MD -0.12 (-0.20, -0.04)                         |
| N achieving INR control           | Moderate     | NA          | Indirect (surrogate) | Precise   | Low   | <b>In favor of combination treatment</b><br>N achieving INR control<br>RR 1.30 (1.04, 1.62) |
| N achieving stable INR            | Moderate     | NA          | Indirect (surrogate) | Precise   | Low   | <b>In favor of combination treatment</b><br>N achieving stable INR<br>RR 2.56 (1.24, 5.28)  |

**Note:** \* Range for mean difference (or risk ratio) given only when evidence consists of multiple studies that were not pooled. Intervention denotes dietary supplement arm; Control denotes placebo or no treatment arm. Range given if evidence consists of multiple studies.

**Abbreviations:** CI = confidence interval; INR = International Normalized Ratio; MD = mean difference; N = number; NA = not applicable; SD = standard deviation.

### Key Question 2a. Do the effect estimates of intermediate cardiovascular outcomes vary by age, ethnicity, gender, or health status?

No studies for any supplement-drug combination of interest precluded exploration of heterogeneity in the effect estimates across preidentified subgroups for intermediate outcomes.

### Key Question 2b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for intermediate cardiovascular outcomes?

Two studies contributed to the evidence regarding statistical interaction between cardiovascular drugs and dietary supplements for this section.<sup>44,78</sup> One study assessed statistical interaction using general linear modeling.<sup>44</sup> No significant interactions were observed between the combination of omega-3 fatty acids (4 g/day) and statins with regards to changes in lipid profile (HDL-C, LDL-C, total cholesterol, triglycerides, non-HDL-C) in 52 obese men with dyslipidaemia and insulin resistance (moderate/moderately high risk for CHD).<sup>44</sup> Authors of another trial<sup>78</sup> conducted a formal assessment of statistical interaction using ANOVA and found that the decrease in triglyceride levels resulting from the combination of omega-3 fatty acids (4

g/day) and niacin was more than twice the additive effect of either therapies alone in 29 participants with atherogenic dyslipidemia (unclear CHD risk).

## Main Points for Key Question 2—Intermediate Outcomes

We compared a dietary supplement coadministered with a cardiovascular drug(s), with the cardiovascular drug(s) alone (or in conjunction with another supplement) to investigate comparative intermediate cardiovascular efficacy outcomes, subgroup effects and statistical interactions.

- Fifty-seven RCTs, two controlled clinical trials and no observational studies addressed this Key Question.
- No study addressed the following outcomes: incidence of metabolic syndrome; carotid-intima media thickness; and change in 10-year Framingham risk profile.
- Exploration of heterogeneity for preidentified subgroups (e.g., males/females, ethnic groups, and the elderly) was not possible due to sparse data found for each supplement-drug combination of interest.
- No evidence was found for intermediate outcomes for the following supplements in combination with cardiovascular drugs: red yeast rice extract; resveratrol; vitamin A; or vitamin D with or without calcium.
- Most evidence was from small, underpowered RCTs that provided inconclusive results.
- The strength of evidence for gradable outcomes was generally insufficient due to inconsistencies in the treatment effect direction and the wide confidence interval compatible to potential for both clinical benefits and harms.
- Low grade evidence indicated improvement in a few intermediate outcomes in the following dietary supplement plus cardiovascular drug versus cardiovascular drug alone:
  - HDL-C: garlic plus nitrates, garlic plus warfarin; coenzyme Q10 plus fenofibrate
  - Triglyceride: garlic plus nitrates, omega-3 fatty acids in addition to calcium channel blockers and aspirin, calcium channel blockers, statins plus aspirin and dipyridamole (in participants with mean baseline TG levels of 200 mg/dL or higher); vitamin E plus nifedipine;
  - LDL-C: vitamin E plus nifedipine;
  - Systolic blood pressure: omega-3 fatty acids plus statins;
  - INR (percentage of time INR in therapeutic range, proportion of subjects achieving INR, proportion of subjects with stable INR): vitamin K plus anticoagulant (warfarin, coumarin derivatives);
  - Bleeding time: *Ginkgo biloba* plus cilostazol;
  - Coronary artery calcification (volume calcium score): *Ginkgo biloba* plus cilostazol;
  - Proteinuria (participants with 50 percent or greater reduction): omega-3 fatty acids plus ACE inhibitors.
- Low grade evidence indicated no difference between omega-3 fatty acids plus statins compared with statins alone in the following measures: HDL-C, LDL-C, achieving LDL-C and HDL-C targets; diastolic blood pressure; C-reactive protein; blood coagulation parameters; and bleeding time.
- Evidence was insufficient (type II error could not be excluded due to the low power of studies) for the following supplement plus cardiovascular drug combinations compared with the cardiovascular drug alone:

- lipid profile: coenzyme Q10 plus statins; coenzyme Q10 plus fenofibrate; garlic plus statins and aspirin; *Ginkgo biloba* plus aspirin; magnesium plus hydrochlorothiazide; omega-3 fatty acids plus fenofibrates; omega-3 fatty acids plus calcium channel blockers; omega-3 fatty acids plus niacin and aspirin; omega-3 fatty acids plus aspirin; vitamin E plus gemfibrozil, or statins;
- HDL-C: vitamin E plus nifedipine; omega-3 fatty acids plus calcium channel blockers and aspirin, calcium channel blockers plus aspirin and dipyridamole;
- Triglycerides: niacin plus propranolol; garlic plus nitrates; omega-3 fatty acids plus ACE inhibitors; omega-3 fatty acids plus statins (in participants with lower baseline TG levels); magnesium-hydrochlorothiazide; magnesium plus beta-adrenergic antagonists; vitamin E plus antiplatelet agents;
- LDL-C: omega-3 fatty acids plus calcium channel blockers and aspirin;
- Blood pressure: garlic plus warfarin; *Ginkgo biloba* plus aspirin, or antiplatelet thienopyridines, or cilostazol; magnesium plus hydrochlorothiazide, or beta-adrenergic antagonists; omega-3 fatty acids plus aspirin, or beta-blockers; vitamin E plus furosemide; vitamin E plus nifedipine; vitamin E plus gemfibrozil;
- INR: *Echinacea* plus warfarin; garlic plus warfarin; ginger plus warfarin; *Ginkgo biloba* plus warfarin; ginseng plus warfarin (peak INR, AUC<sub>INR</sub>); and omega-3 fatty acids plus warfarin.
- No statistical interaction was found for combination of omega-3 fatty acids plus statins for lipid parameters HDL-C, LDL-C, total cholesterol, triglycerides, and non-HDL-C.
- A positive interaction was found for the combination of omega-3 fatty acids plus niacin and aspirin for triglycerides. The decrease in triglycerides resulting from combination treatment was more than twice the additive effect of the therapies alone.

**Key Question 3.** In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement(s]) on clinical or intermediate harms outcomes (e.g., organ toxicity, serious adverse events, withdrawal due to adverse events)

- a. Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?
- b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

## Overview

A total of 58 unique studies were included for Key Question 3 (Table 34).<sup>39,44,46,47,49,51-53,55,56,78,81-84,86,87,91,92,96,97,99,100,36-38,40-42,48,54,57-69,71-77,88-90,93-95,98</sup>

One of the included studies was a retrospective cohort study,<sup>88</sup> while the rest were RCTs. Summary characteristics of the study and population is shown in Table 35.

One study examined the statistical interaction between vitamin E and aspirin<sup>100</sup> on harms. The characteristics of included studies are summarized in Table 34. Overall, the studies were generally of moderate risk of bias across all gradable harms, as summarized in Table 36. The harms outcomes examined across the included studies ranged from minor (e.g., flatulence) to serious (e.g., major bleeding). Although a higher proportion of the harms outcomes were

reported as continuous data rather than dichotomous data, the dichotomous outcomes were the focus of the present work, as these are the most suitable type of data for examining harms. A carryover effect was not a major concern in the crossover trials because most of the studies incorporated adequate washout periods in their design – well over five times the half-life of the drug supplement under investigation. However, a carryover effect may have influenced the results of 5 of the included crossover studies because it was not clearly reported,<sup>37</sup> the washout period was only one week,<sup>99</sup> or there was no washout period.<sup>42,75,86</sup> Detailed study characteristics and data from each of the included studies are available in Appendix C. For each supplement examined, we compared the different cardiovascular drug and supplement combination(s) versus the cardiovascular drug alone. For most supplement-cardiovascular drug related harms outcomes, data were either absent or too sparse with occasional events, precluding meaningful synthesis (Appendix C). Where subgroup analysis could be carried out, we report subgroup results as an additional consideration under the corresponding supplement.

No data were found for the following supplements: red yeast rice, resveratrol, vitamin A, vitamin D (with or without calcium).

**Table 34. Overview of availability of evidence for harms outcomes—Key Question 3**

| Dietary Supplement                  | N of Studies Included                                   | Cardiovascular Drug(s)   | Study Design(s)  |
|-------------------------------------|---|--|--|
| Coenzyme Q10                        | 5 <sup>38,54,57,58,89</sup>                             | Atorvastatin, simvastatin, fenofibrate, ACE-Inhibitors   | 4 Parallel RCT, 1 crossover RCT                          |
| Echinacea                           | 1 <sup>59</sup>   | Warfarin   | Crossover RCT  |
| Garlic                              | 4 <sup>60-63</sup>                                      | Warfarin, nitrates, statin + aspirin   | 3 Parallel RCT, 1 crossover RCT                          |
| Ginger                              | 1 <sup>64</sup>   | Warfarin (single dose)   | 1 Crossover RCT  |
| Ginkgo biloba                       | 7 <sup>48,64-68,90</sup>                                | Warfarin, aspirin, aspirin and/or pentoxiphylline, digoxin, nitrates, statin + aspirin, ticlopidine                                      | Parallel RCT (2), crossover RCT (5)                      |
| Ginseng                             | 3 <sup>69-71</sup>                                      | Warfarin   | 1 crossover, and 2 parallel RCTs                         |
| Hawthorne                           | 1 <sup>72</sup>   | Digoxin  | Crossover RCT  |
| Magnesium (oral)                    | 3 <sup>42,73,74</sup>                                   | Hydrochlorothiazide, metoprolol, atenolol, pindolol, propanolol  | 2 Parallel RCTs and 1 crossover RCT                      |
| Niacin (≤ 250 mg/d)                 | 1 <sup>75</sup>   | Propanolol   | Crossover RCT  |
| Omega- 3 fatty acids (or fish oils) | 22 <sup>36,37,40,44,47,51-53,55,56,76-78,88,92-99</sup> | Statins; Aspirin; Aspirin + Clopidogrel; Aspirin + Dipyridamole + Ca Channel Blockers; Warfarin; Ramipril and/or irbesartan; Fenofibrate | 13 Parallel RCT, 8 crossover RCT, 1 retrospective cohort |
| Vitamin E                           | 10 <sup>39,46,49,81-84,86,87,100</sup>                  | Aspirin, simvastatin, atorvastatin, pravastatin, furosemide  | 8 Parallel RCT and 2 crossover RCT                       |
| Vitamin K                           | 2 <sup>41,143</sup>                                     | Warfarin, phenprocoumon  | Parallel RCT   |

**Abbreviations:** ACE-I = Angiotensin-converting enzyme inhibitors; N = total number; RCT = randomized controlled trial

**Table 35. Summary of study characteristics—Key Question 3**

| Study Characteristic | Distribution  |
|----------------------|---|
| Sample CHD risk      | Low 17.5%<br>Moderate to moderately high 1.8%<br>High 22.8%<br>Mixed 25.3%<br>Unclear 32.6%   |
| Geographical region  | North America 19.3%<br>Europe 28.1%<br>Australia/New Zealand 5.3%<br>East Asia 4.3%<br>Rest of Asia 5.3%<br>NR/Other 37.8%  |
| Setting              | Primary care/community 36.1%<br>Specialty care 24.6%<br>NR 39.4%  |
| Duration             | Mean 21 weeks, range 1 day to 10 years  |
| Total N randomized   | Mean, 775.2, range 8 to 19,934, total across studies = 23,474   |
| Age                  | Mean age 55 years   |
| Gender               | Ten trials exclusively in males, <sup>44,52,59,61,64,65,67,68,71,98</sup> and two in females. <sup>39,100</sup> Of the mixed gender studies, 77% included females representing less than 40% of study sample.                   |
| Race/Ethnicity       | Seventeen studies reported race/ethnicity distribution. Eight included a majority of Caucasians. <sup>36,37,39-41,49,65,74</sup> Two studies included all Asians, <sup>57,68</sup> and two majority Hispanics. <sup>55,95</sup> |

**Table 36. Risk of bias and potential for conflict of interest—Key Question 3**

| Item   |      |      |         |
|--|------|------|---------|
| All RCTs (N = 57)  | Yes  | No   | Unclear |
| Adequate generation of allocation sequence                   | 23   | 0    | 77      |
| Allocation concealment                                       | 9    | 0    | 91      |
| Comparability of groups                                      | 49   | 18   | 33      |
| Purity of supplement   | 83   | 14   | 4       |
| Blinding of allocated intervention                           | 26   | 25   | 49      |
| Adequately addressed missing data                            | 61   | 4    | 35      |
| Freedom from potential for conflict of interest              | 23   | 33   | 44      |
| Crossover RCTs (N = 21)                                      |      |      |         |
| Suitability of crossover design for the study condition      | 100  |      |         |
| Freedom from carryover effect                                | 19.0 | 71.4 | 9.5     |
| Appropriateness of statistical analysis for crossover design | 23.8 | 14.3 | 61.9    |
| Comparability of groups between periods 1 and 2              | 9.5  | 0.0  | 90.5    |
| Freedom from bias introduced by dropouts                     | 76.2 | 9.5  | 14.3    |

**Abbreviations:** N = total number; RCTs = randomized controlled trials.

## Coenzyme Q10

Four RCTs examined coenzyme Q10 plus statins, fenofibrate or angiotensin-converting enzyme (ACE) inhibitors versus statins, fenofibrate, or ACE inhibitors alone.<sup>38,54,57,58</sup> One study examined coenzyme Q10 plus statins compared with vitamin E plus statins.<sup>89</sup> The included patients ranged from those with ischemic or idiopathic dilated cardiomyopathy,<sup>54</sup> or diabetes,<sup>58</sup>

to individuals with myalgia,<sup>38</sup> or myopathic pain.<sup>89</sup> The majority of studies were parallel RCTs (one crossover RCT<sup>54</sup>) with moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

### **Coenzyme Q10 Plus Statins Versus Statins Alone**

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus statins versus statins alone, including serious adverse events,<sup>57</sup> withdrawal due to adverse events,<sup>38,57</sup> hepatotoxicity (elevated alanine transaminase,<sup>38</sup> or elevated aspartate aminotransferase<sup>38</sup>), and renal dysfunction (abnormal glomerular filtration rate<sup>38</sup>) (Table 36). None of the included studies examined the gradable outcome bleeding. One RCT examined adverse events in general and zero events were observed.<sup>57</sup> One small pilot RCT examined myalgia in 44 participants using visual Analogue Scale and did not find a statistically significant difference between coenzyme Q10 (200 mg/day) plus statins (simvastatin 10 to 40 mg/day) versus statins alone (median 6.0 [inter quartile range 2.1, 8.8] vs. 2.3 [interquartile range 0.0, 12.8], p 0.63).<sup>38</sup> Similarly, in this trial there was no statistically significant difference between coenzyme Q10 plus statin and statin alone groups in proportion of patients tolerating statin (16/22 versus 13/22, p 0.47; RR 1.23, 95 percent CI 0.80, 1.90). Note that this RCT<sup>38</sup> was powered to detect a 9 mm difference in myalgia scores between treatment groups. Study designers assumed that less than 10 percent of patients would tolerate high dose simvastatin (40 mg/day) alone compared with 50 percent tolerating combined therapy, and that 50 percent of patients would tolerate lower dose simvastatin (10 mg/day or more) compared with greater than 90 percent tolerating combination therapy at the comparable simvastatin dose.

Two RCTs examined fasting blood glucose as a continuous outcome; no differences were observed with 100 mg<sup>57</sup> or 200 mg<sup>58</sup> of coenzyme Q10 added to atorvastatin,<sup>57</sup> or fenofibrate<sup>58</sup> versus these cardiovascular drugs alone. Other continuous outcomes reported for the statins included myoglobin,<sup>57</sup> creatine kinase (CK), or creatine phosphokinase (CPK);<sup>57</sup> no statistically significant differences were observed.

### **Coenzyme Q10 Plus Statins Versus Vitamin E Plus Statins**

One small pilot RCT found a higher frequency of decreased myopathic pain in the coenzyme Q10 (100 mg/day) plus statin group (16/18) versus the vitamin E (400 IU/day) plus statin group (3/14), and the relative risk (RR) was 4.18 (95 percent CI 1.50, 11.46).<sup>89</sup> Similarly, significantly lower pain severity scores on the four pain intensity items of the Brief Pain Inventory Questionnaire (MD -1.76 (95 percent CI -2.93, -0.58]) and lower average pain interference scores on the seven items of the Questionnaire (MD -1.43 (95 percent CI -2.76, -0.10]) were observed in the coenzyme Q10 plus statins versus the vitamin E plus statins group.<sup>89</sup> No statistically significant differences were observed in phosphokinase levels. Participants in this trial used various type of statins in varying doses.

### **Coenzyme Q10 Plus Fenofibrate Versus Fenofibrate Alone**

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 plus fenofibrate versus fenofibrate alone, including withdrawal due to adverse events,<sup>58</sup> elevated alanine transaminase,<sup>58</sup> and elevated creatinine<sup>58</sup> (Table 36). None of the included studies examined the gradable outcomes serious adverse events or bleeding. RCTs also reported abnormal electrocardiogram (ECG)<sup>58</sup> and abnormal CK/CPK,<sup>58</sup> zero events were observed. In another RCT, frequency of retinopathy was the same with

coenzyme Q10 plus fenofibrates (5/20) versus fenofibrate alone (6/20).<sup>58</sup> One RCT examined fasting blood glucose as a continuous outcome; no differences were observed.<sup>58</sup>

## Coenzyme Q10 Plus ACE Inhibitors Versus ACE Inhibitors Alone

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for coenzyme Q10 (33 mg three times daily) plus ACE inhibitors versus ACE inhibitors alone, including hepatotoxicity (elevated alanine transaminase,<sup>54</sup> aspartate aminotransferase<sup>54</sup>) and renal dysfunction (creatinine,<sup>54</sup> blood urea nitrogen<sup>54</sup>) (Table 37). None of the included studies examined the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT also reported adverse events in general;<sup>54</sup> zero events were observed.

**Table 37. Strength of evidence for coenzyme Q10 with or without cardiovascular drugs—Harms outcomes**

| Cardiovascular Drugs(s)/Harm   | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Coenzyme Q10</b>  |              |             |                    |           |              |  |
| Serious adverse events [1 study]   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| Withdrawal due to adverse events [2 studies]   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>Study 1: 0 events<br>Study 2: no significant differences; 6/22 events in intervention group versus 4/22 events in placebo group |
| Renal dysfunction (glomerular filtration rate [1 study])                                   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| Hepatotoxicity hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study]) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| <b>Fenofibrate</b>   |              |             |                    |           |              |  |
| Withdrawal due to adverse events [1 study]   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>2 events total (not reported by group)  |
| Renal dysfunction (creatinine [1 study])   | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences between groups, number of events not reported  |

**Table 37. Strength of evidence for coenzyme Q10 with or without cardiovascular drugs—Harms outcomes (continued)**

| Cardiovascular Drugs(s)/Harm  | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect              |
|---|--------------|-------------|--------------------|-----------|--------------|--|
| Hepatotoxicity (alanine transaminase [study])                               | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed |
| <b>ACE inhibitors</b>   |              |             |                    |           |              |  |
| Renal dysfunction (creatinine, blood urea nitrogen [n=1 study])             |              |             |                    |           |              | 0 events observed in 1 study             |
| Hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study]) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | 0 events observed in 1 study             |

**Abbreviations:** ACE = angiotensin-converting enzyme; NA = not applicable.

## *Echinacea*

A randomized open-label crossover trial in 12 healthy, non-smoking males with known CYP2C9 genotype reported zero total adverse events and withdrawal due to adverse events. The participants in this trial received a single dose of warfarin (25 mg/day) alone or after two weeks of pre-treatment with of 600 mg of *Echinacea angustifolia* roots plus 675 mg of *E. purpurea* root given four times a day<sup>59</sup> Insufficient evidence was noted for the gradable outcome withdrawal due to adverse events (Table 38). Furthermore, this study did not report data on any of the other gradable outcomes (serious adverse events, bleeding, renal dysfunction or hepatotoxicity).<sup>59</sup>

**Table 38. Strength of evidence for warfarin with or without *Echinacea*—Harms outcomes**

| Cardiovascular Drugs(s)/Harm               | Risk of Bias | Consistency | Directness | Precision | Grade        | Conclusion Treatment Effect              |
|--|--------------|-------------|------------|-----------|--------------|--|
| Withdrawal due to adverse events [1 study] | Moderate     | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed |

**Abbreviation:** NA = not applicable.

## **Garlic**

Four RCTs examined garlic (4 to 10 g/day) plus warfarin, nitrates, or statins/ aspirin versus warfarin, nitrates, or statins/ aspirin alone.<sup>60-63</sup> The included patients ranged from healthy, non-smoking males<sup>61</sup> to individuals with cardiac conditions.<sup>60,62,63</sup> The majority of studies were parallel RCTs (one crossover RCT<sup>61</sup>) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

### **Garlic Plus Warfarin Versus Warfarin Alone**

Insufficient evidence was available for the gradable harm bleeding for garlic (4 to 10 g/day) plus warfarin versus warfarin alone (Table 39).<sup>60,61</sup> In one study, bleeding was defined as hemorrhage, epistaxis, hemoptysis, hematuria, bloody stools, hemorrhage into organs, hemarthrosis, hematomas, or bruising.<sup>60</sup> The other study simply indicated major bleeding



episodes.<sup>61</sup> None of the included RCTs examined the gradable outcomes serious adverse events, withdrawal due to adverse events, renal dysfunction or hepatotoxicity. One RCT examined fasting blood glucose and anemia;<sup>60</sup> no statistically significant effects were observed.

### Garlic Plus Nitrates Versus Nitrates Alone

One RCT examined garlic (4 g/day) plus nitrates versus nitrates alone and did not report the results for any of the gradable harms.<sup>62</sup> This RCT reported only one harm (fasting blood glucose as a continuous outcome) and found no statistically significant effects.<sup>62</sup>

### Garlic Plus Statins/Aspirin Versus Statins/Aspirin Alone

Insufficient evidence was noted for the gradable outcomes renal dysfunction<sup>63</sup> and hepatotoxicity<sup>63</sup> for garlic (4 mL/day) plus statins/aspirin versus statins/aspirin alone (Table 39). This RCT<sup>63</sup> also reported harms data related to leukopenia and fasting blood glucose; no statistically significant effects were observed.

**Table 39. Strength of evidence for warfarin with or without garlic—Harms outcomes**

| Cardiovascular Drugs(s)/Harm   | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Warfarin</b>  |              |             |                    |           |              |  |
| Bleeding [2 studies]   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| <b>Aspirin</b>   |              |             |                    |           |              |  |
| Renal dysfunction* (creatinine, serum potassium [1 study])   | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed |
| Hepatotoxicity* (aspartate aminotransferase, alanine transaminase, alkaline phosphatase [1 study]) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed |

**Note:** \* continuous data only (dichotomous data not available).

**Abbreviation:** NA = not applicable.

### Ginger

No evidence of gradable outcomes was identified for this supplement. Mild diarrhea in 1/12 subjects was found in one RCT after two days of supplementation with ginger (3.6 g/day) plus a single dose of warfarin.<sup>64</sup>

### Ginkgo Biloba

Seven RCTs examined *Ginkgo biloba* plus warfarin, aspirin, aspirin and/or pentoxifylline, digoxin, statin/aspirin, cilostazol/clopidogrel or ticlopidine versus these cardiovascular medications alone.<sup>48,64-68,90</sup> Two of these studies included a single dose of a cardiovascular medication so their results should be interpreted with caution.<sup>67,68</sup> The included patients ranged from those at risk for peripheral artery disease<sup>66</sup> or stroke,<sup>48</sup> to healthy adults<sup>65,90</sup> and all

males.<sup>64,67,68</sup> The majority of studies were crossover RCTs (two parallel RCTs<sup>48,66</sup>) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

### ***Ginkgo Biloba* Plus Aspirin Versus Aspirin Alone**

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for *G. biloba* (240 mg/day,<sup>65</sup> or 300 mg/day<sup>66</sup>) plus aspirin versus aspirin alone, including withdrawal due to adverse events,<sup>66</sup> bleeding (nosebleeds and/or unusual bleeding),<sup>66</sup> renal dysfunction,<sup>65</sup> and hepatotoxicity<sup>65</sup> (Table 40). None of the included studies examined the gradable outcome serious adverse events. No statistically significant differences were observed across the total adverse events (11/34 combination group versus 15/33 control group) and upset stomach (6/34 combination group versus 5/33 aspirin alone group) harms.<sup>66</sup> One RCT reported anemia and white blood cell count using continuous data but found no significant differences between the groups taking *G. biloba* plus aspirin group and aspirin alone.<sup>65</sup>

### ***Ginkgo Biloba* Plus Aspirin and/or Pentoxiphylline Versus Aspirin and/or Pentoxiphylline Alone**

Insufficient evidence was noted for the gradable harm withdrawal due to adverse events for *G. biloba* (40 mg every 6 hours) plus aspirin and/or pentoxiphylline versus aspirin and/or pentoxiphylline alone<sup>48</sup> (Table 40). This RCT reported 4/33 gastrointestinal events in the *G. biloba* plus aspirin and/or pentoxiphylline group compared with 3/29 events in the control group,<sup>48</sup> which was not statistically significant. There was no report of any of the gradable outcomes serious adverse events, bleeding, renal dysfunction or hepatotoxicity.

### ***Ginkgo Biloba* Plus Ticlopidine Versus Ticlopidine Alone**

Insufficient evidence was noted for the gradable harms renal dysfunction (raised creatinine,<sup>68</sup> or abnormal blood urea nitrogen<sup>68</sup>) and hepatotoxicity (elevated aspartate aminotransaminase,<sup>68</sup> or elevated alkaline phosphatase<sup>68</sup>) for *G. biloba* (80 mg single dose) plus ticlopidine versus ticlopidine alone (Table 40). The included RCTs did not examine any of the gradable outcomes serious adverse events, withdrawal due to adverse events or bleeding. One RCT examined the effects of *G. biloba* plus ticlopidin versus ticlopidin alone on hypoglycemia, hyperglycemia, leukopenia, thrombocytopenia, anemia, and abnormal ECG; zero events were observed.<sup>68</sup>

### ***Ginkgo Biloba* Plus Warfarin Versus Warfarin Alone**

Insufficient evidence was noted for the gradable harms serious adverse events and withdrawal due to adverse events for *G. biloba* (two tablets three times daily—each tablet with equivalent of 2 g of *Ginkgo biloba* leaf, 9.6 mg of ginkgo flavonglycosides, 2.4 mg of ginkgolides and bilobalide) plus warfarin versus warfarin alone (Table 40).<sup>64</sup> This RCTs did not examine any of the other gradable harms, including bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were observed for constipation and no statistically significant differences were reported for diarrhea (0/12 combination group versus 1/12 control group).<sup>64</sup>

### ***Ginkgo Biloba* Plus Digoxin Versus Digoxin Alone**

Insufficient evidence was noted for *G. biloba* (80 mg three times daily) plus digoxin versus digoxin alone related to withdrawal due to adverse events (Table 40).<sup>90</sup> However, no data were

available on the other gradable harms, including serious adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore, zero events were reported for adverse events and no statistically significant differences were noted for gastrointestinal adverse events (1/8 combination group versus 0/8 control group).<sup>90</sup>

## **Ginkgo Biloba Plus Cilostazol/Clopidogrel Versus Cilostazol/Clopidogrel Alone**

Insufficient evidence was noted for *Ginkgo biloba* (120, and 240 mg/day) plus cilostazol/clopidogrel versus cilostazol/clopidogrel alone across all gradable outcomes, as none of these were reported.<sup>67</sup> One RCT examined total adverse events; zero events were reported.<sup>67</sup>

**Table 40. Strength of evidence for cardiovascular drugs with or without *G. biloba*—Harms outcomes**

| <b>Cardiovascular Drugs(s)/Harm</b>        | <b>Risk of Bias</b> | <b>Consistency</b> | <b>Directness</b>  | <b>Precision</b> | <b>Grade</b> | <b>Conclusion Treatment Effect</b>  |
|--|---------------------|--------------------|--------------------|------------------|--------------|---|
| <b>Aspirin</b>                             |                     |                    |                    |                  |              |   |
| Withdrawal due to adverse events [1 study] | Low                 | NA                 | Direct             | Imprecise        | Insufficient | <b>Inconclusive</b><br>No statistically significant differences, 3/34 intervention group versus 2/33 control group              |
| Bleeding [1 study]                         | Low                 | NA                 | Direct             | Imprecise        | Insufficient | <b>Inconclusive</b><br>No statistically significant difference; 5/34 events intervention group versus 4/33 events control group |
| Renal dysfunction* (1 study)               | Moderate            | NA                 | Indirect surrogate | Imprecise        | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed  |
| Hepatotoxicity* (1 study)                  | Moderate            | NA                 | Indirect surrogate | Imprecise        | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed  |
| <b>Aspirin and/or pentoxifylline</b>       |                     |                    |                    |                  |              |   |
| Withdrawal due to adverse events [1 study] | Moderate            | NA                 | Direct             | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| <b>Ticlopidine</b>                         |                     |                    |                    |                  |              |   |
| Renal dysfunction (1 study)                | Moderate            | NA                 | Indirect surrogate | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| Hepatotoxicity (1 study)                   | Moderate            | NA                 | Indirect surrogate | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| <b>Warfarin</b>                            |                     |                    |                    |                  |              |   |
| Serious adverse events [1 study]           | Moderate            | NA                 | Direct             | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| Withdrawal due to adverse events [1 study] | Moderate            | NA                 | Direct             | Imprecise        | Insufficient | <b>Inconclusive</b><br>0 events observed  |

**Table 40. Strength of evidence for cardiovascular drugs with or without *G. biloba* - Harms outcomes (continued)**

| Cardiovascular Drugs(s)/Harm                  | Risk of Bias | Consistency | Directness | Precision | Grade        | Conclusion Treatment Effect              |
|---|--------------|-------------|------------|-----------|--------------|--|
| <b>Digoxin</b>                                |              |             |            |           |              |  |
| Withdrawal due to adverse events<br>[1 study] | Moderate     | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed |

**Note:** \* continuous data only (dichotomous data not available). Renal dysfunction indication measures by creatinine, and or blood urea nitrogen levels; Hepatotoxicity measured by raised levels of aspartate aminotransaminase, and or alanine transaminase

**Abbreviation:** NA = not applicable.

## Ginseng

One parallel RCT examined the effects of 1.5 g/day *Panax ginseng* (aqueous extract containing 0.5 grams three times daily) plus warfarin versus warfarin alone among patients who had experienced a stroke.<sup>69</sup> Another parallel RCT examined the same comparison with 2 g/day American ginseng among healthy patients,<sup>70</sup> while a crossover RCT examined the same comparison but with 3 g/day Korean ginseng among healthy non-smoking males.<sup>71</sup> All three RCTs were of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes. Insufficient evidence was noted across the gradable clinical adverse events, including withdrawal due to adverse events<sup>71</sup> and bleeding (no description provided)<sup>69</sup> (Table 41). None of the included RCTs examined the gradable outcome serious adverse events. Furthermore, insufficient evidence was noted for the organ toxicity outcomes (elevated creatinine,<sup>69</sup> abnormal blood urea nitrogen,<sup>69</sup> elevated aspartate aminotransaminase,<sup>69</sup> and elevated alanine transaminase<sup>69</sup>), yet these were based on continuous data only (dichotomous data were not available). One RCT also examined prothrombin time, total adverse events, headache, dizziness, indigestion, INR above 3.5, diarrhea, and constipation,<sup>69</sup> zero events were observed across all of these outcomes. Another RCT reported zero adverse events of clinical importance.<sup>70</sup> One RCT examined the outcomes hematocrit and anemia using continuous data,<sup>69</sup> no statistically significant differences were observed between intervention and control groups.

**Table 41. Strength of evidence for warfarin with or without ginseng—Harms outcomes**

| Cardiovascular Drugs(s)/Harm  | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|---|--------------|-------------|--------------------|-----------|--------------|--|
| Withdrawal due to adverse events                                    | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| Bleeding  | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| Renal dysfunction* (creatinine, blood urea nitrogen)                | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed |
| Hepatotoxicity* (aspartate aminotransaminase, alanine transaminase) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed |

**Note:** \* continuous data only (dichotomous data not available).

**Abbreviation:** NA = not applicable.

## **Hawthorn**

Tankanow and colleagues investigated the occurrence of harms with hawthorn and digoxin in eight healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10-day period plus 900 mg/day of extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidines for a 21 day period, versus digoxin alone for 10 days.<sup>72</sup> This RCT did not report results for any of the gradable harms, including serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Furthermore, with sparse events, evidence was inconclusive for a difference between groups in flatulence, insomnia, headache, and dizziness.

## **Magnesium**

One parallel RCT examined the effects of 4.5 g/day oral magnesium plus hydrochlorothiazide versus hydrochlorothiazide alone,<sup>73</sup> while another examined the same comparison with 15.78 mmol twice daily among hypertensive patients.<sup>74</sup> In addition, one crossover RCT examined the effects of 365 mg/day oral magnesium plus various beta adrenergic antagonists versus beta adrenergic antagonists alone among hypertensive patients.<sup>42</sup> All three RCTs had moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

### **Magnesium Plus Hydrochlorothiazide Versus Hydrochlorothiazide Alone**

Insufficient evidence was noted across all of the gradable clinical adverse events and organ toxicity outcomes for magnesium plus hydrochlorothiazide versus hydrochlorothiazide alone, including withdrawal due to adverse events<sup>73</sup> and renal dysfunction (elevated creatinine<sup>74</sup>) (Table 42). None of the included RCTs examined the gradable outcomes serious adverse events, bleeding or hepatotoxicity. One RCT examining hydrochlorothiazide observed zero events across diarrhea, vomiting, nausea, adverse events, hypercalcemia, and fasting blood glucose harms.<sup>73</sup> Furthermore, no statistically significant differences were observed for abnormal ECG (number of events not reported).<sup>73</sup>

### **Magnesium Plus Beta Adrenergic Antagonists Versus Beta Adrenergic Antagonists Alone**

Insufficient evidence was noted for magnesium (365 mg/day) plus beta adrenergic antagonists versus beta adrenergic antagonists alone for the gradable harms serious adverse events,<sup>42</sup> withdrawal due to adverse events,<sup>42</sup> and renal dysfunction (abnormal serum potassium<sup>42</sup>) (Table 42). None of the studies reported the gradable outcomes bleeding or hepatotoxicity.

**Table 42. Strength of evidence for cardiovascular drugs with or without magnesium—Harms outcomes**

| Cardiovascular Drugs(s)/Harm         | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--------------------------------------|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Hydrochlor-thiazide</b>           |              |             |                    |           |              |  |
| Withdrawal due to adverse events     | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| Renal dysfunction (creatinine)       | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| <b>Beta-adrenergic antagonists</b>   |              |             |                    |           |              |  |
| Serious adverse events               | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| Withdrawal due to adverse events     | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed                                 |
| Renal dysfunction* (serum potassium) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences observed |

**Note:** \* continuous data only (dichotomous data not available).

**Abbreviation:** NA = not applicable.

## Niacin (Not More Than 250 mg)

Harms were investigated among 20 patients with hyperlipoproteinemia in an open-label, randomized crossover trial of niacin (250 mg/day) plus propranolol (20 mg/day) versus propranolol alone for 1 month.<sup>75</sup> There was insufficient evidence for the gradable outcome withdrawals due to adverse events (Table 43).<sup>75</sup> This study did not report gradable harms, such as serious adverse events, bleeding, renal dysfunction or hepatotoxicity. Furthermore, there were no statistically significant differences in nausea plus flushing (zero events) or hypotension plus asthenia (0/10 intervention group versus 1/10 control group).

**Table 43. Strength of evidence for propranolol with or without niacin—Harms outcomes**

| Cardiovascular Drugs(s)/Harm                 | Risk of Bias | Consistency | Directness | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|-------------|------------|-----------|--------------|--|
| Withdrawal due to adverse events [n=1 study] | High         | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences; 0/10 intervention group versus 1/10 control group |

**Abbreviation:** NA = not applicable.

## Omega-3 Fatty Acids/Fish Oils

Twenty-two studies (21 RCTs, and one retrospective cohort study) examined omega-3 fatty acids plus statins,<sup>36,37,40,53,92-97</sup> aspirin,<sup>47,52,78,98,99,99</sup> aspirin and clopidogrel,<sup>88</sup> aspirin in

combination with dipyridamole and calcium channel blockers,<sup>52</sup> warfarin,<sup>47,55</sup> rampril,<sup>77</sup> or fenofibrate,<sup>56</sup>. The included participants ranged from elderly patients with CHD,<sup>82</sup> to adults with diabetes<sup>87</sup> or stroke,<sup>49</sup> to healthy males<sup>39</sup> or adults.<sup>36,93,95,99</sup> The majority of studies were parallel RCTs, yet there were 7 crossover RCTs,<sup>36,37,93,95-97,99</sup> and one retrospective cohort study.<sup>88</sup> The majority were deemed as having moderate risk of bias, although two had low risk of bias<sup>51,92</sup> and one had high risk of bias.<sup>55</sup> Meta-analysis was only possible for the statins; for all other cardiovascular medications, low event rates across all of the harms outcomes precluded pooling.

## **Omega-3 Fatty Acids/Fish Oils Plus Statins Versus Statins Alone**

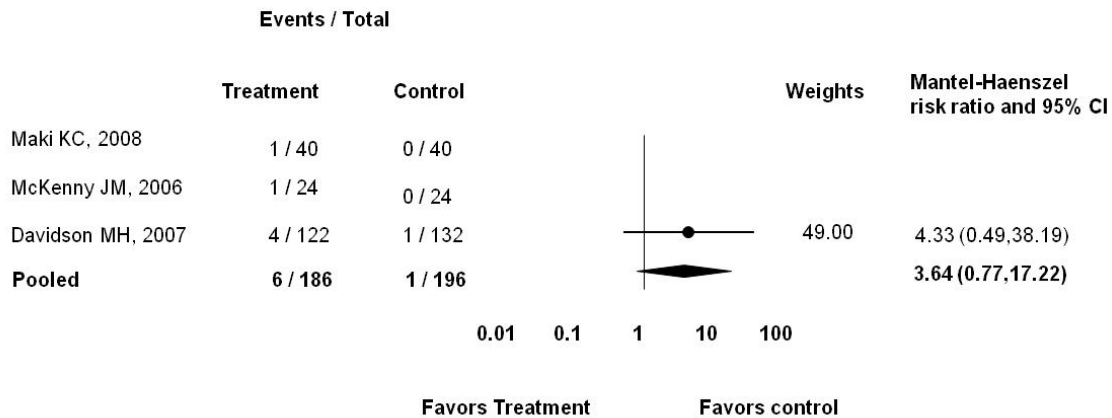
Eleven RCTs examined omega-3 fatty acids (2 to 9.2 g/day) plus statins versus statins alone.<sup>36,37,40,53,91-97</sup> One RCT had low risk of bias,<sup>92</sup> while the rest were of moderate risk of bias, including the seven RCTs included in the meta-analyses.<sup>36,37,40,91,93-96</sup> Insufficient evidence was noted across all gradable outcomes, including serious adverse events meta-analysis (Figure 19), withdrawal due to adverse events meta-analysis (Figure 20), aminotransaminase meta-analysis (Figure 21), and alanine transaminase meta-analysis (Figure 22, Table 44). None of the included RCTs examined the gradable outcome bleeding.

Meta-analysis was also possible for total adverse events (5 studies; RR 0.94 [95 percent CI 0.78, 1.12] Figure 23), dyspepsia (2 studies; odds ratio [OR] 1.61 [95 percent CI 0.46, 5.55] Figure 24), headache (2 studies; OR 0.76 [95 percent CI 0.25, 2.30] Figure 25), constipation (2 studies; RR 0.94 [95 percent CI 0.63, 1.39] Figure 26), upper respiratory infection (2 studies; RR 1.33 [95 percent CI 0.34, 5.21] Figure 27), and CK/CPK (3; RR 1.50 [95 percent CI 0.43, 5.25] Figure 28); no statistically significant effects were observed. Results were consistently not statistically significant despite differences in low<sup>36,93,95</sup> versus moderate<sup>37,40,94,96</sup> CHD risk, and healthy patients<sup>36,93,95</sup> versus those with hyperlipidemia or dyslipidemia<sup>37,40,94,96</sup>.

We were unable to discern any effects of sex, ethnicity or age on the results, as these were not examined in the RCTs for which meta-analysis was deemed appropriate.

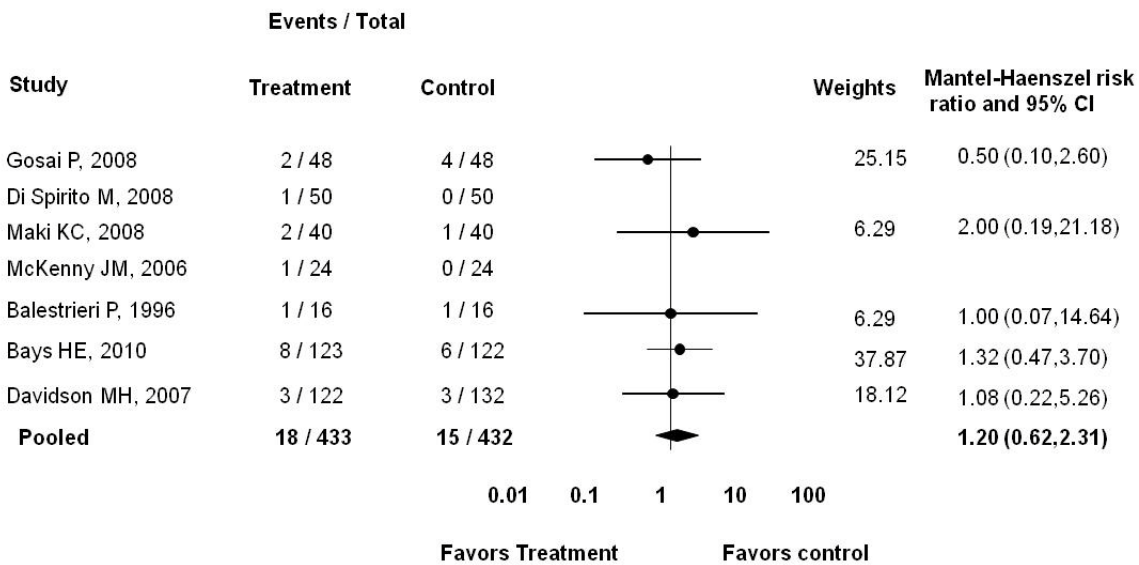
RCTs also reported many other harms outcomes for which no statistically significant differences were observed, such as diarrhea (3/122 intervention versus 3/132 control),<sup>40</sup> flatulence (5/50 intervention versus 5/50 control),<sup>36</sup> generalized edema (0/40 intervention versus 2/40 control),<sup>37</sup> hyperglycemia (2/40 intervention versus 1/40 control),<sup>37</sup> hypoglycemia (1/40 intervention versus 1/40 control),<sup>37</sup> infection (4/122 intervention versus 1/132 control),<sup>40</sup> myalgia (1/40 intervention versus 1/40 control),<sup>37</sup> and sinusitis (0/40 intervention versus 2/40 control).<sup>37</sup> The RCTs also examined harms outcomes as continuous variables, such as leukopenia,<sup>97</sup> anemia,<sup>97</sup> red blood cell count,<sup>97</sup> hematocrit,<sup>97</sup> glycosylated hemoglobin,<sup>94</sup> and fasting blood glucose,<sup>37,40,44,53,76,91,92,94</sup> and one RCT found a statistically significant elevated fasting blood glucose in the omega-3 fatty acids plus statins versus statins alone group.<sup>40</sup>

**Figure 19. Forest plot of serious adverse events with statins, with or without omega-3 fatty acids**



Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.05$ ,  $p\text{-value}=0.97$

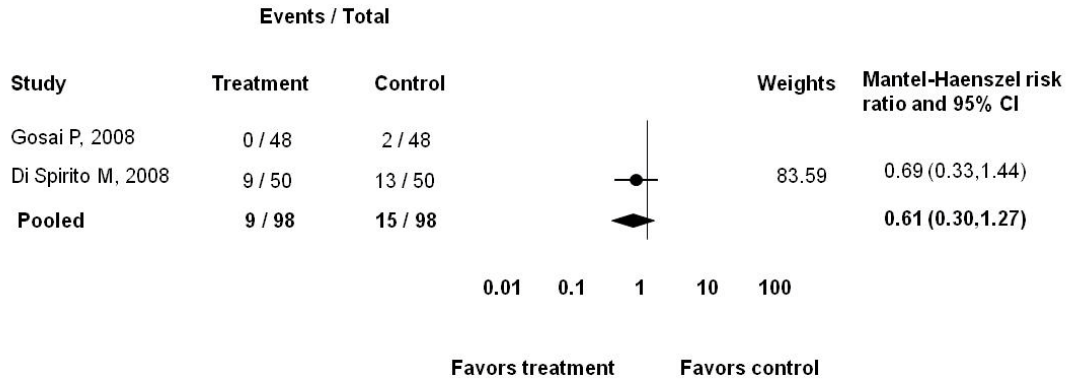
**Figure 20. Forest plot of withdrawal due to adverse events with statins, with or without omega-3 fatty acids**



Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=1.98$ ,  $p\text{-value}=0.92$

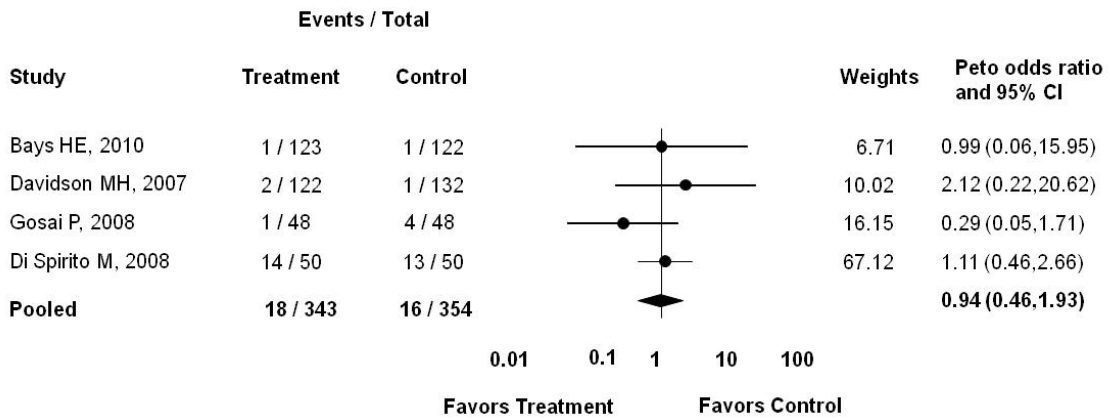


**Figure 21. Forest plot of aminotransaminase with statins, with or without omega-3 fatty acids**



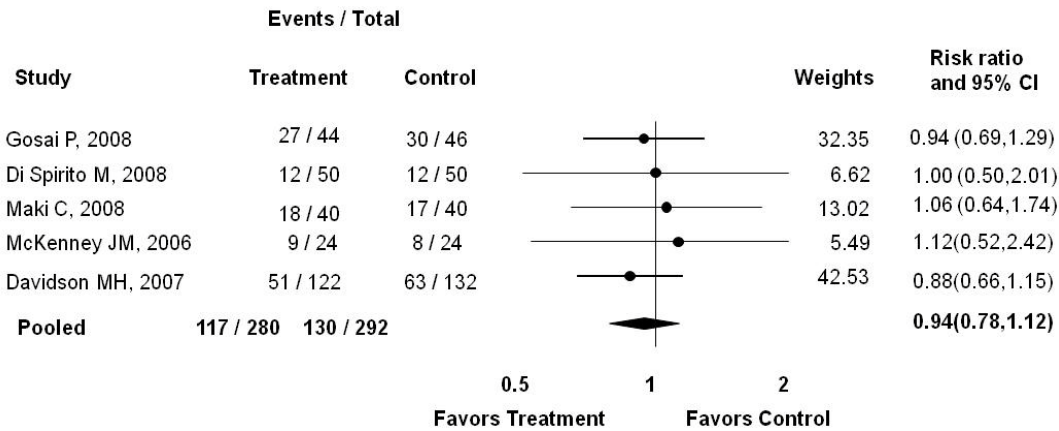
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.63$ ,  $p\text{-value}=0.43$

**Figure 22. Forest plot of alanine transaminase with statins, with or without omega-3 fatty acids**



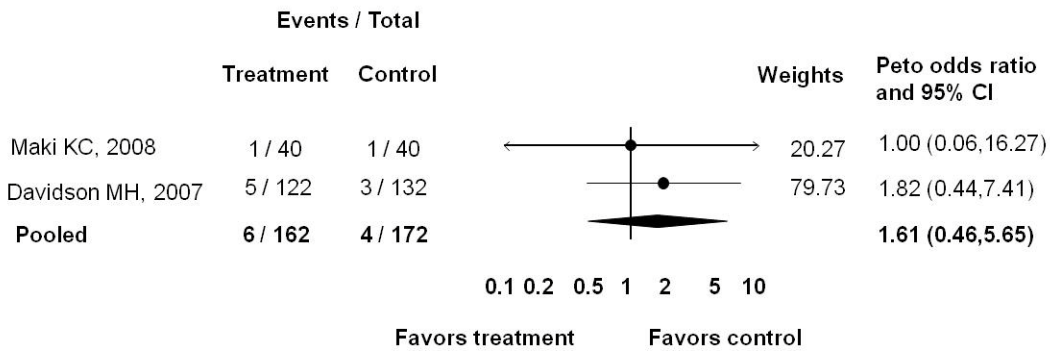
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=2.32$ ,  $p\text{-value}=0.51$

**Figure 23. Forest plot of total adverse events with statins, with or without omega-3 fatty acids**



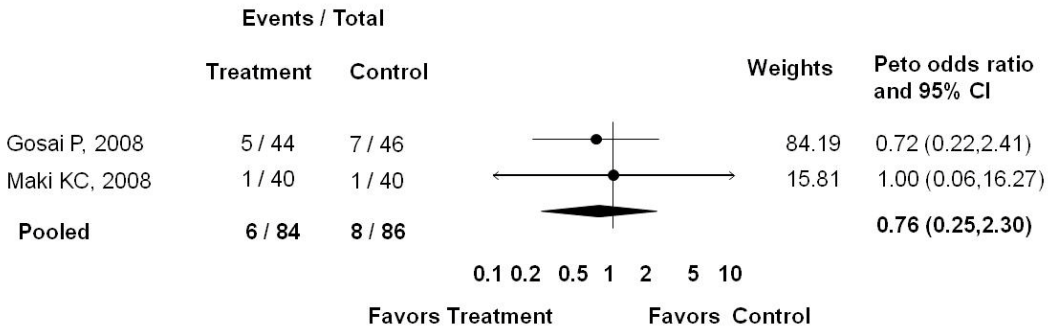
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.72$ ,  $p\text{-value}=0.95$

**Figure 24. Forest plot of dyspepsia with statins with or without omega-3 fatty acids**



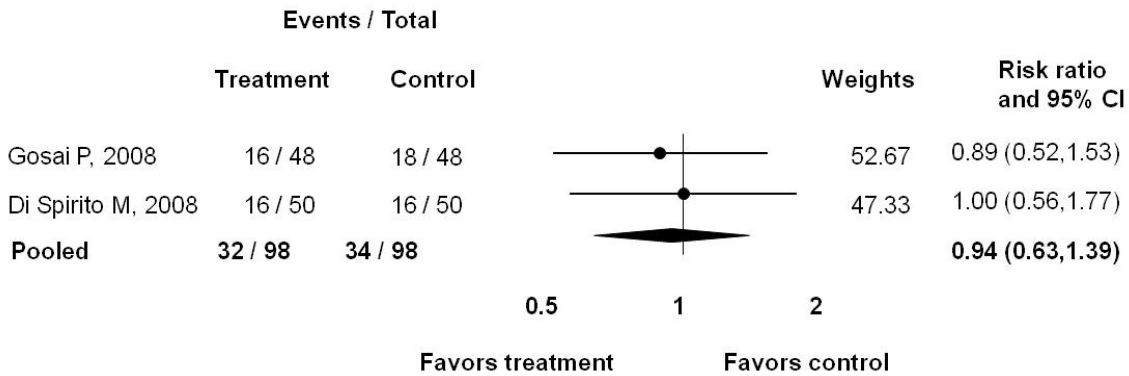
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.14$ ,  $p\text{-value}=0.71$

**Figure 25. Forest plot of headache with statins, with or without omega-3 fatty acids**



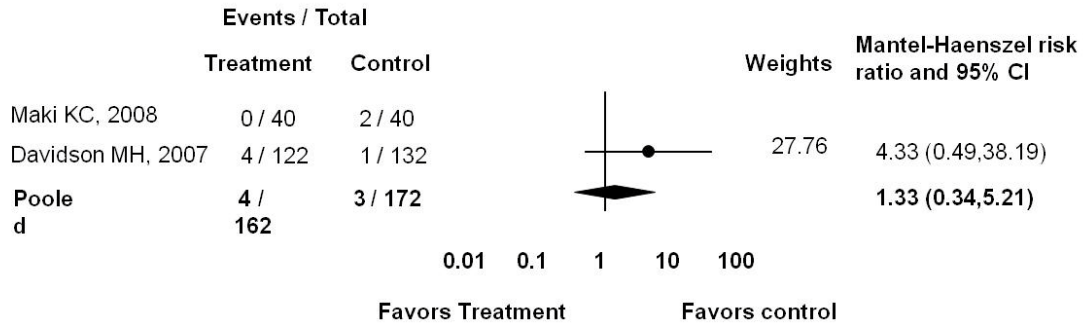
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.04$ ,  $p\text{-value}=0.83$

**Figure 26. Forest plot of constipation with statins, with or without omega-3 fatty acids**



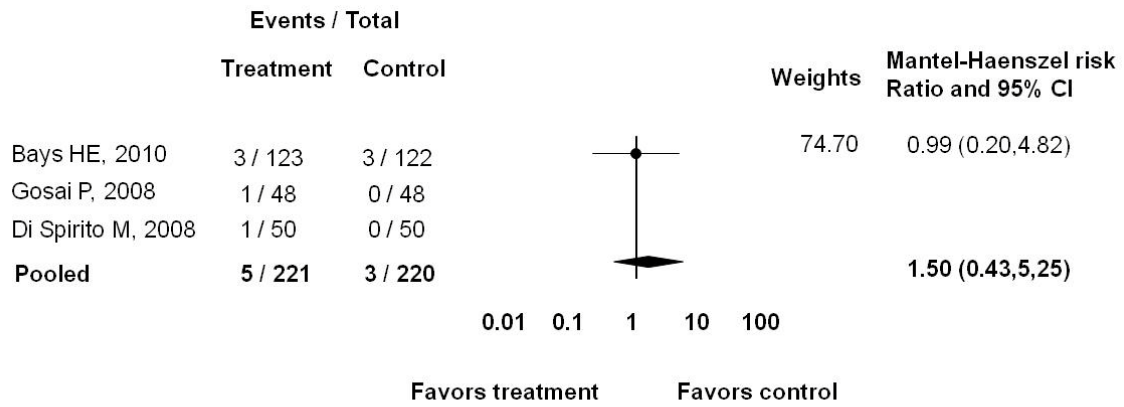
Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.09$ ,  $p\text{-value}=0.77$

**Figure 27. Forest plot of upper respiratory infection with statins, with or without omega-3 fatty acids**



Heterogeneity:  $I^2= 0.0\%$ ,  $Chi^2=2.66$ ,  $p\text{-value}=0.10$

**Figure 28. Forest plot of CK/CPK with statins, with or without omega-3 fatty acids**



Heterogeneity:  $I^2=0.0\%$ ,  $Chi^2=0.63$ ,  $p\text{-value}=0.73$

## **Omega-3 Fatty Acids/Fish Oils Plus Aspirin Versus Aspirin Alone**

Six RCTs examined omega-3 fatty acids (4 to 10 mg/day) plus aspirin versus aspirin alone.<sup>47,52,78,98,99,99</sup> Two of these RCTs were conducted among males only.<sup>52,98</sup> Insufficient evidence was noted for all gradable outcomes, including withdrawal due to adverse events<sup>78</sup> and bleeding<sup>47,99</sup> (Table 44). Bleeding in one study was defined as those episodes leading to deviation from the protocol (major and minor bleeding episodes: major bleeding defined as bleeding necessitating operation or blood transfusion; minor bleeding defined as all other episodes).<sup>47</sup> The second study reported bleeding episodes of any type.<sup>99</sup>

None of the included RCTs examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. No significant differences were observed across all harms, including constipation (1/12 intervention group versus 0/12 control group),<sup>99</sup> diarrhea (0/12 intervention group versus 1/12 control group),<sup>99</sup> fishy taste (4/12 intervention group versus 0/12 control group),<sup>99</sup> gastrointestinal adverse events (7/143 intervention group versus 12/148 control group),<sup>47</sup> flatulence (0/12 intervention group versus 1/12 control group),<sup>99</sup> headache (1/12 intervention group versus 1/12 control group),<sup>99</sup> and nausea (3/12 intervention group versus 3/12 control group).<sup>99</sup> One RCT reported leukopenia as a continuous outcome, with no statistically significant differences observed.<sup>99</sup>

## **Omega-3 Fatty Acids/Fish Oils Plus Aspirin and Clopidogrel Versus Aspirin and Clopidogrel Alone**

One retrospective cohort study examined the effect of fish oils (mean dose 3 g/day plus/minus 1.25 g/day) in combination with aspirin and clopidogrel in 182 elderly subjects with coronary artery disease.<sup>88</sup> An age and gender matched control group of subjects taking aspirin and clopidogrel alone was selected. Major and minor bleeding episodes were noted after a follow-up of 33 months. Major bleeding was defined as a decrease in hemoglobin of more than two grams, intracerebral hemorrhage, or any bleeding episode that required hospitalization. Minor bleeding was defined as epistaxis, abnormal bruising, and gastrointestinal bleeding that did not require hospitalization or lead to a decrease in hemoglobin of more than 2 grams. No significant differences were found between intervention and control groups. Strength of evidence for bleeding was insufficient (Table 44).

## **Omega-3 Fatty Acids/Fish Oils Plus Aspirin, Dipyridamole, and Calcium Channel Blockers Versus Aspirin, Dipyridamole, and Calcium Channel Blockers**

One RCT also examined the effects of omega-3 fatty acids (eicosapentaenoic 3.2 g/day) plus aspirin, dipyridamole, and calcium channel blockers versus aspirin, dipyridamole, and calcium channel blockers alone.<sup>52</sup> Another RCT with a low risk of bias examined omega-3 fatty acids (3 g/day) plus aspirin and calcium channel blockers versus aspirin and calcium channel blockers alone.<sup>51</sup> Insufficient evidence was noted for the gradable outcomes bleeding (described as bleeding complications)<sup>51,52</sup> and withdrawal due to adverse events<sup>51</sup> (Table 44). None of the included RCTs examined serious adverse events, renal dysfunction or hepatotoxicity. No statistically significant differences were observed regarding gastrointestinal events (7/43 intervention group versus 3/39 control group<sup>52</sup>).

## **Omega-3 Fatty Acids/Fish Oils Plus Warfarin Versus Warfarin Alone**

Two RCTs examined the effects of omega-3 fatty acids (3-6 g/day) plus warfarin versus warfarin alone.<sup>47,55</sup> Insufficient evidence was noted for the gradable outcomes bleeding<sup>47,55</sup> and withdrawals due to adverse events<sup>55</sup> (Table 44). Bleeding in one study was defined as those episodes leading to deviation from the protocol (major and minor bleeding episodes: major bleeding defined as bleeding necessitating operation or blood transfusion; minor bleeding defined as all other episodes).<sup>47</sup> The other study reported major bleeding (defined as bleeding episodes causing death or requiring hospitalization, vitamin K, or blood transfusion) and minor bleeding (defined as any bleeding episode that did not qualify as a major bleed but that required a change in warfarin dosage or referral).<sup>55</sup> None of the included studies examined the gradable outcomes serious adverse events, renal dysfunction or hepatotoxicity. Furthermore, three patients with an unstable international normalized ratio withdrew. Data were not reported by treatment groups.<sup>55</sup> One of the RCTs reported gastrointestinal events, which did not differ significantly between groups (9/174 intervention versus 0/145 control).<sup>47</sup>

## **Omega-3 Fatty Acids/Fish Oils Plus Ramipril and/or Irbesartan Versus Ramipril and/or Irbesartan Alone**

One RCT with a moderate risk of bias examined the effects of fish or marine oils (3 g/day) plus ramipril among patients at low risk of CHD.<sup>77</sup> Insufficient evidence was noted for the gradable outcomes withdrawal due to adverse events, bleeding (erythrocyturia grade 3), and renal dysfunction (glomerular filtration rate) (Table 44). This RCT did not report the results for other gradable harms, such as serious adverse events and hepatotoxicity. Furthermore, zero events were observed for hypercalcemia.

## **Omega-3 Fatty Acids/Fish Oils Plus Fenofibrate Versus Fenofibrate Alone**

One RCT with a moderate risk of bias examined the effects of omega-3 fatty acids (4 g/day) plus fenofibrate versus corn oil plus fenofibrate among patients with low CHD risk.<sup>56</sup> Insufficient evidence was noted for the gradable harms serious adverse events, withdrawal due to adverse events, and renal dysfunction (elevated creatinine) (Table 44). This RCT did not report results for the gradable harms bleeding or hepatotoxicity. Furthermore, no statistically significant differences were observed for constipation (1/84 intervention group versus 5/83 control group), diarrhea (4/84 intervention group versus 5/83 control group), flatulence (1/84 intervention group versus 3/83 control group), gastrointestinal adverse events (7/84 intervention group versus 5/83 control group) and nausea (5/84 intervention group versus 3/83 control group).

**Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes**

| Cardiovascular Drugs(s)/Harm   | Risk of Bias | Consistency  | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|--------------|--------------------|-----------|--------------|--|
| <b>Statins</b>   |              |              |                    |           |              |  |
| Serious adverse events [meta-analysis including 3 studies]               | Moderate     | Consistent   | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences; 0/10 intervention group versus 1/10 control group   |
| Withdrawal due to adverse events [meta-analysis including 7 studies]     | Moderate     | Inconsistent | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences; RR 3.6 (95% CI 0.8, 17.2)   |
| Renal dysfunction* (creatinine)  | Moderate     | NA           | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences; OR 1.2 (95% CI 0.6, 2.4)  |
| Hepatotoxicity: aminotransaminase [meta-analysis including 2 studies]    | Moderate     | Consistent   | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences  |
| Hepatotoxicity: alanine transaminase [meta-analysis including 4 studies] | Moderate     | Inconsistent | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences; RR 0.61 (95% CI 0.30, 1.27)   |
| <b>Aspirin</b>   |              |              |                    |           |              |  |
| Withdrawal due to adverse events   | Moderate     | NA           | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| Bleeding [n=2 studies]   | High         | NA           | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences:<br>Study 1: 0 events observed<br>Study 2: 3/143 intervention group versus 2/148 control group                                     |
| <b>Aspirin + clopidogrel</b>   |              |              |                    |           |              |  |
| Bleeding   | Moderate     | NA           | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences:<br>Major Bleeding: 1/182 intervention versus 0/182 control group<br>Minor Bleeding: 4/182 intervention versus 7/182 control group |

**Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes (continued)**

| Cardiovascular Drugs(s)/Harm                             | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Aspirin + dipyridamole + calcium channel blockers</b> |              |             |                    |           |              |  |
| Bleeding   | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences: 3/43 intervention group versus 1/39 control group   |
| <b>Aspirin+ calcium channel blockers</b>                 |              |             |                    |           |              |  |
| Withdrawal due to adverse events                         | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| Bleeding [1 study]                                       | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| <b>Warfarin</b>  |              |             |                    |           |              |  |
| Withdrawal due to adverse events                         | High         | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed   |
| Bleeding [2 studies]                                     | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences:<br>Study 1: 0 events observed<br>Study 2: 2/174 intervention group versus 2/145 control group |
| <b>Ramipril and/or irbesartan</b>                        |              |             |                    |           |              |  |
| Withdrawal due to adverse events [1 study]               | Moderate     | NA          | Direct             | Imprecise | Insufficient | 0 events observed  |
| Bleeding (Grade 3 erythrocyturia)                        | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences:<br>4/15 intervention group versus 1/15 control group  |
| Renal dysfunction* [glomerular filtration rate]          | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | No statistically significant difference  |



**Table 44. Strength of evidence for cardiovascular drugs with or without omega-3 fatty acids/fish oils—Harms outcomes (continued)**

| Cardiovascular Drugs(s)/Harm     | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|----------------------------------|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Fenofibrate</b>               |              |             |                    |           |              |  |
| Serious adverse events           | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences; 3/84 intervention group versus 4/83 control group   |
| Withdrawal due to adverse events | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences<br>4/84 intervention group versus 4/83 control group |
| Renal dysfunction (creatinine)   | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant differences<br>0/84 intervention group versus 1/83 control group |

**Note:** \* continuous data only (dichotomous data not available).

**Abbreviation:** NA = not applicable.

## Vitamin E

Ten RCTs examined vitamin E plus aspirin, statins, or furosemide versus these cardiovascular medications alone.<sup>39,46,49,81-84,86,87,100</sup> The included participants ranged from the elderly with CHD,<sup>82</sup> to those with diabetes,<sup>87</sup> or stroke,<sup>49</sup> to healthy females.<sup>39</sup> The majority of studies were parallel RCTs (with two crossover RCTs<sup>82,86</sup>) of moderate risk of bias. Meta-analysis was not possible due to the low event rate across all of the harms outcomes.

### Vitamin E Plus Aspirin Versus Aspirin Alone

Three RCTs examined vitamin E plus aspirin versus aspirin alone.<sup>39,49,100</sup> Insufficient evidence was noted for the gradable harms of bleeding (hemorrhagic events) after two years supplementation with vitamin E (400 IU/day) plus aspirin (325 mg/day) versus aspirin alone,<sup>49</sup> and for withdrawals due to adverse events after 10 days of vitamin E supplementation (200 mg/day) plus low dose aspirin (80 mg/day) or aspirin alone<sup>100</sup> (Table 45). None of the RCTs reported data related to the gradable harms serious adverse events, renal dysfunction or hepatotoxicity. No statistically significant differences were observed in the number of patients experiencing headache (28/121 intervention group versus 20/122 control group), gastrointestinal discomfort (14/121 intervention group versus 10/122 control group) or total adverse events (23/121 intervention group versus 24/122 control group) with 10 days of vitamin E supplementation (200 mg/day) plus low dose aspirin or aspirin alone.<sup>100</sup> One RCT examined the occurrence of cancer, and no statistically significant differences were observed (716/9966 intervention group versus 722/9968 control group) in a large sample of women (aged 45 years or older) supplemented with vitamin E (600 IU/day) plus low dose aspirin (100 mg/day) or aspirin alone over the period of 10 years.<sup>39</sup>

### **Vitamin E Plus Nifedipine Versus Nifedipine Alone**

One crossover RCT examined the effects of vitamin E (900 mg/day) plus nifedipine versus nifedipine alone over four months in 30 elderly and moderately obese participants with stable effort angina. Insufficient evidence was noted across all of the gradable harms, including withdrawal due to adverse events, renal dysfunction, and hepatotoxicity (zero events were observed).<sup>82</sup> (Table 45) This RCT did not report on the gradable outcomes serious adverse events or bleeding. Furthermore, fasting plasma glucose was examined as a continuous outcome and no statistically significant difference was observed.<sup>82</sup>

### **Vitamin E Plus Furosemide Versus Furosemide Alone**

One parallel RCT examined the effects of vitamin E (600 mg/day) plus furosemide versus furosemide alone over 4 weeks in 24 hypertensive participants, and did not report the results of any of the gradable outcomes. Fasting blood glucose was reported as a continuous outcome; no statistically significant effect was observed.<sup>81</sup>

### **Vitamin E Plus Statins Versus Statins Alone**

Five RCTs examined the effects of vitamin E plus statins versus statins alone in hypercholesterolemic or hyperlipidemic,<sup>46,83,84,86</sup> or diabetic participants.<sup>87</sup> In one trial very low dose of vitamin E was administered (100 IU/day) over three months<sup>46</sup> in contrast to two other trials using higher doses (750 IU/day,<sup>87</sup> and 1000 IU/day<sup>84</sup>) over six months. Insufficient evidence was noted across the gradable harms: organ toxicity (elevated alanine transaminase) with 100 IU/day vitamin E plus statins<sup>46</sup> or 1000 IU/day vitamin E plus statins over six months,<sup>84</sup> aspartate aminotransferase (100 IU/day),<sup>46</sup> abnormal alkaline phosphatase (100 IU/day),<sup>46</sup> elevated creatinine (100 IU/day),<sup>46</sup> abnormal blood urea nitrogen (100 IU/day)<sup>46</sup>, and QT intervals (measured as continuous variable) with 400 IU/day over eight weeks<sup>83</sup> (Table 45). None of the RCTs reported data on the gradable harms serious adverse events, withdrawal due to adverse events or bleeding. Furthermore, glycosylated hemoglobin,<sup>87</sup> leukopenia,<sup>46</sup> and anemia,<sup>46</sup> were examined as continuous outcomes and no statistically significant difference was observed. Change in urinary creatinine levels were not significantly different after 1 month supplementation with vitamin E (600 mg/day) plus statins versus 1 month statins treatment alone in one trial reporting this outcomes as a continuous variable.<sup>86</sup>

**Table 45. Strength of evidence for cardiovascular drugs with or without vitamin E—Harms outcomes**

| Cardiovascular Drugs(s)/Harm  | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect   |
|---|--------------|-------------|--------------------|-----------|--------------|---|
| <b>Aspirin</b>  |              |             |                    |           |              |   |
| Withdrawal due to adverse events [1 study]  | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant difference; 29/121 intervention group versus 19/122 control group |
| Bleeding [1 study]  | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant difference; 3/52 intervention group versus 3/48 control group     |
| <b>Nifedipine</b>   |              |             |                    |           |              |   |
| Withdrawal due to adverse events [n=1 study]  | Moderate     | NA          | Direct             | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| Renal dysfunction (creatinine [1 study])  | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| Hepatotoxicity (alanine transaminase, aspartate aminotransferase [1 study])                                   | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| <b>Statins</b>  |              |             |                    |           |              |   |
| Renal dysfunction (creatinine, blood urea nitrogen* [1 study])  | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| Hepatotoxicity (alanine transaminase [2 studies], aspartate aminotransferase, alkaline phosphatase [1 study]) | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |
| QT interval (continuous data)   | Moderate     | NA          | Indirect Surrogate | Imprecise | Insufficient | <b>Inconclusive</b><br>No significant difference observed.  |

**Note:** \* continuous data only (dichotomous data not available).

**Abbreviation:** NA = not applicable.

## Vitamin K

One parallel RCT (moderate risk of bias) examined the effects of vitamin K plus warfarin versus warfarin alone.<sup>41</sup>

## Vitamin K Plus Warfarin Versus Warfarin Alone

One RCT examined the effects of vitamin K (phytomenadione 150 µg/day) plus warfarin versus warfarin alone.<sup>41</sup> Insufficient evidence was observed for the gradable harms of bleeding episodes (no further description provided) and withdrawals due to adverse events (Table 46). This RCT did not report the gradable harms serious adverse events, renal dysfunction or hepatotoxicity.

**Table 46. Strength of evidence for anticoagulants with or without vitamin K—Harms outcomes**

| Cardiovascular Drugs(s)/Harm     | Risk of Bias | Consistency | Directness | Precision | Grade        | Conclusion Treatment Effect   |
|----------------------------------|--------------|-------------|------------|-----------|--------------|---|
| <b>Phenprocoumon</b>             |              |             |            |           |              |   |
| Bleeding [1 study]               | Moderate     | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences for minor bleeding; Minor bleeding: 7/94 intervention group versus 10/95 control group<br>Major bleeding: 2/94 intervention group versus 0/95 control group |
| <b>Warfarin</b>                  |              |             |            |           |              |   |
| Withdrawal due to adverse events | Moderate     | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>No statistically significant differences; 0/35 intervention group versus 2/33 control group  |
| Bleeding                         | Moderate     | NA          | Direct     | Imprecise | Insufficient | <b>Inconclusive</b><br>0 events observed  |

**Abbreviation:** NA = not applicable.

### Key Question 3a. Do the effect estimates of harms outcomes vary by age, ethnicity, gender, or health status?

A lack of evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.

### Key Question 3b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for harms outcomes?

One RCT presented data that would allow examination of the interaction between vitamin E supplements and the cardiovascular medication aspirin. Participants in this study were 486 Norplant contraceptive implant receivers from five Asian centers. The main outcome of this study was vaginal bleeding, which is not discussed here (it was not an included outcome for the present review). This RCT found no significant difference in the rates of adverse events (headache, gastrointestinal discomfort, and withdrawal due to adverse events) among treatment regimes.<sup>100</sup>

## Main Points for Key Question 3—Harms Outcomes

In this section we examined the evidence on harms outcomes, comparing dietary supplement(s) coadministered with cardiovascular drug(s), to cardiovascular drug(s) alone.

- Fifty-seven RCTs and one retrospective cohort study contributed to the evidence.
- Overall, the studies were of moderate risk of bias across all harms, which ranged from minor (e.g., flatulence) to severe (e.g., leukopenia, hemorrhaging).
- No evidence was identified for the effects of ginger, red yeast rice extract, resveratrol, vitamin A, or vitamin D in combination with cardiovascular drugs on clinical harms.
- No evidence for the following prespecified clinical harms were found: neurologic adverse events (e.g., neuropathy, seizure), and allergic reactions (anaphylaxis, skin, transient acute airway disease).
- Sparse evidence precluded exploration of heterogeneity in the effect estimates for harms across preidentified subgroups.
- Meta-analysis was not possible due to the low event rate across all of the reported harms outcomes for all supplements examined except for omega-3 fatty acids.
- A majority of the studies reported no events or no statistically significant differences across all harms and all supplements, including *Echinacea*, garlic, *G. biloba*, ginseng, hawthorn, oral magnesium, niacin (not more than 250 mg/day), omega-3 fatty acids, vitamin E, and vitamin K.
- For all gradable outcomes for which evidence was found, the strength of evidence was graded insufficient because type II error could not be excluded due to low power of studies to examine harms.
- Four RCTs examined the effects of coenzyme Q10 plus statins, fenofibrate or ACE-inhibitors versus these medications alone.
- The evidence for benefit of coenzyme Q10 in reducing myalgia, based on two small pilot studies, was inconclusive. One RCT found superior effect of coenzyme Q10 plus statin versus vitamin E plus statins in reducing myalgia. Another RCT found no significant difference in posttreatment myopathic pain between coenzyme Q10 plus statin and statin alone groups.
- Insufficient evidence was noted for meta-analyses for serious adverse events, withdrawal due to adverse events, and hepatic toxicity (abnormal levels of aminotransaminase, and alanine transaminase) for omega-3 fatty acids plus statins versus statins alone.
- No statistically significant effects were observed for meta-analyses of omega-3 fatty acids/statins for the following outcomes: dyspepsia, headache, constipation, upper respiratory tract infection, and creatine kinase. None of the other omega-3 fatty acids RCTs found statistically significant results across all harms, except for one RCT that found a statistically significant elevated fasting blood glucose level. Six other RCTs did not observe a statistically significant difference for the blood glucose levels.

Key Question 4. In adults taking cardiovascular drugs, what are the effects of concomitant use of specific dietary supplements (when compared to cardiovascular drugs alone or cardiovascular drugs and a different dietary supplement[s]) on pharmacokinetic outcomes (e.g., half-life [t<sub>1/2</sub>], area under the concentration curve [AUC]) of cardiovascular drugs of interest?

a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?

## b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?

### Overview

A total of 15 unique studies were screened in.<sup>36,59,61,64,68,70-72,90,93,95,101,142,145,147</sup> Three studies were removed from evidence synthesis because the dose of the dietary supplement was not reported,<sup>145</sup> a cardiovascular drug was used that is not marketed in the United States,<sup>142</sup> and finally a poorer study design sequential, single group before-after *Ginkgo biloba* and ticlopidine interaction study did not add to the available randomized controlled trial (RCT) evidence.<sup>147</sup> Thus, a total of 12 studies contributed evidence on exposure and pharmacokinetic outcomes (Table 47). Generally, these studies were open-label, crossover RCTs, of moderate risk of bias for outcomes of interest, and included between eight and 50 healthy volunteers (Table 48).

Seven studies investigated cardiovascular drug kinetics following a single dose.<sup>59,61,64,68,71,90,101</sup> In keeping with the United States Food and Drug Administration guidance,<sup>30</sup> seven studies reported pharmacokinetic outcomes potentially indicating cardiovascular drug interactions such as the area under the concentration curve (AUC) and maximum concentration ( $C_{max}$ ) as geometric mean ratios (dietary supplement plus cardiovascular drug: drug alone) with corresponding 90 percent confidence intervals.<sup>36,59,61,64,68,71,93</sup> Others reported data as posttreatment means or median changes from baseline or geometric mean ratio with 95 percent confidence intervals. Carryover effects in these crossover trials was not a major concern because all study designs incorporated adequate washout periods, that were well over five times the half-lives of the drugs and supplements under investigation. Detailed study characteristics and data are tabulated in Appendix C. Statistical analyses were undertaken to compare the combination of dietary supplement plus cardiovascular drug with the cardiovascular drug alone.

No evidence addressing Key Question 4 subquestions (a) or (b) was identified. No data were available on bioavailability and volume of distribution.

No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K, and a cardiovascular drug.

**Table 47. Overview of included studies for pharmacokinetic outcomes—Key Question 4**

| Dietary Supplement   | N of Studies Included for KQ 4 | Cardio-vascular Drug(s)                     | Study Design(s)               | Participants               | Study Region                                       | Race/Ethnicity                                | Industry Funding or Potential for Conflict of Interest         |
|----------------------|--------------------------------|---|-------------------------------|----------------------------|--|---|--|
| <i>Echinacea</i>     | 1 <sup>59</sup>                | Warfarin                                    | Crossover RCT                 | Healthy non-smoking males  | Australia/New Zealand                              | Mixed – Caucasians and Asians/South Asians    | Yes  |
| Garlic               | 2 <sup>61,101</sup>            | Warfarin, simvastatin, and pravastatin      | Crossover RCT                 | Healthy males              | Australia/New Zealand and Europe                   | Mixed – Caucasians and Asians                 | No<br>Yes <sup>101</sup>                                       |
| Ginger               | 1 <sup>64</sup>                | Warfarin                                    | Crossover RCT                 | Healthy non-smoking males  | Australia/New Zealand                              | Mixed – Caucasians and Asians                 | No   |
| <i>Ginkgo biloba</i> | 3 <sup>64,68,90</sup>          | Ticlopidine, digoxin, and warfarin          | Crossover RCT                 | Healthy adults             | East Asia, North America and Australia/New Zealand | Asians, NR, and Mixed – Caucasians and Asians | Yes <sup>68</sup><br>Unclear <sup>90</sup><br>No <sup>64</sup> |
| Ginseng              | 2 <sup>70,71</sup>             | Warfarin                                    | 1 crossover<br>1 parallel RCT | Healthy adults             | Australia/New Zealand and North America            | Mixed – Caucasians Asians and Hispanics       | No   |
| Hawthorn             | 1 <sup>72</sup>                | Digoxin                                     | Crossover RCT                 | Healthy non-smoking adults | North America                                      | NR  | Unclear  |
| omega-3 fatty acids  | 3 <sup>36,93,95</sup>          | Rosuvastatin, atorvastatin, and simvastatin | Crossover RCT                 | Healthy adults             | North America                                      | Mostly Caucasians, or mostly Hispanics        | Yes  |

**Abbreviations:** NR = not reported; RCT = randomized controlled trial.

**Table 48. Risk of bias and potential for conflict of interest—Key Question 4**

| Item   | % of Total RCT Studies |    |         |
|--|------------------------|----|---------|
|  | Yes                    | No | Unclear |
| <b>All RCTs (N=12)</b>                                       |                        |    |         |
| Adequate generation of allocation sequence                   | 18                     | 0  | 91      |
| Allocation concealment                                       | 0                      | 0  | 109     |
| Comparability of groups                                      | 91                     | 0  | 18      |
| Purity of supplement   | 82                     | 18 | 9       |
| Blinding of allocated intervention                           | 109                    | 0  | 0       |
| Adequately addressed missing data                            | 64                     | 9  | 36      |
| Freedom from potential for conflict of interest              | 45                     | 45 | 18      |
| <b>Crossover RCTs (N=11)</b>                                 |                        |    |         |
| Suitability of crossover design for the study condition      | 109                    | 0  | 0       |
| Free of carryover effect                                     | 109                    | 0  | 0       |
| Appropriateness of statistical analysis for crossover design | 27                     | 10 | 70      |
| Comparability of groups between periods 1 and 2              | 0                      | 0  | 109     |
| Freedom from bias introduced by dropouts                     | 60                     | 18 | 20      |

**Abbreviations:** N = total number; RCTs = randomized controlled trials.

## *Echinacea*

A randomized open-label crossover trial investigated exposure and pharmacokinetic interactions between a mixture of 600 mg of *Echinacea angustifolia* root plus 675 mg of *E. purpurea* root given four times a day for a period of two weeks, with a single dose of 25 mg warfarin versus warfarin alone.<sup>59</sup> Both S- and R-warfarin enantiomer specific pharmacokinetic parameters were reported, including  $AUC_{\infty}$ ,  $C_{max}$ , half-life, clearance and volume of distribution in 12 healthy males of known CYP2C9 and VKORC1 genotype. The 90 percent CIs for the geometric means of all parameters were all within the bioequivalence range of 80 percent to 125 percent. Although not considered to be clinically significant, a statistically significant decrease in S-warfarin  $AUC_{\infty}$ , and increases in drug clearance and apparent volume of distribution were noted with coadministration of the supplement (GMRs [90 percent CIs]: 0.92[0.85, 0.99]; 1.09[1.01, 1.18]; and 1.09 [1.03, 1.18] respectively).<sup>59</sup> Strength of evidence is summarized in Table 49.

**Table 49. Strength of evidence for warfarin with or without *Echinacea*, for Key Question 4**

| Gradable Outcomes   | Risk of Bias | Consistency | Directness         | Precision | Grade | Conclusion Treatment Effect            |
|---|--------------|-------------|--------------------|-----------|-------|--|
| $AUC_{\infty}$ , $C_{max}$ , half-life, and clearance for S- and R-warfarin | Moderate     | NA          | Indirect surrogate | Precise   | Low   | No clinically significant interactions |

**Abbreviations:**  $AUC_{\infty}$  = area under the concentration curve extrapolated to infinity;  $C_{max}$  = maximum concentration; NA = not applicable.



## Garlic

An open-label, randomized, crossover trial of allicin (7.4 mg/day) pretreatment for two weeks plus a single dose of 25 mg warfarin versus a single dose of warfarin alone was conducted in 16 healthy males.<sup>61</sup> Four participants were lost to followup or withdrew, so only 12 participants completed the study. GMRs of S- and R-warfarin  $AUC_{\infty}$ ,  $C_{max}$ , half-life and clearance for S- and R-warfarin were not statistically different; however, the 90 percent CIs went beyond the 0.8 to 1.25 clinical bioequivalence boundaries for  $C_{max}$  of both S- and R-warfarin (GMR [90 percent CI] S-warfarin 1.06 [0.77, 1.47]; R-warfarin 1.02 [0.8, 1.4]).<sup>61</sup> Strength of evidence is summarized in Table 50.

A crossover randomized trial investigated changes in baseline statin pharmacokinetics following coadministration with 3600 $\mu$ g of allicin given twice daily. The study randomized 10 healthy adults to single doses of simvastatin 20 mg and pravastatin 20 mg with a crossover after 24 hours.<sup>101</sup> Subsequently all patients were administered garlic tablet additionally continuing 12000 $\mu$ g of gamma glutamylcysteine and 3800 $\mu$ g of thiosulfinates for 21 days in the last 2 days randomized to single dose of one of the statins with a second crossover to the other. Hence, the investigation of change in statin pharmacokinetic with addition of garlic essentially originated in a nonrandomized before-after experimental study. Ninety-five percent geometric mean ratios of  $AUC_{0-24\text{ h}}$  and half-life of statins were reported which included but went beyond the FDA specified margins of bioequivalence based on 90 percent GMR. The difference in pre and postgarlic means in the outcomes of clearance,  $C_{max}$ , and time to the maximum concentration ( $t_{max}$ ) were not statistically significant, however, the data were not analyzed GMR with 90 percent CIs.

**Table 50. Strength of evidence for warfarin and statins with or without garlic, for Key Question 4**

| Gradable Outcomes   | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|---|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Warfarin</b>   |              |             |                    |           |              |  |
| $AUC_{\infty}$ , half-life, and clearance for S- and R-warfarin | Moderate     | NA          | Indirect surrogate | Precise   | Low          | No clinically significant interactions   |
| $C_{max}$ S- and R-warfarin                                     | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Clinically significant interactions could not be ruled out in either direction                         |
| <b>Simvastatin</b>  |              |             |                    |           |              |  |
| $AUC_{0-24\text{ h}}$ and half-life                             | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Clinically significant interactions could not be ruled out in either direction based on 95% CI of GMRs |
| Clearance, $C_{max}$  | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Inconclusive results because type II error could not be excluded                                       |
| <b>Pravastatin</b>  |              |             |                    |           |              |  |
| $AUC_{0-24\text{ h}}$ and half-life                             | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Clinically significant interactions could not be ruled out in either direction based on 95% CI of GMRs |
| Clearance, $C_{max}$  | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Inconclusive results because type II error could not be excluded                                       |

**Abbreviations:**  $AUC_{\infty}$  = area under the concentration curve extrapolated to infinity;  $C_{max}$  = maximum concentration; NA = not applicable.

## Ginger

Twelve healthy males participated in a study of ginger interaction with warfarin, in an open-label randomized crossover trial.<sup>64</sup> A single dose of 25 mg warfarin was preceded and followed by either no supplement or ginger (3.6 g of ginger rhizome per day) for 7 days. Statistically significant decreases in the  $t_{max}$  were observed for both S- and R-warfarin enantiomers (GMR [90 percent CI] S-warfarin 0.79 [0.73, 0.85]; R-warfarin 0.79 [0.73, 0.85]); the clinical significance of these findings is unclear. No interactions were noted for  $AUC_{\infty}$ ,  $C_{max}$ , half-life, clearance and volume of distribution; the GMR 90 percent CIs were not statistically significant, and were within the bioequivalence boundaries of 80 percent to 125 percent (Table 51).<sup>64</sup>

**Table 51. Strength of evidence for ginger plus warfarin versus warfarin alone, for Key Question 4**

| Gradable Outcomes   | Risk of Bias | Consistency | Directness         | Precision | Grade | Conclusion Treatment Effect            |
|---|--------------|-------------|--------------------|-----------|-------|--|
| $AUC_{\infty}$ , $C_{max}$ , half-life, and clearance for S- and R-warfarin | Moderate     | NA          | Indirect surrogate | Precise   | Low   | No clinically significant interactions |

**Abbreviations:**  $AUC_{\infty}$  = area under the concentration curve extrapolated to infinity;  $C_{max}$  = maximum concentration; NA = not applicable.

## Ginkgo Biloba

Three studies examined pharmacokinetic interaction of *Ginkgo biloba* and specific cardiovascular drugs.<sup>64,68,90</sup> All three studies were randomized crossover trials in healthy adults.

In a study of 24 young healthy Korean males, single doses of ticlopidine (250 mg) were administered with or without *G. biloba* (80 mg).<sup>68</sup> GMRs of  $AUC_{\infty}$  and  $C_{max}$  of ticlopidine were not statistically different from unity, and were clinically nonsignificant (Appendix C). Ticlopidine mean half-life and median  $t_{max}$  were not significantly affected by coadministration with *G. biloba*.<sup>68</sup>

In eight healthy adults, digoxin mean  $AUC_{\infty}$ ,  $C_{max}$ , clearance, elimination rate constant,  $t_{max}$  and half-life were not statistically different with 7 day treatment with *G. biloba* (240 mg/day) plus a single dose of 0.5 mg of oral digoxin on the last day, versus a single dose of 0.5 mg digoxin alone.<sup>90</sup> GMRs were not reported, or could be calculated in the absence of individual patient data; therefore, we could not rule out clinical interaction based on the predefined GMR margins of bioequivalence.<sup>90</sup>

In 12 healthy male participants, no statistically or clinically significant differences were noted in geometric mean ratios of  $AUC_{\infty}$ ,  $C_{max}$ , half-life, clearance and volume of distribution of warfarin when administered as a 25 mg single dose with 7 day pre-treatment with *Ginkgo biloba* (12 g/day) or alone.<sup>64</sup> However, there was significant reduction in  $t_{max}$  of both S- and R-warfarin enantiomers (GMR [90 percent CI]: 0.68 [0.63, 0.73]; 0.72 [0.67, 0.77], respectively). Based on the available data by group, we estimated that this decrease amounted to approximately 33 percent and 23 percent decreases in  $t_{max}$  arithmetic means for S- and R-warfarin enantiomers respectively.<sup>64</sup>

Strength of evidence is summarized in Table 52.

**Table 52. Summary and strength of evidence for ticlopidine, digoxin and warfarin with or without *G. biloba*, for Key Question 4**

| Gradable Outcomes  | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect                                      |
|--|--------------|-------------|--------------------|-----------|--------------|--|
| <b>Ticlopidine</b>   |              |             |                    |           |              |  |
| AUC <sub>∞</sub> , Half-life and C <sub>max</sub>                                    | Moderate     | NA          | Indirect surrogate | Precise   | Low          | No clinically significant interactions                           |
| Clearance  | -            | -           | -                  | -         | Insufficient | Data not reported  |
| <b>Digoxin</b>   |              |             |                    |           |              |  |
| AUC <sub>∞</sub> , C <sub>max</sub> , half-life, and clearance                       | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Inconclusive results because type II error could not be excluded |
| <b>Warfarin</b>  |              |             |                    |           |              |  |
| AUC <sub>∞</sub> , C <sub>max</sub> , half-life, and clearance for S- and R-warfarin | Moderate     | NA          | Indirect surrogate | Precise   | Low          | No clinically significant interactions                           |

**Abbreviations:** AUC<sub>∞</sub> = area under the concentration curve extrapolated to infinity; C<sub>max</sub> = maximum concentration; NA = not applicable.

## Ginseng

Interactions between American ginseng (*Panax quinquefolius*, 2 g/day from weeks 2 to 4) and warfarin (5 mg/day for 3 consecutive days of weeks 1 and 4) given over 4 weeks were investigated in a parallel randomized double blind placebo controlled trial in 20 healthy volunteers.<sup>70</sup> Compared with controls administered warfarin alone, a statistically significant reduction in the warfarin AUC was noted when ginseng was coadministered (between group difference in median change between week 4 and week 1 -0.64 µg/mL per day [95 percent CI, -1.25, -0.13]).<sup>70</sup> The clinical significance of this finding is unclear because analysis was not based on geometric mean ratios.

A second open-label randomized crossover trial in 12 healthy males of a single dose of 25 mg warfarin coadministered with a 7 day pretreatment with Korean ginseng (2 capsules 3 times a day, each capsule containing 0.5 g *Panax ginseng* root and 8.93 mg ginsenosides) or alone, found clinically interpretable results.<sup>71</sup> The geometric mean ratios of S- and R-warfarin AUC<sub>∞</sub>, C<sub>max</sub>, half-life, clearance and volume of distribution were neither statistically nor clinically different, indicating no interaction. The GMR for t<sub>max</sub> of both S- and R-warfarins showed statistically nonsignificant results, but the lower and upper bounds of the 90 percent CI crossed the predefined bioequivalence boundaries (S- and R-warfarin tmax GMR [90 percent CI]: 1.20 [0.77, 1.62]; 1.11 [0.78, 1.44], respectively).<sup>71</sup>

Strength of evidence is summarized in Table 53.

**Table 53. Summary and strength of evidence for warfarin with or without ginseng, for Key Question 4**

| Gradable Outcomes  | Risk of Bias | Consistency  | Directness         | Precision | Grade        | Conclusion Treatment Effect  |
|--|--------------|--------------|--------------------|-----------|--------------|--|
| $C_{max}$ , half-life, and clearance for S- and R-warfarin | Moderate     | NA           | Indirect surrogate | Precise   | Low          | No clinically significant interactions for Korean and American ginseng   |
| $AUC_{\infty}$   | Moderate     | Inconsistent | Indirect surrogate | Imprecise | Insufficient | The evidence of American ginseng and warfarin interaction is unclear because statistically significant reduction in AUC of warfarin was noted, but clinical significance is unclear. |

**Abbreviations:**  $AUC_{ss}$  = steady state area under the concentration curve; NA = not applicable.

## Hawthorn

Pharmacokinetic interactions between hawthorn (*Craetagus oxycantha*) and digoxin were investigated in eight healthy male volunteers in an open-label, randomized crossover trial of digoxin 0.25 mg/day for a 10 day period plus 900 mg/day of extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidins for a 21 day period, versus digoxin alone for ten days.<sup>72</sup> Using a paired analysis, the differences in means of  $AUC_{\infty}$ ,  $C_{max}$ ,  $t_{max}$ , half-life, and clearance did not reach statistical significance.

Strength of evidence is summarized in Table 54.

**Table 54. Strength of evidence for digoxin with or without hawthorn, for Key Question 4**

| Gradable Outcomes   | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect                                      |
|---|--------------|-------------|--------------------|-----------|--------------|--|
| Digoxin $AUC_{\infty}$ , $C_{max}$ , half-life, and clearance | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Inconclusive results because type II error could not be excluded |

**Abbreviations:**  $AUC_{ss}$  = steady state area under the concentration curve; NA = not applicable.

## Omega-3 Fatty Acids/Fish Oils

Three open-label randomized crossover studies in 24 to 50 healthy adult volunteers investigated interactions between omega-3 fatty acids and various statins.<sup>36,93,95</sup> Each study compared statin (rosuvastatin 40 mg/day, atorvastatin 80 mg/day, or simvastatin 80 mg/day) coadministered with 4 g/day of omega-3 fatty acids, with statin alone over a 14 day period. Due to the differences in first pass metabolism among various statins,<sup>166</sup> we did not conduct meta-analysis of outcomes data. No statistically or clinically significant differences were noted for steady state AUC and  $C_{max}$  GMRs for rosuvastatin, atorvastatin, 2-hydroxyatorvastatin, and 4-hydroxyatorvastatin. No statistically significant changes were observed in steady state  $\beta$ -hydroxysimvastatin arithmetic means of AUC,  $C_{max}$ ,  $t_{max}$ , clearance and half-life.<sup>36,93,95</sup>

Strength of evidence is summarized in Table 55.

**Table 55. Strength of evidence for statins with or without omega-3 fatty acids/fish oil—Harms outcomes**

| Gradable Outcomes   | Risk of Bias | Consistency | Directness         | Precision | Grade        | Conclusion Treatment Effect                                      |
|---|--------------|-------------|--------------------|-----------|--------------|--|
| Rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin in AUC <sub>ss</sub> , C <sub>max</sub>   | Moderate     | NA          | Indirect surrogate | Precise   | Low          | No clinically significant interactions                           |
| Half-life, and clearance of rosuvastatin, atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin<br><br>Beta-hydroxy-simvastatin AUC <sub>ss</sub> , C <sub>max</sub> , half-life, and clearance | Moderate     | NA          | Indirect surrogate | Imprecise | Insufficient | Inconclusive results because type II error could not be excluded |

**Abbreviations:** AUC<sub>ss</sub> = steady state area under the concentration curve; C<sub>max</sub> = maximum concentration; NA = not applicable.

**Applicability.** Evidence of interaction affecting pharmacokinetic outcomes may not translate into altered clinical effectiveness or harms. Evidence originating in healthy young adults is not representative of older patients taking cardiovascular drugs. Metabolism of cardiovascular drugs may differ between the populations studied in these trials and CHD patients.

**Key Question 4a. Do the effect estimates of pharmacokinetic outcomes vary by age, ethnicity, gender, or health status?**

A paucity of evidence for supplement-drug combinations precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender.

**Key Question 4b. Is there a measurable interaction between cardiovascular drugs and dietary supplements for pharmacokinetic outcomes?**

Statistical interaction data were not reported in any pharmacokinetic study.

## **Main Points for Key Question 4—Pharmacokinetic Outcomes**

In this section we examined the evidence on pharmacokinetics of cardiovascular drugs when coadministered with or without a dietary supplement. Clinical significance of interaction was evaluated using the FDA guidance. According to the guidance, a statistically significant interaction does not determine clinical significance of interactions unless the 90 percent confidence intervals of the geometric mean ratios fall outside of the defined no effect range of 0.80 to 1.25.

- Twelve randomized controlled trials contributed evidence on pharmacokinetic outcomes.
- All trials were conducted in small numbers of healthy participants.

- No studies were found examining pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (not more than 250 mg/day), red yeast rice extract, resveratrol, vitamin A, vitamin D with or without calcium supplementation, vitamin E, or vitamin K, and a cardiovascular drug.
- No clinically significant interactions were noted when *Echinacea*, ginger, or *Ginkgo biloba* were coadministered with warfarin, and when *Ginkgo biloba* was coadministered with ticlopidine. The strength of evidence for these findings was graded as low because evidence was limited to single pharmacokinetic studies with moderate risk of bias. Available evidence was insufficient, precluding meaningful conclusions about interactions between garlic and warfarin, garlic and statins, *Ginkgo biloba* and digoxin, omega-3 fatty acids and simvastatin, and hawthorn and digoxin. Interactions between ginseng and warfarin, and omega-3 fatty acids and rosuvastatin or atorvastatin were unclear; for some of the pharmacokinetic outcomes there was low strength of evidence suggesting no clinically relevant interactions, and insufficient evidence for others.
- A paucity of studies of supplement-drug combinations for which data were available precluded exploration of heterogeneity in terms of preidentified subgroups such as age and gender. Statistical interaction was not investigated in any pharmacokinetic study.

# Discussion

## Key Findings and Strength of Evidence

Billions of dollars are spent annually in the United States on complementary and alternative medicine (CAM), and a large portion of this expenditure is spent directly on dietary supplements.<sup>8</sup> Given the high prevalence of cardiovascular disease and frequency of polypharmacy in this population, the risk of drug-supplement interactions deserves serious consideration primarily to avoid potential harm; either as a result of decreasing clinical effect of drugs, or increased toxicity. There is also a real possibility of drug interactions leading to synergistic effects and positive clinical outcomes. A more thorough understanding and knowledge of potential drug-supplement interactions is important to provide specific evidence-based recommendations that do not call for universal avoidance of all dietary supplements in conjunction with pharmaceutical treatments to treat or to prevent cardiovascular disease. Without such precision, recommendations may result in the avoidance of potentially beneficial supplements or more importantly might be more readily ignored, leading to greater likelihood for harm through negative interaction.

This systematic review identifies a considerable knowledge gap regarding the impact of combining dietary supplements with cardiovascular drugs in patients with cardiovascular disease. We sought to identify the direct and indirect evidence for cardiovascular drug-dietary supplement interactions and their outcomes, and found 69 unique studies contributed evidence for synthesis. With few exceptions there is insufficient evidence to draw any strong conclusions on particular interactions between dietary supplements and cardiovascular drugs. In addition to an overall lack of evidence, the studies that were included were generally not powered to assess the clinically relevant outcomes we pre-identified as being most relevant. In addition, many of the studies had important methodological limitations or were poorly generalizable to the population of relevance. The strength of the evidence found was frequently compromised by poor allocation concealment and issues related to blinding, study reporting, and potential for conflict of interest.

Evidence of direct impact (or lack thereof) on clinical outcomes such as heart attack or stroke is most useful for patients and providers. Twenty-two randomized controlled trials reported direct evidence of drug-supplement interactions on predetermined gradable clinical outcomes; however, most of the trials were grossly underpowered to demonstrate any real effect, and often were of moderate risk of bias, leading to insufficient grades for strength of evidence. We found evidence of impact on clinical outcomes from studies that evaluated two non-gradable outcomes. In one randomized controlled trial (RCT) postangiography restenosis rates were improved through consumption of 3.2 grams of eicosapentaenoic acid taken along with aspirin, dipyridamole, and calcium channel antagonists for a duration of six months.<sup>52</sup> This finding was not supported by a similar but lower quality trial in India.<sup>51</sup> The second non-gradable clinical outcome of note came from a large long-term pragmatic trial in which 19,934 women were randomized to 600 IU of vitamin E plus 100 mg/day of aspirin versus aspirin taken alone for 10 years. In this trial, no significant differences occurred between groups in a composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke, and vascular death (RR 0.95 [95 percent confidence interval (CI) 0.79, 1.13]).<sup>39</sup>

Anticipating a paucity of evidence describing the influence of cardiovascular drug-dietary supplement interaction on meaningful clinical outcomes, we also sought indirect evidence of such interactions. Fifty-nine studies were identified that addressed intermediate cardiovascular

outcomes (blood pressure, lipid profile, International Normalized Ratio (INR), metabolic syndrome, change in 10-year Framingham risk profile, and QT prolongation). Again, these were mostly underpowered studies of highly selected individuals, with considerable risk of study bias attributed to inadequate blinding, and allocation concealment. As a result, the most frequently graded strength of the evidence was “insufficient,” with a few outcomes graded as “low”.

In our review, we found some of the richest evidence on the combination of omega-3 fatty acids with cardiovascular drugs. Out of a total of 24 RCTs that measured both gradable and non-gradable surrogate outcomes, 13 assessed the combination of omega-3 fatty acids with statins (atorvastatin, simvastatin, lovastatin). From pooled results of six trials<sup>40,44,53,96,151,163</sup> and five trials<sup>40,44,53,96,151</sup> respectively, no beneficial or harmful effect on HDL-C or LDL-C was found (low strength of evidence). While the evidence for total cholesterol and triglycerides was inconclusive (i.e., statistically non-significant pooled estimates with wide 95 percent confidence interval), there appeared to be some trend indicating possible improvement in these outcomes for patients taking omega-3 fatty acids with statins, which might not have reached the level of statistical significance due to low power of the meta-analyses. Results regarding non-HDL-C and total cholesterol/HDL-C ratio were inconsistent across studies. In addition, there was evidence of low strength from one parallel arm RCT<sup>92</sup> and one crossover RCT<sup>37</sup> that systolic blood pressure was improved when statins were taken with omega-3 fatty acids.

The addition of omega-3 fatty acids to statins (only in participants with high baseline levels of TG) or the combination of aspirin and a calcium channel blocker with or without dipyridamole appears to reduce triglyceride levels but not HDL-C or LDL-C.<sup>40,51,52,76</sup> It is likely that the triglyceride drop reflects the activity of omega-3 fatty acids alone rather than a synergistic or additive effect in combination with antiplatelet agents and calcium channel blockers. The combination of omega-3 fatty acids with ACE-inhibitors appears to have no significant effect on blood pressure and also demonstrates evidence consistent with omega-3 fatty acids having an independent benefit for triglyceride reduction.<sup>152</sup> In patients with biopsy proven IgA nephropathy, a single 6-month duration RCT found that the inclusion of omega-3 fatty acids with renin–angiotensin system blockers reduced the degree of proteinuria in comparison to the cardiovascular drugs.<sup>77</sup> In the only trial that assessed for pharmacodynamic interaction between warfarin and omega-3 fatty acids, there was no evidence of differences in coagulation based on INR; however this was a very small study (11 participants) and neither data nor confidence intervals were provided to evaluate this further.<sup>55</sup>

The inclusion of coenzyme Q10 with statin drugs seems to have no significant effect on any parameter of lipid profile predetermined to be a gradable outcome (high- or low-density lipoprotein-cholesterol (HDL-C or LDL-C), triglycerides, and non-HDL-C). Only one study explored the effect of coenzyme Q10 with fenofibrate on cholesterol levels and hypertension.<sup>58</sup> Although the trial failed to demonstrate any interaction, the RCT was underpowered to find any significant results. A similar situation applies to a small sized RCT comparing the combination of coenzyme Q10 with an angiotensin-converting enzyme (ACE) inhibitor on ejection fraction among patients with heart failure.<sup>54</sup> One RCT of 60 patients with coronary artery disease (CAD) suggests that the combination of 4 g/day of garlic oil taken with nitrates has a positive effect on HDL-C levels compared with nitrates taken alone.<sup>62</sup> This result, while statistically significant, may not be clinically meaningful and likely does not reflect an interaction between the two agents so much as an isolated effect of garlic, since nitrates are not known to affect HDL-C.

In a single RCT conducted in an elderly population (at least 65 years), platelet adhesion (a non-gradable outcome) decreased significantly through concomitant use of vitamin E with



aspirin.<sup>49</sup> In another RCT, supplementation with vitamin E in patients taking nifedipine led to a significant beneficial change in LDL-C (low strength of evidence). Again, we suspect this is an isolated effect of the dietary supplement rather than reflective of an interaction between vitamin E and nifedipine itself. Finally, supplementation with low doses of vitamin K (0.1 to 0.15 mg/day) in patients anticoagulated with warfarin appeared to provide stability to INR titration and increase time within the therapeutic range based on one study in participants of unknown ethnicity.<sup>41</sup> The stabilizing effect of vitamin K was independent of pre-specified subgroup status including gender (male/female) and age (younger or older than 65 years) in one of the studies where this was evaluated.<sup>159</sup>

Outcomes related to harms associated with drug interactions between dietary supplement and cardiovascular drugs were reported in 57 unique studies, most of which were considered to be at moderate risk of bias. Gradable harms outcomes included serious adverse events, withdrawal due to adverse events, bleeding, renal dysfunction, and hepatotoxicity. Of the studies that assessed harms outcomes, reported adverse events ranged from mild (e.g., flatulence) to severe (e.g., leucopenia, major bleeding), but for all the gradable outcomes for which evidence was found, the strength of evidence was judged insufficient primarily due to a lack of power contributing to the possibility of a type II error. Furthermore, very few studies systematically screened for predefined adverse events. With respect to non-gradable harms outcomes, results on benefit of coenzyme Q10 in reducing statin induced myopathic pain were inconclusive. Two pilot trials with small sample sizes reported conflicting results regarding myopathic pain. One of these trials,<sup>89</sup> reported potential benefit of coenzyme (100 mg/day) added to statins (varying types and doses) compared with vitamin E added to statins. The other study,<sup>38</sup> reported no significant differences in reduction of myalgia or number of participants tolerating statin between groups treated with combination of coenzyme Q10 (200 mg/day) or simvastatin (10 to 40 mg/day) alone. In one RCT significantly elevated fasting blood glucose occurred in the omega-3 fatty acids plus statins group versus the statins alone group.<sup>40</sup>

Finally, evidence for interactions between cardiovascular drugs and dietary supplements was sought from studies that assessed for direct changes in drug pharmacokinetics when combined with any of the supplements in question. Gradable pharmacokinetic outcomes included area under the concentration curve (AUC), maximum concentration ( $C_{max}$ ), clearance, and drug half-life. Eleven studies contributed pharmacokinetic evidence, all of which had moderate risk of bias. We found no clear evidence of drug-supplement pharmacokinetic interaction. Evidence was either low or insufficient to rule in or out clinically important pharmacokinetic interactions, or showed no clinically important interactions. The following findings were graded as having low strength of evidence. Coadministration of *Echinacea* with warfarin may reduce the AUC of warfarin with statistical significance, but warfarin was still within the range of clinical bioequivalence. Supplementation with *Ginkgo biloba*, garlic, *Panax ginseng* or ginger extracts in patients taking warfarin does not appear to change measurably any clinically relevant warfarin pharmacokinetics. American ginseng demonstrated a shift in AUC of warfarin; however the clinical significance of this shift is not clear. No pharmacokinetic interaction between *G. biloba* and ticlopidine was identified. Finally interactions between omega-3 fatty acids and statins (rosuvastatin, simvastatin, and atorvastatin) are unclear – while for some important pharmacokinetic outcomes there was evidence of no clinically important interactions (low strength of evidence), others remained inconclusive (insufficient evidence). No studies examined pharmacokinetic interactions between coenzyme Q10, magnesium, niacin (up to 250 mg/day),

red yeast rice extract, resveratrol, vitamin A, vitamin D (with or without calcium supplementation), vitamin E, and vitamin K with any of the cardiovascular drugs.

## **Clinical Context and Applicability of Evidence for Decisionmaking**

The purpose of this review was to synthesise the available evidence regarding the clinical significance of drug interactions between dietary supplements and cardiovascular drugs, in order to provide recommendations for medication management to care providers and patients. Ideally, any such recommendations would arise from the synthesis of studies that evaluate meaningful clinical outcomes in the context of relevant drug interactions. In the absence of studies that provide enough data to make strong recommendations we employed a search for a hierarchy of outcomes including meaningful clinical outcomes (i.e., stroke, myocardial infarction), intermediate or surrogate outcomes (i.e., lipid profile, anticoagulation parameters), harms outcomes (i.e., bleeding, adverse drug effects) and finally, pharmacokinetic evidence of interaction (i.e., changes in AUC, drug clearance). Decision makers should be aware that when a strong recommendation cannot be supported by clinical outcome data, recommendations can still be made with intermediate, harms and pharmacokinetic outcomes but the strength of these recommendations cannot be considered to be equal. The correlation between surrogate and clinical outcomes relies on the clinical rationale that surrogate outcome measures truly predict the clinical outcome. Anticipating that the evidence linking drug interactions to clinical outcomes would be sparse, we were careful to ensure appropriate selection of intermediate, harms and pharmacokinetic outcomes by soliciting expert opinion and a strong clinical rationale for each chosen surrogate outcome. Our findings organised according to this hierarchy is provided in Table 56.

Furthermore, interpretation of this report and assessment of its clinical relevance requires acknowledgment of some of the limitations of the data within. The reader must recognize that dietary supplements in the US are not regulated in the same manner as prescription drugs. This has led to some fundamental barriers to conducting and interpreting clinical research with dietary supplements. Manufacturers of supplements are not held to the same standards as manufacturers of prescription and over-the-counter drugs with respect to providing evidence of efficacy and safety prior to marketing.<sup>109</sup> Dietary supplements do not require FDA approval, nor are there any FDA regulations that require evidence of purity, quality or composition prior to marketing. This has resulted in a lack of standardization of these products among manufacturers and even among products from a single manufacturer. Products that claim to have standardized composition of active ingredients (if known) most often cannot claim standardization of biologic activity. Furthermore, postmarketing assessment of “standardized” herbal preparations often reveal that claims on the product label are not true.<sup>167-170</sup> These products are available in pharmacies, grocery stores, health food stores, and via the internet, and are sold by many different vendors. Lack of manufacturing regulations, and labelling standards may result in significant differences between products, unbeknownst to the consumer, that limit the external validity of clinical trials. In addition to concerns over quality and quantity of active ingredients, concerns over purity can be troubling. Botanical products and herbal remedies can on occasion be contaminated with heavy metals or interact with other medications. If present, this interference puts patients at risk for toxicity and interactions from other substances that otherwise would be attributed to the supplement.<sup>170-173</sup> Finally, there is little reliable, published information regarding the safety of dietary supplements. Until only recently, manufacturers of dietary supplements were not obliged

to report serious adverse events. This represents a gross discrepancy compared with what is required of prescription drugs. Although, the FDA has recently taken steps to make serious adverse event reporting mandatory, most of the data in this report predates that mandate, and even since 2008 when the mandate was put in place, the FDA believes that adverse events are significantly underreported.<sup>174</sup>

**Table 56. Summary and hierarchy of significant findings**

| Strength of Evidence  | Dietary Supplement  | Cardiovascular Drug(s)                            | Outcome                                       | Findings                |
|---|---------------------|---|---|-------------------------|
| <b>Clinical Outcomes – None with strength of evidence “Low” or better</b> |                     |   |   |                         |
| <b>Intermediate Outcomes</b>  |                     |   |   |                         |
| Low   | CoEnzyme Q10        | Fenofibrate                                       | HDL-C   | No additional benefit   |
| Low   | Garlic              | Warfarin  | HDL-C   | In favor of combination |
| Low   | Garlic              | Nitrates  | HDL-C   | In favor of combination |
| Low   | Omega-3 fatty acids | Statins   | HDL-C   | No additional benefit   |
| Low   | Omega-3 fatty acids | Statins   | LDL-C   | No additional benefit   |
| Low   | Omega-3 fatty acids | Statins   | TG  | In favor of combination |
| Low   | Omega-3 fatty acids | Statins   | Systolic blood pressure                       | In favor of combination |
| Low   | Omega-3 fatty acids | Statins   | Diastolic blood pressure                      | No additional benefit   |
| Low   | Omega-3 fatty acids | ACE inhibitors                                    | Systolic blood pressure                       | No additional benefit   |
| Low   | Omega-3 fatty acids | ACE inhibitors                                    | Diastolic blood pressure                      | No additional benefit   |
| Low   | Omega-3 fatty acids | Calcium channel blockers and ASA                  | Triglycerides                                 | In favor of combination |
| Low   | Omega-3 fatty acids | Calcium channel blockers and ASA and dipyridamole | LDL-C   | In favor of combination |
| Low   | Omega-3 fatty acids | Calcium channel blockers and ASA and dipyridamole | Triglycerides                                 | In favor of combination |
| Low   | Vitamin E           | Nifedipine  | LDL-C   | In favor of combination |
| Low   | Vitamin E           | Nifedipine  | Triglycerides                                 | In favor of combination |
| Low   | Vitamin K           | Coumarin derivatives                              | % time in INR therapeutic range               | In favor of combination |
| Low   | Vitamin K           | Coumarin derivatives                              | Variability (SD) of INR                       | In favor of combination |
| Low   | Vitamin K           | Coumarin derivatives                              | N in therapeutic range (INR) 100% of the time | In favor of combination |
| Low   | Vitamin K           | Coumarin derivatives                              | N achieving target INR                        | In favor of combination |
| Low   | Vitamin K           | Coumarin Derivatives                              | N achieving stable INR                        | In favor of combination |

**Table 56. Summary and hierarchy of significant findings (continued)**

| Strength of Evidence   | Dietary Supplement   | Cardiovascular Drug(s)     | Outcome                         | Findings                   |
|--|----------------------|----------------------------|---------------------------------|----------------------------|
| <b>Harms Outcomes</b> – None with strength of evidence “Low” or better |                      |                            |                                 |                            |
| <b>Pharmacokinetic Outcomes</b>  |                      |                            |                                 |                            |
| Low  | <i>Echinacea</i>     | Warfarin                   | AUC, Cmax, Half-life, clearance | No evidence of interaction |
| Low  | Garlic               | Warfarin                   | AUC, half-life, clearance       | No evidence of interaction |
| Low  | Ginger               | Warfarin                   | AUC, Cmax, half-life, clearance | No evidence of interaction |
| Low  | <i>Ginkgo biloba</i> | Ticlopidine                | AUC, half-life, Cmax            | No evidence of interaction |
| Low  | <i>Ginkgo biloba</i> | Warfarin                   | AUC, Cmax, half-life, clearance | No evidence of interaction |
| Low  | Ginseng              | Warfarin                   | Cmax, half-life, clearance      | No evidence of interaction |
| Low  | Omega-3 fatty acids  | Rosuvastatin, Atorvastatin | AUC, Cmax                       | No evidence of interaction |

**Abbreviations:** AUC = area under the curve; Cmax = maximum concentration; HDL-C = high density lipoprotein-cholesterol; INR = International Normalized Ratio; LDL-C = low density lipoprotein cholesterol.

Most of the studies included in this review that measured clinical outcomes provided inconclusive findings, primarily due to limitations in study design (underpowered), and risk of bias (allocation concealment, randomization). The weakness of the evidence itself, and its clinical relevance is compounded by a general lack of evidence on dietary supplement-cardiovascular drug interactions in the literature overall. Ultimately this limited information makes it impossible to translate our findings into clear advice and tools for clinical decision-making. The limited evidence also did not permit an effective dose-response evaluation to distinguish dose thresholds at which interactions may result.

Without an adequate evidence base from the literature, variability in effects across clinically important subgroups (i.e., stratified by age, ethnicity, gender or health status) could not be assessed. The evidence on clinical outcomes was generally inconclusive and applicability of inconclusivity was meaningless. The trials were generally efficacy studies in highly selected cardiovascular populations lasting for a short period of observation, along with some single-dose studies in healthy individuals. Reported benefits or “lack of harm” from studies not powered to assess these outcomes, or those in healthy volunteers may not translate into efficacy or safety in the elderly population with cardiovascular disease. As such we are unfortunately left with the unsatisfying yet fundamentally important call for more research with focused consideration and evaluation of dietary supplement-drug interaction in both clinical and observational studies.

The limit of good clinical outcomes data on which to base recommendations, leads to predicting hypothetical interactions wherein indirect evidence is the most prevalent albeit least reliable information source. The study of pharmacokinetic outcomes and changes in these outcomes are best suited to address this area. However, evidence of pharmacokinetic alterations due to interaction may not translate into altered clinical effectiveness or harms even if well characterized. Pharmacokinetic studies are generally conducted in healthy volunteers and as such the evidence may not reflect the compromised physiologic processes of the elderly and the diseased.

With relatively limited findings given its scope, the value in this review is that it points out the need for further consideration of the question of interactions and comparative effectiveness

for dietary supplements when considered in conjunction with cardiovascular drugs. Aside from further research in the area of dietary supplement-drug interactions, better documentation of supplement use by cardiovascular patients is critical to better define where interactions may result in clinically relevant sequelae.

## Review of Other Systematic Reviews

Recent systematic reviews related to the topic of dietary supplement-drug interactions do not address the same scope, are not comprehensive, or involve different populations of interest. Mills and colleagues published a systematic review in 2005 focused on the effect of natural health products on the metabolism of conventional medicines.<sup>115</sup> Their focus was not cardiovascular drugs or patients in particular, and they described the evidence for dietary supplement–drug interactions for any conventional drug category. The evidence in the review is compiled from 41 pharmacokinetic studies. Mills’ review identified a lack of evidence supporting any interaction between coenzyme Q10 and warfarin, *Ginkgo biloba* and warfarin, and *G. biloba* and digoxin. These findings are consistent with those in our review. Both reviews identified a shift in AUC of INR when American ginseng was taken in conjunction with warfarin; however, we question the clinical significance of this finding.

Also in 2005, Desai and colleagues published a review of interactions between dietary supplements and antiplatelet agents.<sup>175</sup> The review included both clinical trials and case reports. With respect to the dietary supplements considered in our review, Desai concluded that omega-3 fatty acids given in conjunction with aspirin led to comparatively significant reductions in ADP induced platelet aggregation, blood platelet count, thromboxane B2, and restenosis rates, and also led to a prolongation in bleeding time. The addition of vitamin E to aspirin led to comparatively significant reductions in platelet adhesion, ischemic stroke, recurrent episodes of TIA, and prolonged dental bleeding time. Unlike our review, the Desai review did not attempt to grade the outcomes extracted and while findings are largely consistent, the graded evaluation we completed did not allow the same confidence in conclusions regarding the interactions from these agents based on the directness and overall strength of evidence.

In one of the more relevant reviews published by Izzo and colleagues in 2005, Pubmed was searched to Feb 2003 for drug interactions with cardiovascular drugs, and evidence was included from case reports (43 studies) and clinical trials (eight studies).<sup>116</sup> This review did not systematically evaluate the quality of evidence, nor was there any grading of the strength of their recommendations. For example, drug interactions between *Ginkgo*, garlic, and ginseng were identified based on few or single case reports while our review found low or insufficient evidence of any interaction from trials of both direct and indirect evidence. In a 2009 review by Izzo and Ernst, the evidence was again extracted from case reports (41 studies) and clinical studies (17 studies) but did not focus on drug interactions with cardiovascular drugs.<sup>119</sup> None of their 17 clinical studies provided evidence for dietary supplement-cardiovascular drugs within the scope of our review.

Skalli and colleagues published a review in 2007, wherein the majority of evidence for supplement-drug interactions was generated from case reports, and there was no focus on cardiovascular drugs.<sup>176</sup> The authors identified interactions between warfarin and all of the following: ginger; *Ginkgo biloba*; garlic; and ginseng. This was again primarily from single case reports or case series. Our review found no evidence of such interactions from clinical trials providing direct or indirect evidence (insufficient or low levels of evidence). The reviewers also

suggest that *G.biloba* can counteract the effect of thiazide diuretics by increasing blood pressure (based on case report data). We found insufficient evidence to support this claim.

The most recent systematic review on dietary supplement-drug interactions was published in 2010 by Kennedy and Seely, and examined herb-drug interactions identified from trials whereby herbal impact on hepatic metabolism via cytochrome P450 isoenzymes could be ascertained.<sup>121</sup> In this review, the target population was not specific to cardiovascular patients or drugs, and the review evaluated indirect evidence limited to herbs metabolized via the cytochrome P450 system. While the information from this review provides an evaluation of primarily indirect data regarding possible pharmacokinetic interactions, the results do not overlap meaningfully with the findings from our review, which addresses only direct evidence for pharmacokinetic interaction.

## Limitations of the Review

Limitations of our systematic review process include our restriction of the number of dietary supplements of interest to 16 of the most commonly used; this was necessary given limitations of resources and review time. Up to 30 percent of included studies were assessed to have the potential for financial conflict of interest and approximately 45 percent did not report funding information. Given the uncertainties involved in interpreting asymmetry tests for publication bias in most reviews, especially in presence of heterogeneity in effect estimates, we did not plan to investigate publication bias in this review.<sup>102,103</sup> In fact, a recent recommendation is that tests for funnel plot asymmetry should be used only in a minority of meta-analyses including at least ten studies of unequal sizes per analysis without substantial heterogeneity in their effect sizes.<sup>104</sup> However, other means of evaluating publication bias and selective outcome reporting exist, such as comparing publications with study protocol, which we did not adopt because of time and resource limitations. Seemingly, another limitation could be the exclusion of indirect evidence of drug interactions derived from surrogate measures such as alterations in probe drug metabolism, that highlight effects on enzymes involved in drug metabolism.<sup>121</sup> As such, evidence traditionally originates in healthy volunteers; applicability of such evidence would have been as much of a concern as for the pharmacokinetic outcomes we examined, the applicability of which was restricted to healthy volunteers with uncompromised drug metabolism. In order to make causal inferences possible for translation into practice, we also excluded combinations of multiple dietary supplements with cardiovascular drugs. For example, a given combination of multivitamins coadministered with a cardiovascular drug(s) would be limited both in causal inference of supplement-drug(s) interactions and applicability to the specific doses and combinations of vitamins employed as intervention in the study.

Empiric evidence indicates that authors are more likely to report in an international English-language journal if results are positive, while publishing negative findings in German-language literature.<sup>177</sup> We restricted eligibility criteria to English and German language records. We are unsure as to the magnitude (if any) and direction of language bias introduced as a result of excluding Chinese language literature for several reasons. First, traditional Chinese, and Ayurvedic medications, which are often concoctions of many herbs, were not included in this review. Secondly, most reports of randomized controlled trials published in Chinese journals lack an adequate description of randomization, and many non-randomized controlled trials have been published as randomized controlled trials.<sup>178</sup> Thirdly, negative CAM findings are more likely to be published in mainstream medical journals (that is, English-language journals), while positive CAM findings are more likely to be published in CAM journals (which tend to be non-English-language journals).<sup>179</sup> Lastly, there is evidence that countries such as China, Japan,

Russia, and Taiwan publish more CAM studies with positive results than studies with negative results; this imbalance may reflect publication bias.<sup>180</sup>

## Conclusions

With limited data to discern evidence on dietary supplement-drug interactions, it is difficult to provide clear guidance to clinicians and patients regarding advice on the choices to be made in this area. Drug interactions that may result in positive or negative outcomes likely exist, and occur, but the evidence available and identified in this review is insufficient to provide clinical recommendations with confidence. The strength of evidence that we did find was low at best, with poor grading resulting from risks of bias, and small sample sizes greatly increasing the risk of type II error. In addition, the etiology for results are difficult to determine effectively as changes in a measured outcome could be due to either a real therapeutic effect that comes from the dietary supplement itself or be due to an interaction between the drug and the supplement in question.

With these caveats in mind, and the fact that the most reliable data comes from indirect intermediate outcomes associated with clinical results, the following is a summary of the clearer indications of interactions from the evidence reviewed:

- Omega-3 fatty acids (2 to 4 g/day) from fish and/or supplements likely do not interfere with the efficacy of statin therapy or calcium channel blockers in presence of antiplatelet agents, and may provide independent benefit in resolving hypertriglyceridemia.
- Vitamin K (0.1 to 0.15 mg/day) may help to stabilize INR when given with warfarin.
- Garlic (4 to 10 g/day) may not interact negatively with nitrates and warfarin and may confer independent benefit in improving HDL and total cholesterol.

Our confidence, however, in the validity and reproducibility of these findings is low.

## Limitations of the Evidence Base

The literature search applied in this review was comprehensive in exploring multiple sources for human level evidence, yet despite this, there was a decided lack of relevant evidence. The available literature came primarily from small trials of highly selected patients and subjects that limited external validity. While there was data from which we can derive a sense of lack of interaction in many cases, the small size of the trials made it impossible to ascertain the potential for a true clinical interaction. Had the trials been adequately powered, evidence of harm or interaction may have been seen.

The internal validity of most trials was compromised due to flawed designs, lack of appropriate allocation concealment, and risk of bias. There were very few examples where a formal assessment of statistical interaction was completed. One notable exception came from a trial whereby a decrease in triglyceride levels due to combination of omega-3 fatty acids with niacin led to twice the additive effect of the each therapy alone, indicating the possibility for synergy through concurrent use.<sup>78</sup> In the absence of corroborating pharmacokinetic evidence or assessment for interaction, it is often impossible to determine whether a difference in outcome was due to a true pharmacological interaction, or due to more independent combined, or possibly counteracting therapeutic effects. As the goal of this synthesis work was not to complete a comparative effectiveness analysis of dietary supplement versus drugs for cardiovascular disease we did not formally assess for these comparative therapeutic effects.

In terms of the pharmacokinetic evidence assessing Key Question 4, most of the research was conducted on healthy young adults. Thus this level of evidence may not be applicable to older patients taking cardiovascular drugs due to possible differences in metabolism and the existence of comorbidities.

One of the principal limitations of the trials we evaluated was the fact that they were very small and thus susceptible to type II error. A slimly reassuring corollary to this is that if there was a real and dramatic clinical impact due to an interaction then some clinical effect would likely have shown up despite being underpowered for smaller effect sizes. Of greater concern are possible interactions that could arise through polypharmacy of prescription drugs, a situation all too common, in particular for the elderly population.

## Future Research Recommendations

Given the important gap in research in the area of dietary supplement-drug interactions there should be a strategic investment in building research capacity to address relevant questions. With the continued burden of cardiovascular disease in North America, this issue is not going to go away and will likely increase in magnitude if the public continues to increase their use of dietary supplements for self-care.

A focused research strategy regarding dietary supplement-cardiovascular drugs could consider a number of recommendations arising from this review:

1. First and foremost, future research with dietary supplements should involve substances for which the identity of the agents can be clearly ascertained and the chemical composition well characterized, and ideally standardized. If the active ingredients or biologic activity of these substances is not known then studies to characterize these variables, identify mechanisms of action and describe safety should precede clinical efficacy studies. According to the 2011–2015 strategic plan of the National Center for Complementary and Alternative Medicine (NCCAM), clinical trials of dietary supplements will not be supported without documentation of biology and mechanism of action<sup>105</sup>;
2. As extant literature is largely based on few small size efficacy studies of limited internal validity examining intermediate outcomes, future supplement-cardiovascular drug interaction trials should focus on meaningful clinical outcomes, be appropriately powered and rigorously conducted and reported, and provide precise measurements of both clinical effectiveness and harms outcomes;
3. Most studies were conducted in speciality settings, excluded patients with comorbidities, or uncontrolled comorbidities, and did not include ethnic and racial minorities; prospective trials should be representative of the population taking cardiovascular drugs in terms of comorbidities, setting, and racial distribution. They should also collect data and undertake subgroup analysis for age, gender, race, comorbidities (e.g., liver or renal compromise), and genotypic polymorphisms of the cytochrome P450 enzyme;
4. A substantial number of pharmacokinetic interaction studies did not report and analyze pharmacokinetic outcomes as per Food and Drug Administration guidance for bioequivalence studies.<sup>30</sup> As such future experiments of drug interactions must evaluate pharmacokinetic outcomes as geometric mean ratios with predefined margins of bioequivalence. This would help in interpretation of statistically significant and nonsignificant outcomes in terms of clinical significance;



5. Given a dearth of studies examining interactions between specific supplements and cardiovascular drugs, future clinical trials and observational studies that explore the effect of cardiovascular drugs should additionally assess the use of dietary supplements, and include this in the reporting of results. One way to facilitate this would be to consider inclusion of inquiry for dietary supplement use and other CAM care in reporting guidelines such as CONSORT;
6. Phase I trials of cardiovascular drugs should include older populations, and if possible a pharmacokinetic assessment that includes dietary supplement usage;
7. As subgroups were underrepresented in existing studies, future studies investigating supplement-drug interactions should examine vulnerable subgroups such as the elderly, those with compromised renal and liver functions, and patients with multiple comorbidities;
8. Where possible, comparative effectiveness studies should include a statistical analysis for supplement drug interactions, and the trials should be powered accordingly;
9. Until well powered, experimental studies are conducted to examine dietary supplement-drug coadministration, evidence from well-conducted prospective observational studies should be sought. Observational studies compliant with STROBE guidelines should be powered appropriately to address predefined endpoints of both efficacy and safety in a naturalistic setting, where the population sampled is reflective of the population in whom this data would be meaningful;<sup>106</sup> and
10. Given the difficulty and resource intensive nature of clinical trials, other sources of data should be considered to derive information regarding drug-dietary supplement interactions. Possibilities include synthesis of reports of adverse events made to both FDA and the Pharmacovigilance program at Health Canada. In addition, electronic health record linkages between databases of dietary supplement use and cardiovascular drug prescription may also add to the sparse evidence of supplement-cardiovascular drug interaction that currently exist.

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## Appendix A. Search Strategies

Appendix A lists the exact search strings used for each database included in the search of the literature for this review.

### MEDLINE (1950 to September 1, 2011)

1. exp Dietary Supplements/
2. (Neutraceutical\* or Nutraceutical\* or (diet\* adj1 supplement\*) or (nutrition\* adj1 supplement\*) or (food\$1 adj1 supplement\*) or (botanic\* adj1 supplement\*)).ti,ab.
3. exp Vitamins/ or vitamin\$1.ti,ab.
4. exp Minerals/ or exp Calcium/ or exp Chromium/ or exp Copper/ or exp Iron/ or exp Magnesium/ or exp Potassium/ or exp Selenium/ or (mineral\$1 or bone meal or dicalcium or dolomite or chromium or copper or iron or magnesium or potassium or selenium).ti,ab.
5. (diet or diets or dietary or supplement\*).ti,ab. or (dt or tu).fs.
6. (3 or 4) and 5
7. 1 or 2 or 6
8. exp Phytotherapy/
9. exp Plant Preparations/ or exp Plant Extracts/
10. exp Drugs, Chinese Herbal/ or exp Plants, Medicinal/
11. ((medicin\* adj3 herb\$2) or (medicin\* adj3 plant\$1) or (botanical\* adj3 medicin\*) or (botanical\* adj3 drug\$1) or (herb\$2 adj3 drug\$1) or (therapeutic\* adj3 herb\$2) or (therapeutic\* adj3 plant\$1) or (therapeutic\* adj3 botanical\*) or (plant\$1 adj3 pharmacotherap\*) or (plant\$1 adj3 pharmaco-therap\*) or (herb\$2 adj3 pharmacotherap\*) or (herb\$2 adj3 pharmaco-therap\*) or (botanical adj3 pharmacotherap\*) or (botanical adj3 pharmaco-therap\*) or (Chinese adj2 medicin\*) or (Chinese adj2 medicin\*) or (Chinese adj2 drug\$1) or (Chinese adj2 pharmacotherap\*) or (Chinese adj2 pharmaco-therap\*) or phytochemical\* or phyto-chemical\* or phytonutrient\* or phyto-nutrient\* or phytotherap\* or phyto-therap\* or phytomedicin\* or phyto-medicin\*).ti,ab.
12. exp Folic Acid/
13. (folic acid\$1 or folacin or folate or folvite or pteroylglutamic acid or "Vitamin M").ti,ab.
14. exp Glucosamine/ or glucosamin\*.ti,ab.
15. exp Salvia miltiorrhiza/
16. (salvia miltiorrhiza or danshen or horse-racing grass\$2 or rat-tail grass\$2 or red-rooted sage\$1 or red root\$1 or red sage\$1 or red sage root or (root\$1 adj3 purple sage\$1) or scarlet sage\$1).ti,ab.
17. (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or danshensu or fufangdenshen or huang ken or hung ken or pin-ma ts'ao or Radix salviae miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root\$1 or Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or yunzhi-danshen).ti,ab.
18. exp Forskolin/ or (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol).ti,ab.
19. exp Ruscus/ or (butcher\$2 adj broom\$1).ti,ab.
20. exp Cinnamomum zeylanicum/ or (Cinnamomum or Cinnamon\*).ti,ab.
21. exp Taraxacum/ or (Taraxacum or dandelion\* or blowball\$1 or Irish daisy or Irish daisies or (pee adj3 bed) or (lion\* adj2 tooth) or (lion\* adj2 teeth) or (priest\* adj2 crown\$1)).ti,ab.

22. ((Dent adj2 lion\$1) or huang hua di ding or yellow flower earth nail\$1 or puffball\$1 or swine snout\$1).ti,ab.
23. exp Lycium/ or (wolfberr\* or wolf berr\* or gojiberr\* or goji berr\*).ti,ab.
24. exp Echinacea/ or (Echinacea or American coneflower\$1 or purple coneflower\$1 or Rudbeckia purpurea or Black Sampson or combflower\$1 or Kansas snake root\$1 or scurvy root\$1).ti,ab.
25. exp Mentha piperita/ or exp Glycyrrhiza/ or (mentha piperita or peppermint\$1 or glycyrrhiza or licorice\$1 or liquorice\$1).ti,ab.
26. exp Tanacetum parthenium/ or exp Tinospora/ or (Tanacetum parthenium or feverfew or bachelor\* adj button\$1) or featherfew or febrifuge plant\$1 or featherfoil or tinospora or guduchi).ti,ab.
27. Chrysanthemum parthenium.ti,ab.
28. exp Garlic/
29. (garlic or allium or (nectar adj2 god\$1) or pa-se-waa or poor man's treacle or stinking rose\$1).ti,ab.
30. exp Ginkgo biloba/
31. (Ginkgo or Ginkgophyta or Maidenhair Tree\$1 or Maiden Hair Tree\$1 or Fossil Tree\$1 or Duckfoot tree\$1 or Duck foot tree\$1 or Japanese silver apricot\$1 or kew tree\$1 or silver apricot\$1).ti,ab.
32. exp Panax/
33. (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng).ti,ab.
34. (Guggulipid\$1 or guggul\$1 or gugulipid\$1 or gugulu or gugululipid\$1 or guggulsterone\$1 or yogaraj-guggulu).ti,ab.
35. (mukul or myrrh).ti,ab.
36. exp Gymnema/
37. (Gymnema or (Periploca adj3 wood\$1) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi).ti,ab.
38. exp Crataegus/ or (hawthorn\$2 or Crataegus oxycantha or (bread adj2 cheese tree\$1) or cockspur thorn\$1 or Chinese hawthorn\$2 or May bush\$2 or May tree\$1 or May blossom\$1 or May flower\$1 or mayflower\$1 or quickset or thorn-apple tree\$1 or thornapple tree\$1 or white thorn\$1 or whitethorn\$1).ti,ab.
39. exp Convallaria/
40. (Convallaria or (lily adj3 valley) or lady\$2 tears or ladies tears or may lily or may lilies or may bell\$1 or maybell\$1 or conval lily or conval lilies or lily constancy or (ladder\$1 adj2 heaven) or male lily or male lilies).ti,ab.
41. exp Leonurus/
42. (Motherwort\* or Leonorus cardiaca or lion\$2 tail\$1 or lion\$2 ear\$1 or throwwort\*).ti,ab.
43. exp Milk Thistle/
44. (Milk Thistle\$1 or Silybum marianum or Carduus marianus or Holy thistle\$1 or marythistle\$1 or Mary\$2 thistle\$1 or Marian\$2 thistle\$1).ti,ab.
45. exp Rauwolfia/
46. (Rauwolfia or Rauvolfia or Indian snakeroot\$1 or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika).ti,ab.
47. (red yeast rice extract\* or Monascus purpureus or (mould species adj3 rice\$1) or (red adj2 yeast\$1) or (red adj2 rice\$1) or red koji or red leaven\$1).ti,ab.

48. exp Eleutherococcus/
49. (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or devil\$2 shrub\$1).ti,ab.
50. ((Thorny bearer adj2 free) or ussurian thorny pepperbrush\$2 or ussurian thorny pepper brush\$2).ti,ab.
51. exp Hypericum/
52. (Hypericum or John\$2 wort\$1 or Johnswort\$1 or Amber or (touch adj2 heal) or goat weed\$1 or Hardhay\$1 or Klamath weed\$1 or Rosin rose\$1 or Tipton weed\$1 or (balm adj2 warrior\$1)).ti,ab.
53. (Devil\$2 scorge\$1 or goatweed\$1 or klammath weed\$1).ti,ab.
54. exp Curcuma/
55. (Turmeric or curcuma or Indian saffron or Indian yellow root\$1 or Zedoary zedoaria).ti,ab.
56. exp Valerian/
57. (Valerian\* or vandal root\$1 or all-heal\$1 or setwall\$1).ti,ab.
58. exp Selenoproteins/ or Selenoprotein\$1.ti,ab.
59. exp Thioctic Acid/ or (thioctic acid\$1 or Alpha lipoic acid\$1 or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam).ti,ab.
60. ("Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10").ti,ab.
61. exp Fish Oils/
62. (fish adj2 oil\$1).ti,ab.
63. exp Fatty Acids, Omega-3/
64. ("omega 3" or "omega 3s" or omega three\$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA").ti,ab.
65. (Eicosapentanoic acid\$1 or decosahexanoic acid\$1 or alpha linoleic acid\$1).ti,ab.
66. (green tea\$1 or black tea\$1 or Camellia sinensis or Japanese tea\$1 or Matsu-cha tea\$1).ti,ab.
67. exp Phytosterols/
68. (Phytosterol\$1 or plant sterol\$1 or plant stanol\$1 or Beta-sitosterol\$1 or sterolin\$1).ti,ab.
69. exp beta-Glucans/
70. beta-Glucan\$1.ti,ab.
71. exp Kava/
72. (kava or kawa or Piper methysticum).ti,ab.
73. exp Psyllium/
74. (Psyllium or Plantago ovata or flea seed\$1 or fleawort or hemicelluloses or plantago seed\$1 or ispaghula husk\$1 or ispagula husk\$1 or ispaghula seed\$1 or ispagula seed\$1 or Plantago arenaria or Plantago isphagula or Plantago ispagula).ti,ab.
75. exp Soy Foods/
76. (soy or miso or natto or tempeh or tofu).ti,ab.
77. exp Arginine/
78. (Arginine or L-Arginine).ti,ab.

79. (Chia or *Salvia columbariae* or *Salvia hispanica* or salba).ti,ab.
80. exp Chitosan/
81. (Chitin or chitosan or "N-carboxybutyl" or Poliglusam).ti,ab.
82. exp Cynara/
83. (Cynara or globe artichoke\$1 or cardoon\$1).ti,ab.
84. exp Carnitine/
85. (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261).ti,ab.
86. (Pantethine or "Vitamin B5" or bile acid sequestrant\$1 or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid\$1 or sulfopantetheine).ti,ab.
87. (Policosanol\$1 or D003 or hexacontanol\$1 or isopolicosanol\$1 or "Octa-60" or octacosanoic acid\$1 or octacosanol\$1 or ricewax\$2 or winteriser cake\$1 or winterizer cake\$1 or sugar cane policosanol\$1 or sunflower seed policosanol\$1 or triacontanol\* or wheat germ policosanol\$1).ti,ab.
88. exp Withania/ or (*Withania* or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng).ti,ab.
89. exp Aesculus/ or exp Aloe/ or (aesculus or buckeye\$1 or horse chestnut\$1 or conqueror tree\$1 or aloe vera or aloe barbadensis).ti,ab.
90. exp Ginger/ or (ginger or *Zingiber officinale* or Gamma oryzanol).ti,ab.
91. exp Ephedra/ or exp Trigonella/ or (ephedra or ginger trigonella or fenugreek or foenumgraecum or poenumgraecum).ti,ab.
92. (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjisiong).ti,ab.
93. exp Hydrastis/
94. (hydrastis or Golden Seal or Goldenseal).ti,ab.
95. or/7-94
96. exp Functional Food/
97. (functional food\$1 or (therapeutic\* adj2 food\$1)).ti,ab.
98. Citrus paradisi/ or Vaccinium macrocarpon/ or Viburnum/ or Blueberry Plant/ or Punicaceae/
99. (Citrus paradisi or Vaccinium macrocarpon or Viburnum or Punicaceae or blueberr\* or cranberr\* or grapefruit\* or Toronja\* or pomegranate\* or Punica granatum or bitter orange or citrus auranticum or kijitsu or shangzhou zhiqiao or zhi shi).ti,ab.
100. exp beverages/ or (beverage\* or drink\* or juice\* or tea or teas).ti,ab.
101. (98 or 99) and 100
102. exp Plant oils/ or exp Olea/
103. ((botanic\* or plant or plants or vegetable\* or clove or cloves or corn or corns or cottonseed\* or croton\* or olive or olives or safflower\* or sesame\* or soybean\* or teatree\*) and (oil or oils)).ti,ab.
104. Linaceae/ or Flax/ or (Linaceae or flax or flaxseed\* or Linum or linseed\*).ti,ab.
105. exp Dietary Fiber/ or ((diet or diets or dietary) and (fibre or fibres or fiber or fibers or roughage or (wheat adj bran) or cereal\*)).ti,ab.
106. exp Caffeine/ or caffein\*.ti,ab.

107. or/102-106
108. 96 or 97 or 101 or 107
109. 95 or 108
110. exp Cardiovascular diseases/dt
111. exp Adrenergic beta-Antagonists/
112. (Adrenergic adj2 Antagonist\*).ti,ab.
113. ((beta adj1 Adrenergic adj2 block\*) or beta block\*).ti,ab.
114. exp Acebutolol/
115. (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent).ti,ab.
116. exp Betaxolol/
117. (betaxolol or Kerlon or Kerlone).ti,ab.
118. exp Bisoprolol/
119. (bisoprolol or Concor or Concore or Zebeta or Monocor).ti,ab.
120. (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex).ti,ab.
121. exp Labetalol/
122. (labetalol or Labetolol or Normodyne or Trandate).ti,ab.
123. exp Metoprolol/
124. (metoprolol or Betaloc or Betalok or Lopressor or Seloken).ti,ab.
125. exp Nadolol/
126. (nadolol or Corgard or Solgol).ti,ab.
127. (nebivolol or Nebilet or Silostar).ti,ab.
128. exp Pindolol/
129. (pindolol or Visken).ti,ab.
130. exp Propranolol/
131. (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan).ti,ab.
132. exp Sotalol/
133. (sotalol or Darob).ti,ab.
134. exp Timolol/
135. (timolol or Blocadren).ti,ab.
136. exp Calcium Channel Blockers/
137. ((calcium block\* adj2 exogenous) or (calcium antagonist\* adj2 exogenous) or (calcium inhibitor\* adj2 exogenous) or calcium channel block\*).ti,ab.
138. (Dihydropyridine or Lemildipine).ti,ab.
139. exp Amlodipine/
140. (amlodipine or Norvasc or Istin).ti,ab.
141. exp Felodipine/
142. (felodipine or Plendil or Renedil).ti,ab.
143. exp Isradipine/
144. (isradipine or DynaCirc or Lomir or Prescal).ti,ab.
145. exp Nicardipine/
146. (nicardipine or Cardene).ti,ab.
147. exp Nifedipine/
148. (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia).ti,ab.
149. exp Nimodipine/
150. (nimodipine or Nimotop).ti,ab.



151. exp Nisoldipine/
152. (nisoldipine or Sular).ti,ab.
153. exp Diltiazem/
154. (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac).ti,ab.
155. exp Verapamil/
156. (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan).ti,ab.
157. exp Angiotensin-Converting Enzyme Inhibitors/
158. ((Angiotensin-Converting Enzyme adj1 Inhibitor\*) or ACE inhibitor\* or (Angiotensin-Converting Enzyme adj1 antagonist\*).ti,ab.
159. (dipeptidyl carboxypeptidase inhibitor\* or (Kininase II adj2 inhibitor\*) or (Kininase II adj2 antagonist\*).ti,ab.
160. (benazepril or Cibacen or Lotensin).ti,ab.
161. exp Captopril/
162. (captopril or Capoten or Lopirin).ti,ab.
163. exp Enalapril/
164. (enalapril or Renitec or Renitek or Vasotec).ti,ab.
165. exp Fosinopril/
166. (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil).ti,ab.
167. exp Lisinopril/
168. (lisinopril or Lysinopril or Prinivil or Zestril).ti,ab.
169. (moexipril or Perdix or Univasc).ti,ab.
170. exp Perindopril/
171. (perindopril or Aceon or Coversyl or Prestarium).ti,ab.
172. (Quinapril or Accupril).ti,ab.
173. exp Ramipril/
174. (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil).ti,ab.
175. (Trandolapril or Gopten or Mavik or Odrik).ti,ab.
176. (Candesartan or Atacand).ti,ab.
177. (eprosartan or Teveten).ti,ab.
178. (irbesartan or Aprovel or Avapro or Karvea).ti,ab.
179. exp Losartan/
180. (losartan or Cozaar).ti,ab.
181. (olmesartan or Benicar).ti,ab.
182. (telmisartan or Micardis or Pritor).ti,ab.
183. (valsartan or Diovan).ti,ab.
184. ((Renin adj1 Inhibit\*) or Renin antagonist\*).ti,ab.
185. (Aliskiren or Tekturna).ti,ab.
186. aldosterone receptor antagonist\$1.ti,ab.
187. (Eplerenone or Inspra).ti,ab.
188. exp Spironolactone/
189. (Spironolactone or Aldactone or Verospirone).ti,ab.
190. exp Vasodilator Agents/
191. Vasodilator\$1.ti,ab.
192. exp Clonidine/
193. (clonidine or Apo-Clonidine or Catapres or Duraclon).ti,ab.

194. exp Guanabenz/
195. (guanabenz or Wytensin).ti,ab.
196. exp Guanfacine/
197. (guanfacine or Intuniv or Tenex).ti,ab.
198. exp Methyldopa/
199. (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt).ti,ab.
200. exp Diazoxide/
201. (Diazoxide or Hyperstat or Proglycem).ti,ab.
202. exp Hydralazine/
203. (Hydralazine or Apo-Hydralazine or Apresoline or Dralzine).ti,ab.
204. exp Minoxidil/
205. (minoxidil or Loniten).ti,ab.
206. exp Isosorbide Dinitrate/
207. (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate).ti,ab.
208. exp Nitroglycerin/
209. (nitroglycerin\$1 or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch).ti,ab.
210. exp Phosphodiesterase inhibitors/
211. ((Phosphodiesterase adj1 Inhibit\*) or (Phosphodiesterase adj1 antagonist\*) or Antiphosphodiesterase\$1 or Anti-phosphodiesterase\$1 or (Phosphoric Diester Hydrolase adj1 Inhibit\*) or (Phosphoric Diester Hydrolase adj1 antagonist\*)).ti,ab.
212. (sildenafil or Revatio or tadalafil or vardenafil).ti,ab.
213. (Cilostazol or Pletal).ti,ab.
214. exp Alprostadil/
215. Alprostadil.ti,ab.
216. exp Epoprostenol/
217. (Epoprostenol or Flolan).ti,ab.
218. exp iloprost/
219. (iloprost or Ciloprost or Ventavis).ti,ab.
220. (Endothelin antagonist\$1 or (Endothelin adj1 inhibit\*)).ti,ab.
221. (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis).ti,ab.
222. exp Papaverine/
223. papaverine.ti,ab.
224. exp Isoxsuprine/
225. (isoxsuprine or Duvadilan).ti,ab.
226. exp Adrenergic alpha-Antagonists/
227. ((alpha-Adrenergic adj2 block\*) or (Adrenergic alpha adj2 block\*) or (alpha-Adrenergic adj2 antagonist\*) or (Adrenergic alpha adj2 antagonist\*) or (alpha block\* adj2 adrenergic) or (alpha antagonist\* adj2 adrenergic)).ti,ab.
228. exp Doxazosin/
229. (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progandol).ti,ab.
230. exp Prazosin/
231. (prazosin or Minipress or Furazosin or Pratsiol).ti,ab.

232. (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol).ti,ab.
233. exp Anti-Arrhythmia Agents/
234. ((Anti-Arrhythmia or Anti-Arrhythmic\* or Antiarrhythmia or Antiarrhythmic\* or Anti-fibrillatory or Antifibrillatory) and (drug or drugs or agent or agents or medication\* or prescription\*)).ti,ab.
235. exp Disopyramide/
236. (disopyramide or Norpace or Rhythmodan).ti,ab.
237. exp Procainamide/
238. (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid).ti,ab.
239. exp Quinidine/
240. (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora).ti,ab.
241. exp Mexiletine/ or Mexiletine.ti,ab.
242. exp Encainide/
243. (encainide or Enkaid).ti,ab.
244. exp Flecainide/
245. (Flecainide or Tambocor).ti,ab.
246. exp Propafenone/
247. (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm).ti,ab.
248. exp Amiodarone/
249. (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex).ti,ab.
250. (dofetilide or Tikosyn).ti,ab.
251. (dronedarone or Multaq).ti,ab.
252. exp Cardiotonic Agents/
253. ((Cardiotonic or Cardioprotective or Cardio-tonic or Cardio-protective) and (drug or drugs or agent or agents or medication\$1 or prescription\$1)).ti,ab.
254. (cardiotonics or cardio-tonics or cardiac stimulant\* or myocardial stimulant\* or inotropic agent\*).ti,ab.
255. exp Digoxin/
256. (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin).ti,ab.
257. exp Antilipemic Agents/
258. (Antilipemic\$1 or anti-lipemic\$1 or hypolipidemic\$1 or hypo-lipidemic\$1).ti,ab.
259. ((Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic) and (drug or drugs or agent or agents or medication\* or prescription\*)).ti,ab.
260. (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics).ti,ab.
261. exp Cholestyramine Resin/
262. (cholestyramin\$1 or colestyramin\$1 or Cuemid or Quantalan or Questran).ti,ab.
263. exp Colestipol/
264. (colestipol or Colestid).ti,ab.
265. (colesevelam or CholestaGel or Welchol).ti,ab.

266. (Bile acid sequestrant\$1 or bile acid-binding drug\$1 or bile acid-binding agent\$1).ti,ab.
267. (Anticholesteremic\$1 or Hypocholesteremic\$1 or (cholesterol adj2 inhibitor\$1) or cholesterol-lowering drug\$1 or cholesterol-lowering agent\$1 or cholesterol-lowering medication\$1).ti,ab.
268. (ezetimibe or Zetia).ti,ab.
269. (fenofibrate or Antara or Fenoglide or Fibracor or Lipofen or Lofibra or TriCor or Triglide or Trilipix).ti,ab.
270. exp Gemfibrozil/
271. (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin).ti,ab.
272. ((Hydroxymethylglutaryl-CoA Reductase adj1 inhibit\*) or (HMG-CoA Reductase adj1 inhibit\*) or (Hydroxymethylglutaryl-CoA adj1 inhibit\$) or (Hydroxymethylglutaryl-Coenzyme A adj1 inhibit\$)).ti,ab.
273. (atorvastatin or Liptor).ti,ab.
274. (fluvastatin or Lescol).ti,ab.
275. exp Lovastatin/
276. (lovastatin or Altacor or Altoprev or Mevacor).ti,ab.
277. exp Pravastatin/
278. (pravastatin or Apo-Pravastatin or Lipostat or Pravasin\$1 or Pravachol or Selektine).ti,ab.
279. (rosuvastatin or Crestor).ti,ab.
280. exp Simvastatin/
281. (simvastatin or Synvinolin or Zocor).ti,ab.
282. exp Niacin/
283. (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinx or Slo-Niacin).ti,ab.
284. exp Anticoagulants/
285. (Anticoagulant\$1 or anti-coagulant\$1 or bloodthinn\* or blood-thinn\*).ti,ab.
286. exp Warfarin/
287. (warfarin or Apo-Warfarin or Coumadin\$1).ti,ab.
288. exp Dalteparin/
289. (dalteparin or Fragmin\$1).ti,ab.
290. exp Heparin/
291. heparin.ti,ab.
292. (tinzaparin or Innohep).ti,ab.
293. exp Platelet Aggregation Inhibitors/
294. (antithrombocytic\* or anti-thrombocytic\* or (platelet\$1 adj2 inhibit\*) or Antiplatelet\$1 or Anti-platelet\$1 or Platelet Antagonist\$1 or Platelet Antiaggregant\$1).ti,ab.
295. exp Aspirin/
296. (Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).ti,ab.
297. exp Ticlopidine/
298. (ticlopidine or Ticlid).ti,ab.
299. (clopidogrel or Plavix).ti,ab.
300. exp Diuretics/
301. (diuretic\$1 or water pill\$1).ti,ab.

- 302. exp Bumetanide/
- 303. (Bumetanide or bumex).ti,ab.
- 304. exp Ethacrynic Acid/
- 305. (etacrynic acid or ethacrynic acid or Edecrin).ti,ab.
- 306. exp Furosemide/
- 307. (furosemide or Errolon or Fursemide or Fusid or Lasix).ti,ab.
- 308. (torsemide or Demadex or torasemide).ti,ab.
- 309. (k-sparing or potassium-sparing).ti,ab.
- 310. exp Amiloride/
- 311. (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide).ti,ab.
- 312. exp Triamterene/
- 313. (triamterene or Dyrenium).ti,ab.
- 314. thiazide diuretic\$.ti,ab.
- 315. exp Bendroflumethiazide/
- 316. (Bendroflumethiazide or Bendrofluazide).ti,ab.
- 317. exp Chlorothiazide/
- 318. (chlorothiazide or Chlotride or Diuril).ti,ab.
- 319. exp Hydrochlorothiazide/
- 320. (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic).ti,ab.
- 321. exp Methyclothiazide/
- 322. (methyclothiazide or Aquatensen or Enduron).ti,ab.
- 323. exp Polythiazide/
- 324. (polythiazide or Renese).ti,ab.
- 325. exp Chlorthalidone/
- 326. (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone).ti,ab.
- 327. exp Indapamide/
- 328. (indapamide or Lozol or Metindamide).ti,ab.
- 329. exp Metolazone/
- 330. (metolazone or Mykrox or Zaroxolyn or Zytanix).ti,ab.
- 331. or/110-330
- 332. exp Herb-Drug Interactions/
- 333. exp Food-Drug Interactions/
- 334. exp Drug Synergism/
- 335. ad.fs.
- 336. ct.fs.
- 337. de.fs.
- 338. me.fs.
- 339. pk.fs.
- 340. to.fs.
- 341. ci.fs.
- 342. (interact\* or react\* or contraindicat\* or contra-indicat\* or chemically induce\* or enhanc\* or potentiat\* or synergis\* or toxic or toxicit\*).ti,ab.
- 343. or/332-342
- 344. 109 and 331 and 343

345. limit 344 to human
346. limit 344 to ("in data review" or "in process" or "pubmednotmedline")
347. 345 or 346
348. limit 347 to "reviews (specificity)"
349. meta analysis.pt.
350. exp meta-analysis as topic/
351. (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).ti,ab.
352. (systematic review\* or systematic overview\* or technology assessment\* or HTA or HTAs).ti,ab.
353. exp Technology assessment, biomedical/
354. health technology assessment winchester england.jn.
355. (evidence report technology assessment or evidence report technology assessment summary).jn.
356. or/349-355
357. 347 and 356
358. 348 or 357
359. (controlled clinical trial or randomized controlled trial).pt.
360. exp randomized controlled trials as topic/ or exp controlled clinical trials as topic/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp placebos/
361. "controlled clinical trial".ti,ab.
362. (random\* or RCT\$1 or placebo\*).ti,ab.
363. ((singl\* or doubl\* or trebl\* or tripl\*) and (mask\* or blind\* or dumm\*)).ti,ab.
364. or/359-363
365. 347 and 364
366. 365 not 358
367. clinical trial.pt.
368. exp Clinical Trials as Topic/
369. "clinical trial".ti,ab.
370. evaluation studies.pt.
371. exp Evaluation Studies as Topic/
372. (volunteer or volunteers or open label\* or nonrandom\* or non random\* or quasirandom\* or quasi-random\*).ti,ab.
373. exp Cohort Studies/ or exp Longitudinal Studies/ or exp Prospective Studies/ or exp Follow-Up Studies/ or exp Retrospective Studies/ or exp Case-Control Studies/
374. (cohort or cohorts or longitudinal or prospective or retrospective).ti,ab.
375. ((observational or follow-up or followup) adj stud\*).ti,ab.
376. (population-based stud\* or population-based analys\* or population stud\* or population analys\*).ti,ab.
377. ((descriptive adj stud\*) or (multidimensional adj stud\*) or (multi-dimensional adj stud\*) or (multicenter adj stud\*) or (multi-center adj stud\*) or (multicentr\* adj stud\*) or (multi-centr\* adj stud\*)).ti,ab.
378. exp Multicenter Study/ or exp Multicenter Studies as Topic/
379. Comparative Study.pt.

380. ((comparative adj study) or (comparative adj studies) or (case adj control\*) or "case series" or (case adj comparison\*) or (case adj history) or (case adj histories)).ti,ab.

381. or/367-380

382. 347 and 381

383. 382 not (358 or 365)

384. (ae or co or mo).fs.

385. exp Harm Reduction/ or exp Intraoperative Complications/ or exp Morbidity/ or exp Mortality/ or exp Postoperative Complications/ or exp Risk/ or exp Safety/ or exp Treatment Outcome/ or exp Teratogens/ or exp Abnormalities, Drug-Induced/

386. (adverse or complication\* or harm or harms or harmful or harming or injurious or morbidit\* or mortalit\* or risk\$1 or side effect\$1 or undersirable or tolerability or teratogen\* or safety).ti,ab.

387. or/384-386

388. 347 and 387

389. 388 not (358 or 365 or 382)

## **AMED (1985 to September 1, 2011)**

1. exp Dietary supplements/

2. (Neutraceutical\* or Nutraceutical\* or (diet\* adj1 supplement\*) or (nutrition\* adj1 supplement\*) or (food\$1 adj1 supplement\*) or (botanic\* adj1 supplement\*)).ti,ab.

3. exp Vitamins/ or vitamin\$1.ti,ab.

4. exp Minerals/ or exp Calcium/ or exp Chromium/ or exp Copper/ or exp Iron/ or exp Magnesium/ or exp Potassium/ or exp Selenium/ or (mineral\$1 or bone meal or dicalcium or dolomite or chromium or copper or iron or magnesium or potassium or selenium).ti,ab.

5. (diet or diets or dietary or supplement\*).ti,ab.

6. (3 or 4) and 5

7. 1 or 2 or 6

8. exp Phytotherapy/

9. exp plant extracts/ or exp plants medicinal/ or exp Herbal Drugs/

10. ((medicin\* adj3 herb\$2) or (medicin\* adj3 plant\$1) or (botanical\* adj3 medicin\*) or (botanical\* adj3 drug\$1) or (herb\$2 adj3 drug\$1) or (therapeutic\* adj3 herb\$2) or (therapeutic\* adj3 plant\$1) or (therapeutic\* adj3 botanical\*) or (plant\$1 adj3 pharmacotherap\*) or (plant\$1 adj3 pharmaco-therap\*) or (herb\$2 adj3 pharmacotherap\*) or (herb\$2 adj3 pharmaco-therap\*) or (botanical adj3 pharmacotherap\*) or (botanical adj3 pharmaco-therap\*) or (Chinese adj2 medicin\*) or (Chinese adj2 medicin\*) or (Chinese adj2 drug\$1) or (Chinese adj2 pharmacotherap\*) or (Chinese adj2 pharmaco-therap\*) or phytochemical\* or phyto-chemical\* or phytonutrient\* or phyto-nutrient\* or phytotherap\* or phyto-therap\* or phytomedicin\* or phyto-medicin\*).ti,ab.

11. exp Folic Acid/

12. (folic acid\$1 or folacin or folate or folvite or pteroylglutamic acid or "Vitamin M").ti,ab.

13. Glucosamin\*.ti,ab.

14. exp Salvia/

15. (salvia miltiorrhiza or danshen or horse-racing grass\$2 or rat-tail grass\$2 or red-rooted sage\$1 or red root\$1 or red sage\$1 or red sage root or (root\$1 adj3 purple sage\$1) or scarlet sage\$1).ti,ab.

16. (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or danshensu or fufangdenshen or huang ken or hung ken or pin-ma ts'ao or Radix salviae miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root\$1 or Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or yunzhi-danshen).ti,ab.
17. (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol).ti,ab.
18. (ruscus or (butcher\$2 adj broom\$1)).ti,ab.
19. exp Cinnamomum/ or (Cinnamomum or Cinnamon\*).ti,ab.
20. exp Taraxacum/ or (Taraxacum or dandelion\* or blowball\$1 or Irish daisy or Irish daisies or (pee adj3 bed) or (lion\* adj2 tooth) or (lion\* adj2 teeth) or (priest\* adj2 crown\$1)).ti,ab.
21. ((Dent adj2 lion\$1) or huang hua di ding or yellow flower earth nail\$1 or puffball\$1 or swine snout\$1).ti,ab.
22. exp Lycium/ or (lycium or wolfberr\* or wolf berr\* or gojiberr\* or goji berr\*).ti,ab.
23. exp Echinacea/ or (Echinacea or American coneflower\$1 or purple coneflower\$1 or Rudbeckia purpurea or Black Sampson or combflower\$1 or Kansas snake root\$1 or scurvy root\$1).ti,ab.
24. exp Mentha piperita/ or exp Glycyrrhiza/ or (mentha piperita or peppermint\$1 or glycyrrhiza or licorice\$1 or liquorice\$1).ti,ab.
25. exp Tanacetum parthenium/ or (Tanacetum parthenium or feverfew or (bachelor'\* adj button\$1) or featherfew or febrifuge plant\$1 or featherfoil or tinospora or guduchi).ti,ab.
26. Chrysanthemum parthenium.ti,ab.
27. exp Allium sativum/
28. (garlic or allium or (nectar adj2 god\$1) or pa-se-waa or poor man's treacle or stinking rose\$1).ti,ab.
29. exp Ginkgo biloba/
30. (Ginkgo or Ginkgophyta or Maidenhair Tree\$1 or Maiden Hair Tree\$1 or Fossil Tree\$1 or Duckfoot tree\$1 or Duck foot tree\$1 or Japanese silver apricot\$1 or kew tree\$1 or silver apricot\$1).ti,ab.
31. exp Panax/
32. (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng).ti,ab.
33. (Guggulipid\$1 or guggul\$1 or gugulipid\$1 or gugulu or guggululipid\$1 or guggulsterone\$1 or yogaraj-guggulu).ti,ab.
34. (mukul or myrrh).ti,ab.
35. (((Gymnema or Periploca) adj3 wood\$1) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi).ti,ab.
36. (hawthorn\$2 or Crataegus oxycantha or (bread adj2 cheese tree\$1) or cockspur thorn\$1 or Chinese hawthorn\$2 or May bush\$2 or May tree\$1 or May blossom\$1 or May flower\$1 or mayflower\$1 or quickset or thorn-apple tree\$1 or thornapple tree\$1 or white thorn\$1 or whitethorn\$1).ti,ab.
37. (Convallaria or (lily adj3 valley) or lady\$2 tears or ladies tears or may lily or may lilies or may bell\$1 or maybell\$1 or conval lily or conval lilies or lily constancy or (ladder\$1 adj2 heaven) or male lily or male lilies).ti,ab.
38. exp Leonurus/
39. (Motherwort\* or Leonorus cardiaca or lion\$2 tail\$1 or lion\$2 ear\$1 or throwwort\*).ti,ab.
40. exp Milk thistle/



41. (Milk Thistle\$1 or Silybum marianum or Carduus marianus or Holy thistle\$1 or marythistle\$1 or Mary\$2 thistle\$1 or Marian\$2 thistle\$1).ti,ab.
42. (Rauwolfia or Rauvolfia or Indian snakeroot\$1 or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika).ti,ab.
43. (red yeast rice extract\* or Monascus purpureus or (mould species adj3 rice\$1) or (red adj2 yeast\$1) or (red adj2 rice\$1) or red koji or red leaven\$1).ti,ab.
44. exp eleutherococcus senticosus/
45. (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or devil\$2 shrub\$1).ti,ab.
46. ((Thorny bearer adj2 free) or ussurian thorny pepperbrush\$2 or ussurian thorny pepper brush\$2).ti,ab.
47. exp Hypericum/
48. (Hypericum or John\$2 wort\$1 or Johnswort\$1 or Amber or (touch adj2 heal) or goat weed\$1 or Hardhay\$1 or Klamath weed\$1 or Rosin rose\$1 or Tipton weed\$1 or (balm adj2 warrior\$1)).ti,ab.
49. (Devil\$2 scorge\$1 or goatweed\$1 or klammath weed\$1).ti,ab.
50. exp Curcuma/
51. (Turmeric or curcuma or Indian saffron or Indian yellow root\$1 or Zedoary zedoaria).ti,ab.
52. (Valerian\* or vandal root\$1 or all-heal\$1 or setwall\$1).ti,ab.
53. Selenoprotein\$1.ti,ab.
54. (thioctic acid\$1 or Alpha lipoic acid\$1 or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam).ti,ab.
55. ("Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10").ti,ab.
56. exp Fish Oils/
57. (fish adj2 oil\$1).ti,ab.
58. ("omega 3" or "omega 3s" or omega three\$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA").ti,ab.
59. (Eicosapentanoic acid\$1 or decosahexanoic acid\$1 or alpha linoleic acid\$1).ti,ab.
60. (green tea\$1 or black tea\$1 or Camellia sinensis or Japanese tea\$1 or Matsu-cha tea\$1).ti,ab.
61. (Phytosterol\$1 or Plant sterol\$1 or Plant stanol\$1 or Beta-sitosterol\$1 or sterolin\$1).ti,ab.
62. beta-Glucan\$1.ti,ab.
63. exp Kava/
64. (kava or kawa or Piper methysticum).ti,ab.
65. (Psyllium or Plantago ovata or flea seed\$1 or fleawort or hemicelluloses or plantago seed\$1 or ispaghula husk\$1 or ispagula husk\$1 or ispaghula seed\$1 or ispagula seed\$1 or Plantago arenaria or Plantago isphagula or Plantago ispagula).ti,ab.
66. exp soy foods/
67. (soy or miso or natto or tempeh or tofu).ti,ab.
68. (Arginine or L-Arginine).ti,ab.

69. (Chia or *Salvia columbariae* or *Salvia hispanica* or salba).ti,ab.
70. (Chitin or chitosan or "N-carboxybutyl" or Poliglusam).ti,ab.
71. exp Cynara/
72. (Cynara or globe artichoke\$1 or cardoon\$1).ti,ab.
73. exp Carnitine/
74. (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261).ti,ab.
75. (Pantethine or "Vitamin B5" or bile acid sequestrant\$1 or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid\$1 or sulfopantetheine).ti,ab.
76. (Policosanol\$1 or D003 or hexacontanol\$1 or isopolicosanol\$1 or "Octa-60" or octacosanoic acid\$1 or octacosanol\$1 or ricewax\$2 or winteriser cake\$1 or winterizer cake\$1 or sugar cane policosanol\$1 or sunflower seed policosanol\$1 or triacontanol\$1 or wheat germ policosanol\$1).ti,ab.
77. exp Withania/
78. (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng).ti,ab.
79. exp Aloe/ or (aesculus or buckeye\$1 or horse chestnut\$1 or conqueror tree\$1 or aloe vera or aloe barbadensis).ti,ab.
80. (ginger or *Zingiber officinale* or Gamma oryzanol).ti,ab.
81. exp Ephedra/ or exp Trigonella/ or (ephedra or trigonella or fenugreek or foenumgraecum or poenumgraecum).ti,ab.
82. (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjisiong).ti,ab.
83. exp Hydrastis/
84. (hydrastis or Golden Seal or Goldenseal).ti,ab.
85. or/7-84
86. ((functional adj food\$1) or (therapeutic\* adj food\$1)).ti,ab.
87. ((Citrus adj paradisi) or (*Vaccinium* adj macrocarpon) or *Viburnum* or Punicaceae or blueberr\* or cranberr\* or grapefruit\* or Toronja\* or pomegranate\* or (*Punica* adj granatum) or (bitter adj orange) or (citrus adj auranticum) or kijitsu or (shangzhou adj zhiqiao) or (zhi adj shi)).ti,ab.
88. exp beverages/ or (beverage\* or drink\* or juice\* or tea or teas).ti,ab.
89. 87 and 88
90. exp Plant oils/
91. exp Olea/
92. ((botanic\* or plant or plants or vegetable\* or clove or cloves or corn or corns or cottonseed\* or croton\* or olive or olives or safflower\* or sesame\* or soybean\* or teatree\*) and (oil or oils)).ti,ab.
93. (Linaceae or flax or flaxseed\* or *Linum* or linseed\*).ti,ab.
94. exp Dietary fiber/
95. ((diet or diets or dietary) and (fibre or fibres or fiber or fibers or roughage or (wheat adj bran) or cereal\*)).ti,ab.
96. exp Caffeine/ or caffein\*.ti,ab.

97. (or/89-96) or 85 or 86
98. exp cardiovascular disease/ and exp drug therapy/
99. (Adrenergic adj2 Antagonist\*).ti,ab.
100. ((beta adj1 Adrenergic adj2 block\*) or beta block\*).ti,ab.
101. (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebulalol or Sectral or Prent).ti,ab.
102. (betaxolol or Kerlon or Kerlone).ti,ab.
103. (bisoprolol or Concor or Concore or Zebeta or Monocor).ti,ab.
104. (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex).ti,ab.
105. (labetalol or Labetolol or Normodyne or Trandate).ti,ab.
106. (metoprolol or Betaloc or Betalok or Lopressor or Seloken).ti,ab.
107. (nadolol or Corgard or Solgol).ti,ab.
108. (nebivolol or Nebilet or Silostar).ti,ab.
109. (pindolol or Visken).ti,ab.
110. (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan).ti,ab.
111. (sotalol or Darob).ti,ab.
112. (timolol or Blocadren).ti,ab.
113. exp Calcium channel blockers/
114. ((calcium block\* adj2 exogenous) or (calcium antagonist\* adj2 exogenous) or (calcium inhibitor\* adj2 exogenous) or calcium channel block\*).ti,ab.
115. (Dihydropyridine or Lemildipine).ti,ab.
116. (amlodipine or Norvasc or Istin).ti,ab.
117. (felodipine or Plendil or Renedil).ti,ab.
118. (isradipine or DynaCirc or Lomir or Prescal).ti,ab.
119. (nicardipine or Cardene).ti,ab.
120. (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia).ti,ab.
121. (nimodipine or Nimotop).ti,ab.
122. (nisoldipine or Sular).ti,ab.
123. (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac).ti,ab.
124. (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan).ti,ab.
125. exp enzyme inhibitors/
126. ((Angiotensin-Converting Enzyme adj1 Inhibitor\*) or ACE inhibitor\* or (Angiotensin-Converting Enzyme adj1 antagonist\*).ti,ab.
127. (dipeptidyl carboxypeptidase inhibitor\* or (Kininase II adj2 inhibitor\*) or (Kininase II adj2 antagonist\*).ti,ab.
128. (benazepril or Cibacen or Lotensin).ti,ab.
129. (captopril or Capoten or Lopirin).ti,ab.
130. (enalapril or Renitec or Renitek or Vasotec).ti,ab.
131. (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil).ti,ab.
132. (lisinopril or Lysinopril or Prinivil or Zestril).ti,ab.
133. (moexipril or Perdix or Univasc).ti,ab.
134. (perindopril or Aceon or Coversyl or Prestarium).ti,ab.
135. (Quinapril or Accupril).ti,ab.
136. (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil).ti,ab.
137. (Trandolapril or Gopten or Mavik or Odrik).ti,ab.

138. (Candesartan or Atacand).ti,ab.
139. (eprosartan or Teveten).ti,ab.
140. (irbesartan or Aprovel or Avapro or Karvea).ti,ab.
141. (losartan or Cozaar).ti,ab.
142. (olmesartan or Benicar).ti,ab.
143. (telmisartan or Micardis or Pritor).ti,ab.
144. (valsartan or Diovan).ti,ab.
145. ((Renin adj Inhibit\*) or Renin antagonist\*).ti,ab.
146. (Aliskiren or Tekturna).ti,ab.
147. aldosterone receptor antagonist\$1.ti,ab.
148. (Eplerenone or Inspra).ti,ab.
149. (Spironolactone or Aldactone or Verospirone).ti,ab.
150. exp Vasodilator agents/
151. Vasodilator\$1.ti,ab.
152. exp Clonidine/
153. (clonidine or Apo-Clonidine or Catapres or Duraclon).ti,ab.
154. (guanabenz or Wytensin).ti,ab.
155. (guanfacine or Intuniv or Tenex).ti,ab.
156. (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt).ti,ab.
157. (Diazoxide or Hyperstat or Proglycem).ti,ab.
158. (Hydralazine or Apo-Hydralazine or Apresoline or Dralzine).ti,ab.
159. (minoxidil or Loniten).ti,ab.
160. (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate).ti,ab.
161. (nitroglycerin\$1 or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch).ti,ab.
162. ((Phosphodiesterase adj1 Inhibit\*) or (Phosphodiesterase adj1 antagonist\*) or Antiphosphodiesterase\$1 or Anti-phosphodiesterase\$1 or (Phosphoric Diester Hydrolase adj1 Inhibit\*) or (Phosphoric Diester Hydrolase adj1 antagonist\*)).ti,ab.
163. (sildenafil or Revatio or tadalafil or vardenafil).ti,ab.
164. (Cilostazol or Pletal).ti,ab.
165. Alprostadil.ti,ab.
166. (Epoprostenol or Flolan).ti,ab.
167. (iloprost or Ciloprost or Ventavis).ti,ab.
168. (Endothelin antagonist\$1 or (Endothelin adj1 inhibit\*)).ti,ab.
169. (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis).ti,ab.
170. papaverine.ti,ab.
171. (isoxsuprine or Duvadilan).ti,ab.
172. ((alpha-Adrenergic adj2 block\*) or (Adrenergic alpha adj2 block\*) or (alpha-Adrenergic adj2 antagonist\*) or (Adrenergic alpha adj2 antagonist\*) or (alpha block\* adj2 adrenergic) or (alpha antagonist\* adj2 adrenergic)).ti,ab.
173. (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Progangdol).ti,ab.
174. (prazosin or Minipress or Furazosin or Pratsiol).ti,ab.

175. (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnurol).ti,ab.
176. ((Anti-Arrhythmia or Anti-Arrhythmic\* or Antiarrhythmia or Antiarrhythmic\* or Anti-fibrillatory or Antifibrillatory) and (drug or drugs or agent or agents or medication\* or prescription\*)).ti,ab.
177. (disopyramide or Norpace or Rhythmodan).ti,ab.
178. (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid).ti,ab.
179. (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora).ti,ab.
180. Mexiletine.ti,ab.
181. (encainide or Enkaid).ti,ab.
182. (Flecainide or Tambocor).ti,ab.
183. (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm).ti,ab.
184. (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex).ti,ab.
185. (dofetilide or Tikosyn).ti,ab.
186. (dronedarone or Multaq).ti,ab.
187. exp Cardiotoxic agents/
188. ((Cardiotoxic or Cardioprotective or Cardio-tonic or Cardio-protective) and (drug or drugs or agent or agents or medication\$1 or prescription\$1)).ti,ab.
189. (cardiotonics or cardio-tonics or cardiac stimulant\* or myocardial stimulant\* or inotropic agent\*).ti,ab.
190. exp Digoxin/
191. (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin).ti,ab.
192. exp Antilipemic agents/
193. (Antilipemic\$1 or anti-lipemic\$1 or hypolipidemic\$1 or hypo-lipidemic\$1).ti,ab.
194. ((Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic) and (drug or drugs or agent or agents or medication\* or prescription\*)).ti,ab.
195. (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics).ti,ab.
196. (cholestyramin\$1 or colestyramin\$1 or Cuemid or Quantalan or Questran).ti,ab.
197. (colestipol or Colestid).ti,ab.
198. (colesevelam or CholestaGel or Welchol).ti,ab.
199. (Bile acid sequestrant\$1 or bile acid-binding drug\$1 or bile acid-binding agent\$1).ti,ab.
200. (Anticholesteremic\$1 or Hypocholesteremic\$1 or (cholesterol adj2 inhibitor\$1) or cholesterol-lowering drug\$1 or cholesterol-lowering agent\$1 or cholesterol-lowering medication\$1).ti,ab.
201. (ezetimibe or Zetia).ti,ab.
202. (fenofibrate or Antara or Fenoglide or Fibracor or Lipofen or Lofibra or TriCor or Triglide or Trilipix).ti,ab.
203. (Gemfibrozil or Apo-Gemfibrozil or Lopid or Trialmin).ti,ab.

204. ((Hydroxymethylglutaryl-CoA Reductase adj1 inhibit\*) or (HMG-CoA Reductase adj1 inhibit\*) or (Hydroxymethylglutaryl-CoA adj1 inhibit\$) or (Hydroxymethylglutaryl-Coenzyme A adj1 inhibit\$)).ti,ab.
205. (atorvastatin or Liptor).ti,ab.
206. (fluvastatin or Lescol).ti,ab.
207. (lovastatin or Altacor or Altoprev or Mevacor).ti,ab.
208. (pravastatin or Apo-Pravastatin or Lipostat or Pravasin\$1 or Pravachol or Selektine).ti,ab.
209. (rosuvastatin or Crestor).ti,ab.
210. (simvastatin or Synvinolin or Zocor).ti,ab.
211. exp Niacin/
212. (niacin or Niacor or Niaspan or Nicobid or Nicoliar or Nicotinx or Slo-Niacin).ti,ab.
213. exp Anticoagulants/
214. (Anticoagulant\$1 or anti-coagulant\$1 or bloodthinn\* or blood-thinn\*).ti,ab.
215. (warfarin or Apo-Warfarin or Coumadin\$1).ti,ab.
216. (dalteparin or Fragmin\$1).ti,ab.
217. exp Heparin/
218. heparin.ti,ab.
219. (tinzaparin or Innohep).ti,ab.
220. (antithrombocytic\* or anti-thrombocytic\* or (platelet\$1 adj2 inhibit\*) or Antiplatelet\$1 or Anti-platelet\$1 or Platelet Antagonist\$1 or Platelet Antiaggregant\$1).ti,ab.
221. exp Aspirin/
222. (Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).ti,ab.
223. (ticlopidine or Ticlid).ti,ab.
224. (clopidogrel or Plavix).ti,ab.
225. exp Diuretics/
226. (diuretic\$1 or water pill\$1).ti,ab.
227. (Bumetanide or bumex).ti,ab.
228. (etacrynic acid or ethacrynic acid or Edecrin).ti,ab.
229. (furosemide or Errolon or Furseamide or Fusid or Lasix).ti,ab.
230. (torsemide or Demadex or torasemide).ti,ab.
231. (k-sparing or potassium-sparing).ti,ab.
232. (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide).ti,ab.
233. (triamterene or Dyrenium).ti,ab.
234. thiazide diuretic\$1.ti,ab.
235. (Bendroflumethiazide or Bendrofluazide).ti,ab.
236. (chlorothiazide or Chlotride or Diuril).ti,ab.
237. (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic).ti,ab.
238. (methyclothiazide or Aquatensen or Enduron).ti,ab.
239. (polythiazide or Renese).ti,ab.
240. (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone).ti,ab.
241. (indapamide or Lozol or Metindamide).ti,ab.

242. (metolazone or Mykrox or Zaroxolyn or Zytanix).ti,ab.
243. or/98-242
244. 97 and 243
245. exp Herb drug interactions/
246. (interact\* or react\* or contraindicat\* or contra-indicat\* or chemically induce\* or enhance\* or potentiat\* or synergis\* or toxic or toxicit\*).ti,ab.
247. 245 or 246
248. 244 and 247
249. meta analysis/
250. meta analysis.pt.
251. (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).ti,ab.
252. (systematic review\* or systematic overview\* or technology assessment\* or HTA or HTAs).ti,ab.
253. health technol assess rep.ja.
254. evid rep technol assess summ.ja.
255. or/249-254
256. 248 and 255
257. (controlled clinical trial or controlled trial or randomised controlled trial or randomized controlled trial).pt.
258. exp Randomized controlled trials/
259. exp Random allocation/
260. exp Double blind method/
261. exp Placebos/
262. (random\* or RCT\$1 or placebo\*).ti,ab.
263. ((singl\* or doubl\* or trebl\* or tripl\*) and (mask\* or blind\* or dumm\*)).ti,ab.
264. controlled clinical trial.ti,ab.
265. or/257-264
266. 248 and 265
267. 266 not 256
268. clinical trial.pt.
269. exp Clinical trials/
270. "clinical trial".ti,ab.
271. (comparative studies or comparative study or evaluation studies or multicenter study or multicentre study).pt.
272. (volunteer or volunteers or open label\* or nonrandom\* or non random\* or quasirandom\* or quasi-random\*).ti,ab.
273. exp cohort studies/ or exp longitudinal studies/ or exp prospective studies/ or exp Follow up studies/ or exp retrospective studies/ or exp case control studies/ or exp Comparative study/
274. (cohort or cohorts or longitudinal or prospective or retrospective).ti,ab.
275. ((observational or follow-up or followup) adj stud\*).ti,ab.
276. (population-based stud\* or population-based analys\* or population stud\* or population analys\*).ti,ab.

277. ((descriptive adj stud\*) or (multidimensional adj stud\*) or (multi-dimensional adj stud\*) or (multicenter adj stud\*) or (multi-center adj stud\*) or (multicentr\* adj stud\*) or (multi-centr\* adj stud\*)).ti,ab.

278. ((comparative adj study) or (comparative adj studies) or (case adj control\*) or "case series" or (case adj comparison\*) or (case adj history) or (case adj histories)).ti,ab.

279. or/268-278

280. 248 and 279

281. 280 not (256 or 266)

282. exp Mortality/ or exp Risk/ or exp Morbidity/

283. exp Adverse effects/ or exp Safety/ or exp Complications/

284. (adverse or complication\* or harm or harms or harmful or harming or injurious or morbidit\* or mortalit\* or risk\$1 or side effect\$1 or undersirable or tolerability or teratogen\* or safety).ti,ab.

285. or/282-284

286. 248 and 285

287. 286 not (256 or 266 or 280)

## **EMBASE (September 1, 2011)**

1. exp diet supplementation/

2. exp cardiovascular agent/

3. 1 and 2

4. 3

5. limit 4 to human

## **Cochrane Library (September 1, 2011)**

#1 MeSH descriptor Herb-Drug Interactions explode all trees

#2 ((herb or herbs or herbal or plant or plants or botanic\*) and (drug or drugs or medication\* or prescription\* or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)):ti,ab,kw

#3 MeSH descriptor Food-Drug Interactions explode all trees

#4 ((food or foods) and (drug or drugs or medication\* or prescription\* or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)):ti,ab,kw

#5 (#1 OR #2 OR #3 OR #4)

#6 MeSH descriptor Dietary Supplements explode all trees

#7 (Neutraceutical\* or Nutraceutical\* or (diet\* NEXT supplement\*) or (nutrition\* NEXT supplement\*) or (food\* NEXT supplement\*) or (mineral\* NEXT supplement\*) or (vitamin\* NEXT supplement\*) or (botanic\* NEXT supplement\*)):ti,ab,kw

#8 MeSH descriptor Vitamins explode all trees

#9 (vitamin or vitamins ):ti,ab,kw or (folic acid):ti,ab,kw

#10 MeSH descriptor Minerals explode all trees

#11 MeSH descriptor Copper explode all trees

#12 MeSH descriptor Iron explode all trees

#13 MeSH descriptor Magnesium explode all trees

#14 MeSH descriptor Potassium explode all trees



- #15 MeSH descriptor Selenium explode all trees
- #16 (copper or iron or magnesium or potassium or selenium):ti,ab,kw
- #17 MeSH descriptor Plant Preparations explode all trees
- #18 MeSH descriptor Plant Extracts explode all trees
- #19 MeSH descriptor Drugs, Chinese Herbal explode all trees
- #20 MeSH descriptor Plants, Medicinal explode all trees
- #21 ((medicin\* NEAR/3 herb\*) or (medicin\* NEAR/3 plant\*) or (botanical\* NEAR/3  
medicin\*) or (botanical\* NEAR/3 drug\*) or (herb\* NEAR/3 drug\*) or (therapeutic\* NEAR/3  
herb\*) or (therapeutic\* NEAR/3 plant\*) or (therapeutic\* NEAR/3 botanical\*) or (plant\*  
NEAR/3 pharmacotherap\*) or (plant\* NEAR/3 pharmaco-therap\*)):ti,ab,kw or ((herb\* NEAR/3  
pharmacotherap\*) or (herb\* NEAR/3 pharmaco-therap\*) or (botanical NEAR/3  
pharmacotherap\*) or (botanical NEAR/3 pharmaco-therap\*) or (Chinese NEAR/2 medicin\*) or  
(Chinese NEAR/2 medicin\*) or (Chinese NEAR/2 drug\*) or (Chinese NEAR/2  
pharmacotherap\*) or (Chinese NEAR/2 pharmaco-therap\*)):ti,ab,kw or (phytochemical\* OR  
phyto-chemical\* OR phytonutrient\* OR phyto-nutrient\*):ti,ab,kw
- #22 MeSH descriptor Glucosamine explode all trees
- #23 (glucosamin\*):ti,ab,kw
- #24 MeSH descriptor Salvia miltiorrhiza explode all trees
- #25 (salvia miltiorrhiza or danshen or horse-racing grass\* or rat-tail grass\* or red-  
rooted sage\* or red root\* or red sage\* or red sage root or (root\* NEAR/3 purple sage\*) or scarlet  
sage\*):ti,ab,kw or (Ch'ih shen or Chinese Salvia or dangshem or dan shen or dan-shen or  
danshensu or fufangdensen or huang ken or hung ken or pin-ma ts'ao or Radix salviae  
miltiorrhizae or Salvia bowelyana or Salvia miltiorrhiza or Salvia przewalskii or Salvia root\* or  
Salvia yunnanensis or sh'ih shen or shu-wei ts'ao or tan seng or tan-shen or tzu tan-ken or  
yunzhi-danshen):ti,ab,kw
- #26 MeSH descriptor Forskolin explode all trees
- #27 MeSH descriptor Ruscus explode all trees
- #28 MeSH descriptor Cinnamomum zeylanicum explode all trees
- #29 (Forskolin or Coleus forskohlii or Indian Coleus or Coleonol):ti,ab,kw or (ruscus  
or (butcher\* NEXT broom\*)):ti,ab,kw or (Cinnamomum or Cinnamon\*):ti,ab,kw
- #30 MeSH descriptor Taraxacum explode all trees
- #31 (Taraxacum or dandelion\* or blowball\* or Irish daisy or Irish daisies or (pee  
NEAR/3 bed) or (lion\* NEAR/2 tooth) or (lion\* NEAR/2 teeth) or (priest\* NEAR/2  
crown\*)):ti,ab,kw or (Dent NEAR/2 lion\*) or huang hua di ding or yellow flower earth nail\* or  
puffball\* or swine snout\*:ti,ab,kw
- #32 MeSH descriptor Echinacea explode all trees
- #33 (Echinacea or American coneflower\* or purple coneflower\* or Rudbeckia  
purpurea or Black Sampson or combflower\* or Kansas snake root\* or scurvy root\*):ti,ab,kw
- #34 MeSH descriptor Tanacetum parthenium explode all trees
- #35 (Tanacetum parthenium or feverfew or (bachelor\* NEXT button\*) or featherfew  
or febrifuge plant\* or featherfoil\*):ti,ab,kw or (Chrysanthemum parthenium):ti,ab,kw
- #36 MeSH descriptor Garlic explode all trees
- #37 (garlic or allium or (nectar NEAR/2 god\*) or pa-se-waa or poor man's treacle or  
stinking rose\*):ti,ab,kw
- #38 MeSH descriptor Ginkgo biloba explode all trees

- #39 (Ginkgo or Ginkgophyta or Maidenhair Tree\* or Maiden Hair Tree\* or Fossil Tree\* or Duckfoot tree\* or Duck foot tree\* or silver apricot\* or kew tree\*):ti,ab,kw
- #40 MeSH descriptor Panax explode all trees
- #41 (Panax or Ginseng or Jen Shen or Ninjin or Renshen or Schinseng or Shinseng):ti,ab,kw or (guggulipid\* or guggul\* or gugulipid\* or gugulu or gugululipid\* or guggulsterone\* or yogaraj-guggulu):ti,ab,kw
- #42 MeSH descriptor Lycium explode all trees
- #43 (wolfberr\* or (wolf NEXT berr\*) or gojiberr\* or (goji NEXT berr\*)):ti,ab,kw
- #44 MeSH descriptor Mentha piperita explode all trees
- #45 MeSH descriptor Glycyrrhiza explode all trees
- #46 MeSH descriptor Tinospora explode all trees
- #47 (Chrysanthemum parthenium or gynura or gynuras or gulvel or gulvels):ti,ab,kw
- #48 MeSH descriptor Gymnema explode all trees
- #49 (Gymnema or (Periploca NEAR/3 wood\*) or small Indian ipecac or vishani or Sarpadarushtrika or Wakandi):ti,ab,kw or (hawthorn\* or Crataegus oxycantha or (bread NEAR/2 cheese tree\*) or cockspur thorn\* or Chinese hawthorn\* or May bush\* or May tree\* or May blossom\* or May flower\* or mayflower\* or quickset or thorn-apple tree\* or thornapple tree\* or white thorn\* or whitethorn\*):ti,ab,kw
- #50 MeSH descriptor Convallaria explode all trees
- #51 (Convallaria or (lily NEAR/3 valley) or (lady\* NEXT tears) or ladies tears or may lily or may lilies or may bell or may bells or maybell\* or conval lily or conval lilies or lily constancy or (ladder\* NEAR/2 heaven) or male lily or male lilies):ti,ab,kw
- #52 MeSH descriptor Leonurus explode all trees
- #53 (Motherwort\* or Leonorus cardiaca or (lion\* NEXT tail\*) or (lion\* NEXT ear\*) or throwwort\*):ti,ab,kw
- #54 MeSH descriptor Milk Thistle explode all trees
- #55 (Milk Thistle\* or Silybum marianum or Carduus marianus or Holy thistle\* or marythistle\* or (Mary\* NEXT thistle\*) or (Marian\* NEXT thistle\*)):ti,ab,kw
- #56 MeSH descriptor Rauwolfia explode all trees
- #57 (Rauwolfia or Rauvolfia or Indian snakeroot\* or Sarpa-gandha or Nakuli or Chota-chand or Kanakachandrika):ti,ab,kw or (red yeast rice extract\* or Monascus purpureus or (mould species NEAR/3 rice\*) or (red NEAR/2 yeast\*) or (red NEAR/2 rice\*) or red koji or red leaven\*):ti,ab,kw
- #58 MeSH descriptor Eleutherococcus explode all trees
- #59 (Eleutherococcus or Siberian ginseng or Ci wu ju or Eleuthero or "touch-me-not" or "touch-me-nots" or (devil\* NEXT shrub\*)):ti,ab,kw or ((Thorny bearer NEAR/2 free) or ussurian thorny pepperbrush\* or ussurian thorny pepper brush\*):ti,ab,kw
- #60 MeSH descriptor Hypericum explode all trees
- #61 (Hypericum or (John\* NEXT wort\*) or Johnswort\* or Amber or (touch NEAR/2 heal) or goat weed\* or goatweed\* or Hardhay\* or Klamath weed\* or Klammath weed\* or Rosin rose\* or Tipton weed\* or (balm NEAR/2 warrior\*) or (Devil\* NEXT scorge\*)):ti,ab,kw
- #62 MeSH descriptor Curcuma explode all trees
- #63 MeSH descriptor Valerian explode all trees
- #64 (Turmeric or curcuma or Indian saffron or Indian yellow root\* or Zedoary zedoaria):ti,ab,kw or (Valerian\* or vandal root\* or all-heal\* or setwall\*):ti,ab,kw
- #65 MeSH descriptor Selenoproteins explode all trees

- #66 MeSH descriptor Thioctic Acid explode all trees
- #67 (Selenoprotein\*):ti,ab,kw or (Alpha lipoic acid\* or Alpha-Lipogamma or Alpha-Lipon Stada or alpha-Liponaure Heumann or Alpha-Liponsaure or Alpha-Lippon or alpha-Vibolex or Alphaflam):ti,ab,kw or "Coenzyme Q10" or "CoQ 10" or CoQ10 or idebenone or ubiquinone or ubidecarenone or ubisemiquinone or "vitamin q10":ti,ab,kw
- #68 MeSH descriptor Fish Oils explode all trees
- #69 MeSH descriptor Fatty Acids, Omega-3 explode all trees
- #70 (fish NEAR/2 oil) of (fish NEAR/2 oils):ti,ab,kw or ("omega 3" or "omega 3s" or omega three\$1 or "n-3 Fatty Acid" or "n-3 Fatty Acids" or "n3 Fatty Acid" or "n3 Fatty Acids" or "n-3 Polyunsaturated Fatty Acid" or "n-3 Polyunsaturated Fatty Acids" or "n3 Polyunsaturated Fatty Acid" or "n3 Polyunsaturated Fatty Acids" or "n-3 PUFA" or "n3 PUFA"):ti,ab,kw
- #71 (Eicosapentanoic acid\* or decosahexanoic acid\* or alpha linoleic acid\*):ti,ab,kw or (green tea or green teas or black tea or black teas or Camellia sinensis or Japanese tea or Japanese teas or Matsu-cha tea or Matsu-cha teas):ti,ab,kw
- #72 MeSH descriptor Phytosterols explode all trees
- #73 MeSH descriptor beta-Glucans explode all trees
- #74 (Phytosterol\* or plant sterol\* or plant stanol\* or beta-sitosterol\* or sterolin\*):ti,ab,kw or (beta-Glucan or beta-Glucans):ti,ab,kw
- #75 MeSH descriptor Calcium explode all trees
- #76 MeSH descriptor Psyllium explode all trees
- #77 (calcium or bone meal or dicalcium or dolomite):ti,ab,kw or (Psyllium or Plantago ovata or flea seed\* or fleawort or hemicelluloses or plantago seed\* or ispaghula husk\* or ispaghula seed\* or Plantago arenaria or Plantago isphagula):ti,ab,kw
- #78 MeSH descriptor Soybeans explode all trees
- #79 MeSH descriptor Arginine explode all trees
- #80 (soy or soybean\* or Glycine max):ti,ab,kw or (Arginine or L-Arginine):ti,ab,kw or (Chia or Salvia columbariae or Salvia hispanica or salba):ti,ab,kw
- #81 MeSH descriptor Chitosan explode all trees
- #82 MeSH descriptor Cynara explode all trees
- #83 MeSH descriptor Carnitine explode all trees
- #84 (Chitin or chitosan or "N-carboxybutyl" or Poliglusam):ti,ab,kw or (Cynara or globe artichoke\* or cardoon\*):ti,ab,kw or (Carnitine or Bicarnesine or "L-Carnitine" or Levocarnitine or "Vitamin BT" or "Acetyl-L-carnitine" or carnitene or carnitor or canitor or "D-carnitine" or "D,L-carnitine" or "L-acetyl-carnitine" or "L-carnitina" or "L-carnitine" or "L-tartrate" or "L-CARNIPURE" or levacecarnine or levocarnitine or "L-propionylcarnitine" or "propionil-L-carnitine" or "propionyl-L-carnitine" or ST261):ti,ab,kw
- #85 (Pantethine or "Vitamin B5" or bile acid sequestrant\* or cyproheptadine or cysteamine or "D-pantethine" or pantetheine or pantetheinase or Pantetina or panthenol or pantomin or pantosin or pantothenic acid\* or sulfopantetheine):ti,ab,kw or (Policosanol\* or D003 or hexacontanol\* or isopolicosanol\* or "Octa-60" or octacosanoic acid\* or octacosanol\* or ricewax\* or winteriser cake\* or winterizer cake\* or sugar cane policosanol\* or sunflower seed policosanol\* or triacontanol\* or wheat germ policosanol\*):ti,ab,kw
- #86 MeSH descriptor Withania explode all trees
- #87 MeSH descriptor Aesculus explode all trees
- #88 MeSH descriptor Aloe explode all trees

- #89 (Withania or Ashwaganda or Indian ginseng or winter cherry or winter cherries or wintercherry or wintercherries or Ayurvedic ginseng):ti,ab,kw or (aesculus or buckeye\* or horse chestnut\* or conqueror tree\* or aloe vera or aloe barbadensis):ti,ab,kw
- #90 MeSH descriptor Ginger explode all trees
- #91 MeSH descriptor Ephedra explode all trees
- #92 MeSH descriptor Trigonella explode all trees
- #93 (ginger or Zingiber officinale or Gamma oryzanol):ti,ab,kw or (ephedra or trigonella or fenugreek or foenumgraecum or poenumgraecum):ti,ab,kw or (Gamma oryzanol or dong quai or tetrandrine or tetradrine or hanjision):ti,ab,kw
- #94 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
- #95 (#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)
- #96 (#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR ( #70 AND OF AND #71 ) OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93)
- #97 MeSH descriptor Phytotherapy explode all trees
- #98 (phytotherap\* or phyto-therap\* or phytomedicin\* or phyto-medicin\*)
- #99 MeSH descriptor Cardiovascular Diseases explode all trees with qualifier: DT
- #100 Any MeSH descriptor with qualifier: TU
- #101 (#97 OR #98 OR #99 OR #100)
- #102 (#94 OR #95 OR #96)
- #103 (#101 AND #102)
- #104 (#6 OR #7 OR #19 OR #20 OR #21)
- #105 (#103 OR #104)
- #106 (#97 OR #98 OR #105)
- #107 MeSH descriptor Functional Food explode all trees
- #108 (functional NEXT food\*) or (therapeutic\* NEXT food\*):ti,ab,kw
- #109 MeSH descriptor Citrus paradisi explode all trees
- #110 MeSH descriptor Vaccinium macrocarpon explode all trees
- #111 MeSH descriptor Viburnum explode all trees
- #112 MeSH descriptor Blueberry Plant explode all trees
- #113 MeSH descriptor Punicaceae explode all trees
- #114 (citrus paradisi or vaccinium macrocarpon or viburnum or puniceae or blueberr\* or cranberr\* or grapefruit\* or toronja\* or pomegranate\* or punica granatum or bitter orange or citrus uranticum or kijitsu or shangzhou zhiqiao or zhi shi):ti,ab,kw
- #115 MeSH descriptor Beverages explode all trees
- #116 (beverage\* or drink\* or juice\* or tea or teas):ti,ab,kw
- #117 (#109 OR #110 OR #111 OR #112 OR #113 OR #114)
- #118 (#115 OR #116)
- #119 (#117 AND #118)
- #120 MeSH descriptor Plant Oils explode all trees
- #121 MeSH descriptor Olea explode all trees

#122 (botanic\* or plant or plants or vegetable\* or clove or cloves or corn or corns or cottonseed\* or croton\* or olive or olives or safflower\* or sesame\* or soybean\* or teatree\*):ti,ab,kw and (oil or oils):ti,ab,kw

#123 MeSH descriptor Linaceae explode all trees

#124 (Linaceae or flax or flaxseed\* or Linum or linseed\*):ti,ab,kw

#125 MeSH descriptor Dietary Fiber explode all trees

#126 (diet or diets or dietary):ti,ab,kw and (fibre or fibres or fiber or fibers or roughage or (wheat NEXT bran) or cereal\*):ti,ab,kw

#127 MeSH descriptor Caffeine explode all trees

#128 (#120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127)

#129 (#107 OR #108 OR #119 OR #128)

#130 MeSH descriptor Cardiovascular Diseases explode all trees with qualifier: DT

#131 MeSH descriptor Adrenergic beta-Antagonists explode all trees

#132 MeSH descriptor Acebutolol explode all trees

#133 MeSH descriptor Betaxolol explode all trees

#134 MeSH descriptor Bisoprolol explode all trees

#135 (Adrenergic NEAR/2 Antagonist\*) OR (beta NEXT block\*) OR ((beta NEAR/1 Adrenergic) NEAR/2 block\*):ti,ab,kw or (acebutolol or acebutalol or Apo-Acebutolol or Apo-Acebualol or Sectral or Prent):ti,ab,kw or (betaxolol or Kerlon or Kerlone):ti,ab,kw or (bisoprolol or Concor or Concore or Zebeta or Monocor):ti,ab,kw or (carvedilol or Apo-carvedilol or Coreg or Dilatrend or Eucardic or Kredex):ti,ab,kw

#136 MeSH descriptor Labetalol explode all trees

#137 MeSH descriptor Metoprolol explode all trees

#138 MeSH descriptor Nadolol explode all trees

#139 MeSH descriptor Pindolol explode all trees

#140 MeSH descriptor Propranolol explode all trees

#141 (labetalol or Labetolol or Normodyne or Trandate):ti,ab,kw or (metoprolol or Betaloc or Betalok or Lopressor or Seloken):ti,ab,kw or (nadolol or Corgard or Solgol or nebivolol or Nebilet or Silostar):ti,ab,kw or (pindolol or Visken):ti,ab,kw or (propranolol or Avlocardyl or Deralin or Dociton or Inderal or Obsidan):ti,ab,kw

#142 MeSH descriptor Sotalol explode all trees

#143 MeSH descriptor Timolol explode all trees

#144 MeSH descriptor Calcium Channel Blockers explode all trees

#145 MeSH descriptor Amlodipine explode all trees

#146 (sotalol or Darob):ti,ab,kw or (timolol or Blocadren):ti,ab,kw or (calcium block\* NEAR/2 exogenous) or (calcium antagonist\* NEAR/2 exogenous) or (calcium inhibitor\* NEAR/2 exogenous) or calcium channel block\*:ti,ab,kw or (Dihydropyridine or Lemildipine):ti,ab,kw or (amlodipine or Norvasc or Istin):ti,ab,kw

#147 MeSH descriptor Felodipine explode all trees

#148 MeSH descriptor Isradipine explode all trees

#149 MeSH descriptor Nicardipine explode all trees

#150 MeSH descriptor Nifedipine explode all trees

#151 MeSH descriptor Nimodipine explode all trees

#152 (felodipine or Plendil or Renedil):ti,ab,kw or (isradipine or DynaCirc or Lomir or Prescal):ti,ab,kw or (nicardipine or Cardene):ti,ab,kw or (nifedipine or Adalat or Cordipin or Nifediac or Nifedical or Procardia):ti,ab,kw or (nimodipine or Nimotop):ti,ab,kw

#153 MeSH descriptor Nisoldipine explode all trees  
 #154 MeSH descriptor Diltiazem explode all trees  
 #155 MeSH descriptor Verapamil explode all trees  
 #156 (nisoldipine or Sular):ti,ab,kw or (diltiazem or Cardizem or Dilacor or Dilzem or Tiazac):ti,ab,kw or (verapamil or Bosoptin or Calan or Cordilox or Covera-HS or Isoptin or Iproveratril or Verelan):ti,ab,kw  
 #157 MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees  
 #158 (Angiotensin-Converting Enzyme NEXT Inhibitor\*) or ACE inhibitor\* or (Angiotensin-Converting Enzyme antagonist\*):ti,ab,kw or (Kininase II NEAR/2 inhibitor\*) or (Kininase II NEAR/2 antagonist\*):ti,ab,kw or (benazepril or Cibacen or Lotensin):ti,ab,kw  
 #159 MeSH descriptor Captopril explode all trees  
 #160 MeSH descriptor Enalapril explode all trees  
 #161 MeSH descriptor Fosinopril explode all trees  
 #162 MeSH descriptor Lisinopril explode all trees  
 #163 MeSH descriptor Perindopril explode all trees  
 #164 (captopril or Capoten or Lopirin):ti,ab,kw or (enalapril or Renitec or Renitek or Vasotec):ti,ab,kw or (fosinopril or Dynacil or Fozitec or Monopril or Staril or Tensocardil):ti,ab,kw or (lisinopril or Lysinopril or Prinivil or Zestril or moexipril or Perdix or Univasc):ti,ab,kw or (perindopril or Aceon or Coversyl or Prestarium or Quinapril or Accupril):ti,ab,kw  
 #165 MeSH descriptor Ramipril explode all trees  
 #166 MeSH descriptor Losartan explode all trees  
 #167 (Ramipril or Acovil or Altace or Triatec or Tritace or Vesdil):ti,ab,kw or (Trandolapril or Gopten or Mavik or Odrik or Candesartan or Atacand):ti,ab,kw or (eprosartan or Teveten or irbesartan or Aprovel or Avapro or Karvea):ti,ab,kw or (losartan or Cozaar or olmesartan or Benicar ):ti,ab,kw or (telmisartan or Micardis or Pritor or valsartan or Diovan):ti,ab,kw  
 #168 (renin NEXT inhibit\*) or renin antagonist\*):ti,ab,kw or (Aliskiren or Tekturna):ti,ab,kw or (aldosterone receptor antagonist\*):ti,ab,kw or (Eplerenone or Inspra):ti,ab,kw  
 #169 MeSH descriptor Spironolactone explode all trees  
 #170 MeSH descriptor Vasodilator Agents explode all trees  
 #171 MeSH descriptor Clonidine explode all trees  
 #172 MeSH descriptor Guanabenz explode all trees  
 #173 MeSH descriptor Guanfacine explode all trees  
 #174 (Spironolactone or Aldactone or Verospirone):ti,ab,kw or (Vasodilator\*):ti,ab,kw or (clonidine or Apo-Clonidine or Catapres or Duraclon):ti,ab,kw or (guanabenz or Wytensin):ti,ab,kw or (guanfacine or Intuniv or Tenex):ti,ab,kw  
 #175 MeSH descriptor Methyldopa explode all trees  
 #176 MeSH descriptor Diazoxide explode all trees  
 #177 MeSH descriptor Hydralazine explode all trees  
 #178 MeSH descriptor Minoxidil explode all trees  
 #179 MeSH descriptor Isosorbide Dinitrate explode all trees  
 #180 (Methyldopa or Apo-Methyldopa or Aldoril or Aldomet or Dopamet or Dopegyt):ti,ab,kw or (Diazoxide or Hyperstat or Proglycem):ti,ab,kw or (Hydralazine or Apo-

Hydralazine or Apresoline or Dralzine):ti,ab,kw or (minoxidil or Loniten):ti,ab,kw or (Isosorbide Dinitrate or Dilatrate or Cedocard or Isoket or Isotrate or Isordil or Sorbitrate):ti,ab,kw

#181 MeSH descriptor Nitroglycerin explode all trees

#182 MeSH descriptor Phosphodiesterase Inhibitors explode all trees

#183 (nitroglycerin\* or Natispray or Nitro-Dur or Nitromist or Nitrospan or Nitrostat or Nitro-Time or Transderm Nitro or Tridil or Trinipatch):ti,ab,kw or (Phosphodiesterase Inhibit\* or Phosphodiesterase antagonist\* or Antiphosphodiesterase\* or Anti-phosphodiesterase\* or Phosphoric Diester Hydrolase Inhibit\* or Phosphoric Diester Hydrolase antagonist\*):ti,ab,kw or (sildenafil or Revatio or tadalafil or vardenafil):ti,ab,kw or (Cilostazol or Pletal):ti,ab,kw

#184 MeSH descriptor Alprostadil explode all trees

#185 MeSH descriptor Epoprostenol explode all trees

#186 MeSH descriptor Iloprost explode all trees

#187 MeSH descriptor Papaverine explode all trees

#188 MeSH descriptor Isoxsuprine explode all trees

#189 (Alprostadil):ti,ab,kw or (Epoprostenol or Flolan or iloprost or Ciloprost or Ventavis):ti,ab,kw or (Endothelin antagonist\* or (Endothelin NEAR/1 inhibit\*)):ti,ab,kw or (treprostinil or Remodulin or bosentan or Tracleer or ambrisentan or Letairis):ti,ab,kw or (papaverine or isoxsuprine or Duvadilan):ti,ab,kw

#190 MeSH descriptor Adrenergic alpha-Antagonists explode all trees

#191 MeSH descriptor Doxazosin explode all trees

#192 MeSH descriptor Prazosin explode all trees

#193 ((alpha-Adrenergic NEAR/2 block\*) or (adrenergic alpha NEAR/2 block\*) or (alpha-adrenergic NEAR/2 antagonist\*) or (adrenergic alpha NEAR/2 antagonist\*) or (alpha block\* NEAR/2 adrenergic) or (alpha antagonist\* NEAR/2 adrenergic)):ti,ab,kw or (doxazosin or Cardura or Carduran or Diblocin or Doxazomerck or Doxazosin or Proglanidol):ti,ab,kw or (prazosin or Minipress or Furazosin or Pratsiol):ti,ab,kw or (terazosin or Adecur or Apo-Terazosin or Deflox or Dysalfa or Flotrin or Heitrin or Hytrin or Hytrine or Magnuroil):ti,ab,kw

#194 MeSH descriptor Anti-Arrhythmia Agents explode all trees

#195 (Anti-Arrhythmia or Anti-Arrhythmic\* or Antiarrhythmia or Antiarrhythmic\* or Anti-fibrillatory or Antifibrillatory):ti,ab,kw and (drug or drugs or agent or agents):ti,ab,kw

#196 MeSH descriptor Disopyramide explode all trees

#197 MeSH descriptor Procainamide explode all trees

#198 MeSH descriptor Quinidine explode all trees

#199 MeSH descriptor Mexiletine explode all trees

#200 MeSH descriptor Encainide explode all trees

#201 (disopyramide or Norpace or Rhythmolan):ti,ab,kw or (procainamide or Apo-Procainamide or Biocoryl or Novocainamide or Novocamid or Procamide or Pronestyl or Procan or Procanbid):ti,ab,kw or (quinidine or Apo-Quinidine or Chinidin or Quinidex or Quinora):ti,ab,kw or (Mexiletine):ti,ab,kw or (encainide or Enkaid):ti,ab,kw

#202 MeSH descriptor Flecainide explode all trees

#203 MeSH descriptor Propafenone explode all trees

#204 MeSH descriptor Amiodarone explode all trees

#205 (Flecainide or Tambacor):ti,ab,kw or (propafenone or Apo-Propafenone or Arythmol or Baxarytmon or Fenoprain or Rythmol or Rytmonorm):ti,ab,kw or (amiodarone or Amiodarona or Cordarone or Cordarex or Pacerone or Trangorex):ti,ab,kw or (dofetilide or Tikosyn):ti,ab,kw or (dronedaronone or Multaq):ti,ab,kw

#206 MeSH descriptor Cardiotonic Agents explode all trees

#207 MeSH descriptor Digoxin explode all trees

#208 (Cardiotonic or Cardioprotective or Cardio-tonic or Cardio-protective):ti,ab,kw  
and (drug or drugs or agent or agents or medication\* or prescription\*):ti,ab,kw

#209 (cardiotonics or cardio-tonics or cardiac stimulant\* or myocardial stimulant\* or inotropic agent\*):ti,ab,kw or (digoxin or Digacin or Digitek or Dilanacin or Lanacordin or Lanicor or Lanoxicaps or Lanoxin or Lenoxin):ti,ab,kw

#210 MeSH descriptor Antilipemic Agents explode all trees

#211 (antilipemic\* or anti-lipemic\* or hypolipidemic\* or hypo-lipidemic\*):ti,ab,kw or (antihyperlipemics or anti-hyperlipemics or antihyperlipidemics or anti-hyperlipidemics):ti,ab,kw

#212 (Antilipemic or anti-lipemic or antihyperlipemic or anti-hyperlipemic or antihyperlipidemic or anti-hyperlipidemic or hypolipidemic or hypo-lipidemic):ti,ab,kw and (drug or drugs or agent or agents or medication\* or prescription\*):ti,ab,kw

#213 MeSH descriptor Cholestyramine Resin explode all trees

#214 MeSH descriptor Colestipol explode all trees

#215 (cholestyramin\* or colestyramin\* or Cuemid or Quantalan or Questran):ti,ab,kw or (colestipol or Colestid):ti,ab,kw or (colesevelam or CholestaGel or Welchol):ti,ab,kw or (Bile acid sequestrant\* or bile acid-binding drug\* or bile acid-binding agent\*):ti,ab,kw or (anticholesteremic\* or hypocholesteremic\* or (cholesterol NEAR/2 inhibitor\*) or cholesterol-lowering drug\* or cholesterol-lowering agent\* or cholesterol-lowering medication\*):ti,ab,kw

#216 MeSH descriptor Gemfibrozil explode all trees

#217 MeSH descriptor Lovastatin explode all trees

#218 MeSH descriptor Pravastatin explode all trees

#219 (ezetimibe or Zetia or fenofibrate or Antara or Fenoglide or Fibricor or Lipofen or Lofibra or TriCor or Triglide or Trilipix):ti,ab,kw or (Gemfibrozil or Apo-Gemfibrozil or Lipid or Trialmin):ti,ab,kw or (Hydroxymethylglutaryl-CoA Reductase inhibit\*) or (HMG-CoA Reductase inhibit\*) or (Hydroxymethylglutaryl-CoA inhibit\*) or (Hydroxymethylglutaryl-Coenzyme A inhibit\*):ti,ab,kw or (atorvastatin or Liptor or fluvastatin or Lescol or lovastatin or Altacor or Altoprev or Mevacor):ti,ab,kw or (pravastatin or Apo-Pravastatin or Lipostat or Pravasin\* or Pravachol or Selektine or rosuvastatin or Crestor):ti,ab,kw

#220 MeSH descriptor Simvastatin explode all trees

#221 MeSH descriptor Niacin explode all trees

#222 MeSH descriptor Anticoagulants explode all trees

#223 MeSH descriptor Warfarin explode all trees

#224 MeSH descriptor Dalteparin explode all trees

#225 (simvastatin or Synvinolin or Zocor):ti,ab,kw or (niacin or Niacor or Niaspan or Nicobid or Nicolar or Nicotinex or Slo-Niacin):ti,ab,kw or (Anticoagulant\* or bloodthinn\* or blood-thinn\*):ti,ab,kw or (warfarin or Apo-Warfarin or Coumadin\*):ti,ab,kw or (dalteparin or Fragmin\*):ti,ab,kw

#226 MeSH descriptor Heparin explode all trees

#227 MeSH descriptor Platelet Aggregation Inhibitors explode all trees

#228 MeSH descriptor Aspirin explode all trees

#229 MeSH descriptor Ticlopidine explode all trees

#230 (heparin or tinzaparin or Innohep):ti,ab,kw or (platelet\* NEAR/2 inhibit\*) or antiplatelet\* or anti-platelet\* or platelet antagonist\* or platelet antiaggregant\*):ti,ab,kw or



(Aspirin or Acetylsalicylic or Acylpyrin or Aloxiprimum or Aspergum or Bufferin or Colfarit or Dispril or Ecotrin or Easprin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin):ti,ab,kw or (ticlopidine or Ticlid):ti,ab,kw or (clopidogrel or Plavix):ti,ab,kw

#231 MeSH descriptor Diuretics explode all trees

#232 MeSH descriptor Bumetanide explode all trees

#233 MeSH descriptor Ethacrynic Acid explode all trees

#234 MeSH descriptor Furosemide explode all trees

#235 MeSH descriptor Amiloride explode all trees

#236 (diuretic\* or water pill\*):ti,ab,kw or (Bumetanide or bumex):ti,ab,kw or (ethacrynic acid or Edecrin):ti,ab,kw or (furosemide or Errolon or Fursemide or Fusid or Lasix or torsemide or Demadex or torasemide or k-sparing or potassium-sparing):ti,ab,kw or (Amiloride or Amidal or Amiduret or Kaluril or Midamor or Midoride or Modamide):ti,ab,kw

#237 MeSH descriptor Triamterene explode all trees

#238 MeSH descriptor Bendroflumethiazide explode all trees

#239 MeSH descriptor Chlorothiazide explode all trees

#240 MeSH descriptor Hydrochlorothiazide explode all trees

#241 MeSH descriptor Methyclothiazide explode all trees

#242 (triamterene or Dyrenium or thiazide diuretic\*):ti,ab,kw or (Bendroflumethiazide or Bendrofluazide):ti,ab,kw or (chlorothiazide or Chlotride or Diuril):ti,ab,kw or (hydrochlorothiazide or Apo-Hydro or Dichlotride or Esidrex or HydroDIURIL or Microzide or Oretic):ti,ab,kw or (methyclothiazide or Aquatensen or Enduron):ti,ab,kw

#243 MeSH descriptor Polythiazide explode all trees

#244 MeSH descriptor Chlorthalidone explode all trees

#245 MeSH descriptor Indapamide explode all trees

#246 MeSH descriptor Metolazone explode all trees

#247 (polythiazide or Renese):ti,ab,kw or (chlorthalidone or Apo-Chlorthalidone or Hygroton or Thalitone):ti,ab,kw or (indapamide or Lozol or Metindamide):ti,ab,kw or (metolazone or Mykrox or Zaroxolyn or Zytanix):ti,ab,kw

#248 (#130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #176 OR #177 OR #178 OR #179 OR #180)

#249 (#181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194 OR #195 OR #196 OR #197 OR #198 OR #199 OR #200 OR #201 OR #202 OR #203 OR #204 OR #205 OR #206 OR #207 OR #208 OR #209 OR #210 OR #211 OR #212 OR #213 OR #214 OR #215 OR #216 OR #217 OR #218 OR #219 OR #220 OR #221 OR #222 OR #223 OR #224 OR #225 OR #226 OR #227 OR #228 OR #229 OR #230)

#250 (#231 OR #232 OR #233 OR #234 OR #235 OR #236 OR #237 OR #238 OR #239 OR #240 OR #241 OR #242 OR #243 OR #244 OR #245 OR #246 OR #247)

#251 (#248 OR #249 OR #250)

#252 (#106 OR #129)

#253 (#251 AND #252)

- #254 (#1 OR #3)
- #255 Any MeSH descriptor with qualifiers: AD,CT,DE,ME,PK,TO
- #256 MeSH descriptor Drug Synergism explode all trees
- #257 (interact\* or react\* or contraindicat\* or enhance\* or metabolis\* or metaboliz\* or pharmacokinetic\* or synergis\* or toxic or toxicit\*):ti,ab,kw
- #258 (#254 OR #255 OR #256 OR #257)
- #259 (#253 AND #258)
- #260 (#5 OR #259)
- #261 (#5 AND #251)
- #262 (#259), from 2005 to 2010
- #263 (#259), from 2000 to 2004
- #264 (#259), from 1990 to 1999
- #265 (#259), from 1950 to 1989
- #266 (#5 AND NOT #261)

## Herb-Drug Interactions

### MEDLINE (1950 to October 26, 2010)

1. exp Herb-Drug Interactions/
2. ((herb or herbs or herbal or plant or plants or botanic\*) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)):ti,ab.
3. exp Food-Drug Interactions/
4. ((food or foods) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)):ti,ab.
5. or/1-4
6. limit 5 to human
7. limit 5 to ("in data review" or "in process" or "pubmednotmedline")
8. 6 or 7
9. limit 8 to "reviews (specificity)"
10. meta analysis.pt.
11. exp meta-analysis as topic/
12. (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*):ti,ab.
13. (systematic review\* or systematic overview\* or technology assessment\* or HTA or HTAs):ti,ab.
14. exp Technology assessment, biomedical/
15. health technology assessment winchester england.jn.
16. "cochrane database of systematic reviews".jn.
17. (evidence report technology assessment or evidence report technology assessment summary).jn.
18. or/10-17
19. 8 and 18

## **EMBASE (1980 to October 26, 2010)**

1. exp herb drug interaction/
2. ((herb or herbs or herbal or plant or plants or botanic\*) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)).ti,ab.
3. exp food drug interaction/
4. ((food or foods) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)).ti,ab.
5. or/1-4
6. limit 5 to human
7. limit 6 to "reviews (2 or more terms high specificity)"
8. exp meta analysis/
9. (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).ti,ab.
10. (systematic review\* or systematic overview\* or technology assessment\* or HTA or HTAs).ti,ab.
11. exp biomedical technology assessment/
12. health technology assessment winchester england.jn.
13. "cochrane database of systematic reviews".jn.
14. evidence report technology assessment.jn.
15. (evidence report technology assessment or evidence report technology assessment summary).jn.
16. or/8-15
17. 6 and 16
18. 7 or 17

## **AMED (1985 to October 26, 2010)**

1. exp Herb drug interactions/
2. ((herb or herbs or herbal or plant or plants or botanic\*) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)).ti,ab.
3. ((food or foods) and (drug or drugs or medication\$1 or prescription\$1 or pharmacotherap\* or pharmaco-therap\*) and (interact\* or react\* or contraindicat\* or metabolis\* or metaboliz\* or pharmacokinetic\* or pharmaco-kinetic\*)).ti,ab.
4. or/1-3
5. meta analysis/
6. meta analysis.pt.
7. (meta-analy\* or metanaly\* or metaanaly\* or met analy\* or integrative research or integrative review\* or integrative overview\* or research integration or research overview\* or collaborative review\*).ti,ab.

8. (systematic review\* or systematic overview\* or technology assessment\* or HTA or HTAs).ti,ab.
9. health technol assess rep.ja.
10. evid rep technol assess summ.ja.
11. cochrane database syst rev.ja.
12. or/5-11
13. 4 and 12

## **International Bibliographic Information on Dietary Supplements (IBIDS)**

(interact\* react\* contraindicat\* enhanc\* pharmacokinetic\* synergis\* toxic\*)  
+(cardiovascular\* "heart disease" "heart diseases") +(drug drugs agent\* medication\*  
prescription\* prescribe\*)

# Appendix B. Scientific Information Packet Requests

Appendix B lists the names of the companies contacted from which to obtain scientific information packets.

## Name of Company

|  |                                      |
|--|--------------------------------------|
| Abbott Laboratories                                      | Lundbeck, Inc.                       |
| Actelion Pharmaceuticals US, Inc                         | Meda Pharmaceuticals                 |
| Alcon Laboratories, Inc.                                 | Merck & Co., Inc.                    |
| Apothecon B.V.   | Mutual Pharma (URL Pharma Inc)       |
| AstraZeneca Pharmaceuticals, LP                          | Mylan Pharmaceuticals                |
| AstraZeneca Pharmaceuticals, LP                          | Mylan Pharmaceuticals                |
| Aton Pharma Inc.   | NitroMed, Inc.                       |
| Bayer HealthCare Pharmaceuticals                         | NovaDel Pharma                       |
| Biovail Pharmaceuticals Inc.                             | Novartis Pharmaceuticals Corporation |
| Boehringer Ingelheim Pharmaceuticals, Inc.               | Otsuka America Pharmaceutical, Inc.  |
| Bristol-Myers Squibb                                     | Paddock Laboratories, Inc.           |
| Daiichi Sankyo, Inc                                      | Pfizer Inc                           |
| Duramed Subsidiary of Barr Pharmaceuticals a.k.a. Teva   | Prometheus Laboratories Inc.         |
| Eisal Medical Research Inc.                              | Promius Pharma, LLC                  |
| EKR Therapeutics, Inc                                    | Salix Pharmaceuticals                |
| Eli Lilly & Co   | Sandoz Inc                           |
| Ferndale   | Sanofi Aventis US                    |
| Forest Pharmaceuticals                                   | Santen Inc.                          |
| Forest Pharmaceuticals                                   | Schering-Plough Corporation          |
| G. Pohl-Boskamp GmbH & Co. KG                            | Shionogi Inc.                        |
| Gilead Sciences  | Teva Pharmaceuticals USA             |
| GlaxoSmithKline  | Teva Pharmaceuticals USA             |
| Graceway Pharmaceuticals, LLC                            | UCB, Inc                             |
| Hospira  | United Therapeutics Corporation      |
| Ivax Pharmaceuticals (Teva Pharmaceuticals)              | Upsher-Smith Laboratories, Inc       |
| Johnson & Johnson Health Care Products & Pharmaceuticals | USL Pharmaceuticals                  |
| Key Pharmaceuticals                                      | Validus Pharmaceuticals LLC          |
| King Pharmaceuticals, Inc.                               | VIVUS, Inc.                          |
| LEO Pharma Inc.  | Wyeth Pharmaceuticals Headquarters   |

## **Appendix C. Evidence Tables**

The purpose of Appendix C is to provide detailed evidence tables that depict the criteria used to determine validity for each study and show the risk of bias assessment made to each study. Furthermore, the tables summarize the evidence described and reflect specific information discussed in the report. The tables are categorized and alphabetized. The categories are: General Characteristics; Interventions; Outcomes by Key Question and outcome; Risk of Bias.

**Evidence Table 57. General characteristics of all studies**

| Author Year             | Population   | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)   | Other Interventions  |
|-------------------------|--|---|---|--|--|--|
| Abdul 2010 <sup>1</sup> | <p>N screened: NR<br/>N included/randomized: 12</p> <p>Age: 24<br/>%female: 0<br/>Ethnicity:<br/>- Caucasian (6)<br/>- Asian (6)</p> <p>Comorbidities (other than indication(s) for CVDs: NR</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: non-smokers and not taking any medication including any herbal medicines or dietary supplements (for at least 2 weeks)</p> <p>Exclusion Criteria: Subjects with any medical condition that could alter warfarin effects, including any clotting disorders, hepatic dysfunction or platelet dysfunction</p> <p>Brief Description: healthy male subjects of known CYP2C9 and VKORC1 genotype</p> | <p>Study Design:<br/>Crossover RCT<br/>Region: NR, likely Australia<br/>Setting: NR</p> <p>Industry Funded:<br/>Yes</p> <p>Treatment Duration supplement(s): 21</p> <p>Treatment DurationCVD Drug(s): Single dose</p> <p>Duration of Followup: 7</p> <p>Duration of Longest Followup: 7</p> | <p>Generic Name(s): warfarin<br/>Drug Category:<br/>Anticoagulants<br/>Mode of Administration:<br/>Oral<br/>Mean Daily Dose: 25mg- 1 dose<br/>Reason for taking CVD drug(s): Pharmacokinetics and pharmacodynamic study</p> | <p>N: 12<br/>Supplement(s):<br/>Echinacea<br/>Form of Administration:<br/>Capsule/Tablet<br/>Daily Dose: 5100 mg</p> | <p>N1 = 12<br/>No treatment</p> <p>N2 = 12<br/>policosanol (non-relevant supplement)</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s):<br/>No</p> <p>Exercise Intervention(s):<br/>No</p> <p>Other Lifestyle Intervention(s):<br/>No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population  | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)   | Other Interventions  |
|-------------------------|---|---|---|--|--|--|
| Aruna 2007 <sup>2</sup> | <p>N screened: 16<br/>N included/randomized: 10</p> <p>Age: 27<br/>%female: 0<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: subjects hypersensitive to study drugs, chronic smokers or alcoholics, and a history of gastrointestinal surgery that could interfere with absorption of study drugs</p> <p>Brief Description: healthy male subjects</p> | <p>Study Design: Crossover RCT</p> <p>Region: Rest of Asia</p> <p>Setting: General community</p> <p>Industry Funded: Unclear</p> <p>Treatment Duration supplement(s): 1</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): cilostazol<br/>Drug Category: Vasodilator:<br/>Nitrates/PDE-5 Inhibitors<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 150mg<br/>Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study</p> <p>Generic Name(s): clopidogrel<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 112.5mg<br/>Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study</p> | <p>N: 10<br/>Supplement(s): Gingko biloba<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 120mg single dose</p> | <p>N1 = 10<br/>No treatment<br/>N2 = 10<br/>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)  | Other Interventions   |
|---------------------------|--|---|---|---|---|---|
| Avogaro 1974 <sup>3</sup> | <p>N screened: NR<br/>N included/randomized: 20</p> <p>Age: NR<br/>%female: NR<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: suffering from hyperlipoproteinemia; high levels of cholesterol and/or serum triglycerides at least twice after being on a balanced diet for two weeks. Classified on the basis of lipids and lipoproteins levels according to the criteria of Fredrickson et al. and recommendations of the WHO</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: Patients suffering from hyperlipoproteinemia</p> | <p>Study Design: Crossover RCT<br/>Region: Europe<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): propranolol<br/>Drug Category: b-blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 20mg OR 60mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 20<br/>Supplement(s): Niacin<br/>Form of Administration: Capsule/tablet<br/>Daily Dose: 250 mg (and non-relevant dose of 750mg/day)</p> | <p>N1 = 20<br/>Placebo<br/>N2 = 20<br/>No treatment<br/>N3 = 20<br/>Intervention3: No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): diet adjusted to bring each patient to ideal weight. The diet provided 45 % carbohydrates, 34 % fats, 15 % proteins and 6 % alcohol; 78% of carbohydrates was given as starches and 22% as sugars. For fats the P/S relationship was 1.87; the amount of dietary cholesterol did not exceed 200 mg.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                   | Population  | Study   | CVD Drug   | Dietary Supplements  | Control Group(s)          | Other Interventions   |
|-------------------------------|---|---|--|--|---------------------------|---|
| Balestrieri 1996 <sup>4</sup> | <p>N screened: NR<br/>N included/randomized: 16</p> <p>Age: 42.5<br/>%female: 44<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: Heterozygous FH diagnosed according to the criteria of Brown and Goldstein; normal thyroid, renal and hepatic function</p> <p>Exclusion Criteria: diabetic, obese</p> <p>Brief Description: Group of heterozygous FH patients on long-term treatment with simvastatin</p> | <p>Study Design: Crossover RCT<br/>Region: Europe<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>Simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: range 10-40mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 8<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/tablet<br/>Daily Dose: 5100mg</p> | <p>N1 = 8<br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): lipid lowering diet (Step 1 AHA diet)</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                  | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)           | Other Interventions  |
|------------------------------|---|--|--|--|----------------------------|--|
| Barbagallo 1999 <sup>5</sup> | <p>N screened: NR<br/>N included/randomized: 24</p> <p>Age: 47.05<br/>%female: 54<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Essential hypertension (outpatient blood pressure &gt;140/90 mm Hg on &gt;=3 occasions and the absence of any history, physical examination, or laboratory evidence of secondary forms of hypertension)</p> <p>Exclusion Criteria: Patients with diabetes mellitus or glucose intolerance</p> <p>Brief Description: Patients with essential hypertension</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): furosemide<br/>Drug Category: Diuretic: Loop<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 25mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 12<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 600mg</p> | <p>N1 = 12<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year            | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                                 | Other Interventions   |
|------------------------|--|--|--|---|--|---|
| Bays 2010 <sup>6</sup> | <p>N screened: 585<br/>N included/randomized: 245</p> <p>Age: 56.15<br/>%female: 42<br/>Ethnicity: Caucasian (89)</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: Between ages 18-79; medically stable; Lipid criteria: non-HDL-C level greater than 160mg/dL and triglycerides between 250 and 599 mg/dL</p> <p>Exclusion Criteria: Use of nonstudy lipid lowering therapy; omega3 supplements; or niacin dosages &gt;400; known allergy to statins or omega3s; symptoms of muscle pain, tenderness or weakness 2mo before study; history of myopathy or rhabdomyolysis</p> <p>Brief Description: patients with combined hyperlipidemia</p> | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Specialty clinic<br/>Industry<br/>Funded: Yes<br/>Treatment Duration supplement(s): 112</p> <p>Treatment Duration CVD Drug(s): 112</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: NR</p> | <p>Generic Name(s): atorvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 10, 20 and 40mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 123<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose:: 4000mg</p> | <p>N1 = 122</p> <p>Placebo plus atorvastatin</p> | <p>Non-CVD Medications: none</p> <p>Dietary Intervention(s): National Cholesterol Education Program therapeutic lifestyle changes diet</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Bays 2009 <sup>7</sup> | <p>N screened: 596<br/>N included/randomized: 167</p> <p>Age: 52.05<br/>%female: 26.35<br/>Ethnicity:<br/>- Caucasian (88)<br/>- African-American (1)<br/>- Hispanic (7)<br/>- Other (4)</p>   | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p>   | <p>Generic Name(s): fenofibrate<br/>Drug Category: Antilipidemic: Fibrate<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 130mg<br/>Reason for taking</p>  | <p>N: 75<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p>   | <p>N1 = 75</p> <p>Placebo</p>                    | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): low saturated fat NCEP Therapeutic Lifestyle Changes (TLC) diet</p>  |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study  | CVD Drug                                      | Dietary Supplements | Control Group(s) | Other Interventions  |
|-------------|--|--|---|---------------------|------------------|--|
|             | <p>Comorbidities (other than indication(s) for CVDs): overweight/obese; Type II Diabetes (20.5%)<br/>                     CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: men and women in good health between 18 and 79 years of age with a body mass index of <math>\geq 25</math> kg/m<sup>2</sup> and <math>\leq 43</math> kg/m<sup>2</sup>; mean fasting TG level of <math>\geq 500</math> mg/dL and <math>&lt; 1300</math> mg/dL as determined by the average of the 2 TG values obtained at 2 weeks before and 1 week prior to randomization; met the criteria for Fredrickson type IV dyslipidemia</p> <p>Exclusion Criteria: use of warfarin, cyclic sex hormone therapy, or other agents known to affect lipid levels during the run-in or treatment period of the study; The use of cyclosporine, systemic corticosteroids, high-dose topical corticosteroids (1500 mg/d), androgens, phenytoin, isotretinoin, or thyroid hormones (except stable-dose replacement therapy for 2 months prior to week 6) during the study also was restricted. Subjects with a known sensitivity to seafood, EPA or DHA, in addition to any history of pancreatitis, significant renal, hepatic, biliary, or gastrointestinal disease, type 1 diabetes mellitus, or uncontrolled type 2 diabetes; Women who were pregnant, lactating, or were of childbearing potential and were not using a medically approved method of contraception</p> | <p>Treatment Duration supplement(s): 56</p> <p>Treatment Duration CVD Drug(s): 56</p> <p>Duration of Followup: 56</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>CVD drug(s): Cardiovascular indication</p> |                     |                  | <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)   | Other Interventions  |
|--------------------------|--|--|--|---|--|--|
|                          | Brief Description: 18-75 years old, overweight/obese, with dyslipidemia  |  |  |   |  |  |
| Bender 1998 <sup>8</sup> | <p>N screened: NR<br/>N included/randomized: 16</p> <p>Age: 53.5<br/>%female: 54.5<br/>Ethnicity:<br/>- African-American (9)<br/>- Hispanic (91)</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: Unclear</p> <p>Inclusion Criteria: between the ages of 18 and 70years, stable anticoagulation status (i.e., INR change no greater than1.63 for at least the past 3 consecutive months, with no warfarin dosage adjustments).</p> <p>Exclusion Criteria: any new medication(s) other than the study medications within 1 month of the study, receiving concurrent therapy with salicylates or other nonsteroidal anti-inflammatory agents, baseline platelet count less than100,000, history of a major bleeding episode while receiving warfarin therapy within the past 5 years, had active peptic ulcer disease within the previous 6 months, or cerebrovascular disease, uncontrolled hypertension, or surgery/trauma within the previous 3 months. Women who</p> | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): warfarin<br/>Drug Category: Anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 3000 or 6000mg</p> | <p>Placebo (matching; R.P. Schering Pharmaceuticals Corporation)</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study   | CVD Drug   | Dietary Supplements  | Control Group(s)       | Other Interventions   |
|--------------------------|--|---|--|--|------------------------|---|
|                          | were pregnant or of child-bearing potential who were not using an acceptable means of contraception<br><br>Brief Description: Patients receiving chronic warfarin therapy for indications requiring oral anticoagulation   |   |  |  |                        |   |
| Bordia 1998 <sup>9</sup> | N screened: NR<br>N included/randomized: 60<br><br>Age: NR<br>%female: NR<br>Ethnicity: NR<br><br>Comorbidities (other than indication(s) for CVDs): Not reported<br>CHD Risk Level: At high risk for CHD<br><br>Inclusion Criteria: Patients with CAD and with old healed MI (> 6 months) with or without angina.<br><br>Exclusion Criteria: NR<br><br>Brief Description: Patients with CAD | Study Design: Controlled clinical trial (CCT)<br>Region: Europe<br>Setting: Not reported<br>Industry<br>Funded: No<br><br>Treatment Duration<br>supplement(s): 90<br><br>Treatment Duration<br>CVD Drug(s): Unclear<br><br>Duration of Followup: End of treatment period<br><br>Duration of Longest Followup: End of treatment period | Generic Name(s): NR<br>Nitrates<br>Drug Category: Vasodilator:<br>Nitrates/PDE-5 Inhibitors<br>Mode of Administration: NR<br>Mean Daily Dose: NR<br>Reason for taking CVD drug(s): Cardiovascular indication | N: 30<br>Supplement(s): Garlic<br>Form of Administration: Capsule/Tablet<br>Daily Dose: 4000mg | N1 = 30<br><br>Placebo | Non-CVD Medications: NR<br><br>Dietary Intervention(s): No<br><br>Exercise Intervention(s): No<br><br>Other Lifestyle Intervention(s): No |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)                                       | Other Interventions   |
|---------------------------|--|---|---|--|--|---|
| Budoff 2004 <sup>10</sup> | <p>N screened: NR<br/>N included/randomized: 23</p> <p>Age: 59.6<br/>%female: 26<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: known coronary artery disease or high risk for coronary artery disease, with a 10-year Framingham risk of developing coronary artery disease of &gt;20%</p> <p>Exclusion Criteria: A contraindication to Aged Garlic Extract therapy including: known hypersensitivity to drug; Weight in excess of 300 lb; Serum creatinine &gt;1.4 mg/d; Triglycerides &gt;400 at visit; Drug or alcohol abuse, or current intake of more than 14 standard drinks per week; Concurrent enrollment in another placebo-controlled Trial; Presence of metal clips or stenting that preclude accurate measure of coronary calcification and angiographic disease by electron beam tomography; Partial ileal bypass or known gastrointestinal disease limiting drug absorption; Current intake of garlic supplement</p> <p>Brief Description: patients with known coronary artery disease or high risk for coronary artery disease</p> | <p>Study Design: Parallel RCT</p> <p>Region: NR, likely North America</p> <p>Setting: NR</p> <p>Industry Funded: Unclear</p> <p>Treatment Duration supplement(s): 365</p> <p>Treatment DurationCVD Drug(s): 365</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Statin</p> <p>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor</p> <p>Mode of Administration: NR</p> <p>Mean Daily Dose: Range of 10-40mg</p> <p>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 9</p> <p>Supplement(s): Garlic</p> <p>Form of Administration: Liquid</p> <p>Daily Dose: 4 ml</p> | <p>N1 = 10</p> <p>Placebo</p> <p>N2 = NA</p> <p>NA</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): All participants were educated on a low-cholesterol diet at entry to the study by the nurse coordinator</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population  | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)                         | Other Interventions   |
|-------------------------|---|---|--|---|--|---|
| Caso 2007 <sup>11</sup> | <p>N screened: NR<br/>N included/randomized: 32</p> <p>Age: 60.63<br/>%female: 47<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: treated for hyperlipidemia with statin; under current NCEP guidelines and reporting myopathic symptoms (only if no other identifiable cause of myopathy could be determined)</p> <p>Exclusion Criteria: Clinical evidence of hepatic, vascular, renal or endocrine disease; coagulopathy; or other serious medical conditions; none were using CoQ10, Vit E or anticoagulants</p> <p>Brief Description: patients using statins with myopathic pain</p> | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: No</p> <p>Treatment Duration supplement(s): 30</p> <p>Treatment DurationCVD Drug(s): 30</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: varying doses for all patients<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 18<br/>Supplement(s): Coenzyme Q10<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 100mg</p> | <p>N1 = 14<br/><br/>Vitamin E, 400IU</p> | <p>Non-CVD Medications: nonsteroidal anti-inflammatory drugs taken by 9 patients</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): patients were already following Adult Treatment Panel III/National Cholesterol Education Program guidelines</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                    | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)   | Other Interventions  |
|--------------------------------|---|--|--|--|--|--|
| Chan 2002 <sup>12</sup>        | <p>N screened: 52<br/>N included/randomized: 52</p> <p>Age: 53.23<br/>%female: 0<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): obese<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: obese (BMI&gt;29kgm-2); dyslipidemia (LDL-C&gt;2.6mmol L-1, non HDL-C&gt;3.4mmolL-1 and triglycerides&gt;1.2mmolL-1); weight-maintenance diet</p> <p>Exclusion Criteria: diabetes;apolipoprotein E2/D2 genotype;macroproteinuria;creatinaemia (&gt;120umolL-1);hypothyroidism;abnormal liver and muscle enzymes; consumed fish oil supplements; more than 30g alcohol</p> <p>Brief Description: viscerally obese men</p> | <p>Study Design: Parallel RCT<br/>Region: NR<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 42</p> <p>Treatment DurationCVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>Atorvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 40mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = Placebo<br/>N2 = fish oil + atorvastatin placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): isocaloric diet</p> <p>Exercise Intervention(s): keep their physical activity constant</p> <p>Other Lifestyle Intervention(s): No</p> |
| d'Arcangues 2004 <sup>13</sup> | <p>N screened: NR<br/>N included/randomized: 9297</p> <p>Age: NR<br/>%female: NR<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p>  | <p>Study Design: Parallel RCT<br/>Region: Multiple (East Asia, Central &amp; South America)<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Unclear</p>  | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 80mg<br/>Reason for taking CVD drug(s): Norplant-induced</p>  | <p>N: 120<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 200mg</p>      | <p>N1 = 122<br/>No treatment<br/>N2 = 123<br/>Placebo</p>    | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p>   |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population  | Study   | CVD Drug   | Dietary Supplements  | Control Group(s)                 | Other Interventions  |
|-----------------------------|---|---|--|--|----------------------------------|--|
|                             | <p>Inclusion Criteria: healthy, between 18 and 38 years old, nonpregnant and nonlactating and had been using the implantable contraceptive Norplant for 1 to 6 months. Able to keep a menstrual diary, willing to return to the clinic at prescribed intervals, agreed not to use vitamins, aspirin, anti-inflammatory drugs, steroids or any other drug that might affect the vaginal bleeding pattern (other than those prescribed in the trial) during the trial or for 3 weeks prior to admission.</p> <p>Exclusion Criteria: they had a last injection of DMPA within 6 months or a last injection of norethisterone enanthate (NET-EN) within 4 months, previous immediate use of Norplant or levonorgestrel-releasing intrauterine device, hemoglobin level lower than 8 g/dl, known hypersensitivity to aspirin or vitamin E or had participated in the pilot study of vitamin E previously conducted in Jakarta.</p> <p>Brief Description: healthy bleeding with Norplant-induced prolonged vaginal bleeding</p> | <p>Treatment Duration supplement(s): 10</p> <p>Treatment Duration CVD Drug(s): 10</p> <p>Duration of Followup: 360</p> <p>Duration of Longest Followup: 360</p> | prolonged vaginal bleeding   |  |                                  |  |
| Davidson 2007 <sup>14</sup> | <p>N screened: 690<br/>N included/randomized: 256</p> <p>Age: 59.8<br/>%female: 42.5<br/>Ethnicity: NR<br/>- Caucasian (95.7)<br/>- African-American (2)<br/>- Hispanic (1.6)</p>   | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Yes</p>   | <p>Generic Name(s): simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose:</p> | <p>N: 123<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 133<br/><br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): NCEP Therapeutic Lifestyle Changes diet</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study   | CVD Drug  | Dietary Supplements | Control Group(s) | Other Interventions  |
|-------------|--|---|---|---------------------|------------------|--|
|             | <p>- Asian (1.2)</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: between ages 18-79;receiving stable doses of statin for control of LDL-C levels for&gt;8weeks;mean fasting TG level&gt;200 and&lt;500mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP</p> <p>Exclusion Criteria: poorly controlled diabetes (HbA1c&gt;8%); history of CV; revascularization procedure or aortic aneurysm within 6mo of screening; history of pancreatitis;sensitivity to statins or omega3s;poorly controlled hypertension (resting blood pressure&gt;160mmHg systolic and/or &gt;100mm Hg; serum creatinine level &gt;2.0 mg/dL;serum transaminase&gt;1.5 times the upper limit of normal;creatinine kinase levels&gt;2 times the ULN</p> <p>Brief Description: patients with persistent hypertriglyceridemia despite statin therapy</p> | <p>Treatment Duration supplement(s): 56</p> <p>Treatment DurationCVD Drug(s): 112</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>40mg</p> <p>Reason for taking CVD drug(s): Cardiovascular indication</p> |                     |                  | <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                    | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)  | Other Interventions   |
|--------------------------------|---|--|---|--|---|---|
| Davidson<br>1997 <sup>15</sup> | <p>N screened: 46<br/>N included/randomized: 30</p> <p>Age: NR<br/>%female: NR<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Serum lipid values determined as mean values from 2 fasting measurements taken 1 week apart. Qualifying lipid concentrations were LDL cholesterol &gt;/ 160 and &lt;/ 240 mg/dl, HDL &lt;/ 50mg/dl for men and &lt;/60 mg/dl for women, and fasting triglycerides of 200 to 600 mg/dl after &gt;/ 4 weeks following a National Cholesterol Education Program Step I Diet.</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: Hyperlipidemic subjects</p> | <p>Study Design: Parallel RCT<br/>Region: NR<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 84</p> <p>Treatment DurationCVD Drug(s): 84</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>Simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 10mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 10<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 10000mg</p> | <p>N1 = 10<br/>No treatment<br/>N2 = 9<br/>Fish oil</p> | <p>Non-CVD Medications: NR<br/>Dietary Intervention(s): No<br/>Exercise Intervention(s): No<br/>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                        | Population  | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                   | Other Interventions  |
|------------------------------------|---|--|--|---|------------------------------------|--|
| De, Caterina<br>2002 <sup>16</sup> | <p>N screened: NR<br/>N included/randomized: 43</p> <p>Age: 63.1<br/>%female: 51<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): diabetes (19%)<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: hypercholesterolemic subjects (Fredrickson IIa or IIb) with serum cholesterol 200 mg/dL and proven vascular (coronary, carotid, or peripheral arterial) disease.</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: hypercholesterolemic subjects with proven vascular disease</p> | <p>Study Design:<br/>Crossover RCT</p> <p>Treatment<br/>Duration: 30</p> <p>Region: NR<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>30</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 30</p> <p>Duration of<br/>Followup: End<br/>of treatment<br/>period</p> <p>Duration of<br/>Longest<br/>Followup: End<br/>of treatment<br/>period</p> | <p>Generic Name(s):<br/>NR</p> <p>simvastatin</p> <p>Drug Category:<br/>Antilipidemic: HMG<br/>Co-A Reductase<br/>Inhibitor</p> <p>Mode of<br/>Administration: Oral</p> <p>Mean Daily Dose:<br/>10mg</p> <p>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> | <p>N: 21</p> <p>Supplement(s):<br/>Vitamin E</p> <p>Form of<br/>Administration:<br/>Capsule/Tablet</p> <p>Daily Dose:<br/>600mg</p> | <p>N1 = 22</p> <p>No treatment</p> | <p>Non-CVD<br/>Medications: NR</p> <p>Dietary<br/>Intervention(s): No</p> <p>Exercise<br/>Intervention(s): No</p> <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)                     | Other Interventions  |
|---------------------------|--|---|---|---|--------------------------------------|--|
| Dehmer 1988 <sup>17</sup> | <p>N screened: 149<br/>N included/randomized: 90</p> <p>Age: 56<br/>%female: 0<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): diabetes 28% in control group; 21% in treatment group<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: male patients referred to laboratory for angioplasty</p> <p>Exclusion Criteria: age over 80 years, severe confounding medical problems, angioplasties for restenosis that had developed after an earlier procedure; acute MI or unstable ischemic symptoms that persisted despite all medical therapies.</p> <p>Brief Description: male patients undergoing angioplasty</p> | <p>Study Design: Parallel RCT<br/>Region: North America<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: No</p> <p>Treatment Duration supplement(s): 187</p> <p>Treatment DurationCVD Drug(s): 187</p> <p>Duration of Followup: 270,360</p> <p>Duration of Longest Followup: 360</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 325mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name: dipyridamole<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 225mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name: NR<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 43<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 3200mg</p> | <p>N1 = 39<br/><br/>No treatment</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Desideri                  | N screened: 67   | Study Design:   | Generic Name(s):  | N: 31   | N1 = 19                              | Non-CVD  |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year        | Population   | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)                                 | Other Interventions   |
|--------------------|--|---|---|--|--|---|
| 2003 <sup>18</sup> | <p>N included/randomized: 67</p> <p>Age: 47.7<br/>%female: 42<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Serum LDL-cholesterol levels of more than 5.2 mmol/liter and less than 7.8 mmol/liter and fasting triglyceride levels of less than 1.7 mmol/liter after 30d on an American heart step I diet. Normal M-mode and B-mode echocardiograms and 12-lead electrocardiogram</p> <p>Exclusion Criteria: age of less than 25 year or higher than 55 year, pregnancy, concomitant diseases, personal history of previous cerebro-or cardiovascular disease, diabetes of either type I or II, hypertension, obesity, smoking, drug consumption (including vitamins, aspirin, birth control) alcohol intake of more than 10g, proteinuria, serum creatinine of more than 100microM or atherosclerotic lesions of the neck and limb vessels, Patients with allergic diathesis regarding both type I and type II immune responses and/or reporting respiratory, GI or genotourinary tracts infections during the last 3 months.</p> <p>Brief Description: Hypercholesterolemic</p> | <p>Parallel RCT<br/>Region: Europe<br/>Setting: Not reported<br/>Industry<br/>Funded:<br/>Unclear<br/>Treatment<br/>Duration<br/>supplement(s): 180</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 180</p> <p>Duration of<br/>Followup: End of treatment period</p> <p>Duration of<br/>Longest<br/>Followup: End of treatment period</p> | <p>NR<br/>Simvastatin<br/>Drug Category:<br/>Antilipidemic: HMG<br/>Co-A Reductase<br/>Inhibitor<br/>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:<br/>40mg<br/>Reason for taking<br/>CVD drug(s):</p> <p>Generic Name: NR<br/>Bezafibrate<br/>Drug Category:<br/>Antilipidemic: Fibrate<br/>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:<br/>800mg<br/>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> | <p>Supplement(s):<br/>Vitamin E<br/>Form of<br/>Administration:<br/>Capsule/Tablet<br/>Daily Dose: 400IU</p> | <p>No treatment<br/>N2 = 17<br/>No treatment</p> | <p>Medications: NR<br/>Dietary<br/>Intervention(s): No<br/>Exercise<br/>Intervention(s): No<br/>Other Lifestyle<br/>Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                   | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                   | Other Interventions  |
|-------------------------------|--|--|--|---|------------------------------------|--|
|                               | patients   |  |  |   |                                    |  |
| Di Spirito 2008 <sup>19</sup> | <p>N screened: 50<br/>N included/randomized: 50</p> <p>Age: 35<br/>%female: 20<br/>Ethnicity:<br/>- Caucasian (98)<br/>- African-American (2)</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: Women who were pregnant or lactating or who were planning a pregnancy; Individuals with a history of hypersensitivity or allergy to study medications</p> <p>Brief Description: healthy non-smoking men and women within 15% of ideal body weight</p> | <p>Study Design: Crossover RCT</p> <p>Region: North America</p> <p>Setting: Research Facility</p> <p>Industry Funded: Yes</p> <p>Treatment Duration supplement(s): 14</p> <p>Treatment DurationCVD Drug(s): 14</p> <p>Duration of Followup: 1</p> <p>Duration of Longest Followup: 1</p> | <p>Generic Name(s): atorvastatin</p> <p>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 80mg</p> <p>Reason for taking CVD drug(s): pharmacokinetics of atorvastatin and P-OM3</p> | <p>N: 50</p> <p>Supplement(s): Omega-3 (EPA, DHA or both)</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 4000mg</p> | <p>N1 = 50</p> <p>No treatment</p> | <p>Non-CVD Medications: hormonal contraceptives (portion NR)</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)  | Other Interventions   |
|--------------------------|--|--|---|---|---|---|
| Duffy 2001 <sup>20</sup> | <p>N screened: NR<br/>N included/randomized: 29</p> <p>Age: 28.7<br/>%female: 54<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: hypercholesterolaemia (total cholesterol and LDL levels were above the 75th percentile for age and gender based on NHFA Risk Factor Prevalence Study)</p> <p>Exclusion Criteria: any other risk factor for CAD, cardiovascular disease, any other major disease; volunteers on CV medications or vitamin supplements</p> <p>Brief Description: young patients with hypercholesterolaemia</p> | <p>Study Design: Parallel RCT<br/>Region: NR (likely Australia)<br/>Setting: Not reported<br/>Industry Funded: No</p> <p>Treatment Duration supplement(s): 180</p> <p>Treatment DurationCVD Drug(s): 180</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: : End of treatment period</p> | <p>Generic Name(s): NA<br/>simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: starting dose 10mg; ending dose 40mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 6<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 1000 IU</p> | <p>N1 = 7<br/>Placebo<br/>N2 = 7<br/>No treatment<br/>N3 = 6<br/>Intervention3: Vitamin E</p> | <p>Non-CVD Medications: estrogen-based oral contraceptives (portion of population)</p> <p>Dietary Intervention(s): dietary advice and information sheets on cholesterol lowering diets</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                  | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)                      | Other Interventions  |
|------------------------------|---|--|---|--|---------------------------------------|--|
| Eritsland 1996 <sup>21</sup> | <p>N screened: NR<br/>N included/randomized: 291</p> <p>Age: 60.49<br/>%female: 12.5<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Diabetes</p> <p>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: admitted for coronary artery bypass grafting without concomitant cardiac surgery.</p> <p>Exclusion Criteria: medical contraindications to any of the treatment principles; refused participation; early (&lt;2 days) perioperative death or complications; presumed lack of compliance; indication for anticoagulation; administrative reasons</p> <p>Brief Description: Subjects undergoing coronary artery bypass grafting without surgery</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Specialty Clinic<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 365</p> <p>Treatment DurationCVD Drug(s): 365</p> <p>Duration of Followup: 365</p> <p>Duration of Longest Followup: 365</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 300mg<br/>Reason for taking CVD drug(s):</p> | <p>N: 143<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 148<br/><br/>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): Verbal and written dietary advice; decreased intake of saturated fatty acids advised; told to refrain from cod-liver oil and other fish oil products; dietary records obtained from a random sample.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                  | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)                    | Other Interventions  |
|------------------------------|---|--|--|--|-------------------------------------|--|
| Eritsland 1996 <sup>21</sup> | <p>N screened: NR<br/>N included/randomized: 319</p> <p>Age: 59.54<br/>%female: 13.8<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Diabetes</p> <p>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: admitted for coronary artery bypass grafting without concomitant cardiac surgery.</p> <p>Exclusion Criteria: medical contraindications to any of the treatment principles; refused participation; early (&lt;2 days) perioperative death or complications; presumed lack of compliance; indication for anticoagulation; administrative reasons</p> <p>Brief Description: Subjects undergoing coronary artery bypass grafting without surgery</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Specialty Clinic<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 365</p> <p>Treatment DurationCVD Drug(s): 365</p> <p>Duration of Followup: 365</p> <p>Duration of Longest Followup: 365</p> | <p>Generic Name(s): warfarin<br/>Drug Category: Anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 174<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 145</p> <p>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): Verbal and written dietary advice; decreased intake of saturated fatty acids advised; told to refrain from cod-liver oil and other fish oil products; dietary records obtained from a random sample.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population  | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)                     | Other Interventions  |
|----------------------------|---|---|---|---|--------------------------------------|--|
| Ferraro 2009 <sup>22</sup> | <p>N screened: NR<br/>N included/randomized: 30</p> <p>Age: 45<br/>%female: 36.6<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: patients with biopsy-proven IgAN and persistent proteinuria (&gt;200 mg) despite treatment with ACE inhibitors and/or ARB. only patients with at least two positive determinations were included</p> <p>Exclusion Criteria: dialysis or kidney transplantation, diabetes mellitus, Henoch-Schoenlein purpura, systemic lupus erythematosus and an active or recent (&lt;1 year) treatment with immunosuppressors and/or PUFA.</p> <p>Brief Description: patients with biopsy-proven IgAN and persistent proteinuria</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Unclear<br/>Treatment<br/>Duration supplement(s): 180</p> <p>Treatment Duration CVD Drug(s): 180</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ramipril<br/>Drug Category: RAAS Antagonist: ACEI<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 10mg<br/>Reason for taking CVD drug(s): IgA nephropathy</p> | <p>N: 15<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 3000mg</p> | <p>N1 = 15<br/><br/>No treatment</p> | <p>Non-CVD Medications: Steroid 60 days prior to randomization in 1 vs. 2 pts (Irbesartan 300mg)</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)           | Other Interventions  |
|----------------------------|---|--|---|--|----------------------------|--|
| Gardner 2007 <sup>23</sup> | <p>N screened: 188<br/>N included/randomized: 67</p> <p>Age: 68.5<br/>%female: 40<br/>Ethnicity:<br/>- Caucasian (75)<br/>- African-American (5)<br/>- Hispanic (13)<br/>- Asian (7)</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: experienced leg pain during walking that was characteristic of the intermittent claudication symptom of PAD, or who might be at risk for PAD due to either a family history of cardiovascular disease (CVD) or elevated CVD risk factors. Older than 18 years of age, had not been taking (for at least 1 month prior to randomization) and did not plan to take (for the duration of the study) any medications or dietary supplements known to affect blood coagulation, and were able to tolerate daily use of aspirin for 6 weeks.</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: adult patients at risk for PAD not taking any medications known to affect blood coagulation and able to tolerate aspirin for 6 weeks</p> | <p>Study Design: Parallel RCT<br/>Region: NR (likely North America)<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment Duration CVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 325mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 29<br/>Supplement(s): Gingko biloba<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 300mg</p> | <p>N1 = 26<br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)                | Other Interventions  |
|-------------------------|---|--|--|--|---------------------------------|--|
| Garg 1995 <sup>24</sup> | <p>N screened: 98<br/>N included/randomized: 62</p> <p>Age: 54.19<br/>%female: 29.6<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): NR<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: acute ischemic stroke, either sex with sudden hemoplegia of either side with or without speech involvement, with cranial CT scan (non-contrast enhanced) showing a hypodense lesion (infarct) in the territory of either middle cerebral artery</p> <p>Exclusion Criteria: ischemia in posterior cerebral territory, overt systemic disease (e.g. recent myocardial infarction, renal failure, severe systemic infection, deeply comatose.</p> <p>Brief Description: patients with acute ischemic stroke</p> | <p>Study Design: Parallel RCT<br/>Region: Rest of Asia<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment<br/>Duration<br/>supplement(s): 7</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): Unclear</p> <p>Duration of<br/>Followup: 14</p> <p>Duration of<br/>Longest<br/>Followup: 14</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 29<br/>Supplement(s): Gingko biloba<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 240mg</p> | <p>N1 = 26<br/><br/>Placebo</p> | <p>Non-CVD Medications: antibiotics and short-term glucocorticoids</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population   | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)                    | Other Interventions   |
|-----------------------------|--|--|--|--|-------------------------------------|---|
| Glynn<br>2007 <sup>25</sup> | <p>N screened: 453787<br/>N included/randomized: 65169</p> <p>Age: NR<br/>%female: 100<br/>Ethnicity:<br/>- Caucasian (94.8)<br/>- African-American (2.3)<br/>- Hispanic (1.1)<br/>- Asian (1.4)<br/>- Other (0.4)</p> <p>Comorbidities (other than indication(s) for CVDs): Obesity (18%), Type II Diabetes (portion), women with deep vein thrombosis or pulmonary embolism were not excluded (portion NR)<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: age 45 years or older; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of adverse effects from aspirin; no use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week, or willingness to forgo their use; no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or beta carotene more than once a week.</p> <p>Exclusion Criteria: women who currently used anticoagulants</p> <p>Brief Description: Healthy women not currently using anticoagulants</p> | <p>Study Design:<br/>Parallel RCT<br/>Region: North America<br/>Setting:<br/>General community<br/>Industry<br/>Funded:<br/>Unclear</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>3650</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 3650</p> <p>Duration of<br/>Followup: 3650</p> <p>Duration of<br/>Longest<br/>Followup: 3650</p> | <p>Generic Name(s):<br/>ASA<br/>Drug Category:<br/>Antiplatelets<br/>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:<br/>100mg/every other<br/>day<br/>Reason for taking<br/>CVD drug(s):<br/>prevention</p> | <p>N: 19,937<br/>Supplement(s):<br/>Vitamin E<br/>Form of<br/>Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>600IU/every other<br/>day</p> | <p>N1 = 19,939<br/><br/>Placebo</p> | <p>Non-CVD<br/>Medications:<br/>Hormone therapy<br/>(30%)<br/><br/>Dietary<br/>Intervention(s): No<br/><br/>Exercise<br/>Intervention(s): No<br/><br/>Other Lifestyle<br/>Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population  | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)                   | Other Interventions  |
|--------------------------|---|--|---|---|------------------------------------|--|
| Gosai 2008 <sup>26</sup> | <p>N screened: NR<br/>N included/randomized: 48</p> <p>Age: 37<br/>%female: 25<br/>Ethnicity:<br/>- Caucasian (42)<br/>- Other (arabic, african or undefined ethnicity) (6)</p> <p>Comorbidities (other than indication(s) for CVDs: NR</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Healthy non-smoking men and women between the ages of 18 and 55 years who were within 15% of ideal body weight</p> <p>Exclusion Criteria: Women who were pregnant, lactating, or planning a pregnancy; individuals with a history of hypersensitivity or allergy to study medications</p> <p>Brief Description: healthy adult volunteers</p> | <p>Study Design: Crossover RCT</p> <p>Region: NR</p> <p>Setting: NR</p> <p>Industry Funded: Yes</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: 1</p> <p>Duration of Longest Followup: 1</p> | <p>Generic Name(s): rosuvastatin</p> <p>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 40mg</p> <p>Reason for taking CVD drug(s): Pharmacokinetics and pharmackodynamic study</p> | <p>N: 48</p> <p>Supplement(s): Omega-3 (EPA, DHA or both)</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 4000mg</p> | <p>N1 = 48</p> <p>No treatment</p> | <p>Non-CVD Medications: hormonal contraceptives (portion NR)</p> <p>Dietary Intervention(s): meal plans provided 4 and 9h after each dosing</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)                   | Other Interventions  |
|--------------------------|--|--|---|--|------------------------------------|--|
| Govil 1979 <sup>27</sup> | <p>N screened: NR<br/>N included/randomized: 80</p> <p>Age: NR<br/>%female: 31<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: congestive cardiac failure</p> <p>Exclusion Criteria: renal insufficiency</p> <p>Brief Description: patients of congestive cardiac failure</p> | <p>Study Design:<br/>Controlled<br/>Clinical Trial</p> <p>Region: Rest of Asia</p> <p>Setting: Primary Care</p> <p>Industry Funded:<br/>Unclear</p> <p>Treatment Duration supplement(s): NR</p> <p>Treatment DurationCVD Drug(s): NR</p> <p>Duration of Followup: 8</p> <p>Duration of Longest Followup: 8</p> | <p>Generic Name(s):<br/>Digoxin</p> <p>Drug Category:<br/>Inotropics</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose:<br/>NR</p> <p>Reason for taking CVD drug(s):Cardiovascular indication</p> <p>Generic Name(s):<br/>Diuretics</p> <p>Drug Category:<br/>Diuretic: Loop</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose:<br/>NR</p> <p>Reason for taking CVD drug(s):Cardiovascular indication</p> | <p>N: 20</p> <p>Supplement(s):<br/>Magnesium</p> <p>Form of Administration:<br/>Liquid</p> <p>Capsule/Tablet Daily Dose: 396 mEq</p> | <p>N1 = 60</p> <p>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population  | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)                                    | Other Interventions  |
|---------------------------|---|--|---|---|---|--|
| Hajda, 2010 <sup>28</sup> | <p>N screened: NR<br/>N included/randomized: 10</p> <p>Age: 28.8<br/>%female: 0<br/>Ethnicity: Caucasian</p> <p>Comorbidities (other than indication(s) for CVDs: None</p> <p>CHD Risk Level: At low risk for CHD</p> <p>Inclusion Criteria: healthy male subjects (based on physical examinations, standard clinical chemistry and hematology analyses)</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: patients of congestive cardiac failure</p> | <p>Study Design: Randomized cross over (the design may not fit the exact description of RCT for this review)</p> <p>Region: Europe</p> <p>Setting: Unclear</p> <p>Industry Funded: Yes</p> <p>Treatment Duration supplement(s): 21 days</p> <p>Treatment Duration<sub>CVD</sub> Drug(s): 21 days</p> <p>Duration of Followup: 21 days</p> <p>Duration of Longest Followup: 22 days</p> | <p>Generic Name(s): Statins (pravastatin, or simvastatin)</p> <p>Mode of Administration: Oral</p> <p>Daily Dose: 20 mg</p> <p>Reason for taking CVD drug(s):non-Cardiovascular indication</p> <p>Generic Name(s): Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: NR</p> <p>Reason for taking CVD drug(s): non-Cardiovascular indication</p> | <p>N: 10</p> <p>Supplement(s): Garlic</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 600 mg bid (twice daily)</p> | <p>N<sub>1</sub> = 10</p> <p>No treatment</p>       | <p>Non-CVD Medications: No</p> <p>Dietary Intervention(s): standardized meals during the study period; all subjects were instructed to abstain from taking any type of medication, including over-the-counter remedies and supplements, grapefruit, caffeine, or alcohol-containing food or beverages for at least 3 days prior to the start of the study and throughout the course of the study.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): NR</p> |
| Hansen 1993 <sup>29</sup> | <p>N screened: NR<br/>N included/randomized: 15</p> <p>Age: 49<br/>%female: 53.3<br/>Ethnicity: NR</p>  | <p>Study Design: Crossover RCT</p> <p>Region: Europe</p> <p>Setting: Primary care</p> <p>Industry</p>  | <p>Generic Name(s): lovastatin</p> <p>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor</p>  | <p>N=15</p> <p>Supplement(s): Fish oils/marine oils</p> <p>Form of</p>  | <p>N=15</p> <p>Placebo (olive oil) + lovastatin</p> | <p>Non-CVD Medications: No</p> <p>Dietary Intervention(s): diet low in cholesterol</p>   |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)   | Other Interventions  |
|-------------|--|--|--|---|--|--|
|             | <p>Comorbidities (other than indication(s) for CVDs): tendon xanthomas (3)</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: hypercholesterolemia, nonobese (within 15% of their ideal body weight) and had a total serum cholesterol level above 9.0 mmol/l and a triglyceride level below 2.0 mmol/l on two occasions after 8-20 weeks on a diet low in cholesterol and saturated fat (American Heart Association step I diet), normal thyroid, renal, and hepatic function, no diabetes, manifest cardiovascular disease, or other chronic illnesses</p> <p>Exclusion Criteria: peptic ulcers, gastrointestinal disorders likely to influence drug absorption, alcoholism, drug abuse, or mental illness</p> <p>Brief Description: hypercholesterolemic patients within 15% of their ideal body weight</p> | <p>Funded:<br/>Unclear</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>42</p> <p>Treatment<br/>Duration<br/>CVD<br/>Drug(s): 42</p> <p>Duration of<br/>Followup: 84</p> <p>Duration of<br/>Longest<br/>Followup: 84</p> | <p>Mode of<br/>Administration: Oral</p> <p>Mean Daily Dose:<br/>40mg</p> <p>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> | <p>Administration:<br/>Capsule/Tablet</p> <p>Daily Dose:<br/>6000mg</p> | <p>N=15<br/>Placebo<br/>(olive oil) +<br/>lovastatin<br/>placebo</p> | <p>and saturated fat<br/>(American Heart<br/>Association step I<br/>diet)</p> <p>Exercise<br/>Intervention(s): No</p> <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)  | Other Interventions   |
|--------------------------|--|---|---|---|---|---|
| Howe 1994 <sup>30</sup>  | <p>N screened: NR<br/>N included/randomized: 61</p> <p>Age: 55<br/>%female: 44.6<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Uncomplicated essential hypertension controlled by ACE inhibitor monotherapy</p> <p>Exclusion Criteria: unstable heart, renal or liver disease, DBP &gt;105mmHg, consumed more than 20 cigarettes or 40mg of alcohol per day, exercised erratically, institutionalized, or have no control over the preparation of their food</p> <p>Brief Description: Uncomplicated essential hypertension controlled by ACE inhibitor monotherapy</p> | <p>Study Design: Parallel RCT<br/>Region: Australia/New Zealand<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 42</p> <p>Treatment DurationCVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Captopril</p> <p>Drug Category: RAAS Antagonist: ACEI<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 28<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 5000mg</p>     | <p>N1 = 28<br/>Placebo</p>  | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): low/vs/normal sodium diet</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Isley 2007 <sup>31</sup> | <p>N screened: 100<br/>N included/randomized: 36</p> <p>Age: 49.93<br/>%female: 31<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): NR</p>  | <p>Study Design: Parallel RCT</p> <p>Region: NR, likely North America</p> <p>Setting: NR</p>  | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 325mg<br/>Reason for taking</p>  | <p>N: 8<br/>Supplement(s): Omega-3 (EPA, DHA or both)<br/>Form of Administration: Capsule/tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 7<br/>Omega-3 placebo (corn oil ethyl esters 4g/d) +- niacin placebo (Calcium</p> | <p>Non-CVD Medications: ibuprofen or acetaminophen were allowed as needed</p> <p>Dietary Intervention(s):</p>   |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study   | CVD Drug   | Dietary Supplements | Control Group(s)  | Other Interventions  |
|-------------|--|---|--|---------------------|---|--|
|             | <p>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: Men and postmenopausal or surgically sterile women ages 21 to 70 years were studied; necessary for fasting serum triglyceride levels to be between 150 and 500 mg/dL; A normal chemistry screen was required to exclude secondary hypertriglyceridemia. HDL-C had to be</p> <hr/> <p>40 mg/dL for men and</p> <hr/> <p>50 mg/dL for women. LDL-C inclusion criteria were based on 1993 National Cholesterol Education Program guidelines:</p> <hr/> <p>130mg/dL with CHD;</p> <hr/> <p>160mg/dL with two or more risk factors; and</p> <hr/> <p>190 mg/dL with one risk factor</p> <p>Exclusion Criteria: Subjects with diabetes mellitus, peptic ulcer disease, gouty arthritis, or hyperuricemia; or known hepatic, renal, autoimmune, or gastrointestinal diseases; taking warfarin, chronic nonsteroidal anti-inflammatory agents, or any medication known to affect lipid metabolism</p> <p>Brief Description: patients with</p> | <p>Industry Funded: No</p> <p>Treatment Duration supplement(s): 135</p> <p>Treatment Duration CVD Drug(s): 90</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>CVD drug(s): cardiovascular indication</p> <p>+/-</p> <p>Immediate-release niacin tablets (Rugby Laboratories, West Hempstead, NY). Patients Administration: Oral Mean Daily Dose: escalating dose 500-3000 mg x3 /d Reason for taking CVD drug(s): cardiovascular indication</p> |                     | <p>gluconate USP; Roxane Laboratories, Columbus, OH).</p> | <p>Subjects were instructed to follow a low-fat, low-cholesterol diet per the National Cholesterol Education Program</p> <p>Exercise Intervention(s): maintain their usual exercise habits</p> <p>Other Lifestyle Intervention(s): abstain from alcohol excess</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                   | Other Interventions  |
|--------------------------|--|--|--|---|------------------------------------|--|
|                          | atherogenic dyslipidemia   |  |  |   |                                    |  |
| Jiang 2005 <sup>32</sup> | <p>N screened: NR<br/>N included/randomized: 12</p> <p>Age: NR<br/>%female: 0<br/>Ethnicity:<br/>- Caucasian (6)<br/>- Asian (6)</p> <p>Comorbidities (other than indication(s) for CVDs: NR</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: All subjects were nonsmokers and were selected on the basis of medical history, physical examination and clinical laboratory test results (including INR, platelet aggregation, creatinine, bilirubin, albumin and total protein)</p> <p>Exclusion Criteria: Subjects with current or past medical conditions that might affect the pharmacokinetic or pharmacodynamic response to warfarin; not taken any medication for at least 2 weeks before commencing the study</p> <p>Brief Description: healthy male subjects</p> | <p>Study Design: Crossover RCT</p> <p>Region: NR likely Australia</p> <p>Setting: Primary Care</p> <p>Industry Funded: No</p> <p>Treatment Duration supplement(s): 7</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): warfarin</p> <p>Drug Category: Anticoagulants</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 25mg – 1 dose</p> <p>Reason for taking CVD drug(s): Pharmacokinetics and pharmacodynamic study</p> | <p>N: 12<br/>Supplement(s): Gingko biloba</p> <p>Form of Administration: Capsule/tablet</p> <p>Daily Dose: 12000mg</p> <p>N: 12<br/>Supplement(s): Ginger</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 3600mg</p> | <p>N1 = 12</p> <p>No treatment</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population  | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)   | Other Interventions  |
|--------------------------|---|--|---|---|--|--|
| Jiang 2004 <sup>33</sup> | <p>N screened: NR<br/>N included/randomized: 12</p> <p>Age: NR<br/>%female: 0<br/>Ethnicity:<br/>- Caucasian (8)<br/>- Asian (4)</p> <p>Comorbidities (other than indication(s) for CVDs: NR</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: All subjects were nonsmokers and were selected on the basis of medical history, physical examination, and clinical laboratory test results (including INR, platelet aggregation, creatinine, bilirubin, albumin and total protein)</p> <p>Exclusion Criteria: Subjects with current or past medical conditions that might affect the pharmacokinetic or pharmacodynamic response to warfarin; had not taken any medication for at least 2 weeks before commencing the study</p> <p>Brief Description: healthy male subjects</p> | <p>Study Design:<br/>Crossover RCT</p> <p>Region: NR</p> <p>Setting: NR<br/>Industry<br/>Funded: No</p> <p>Treatment Duration supplement(s): 7</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: 3</p> <p>Duration of Longest Followup: 3</p> | <p>Generic Name(s):<br/>Warfarin<br/>Drug Category:<br/>Anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose:<br/>25mg – single dose<br/>Reason for taking<br/>CVD drug(s):<br/>Pharmacokinetics and pharmacodynamic study</p> | <p>N: 12<br/>Supplement(s):<br/>Ginseng<br/>Form of Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>3000mg</p> | <p>N1 = 12<br/><br/>No treatment<br/><br/>N2 = 12<br/><br/>non-relevant supplement</p> | <p>Non-CVD Medications: No<br/><br/>Dietary Intervention(s): No<br/><br/>Exercise Intervention(s): No<br/><br/>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                     | Other Interventions  |
|----------------------------|--|--|--|---|--------------------------------------|--|
| Kaul<br>1992 <sup>34</sup> | <p>N screened: NR<br/>N included/randomized: 107</p> <p>Age: 57.37<br/>%female: 15<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): unstable angina 33.64%<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: patients undergoing coronary angioplasty</p> <p>Exclusion Criteria: history of bleeding disorder;on oral anticoagulants;emergency angioplasty;recent MI;angioplasty of a saphenous vein bypass graft;angioplasty for restenosis;inability to perform treadmill test</p> <p>Brief Description: patients undergoing coronary angioplasty</p> | <p>Study Design: Parallel RCT<br/>Region: Rest of Asia<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 180</p> <p>Treatment DurationCVD Drug(s): 180</p> <p>Duration of Followup: 0</p> <p>Duration of Longest Followup: 180</p> | <p>Generic Name(s): NR<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s):</p> <p>Generic Name: ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 150 mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name: heparin<br/>Drug Category: anticoagulants<br/>Mode of administration: IV<br/>Mean daily dose: 1000 units/hour for 24 hours (max. 20,000 units)</p> | <p>N: 58<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 10 capsules given to patients, daily dose NR</p> | <p>N1 = 49<br/><br/>No treatment</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year            | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)                   | Other Interventions  |
|------------------------|---|--|--|--|------------------------------------|--|
| Kim 2010 <sup>35</sup> | <p>N screened: NR<br/>N included/randomized: 24</p> <p>Age: 24.1<br/>%female: 0<br/>Ethnicity: Asian (100)</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: Unclear</p> <p>Inclusion Criteria: Healthy males, confirmed by physical exam and lab testing</p> <p>Exclusion Criteria: Those outside 80%-120% of ideal weight</p> <p>Brief Description: Healthy, adult, Korean males</p> | <p>Study Design: Crossover RCT</p> <p>Region: East Asia</p> <p>Setting: General community</p> <p>Industry Funded: Yes</p> <p>Treatment Duration supplement(s): single dose</p> <p>Treatment Duration CVD Drug(s): Single dose</p> <p>Duration of Followup: 2</p> <p>Duration of Longest Followup: NA</p> | <p>Generic Name(s): Ticlopidine</p> <p>Drug Category: Antiplatelets</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 250mg single dose</p> <p>Reason for taking CVD drug(s): Pharmacokinetics and pharmacodynamic study</p> | <p>N: 12</p> <p>Supplement(s): Ginkgo Biloba</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 80mg single dose</p> | <p>N1 = 12</p> <p>No treatment</p> | <p>Non-CVD Medications: None</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Lee 2008 <sup>36</sup> | <p>N screened: 200<br/>N included/randomized: 34</p> <p>Age: 63.73<br/>%female: 44<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia</p>   | <p>Study Design: Parallel RCT</p> <p>Region: East Asia</p> <p>Setting: Primary Care</p> <p>Industry</p>  | <p>Generic Name(s): Warfarin</p> <p>Drug Category: Anticoagulants</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 3.5mg</p> <p>Reason for taking CVD</p>   | <p>N: 12</p> <p>Supplement(s): Ginseng</p> <p>Form of Administration: aqueous extracts</p> <p>Daily Dose: 1500mg</p>               | <p>N1 = 13</p> <p>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle</p>                       |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population  | Study  | CVD Drug   | Dietary Supplements | Control Group(s) | Other Interventions        |
|-------------|---|--|--|---------------------|------------------|----------------------------|
|             | <p>CHD Risk Level: high risk for CHD</p> <p>Inclusion Criteria: patients with ischemic stroke who received care between Mar 2007 and Aug 2007 in the Korean Medical Hospital, Kyung Hee University Medical Center; diagnosis of stroke was defined as an acute focal or global neurologic deficit lasting more than 24 hrs without an apparent cause other than one of vascular origin, subsequently confirmed by brain CT or MRI scan within 72 hours from onset of the symptoms; Subjects were required to have scores of 3 or more on the Glasgow Outcome Scale</p> <p>Exclusion Criteria: hepatic disease (alanine,aminotransferase and aspartate &gt;2x the upper limit of laboratory normal range); history or presence of renal insufficiency (creatinine&gt; 1.2mg/dL);hematologic abnormalities(thrombocytopenia,low granulocyte count, anemia, hypofibrinogenemia, hemophilia, vascularpurpura, hemopathy with prolongation of bleeding time, a baseline INR above the normal range [more than 1.4]); condition liable to interfere with the absorption, metabolism,or excretion of warfarin; positive test result for hepatitis (B and C) except for vaccinated patients; positive HIV test on admission lab; taking medications such as aspirin and clopidogrel</p> <p>Brief Description: patients with histories</p> | <p>Funded: No</p> <p>Treatment Duration supplement(s): 14</p> <p>Treatment DurationCVD Drug(s): 14</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>drug(s):Pharmacokinetics and pharmackodynamic study</p> |                     |                  | <p>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year            | Population   | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)  | Other Interventions  |
|------------------------|--|--|---|---|---|--|
|                        | of ischemic stroke   |  |   |   |   |  |
| Liu 2003 <sup>37</sup> | <p>N screened: NR<br/>N included/randomized: 88</p> <p>Age: 60<br/>%female: 69.3<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: Mixed - all participants were hyperlipidemic and subjects with obesity, high BMI, high blood pressure or insulin resistance were not excluded</p> <p>Inclusion Criteria: adults with hyperlipidemia, fasting TC &gt; 6.2 mmol/L and/or fasting TG &gt;1.8 mmol/L. Subjects with obesity, high BMI, high blood pressure or insulin resistance were not excluded</p> <p>Exclusion Criteria: Subjects with previously known lipid changes undergoing treatment; allergy to statins; diabetes mellitus; liver or renal disease; other diseases that might influence lipid metabolism; pregnant women; participation in another drug study during the last month; treatment with antimycotic drugs or antibiotics that might interfere with the effects of statins; other drugs that may influence lipid metabolism; cancer or other serious diseases.</p> <p>Brief Description: Adults with hyperlipidemia</p> | <p>Study Design: Parallel RCT<br/>Region: NR (likely Europe)<br/>Setting: Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 84</p> <p>Treatment Duration CVD Drug(s): 84</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral</p> <p>Mean Daily Dose: 10mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 29<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 9.2g</p> | <p>N1 = 18<br/>No treatment<br/>N2 = 22<br/>Low fat diet<br/>N3 = 19<br/>Fish oil</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): decrease intake of fat milk, cream, and fat cheese</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                      | Population  | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)           | Other Interventions   |
|----------------------------------|---|---|---|---|----------------------------|---|
| Lungershausen 1994 <sup>38</sup> | <p>N screened: NR<br/>N included/randomized: 43</p> <p>Age: 61<br/>%female: 69<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: Unclear</p> <p>Inclusion Criteria: uncomplicated essential hypertension being treated with monotherapy (b-blocker and/or diuretic)</p> <p>Exclusion Criteria: history of unstable heart, renal or liver disease, or DBP exceeding 105mmHg consumed more than 20 cigarettes or 40g alcohol per day or exercised erratically</p> <p>Brief Description: volunteers with uncomplicated essential hypertension controlled by monotherapy with beta-blocker or diuretic or combination of 2</p> | <p>Study Design: Crossover RCT<br/>Region: Australia/New Zealand<br/>Setting: Other (recruited by GP)<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 42</p> <p>Treatment DurationCVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>NR<br/>Drug Category: b-blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 42<br/>Supplement(s): Fish oils/marine oils<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 42<br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): told to maintain constant diet and avoid fatty fish</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)                | Other Interventions  |
|----------------------------|--|---|---|---|---------------------------------|--|
| Mabuchi 2007 <sup>39</sup> | <p>N screened: NR<br/>N included/randomized: 49</p> <p>Age: 60.49<br/>%female: 71<br/>Ethnicity: Asian (100)</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: hypercholesterolemic (above 220 mg/dL)</p> <p>Exclusion Criteria: pregnant or lactating women; patients with familial hypercholesterolemia; Patients taking other lipid-lowering drugs; patients taking antioxidants</p> <p>Brief Description: Japanese hypercholesterolemic</p> | <p>Study Design: Parallel RCT<br/>Region: East Asia<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 112</p> <p>Treatment DurationCVD Drug(s): 112</p> <p>Duration of Followup: 28</p> <p>Duration of Longest Followup: 28</p> | <p>Generic Name(s): atorvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 10mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 24<br/>Supplement(s): Coenzyme Q10<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 100mg</p> | <p>N1 = 25<br/><br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): less than 300 mg of low cholesterol diet</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Macan 2006 <sup>40</sup>   | <p>N screened: 66<br/>N included/randomized: 52</p> <p>Age: 55.4<br/>%female: 66.6<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Type II Diabetes, hypertension, hypercholesterolemia (portion NR)</p> <p>CHD Risk Level: At high risk for CHD</p>   | <p>Study Design: Parallel RCT<br/>Region: NR (likely North America)<br/>Setting: Not reported<br/>Industry<br/>Funded: No</p> <p>Treatment Duration supplement(s): 84</p>   | <p>Generic Name(s): Warfarin<br/>Drug Category: Anticoagulants<br/>Mode of Administration: NR<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p>                                      | <p>N: 22<br/>Supplement(s): Garlic<br/>Form of Administration: Liquid<br/>Daily Dose: 10ml</p>                | <p>N1 = 26<br/><br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p>                                       |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population   | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)                | Other Interventions   |
|----------------------------|--|---|--|---|---------------------------------|---|
|                            | <p>Inclusion Criteria: participants diagnosed with deep vein thrombosis, valvular heart disease, atrial fibrillation, or those with prosthetic heart valves. 18 years or older, on warfarin therapy.</p> <p>Exclusion Criteria: any significant medical conditions other than those mentioned, such as the presence of a terminal disease that could shorten the lifespan of the patient (e.g. cancer), a mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, a history of hypersensitivity to garlic or study medication, the presence of anemia (&lt;32 mg %) thrombocytopenia (platelets &lt;75,000/mm<sup>3</sup>), current drug abuse, active bleeding, uncontrolled hypertension, prior treatment with garlic or any related products within 3 months, and treatment with any investigational drugs within 30 days prior to signing the consent.</p> <p>Brief Description: adults on warfarin therapy diagnosed with deep vein thrombosis, valvular heart disease, atrial fibrillation, or those with prosthetic heart valves</p> | <p>Treatment<br/>Duration<br/>CVD<br/>Drug(s): 84</p> <p>Duration of<br/>Followup: End<br/>of treatment<br/>period</p> <p>Duration of<br/>Longest<br/>Followup: End<br/>of treatment<br/>period</p> |  |   |                                 |   |
| Maki<br>2008 <sup>41</sup> | <p>N screened: 98<br/>N included/randomized: 40</p> <p>Age: 58<br/>%female: 64<br/>Ethnicity:<br/>- Caucasian (97)<br/>- Asian (3)</p>   | <p>Study Design:<br/>Crossover RCT<br/>Region: North<br/>America<br/>Setting:<br/>Speciality clinic<br/>Industry<br/>Funded: Yes<br/>Treatment</p>  | <p>Generic Name(s):<br/>Simvastatin<br/>Drug Category:<br/>Antilipidemic: HMG<br/>Co-A Reductase<br/>Inhibitor<br/>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:</p> | <p>N: 20<br/>Supplement(s):<br/>Omega-3<br/>Form of<br/>Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>4000mg</p> | <p>N1 = 20<br/><br/>Placebo</p> | <p>Non-CVD<br/>Medications: NA</p> <p>Dietary<br/>Intervention(s):<br/>Therapeutic<br/>Lifestyle Changes<br/>diet</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study   | CVD Drug  | Dietary Supplements | Control Group(s) | Other Interventions  |
|-------------|--|---|---|---------------------|------------------|--|
|             | <p>Comorbidities (other than indication(s) for CVDs): No<br/>                     CHD Risk Level: At moderate/moderately high risk for CHD (2+ risk factors)</p> <p>Inclusion Criteria: Subjects with mixed dyslipidemia (defined as a mean fasting triglyceride level of 200 to 600 mg/dl and a non-HDL cholesterol level higher than the subject's National Cholesterol Education Program Third Adult Treatment Panel goal); Nonpregnant, nonlactating women who were not planning on becoming pregnant during study period</p> <p>Exclusion Criteria: Recent history of CV event, or revascularization procedure; presence or recent resection of an aortic aneurysm; a lipoprotein lipase impairment or deficiency, known apolipoprotein (apo) CII deficiency, or familial dysbetalipoproteinemia; significant renal (creatinine <math>\geq</math>2.0 mg/dl), pulmonary, hepatic, biliary, or gastrointestinal disease; increased liver enzymes (1.5 times the upper limit of normal); history of pancreatitis; recent history of cancer (except nonmelanoma skin cancer); symptoms of unexplained muscle pain, tenderness or weakness, myopathy, or rhabdomyolysis; or a body mass index <math>\geq</math>40.0 kg/m<sup>2</sup>; poorly controlled hypertension; or poorly controlled diabetes</p> <p>Brief Description: Subjects with mixed dyslipidemia</p> | <p>Duration supplement(s): 42</p> <p>Treatment Duration CVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>20mg</p> <p>Reason for taking CVD drug(s): Cardiovascular indication</p> |                     |                  | <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population  | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)           | Other Interventions   |
|---------------------------|---|---|---|--|----------------------------|---|
| Manuel 2004 <sup>42</sup> | <p>N screened: 32<br/>N included/randomized: 24</p> <p>Age: 51<br/>%female: 13.7<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): T1DM<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: Inclusion criteria were total cholesterol &gt; 4.9 and LDL cholesterol &gt; 3.0 mmol/L but Triglycerides &lt; 4.5 mmol/L and normal blood levels of thyroxin (9.7-23.4 pmol/L) and TSH (0.4-4.0 uU/mL).</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: T1DM patients with high cholesterol</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded:<br/>Unclear</p> <p>Treatment Duration supplement(s): 183</p> <p>Treatment DurationCVD Drug(s): 183</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Atorvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 20mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 11<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/tablet<br/>Daily Dose: 750IU</p> | <p>N1 = 11<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): standard diet for diabetes recommending 7.5 to 8.5 MJ (50% of the energy as carbohydrates, 20% as protein and 30% as fats). This diet assures a daily intake of at least 3 mg Vitamin E, 3000mg Vitamin A, 150 mg Vitamin C and 26 mg flavonoids.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population  | Study   | CVD Drug   | Dietary Supplements  | Control Group(s)                  | Other Interventions   |
|--------------------------|---|---|--|--|-----------------------------------|---|
| Mauro 2003 <sup>43</sup> | <p>N screened: NR<br/>N included/randomized: 8</p> <p>Age: 23<br/>%female: 12.5<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: healthy adult volunteers aged 20 to 35 years willing to sign an informed consent document; All volunteers needed to pass a physical examination, have normal blood and urine chemistry results (SMA-20, CBC, coagulation panel, and urine analysis), a normal electrocardiogram, and, if female, a negative serum pregnancy test.</p> <p>Exclusion Criteria: a history of psychiatric, cardiovascular, renal, gastrointestinal, hepatic, thyroid, neurologic, hematologic, or pulmonary disease; were on medication, had a history of alcohol or drug abuse, a hypersensitivity to digoxin or herbal medications, or a history of chronic smoking or had smoked within the past year.</p> <p>Brief Description: young healthy adults</p> | <p>Study Design: Crossover RCT</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Industry Funded: Unclear</p> <p>Treatment Duration supplement(s): 8</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: 1.5</p> <p>Duration of Longest Followup: 1.5</p> | <p>Generic Name(s): Digoxin</p> <p>Drug Category: Inotropics</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose:0.5mg – single dose</p> <p>Reason for taking CVD drug(s):Pharmacokinetics and pharmackodynamic study</p> | <p>N: 8</p> <p>Supplement(s): Gingko Biloba</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 240mg</p> | <p>N1 = 8</p> <p>No treatment</p> | <p>Non-CVD Medications: Subjects not on any medications</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population  | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                                      | Other Interventions   |
|-----------------------------|---|--|--|---|---|---|
| McDowell 1994 <sup>44</sup> | <p>N screened: NR<br/>N included/randomized: 24</p> <p>Age: 43.8<br/>%female: 37.5<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Type IIa hyperlipidaemia</p> <p>Exclusion Criteria: Taking regular medication for angina or hypertension oxidation</p> <p>Brief Description: Patients with Type IIa hyperlipidaemia</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Primary care<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 28</p> <p>Treatment DurationCVD Drug(s): 28</p> <p>Duration of Followup: 28</p> <p>Duration of Longest Followup: 28</p> | <p>Generic Name(s): simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 20mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 8<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 400IU</p> | <p>N1 = 8<br/>Placebo<br/>N2 = 8<br/>No treatment</p> | <p>Non-CVD Medications: NR<br/>Dietary Intervention(s): NR<br/>Exercise Intervention(s): No<br/>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population   | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)                     | Other Interventions   |
|-----------------------------|--|--|---|--|--------------------------------------|---|
| McKenney 2006 <sup>45</sup> | <p>N screened: NR<br/>N included/randomized: 24</p> <p>Age: 30<br/>%female: 16.7<br/>Ethnicity:<br/>- Caucasian (16.7)<br/>- Hispanic (83.3)</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: healthy male or female volunteers, aged 18 to 55 years and within 15% of ideal weight according to the 1983 Metropolitan Life Insurance Tables; nonsmokers for at least 3 months; Female subjects were required to be past menopause by more than 2 years, sexually abstinent, or using an acceptable method of birth control.</p> <p>Exclusion Criteria: Persons with a history of hypersensitivity or idiosyncratic reaction to HMG-CoA reductase inhibitors or lipid-regulating agents, or allergy or sensitivity to fish; Persons who had used drugs or substances known to be strong inhibitors or inducers of CYP enzymes within 10 days (inhibitors) or 28 days (inducers) of the first dose</p> <p>Brief Description: healthy adults</p> | <p>Study Design:<br/>Crossover RCT</p> <p>Region: NR, likely North America</p> <p>Setting:<br/>Research Unit</p> <p>Industry<br/>Funded: Yes</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>14</p> <p>Treatment<br/>Duration<br/>CVD<br/>Drug(s): 14</p> <p>Duration of<br/>Followup: 1</p> <p>Duration of<br/>Longest<br/>Followup: 1</p> | <p>Generic Name(s):<br/>Simvastatin<br/>Drug Category:<br/>Antilipidemic: HMG<br/>Co-A Reductase<br/>Inhibitor<br/>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:<br/>80mg<br/>Reason for taking<br/>CVD drug(s):<br/>exploratory analysis<br/>of the effects of P-<br/>OM3 on blood<br/>coagulation and/or<br/>platelet aggregation</p> | <p>N: 24<br/>Supplement(s):<br/>Omega-3 (EPA,<br/>DHA or both)<br/>Form of<br/>Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>4000mg</p> | <p>N1 = 24<br/><br/>No treatment</p> | <p>Non-CVD<br/>Medications:<br/>hormonal<br/>contraceptives;<br/>hormone<br/>replacement<br/>therapy allowed<br/>(portion NR)</p> <p>Dietary<br/>Intervention(s): No</p> <p>Exercise<br/>Intervention(s): No</p> <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population   | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)           | Other Interventions  |
|--------------------------|--|---|--|---|----------------------------|--|
| Meyer 2007 <sup>46</sup> | <p>N screened: NR<br/>N included/randomized: 45</p> <p>Age: 56.66<br/>%female: 33<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: subjects on stable statin treatment for hypercholesterolaemia (i.e. already taking statin drug for at least 3 months and expecting to continue on the same dosage during the study period) who had persistent hypertriglyceridaemia (greater than 1.6 mmol/L).</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: subjects on stable statin treatment for hypercholesterolaemia (i.e. already taking statin drug for at least 3 months</p> | <p>Study Design: Parallel RCT<br/>Region: Australia/New Zealand<br/>Setting: Not reported<br/>Industry: Not reported<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 183</p> <p>Treatment DurationCVD Drug(s): 183</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): 19 pts were taking simvastatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 luvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 30<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg or 8000mg</p> | <p>N1 = 15<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                   | Population  | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                    | Other Interventions  |
|-------------------------------|---|--|--|---|-------------------------------------|--|
| Micheletta 2004 <sup>47</sup> | <p>N screened: NA<br/>N included/randomized: 16</p> <p>Age: 60.9<br/>%female: 35<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: patients with carotid atherosclerosis having a lumen stenosis &gt;70% and eligible for carotid endarterectomy</p> <p>Exclusion Criteria: acute and chronic liver disease, cancer, malabsorption syndrome, prior stomach surgery, renal failure, and the use of any supplements containing vitamin E, vitamin C, carotenoids, or iron in the 30 days before the study.</p> <p>Brief Description: patients with carotid atherosclerosis</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Not reported<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 42</p> <p>Treatment DurationCVD Drug(s): 42</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ASA or ticlopidin<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 8<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/tablet<br/>Daily Dose: 900mg</p> | <p>N1 = 8<br/><br/>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population   | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)           | Other Interventions  |
|-----------------------------|--|--|---|--|----------------------------|--|
| Miyamoto 2004 <sup>48</sup> | <p>N screened: NR<br/>N included/randomized: 40</p> <p>Age: 60.9<br/>%female: 35<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): NR</p> <p>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: patients with coronary spastic angina, in whom spontaneous angina occurred at rest.</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: Patients with Coronary spastic angina</p> | <p>Study Design: Parallel RCT<br/>Region: East Asia<br/>Setting: Not reported<br/>Industry<br/>Funded: No</p> <p>Treatment Duration supplement(s): 30</p> <p>Treatment DurationCVD Drug(s): 30</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>Diltiazem<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 100 OR 200 mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 20<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 400mg</p> | <p>N1 = 20<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                       | Population   | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)  | Other Interventions   |
|-----------------------------------|--|---|--|---|---|---|
| Mohammed Abdul 2008 <sup>49</sup> | <p>N screened: 23<br/>N included/randomized: 16</p> <p>Age: 23<br/>%female: 0<br/>Ethnicity:<br/>- Caucasian (58.3)<br/>- Asian, including 3 Indians (41.7)</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: nonsmoking, not taking any medicines including herbal/vitamin supplements for at least 2 weeks and aged 18-34 years</p> <p>Exclusion Criteria: any medical condition that could alter warfarin effects, including any clotting disorders, hepatic dysfunction or platelet dysfunction</p> <p>Brief Description: healthy males</p> | <p>Study Design:<br/>Crossover RCT</p> <p>Region:<br/>Australia/New Zealand</p> <p>Setting: Primary Care</p> <p>Industry Funded: No</p> <p>Treatment Duration supplement(s): 21</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s):<br/>Warfarin<br/>Drug Category:<br/>Anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose:<br/>25mg – single dose<br/>Reason for taking CVD drug(s):<br/>pharmacokinetics and pharmacodynamics</p> | <p>N: 4<br/>Supplement(s):<br/>Garlic<br/>Form of Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>4000mg</p> | <p>N1 = 4<br/>No treatment<br/>N2 = 4<br/>non-relevant supplement<br/>N3 = 4<br/>Intervention3:<br/>non-relevant supplement</p> | <p>Non-CVD Medications:<br/>hormonal contraceptives;<br/>hormone replacement therapy allowed (portion NR)</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                    | Population   | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)               | Other Interventions  |
|--------------------------------|--|--|---|--|--------------------------------|--|
| Motoyama<br>1998 <sup>50</sup> | <p>N screened: NR<br/>N included/randomized: 60</p> <p>Age: 60.3<br/>%female: 49<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: Patients with coronary spastic angina in whom spontaneous angina occurred at rest</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: Patients with angina</p> | <p>Study Design: Parallel RCT<br/>Region: East Asia<br/>Setting: Not reported<br/>Industry<br/>Funded: No</p> <p>Treatment Duration<br/>supplement(s): NR</p> <p>Treatment DurationCVD<br/>Drug(s): NR</p> <p>Duration of Followup: 30</p> <p>Duration of Longest Followup: NR</p> | <p>Generic Name(s): NR<br/>Diltiazem<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 200mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 300mg</p> | <p>Placebo (not described)</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population  | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)             | Other Interventions  |
|----------------------------|---|--|--|--|------------------------------|--|
| Mueller 1991 <sup>51</sup> | <p>N screened: NR<br/>N included/randomized: 12</p> <p>Age: 29.67<br/>%female: 41.7<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: healthy adult volunteers who provided informed consent</p> <p>Exclusion Criteria: Pregnant women, anyone with a known allergy to aspirin or fish, and those taking aspirin, NSAIDs, or oral anticoagulants for a concurrent medical condition; Subjects with known platelet or coagulation disorders and subjects with thrombocytopenia, defined as a platelet count of less than 150,000/mm<sup>3</sup> at baseline; those receiving ethanol</p> <p>Brief Description: healthy adults</p> | <p>Study Design: Parallel RCT</p> <p>Region: NR</p> <p>Setting: NR</p> <p>Industry Funded: Unclear</p> <p>Treatment Duration supplement(s): 21</p> <p>Treatment DurationCVD Drug(s): 1</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ASA</p> <p>Drug Category: Antiplatelets</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 325mg - single dose</p> <p>Reason for taking CVD drug(s): bleeding-time changes associated with aspirin in normal volunteers who ingest omega-3s</p> | <p>N: 6</p> <p>Supplement(s): Omega-3 (EPA, DHA or both)</p> <p>Form of Administration: Capsule/tablet</p> <p>Daily Dose: 8000mg</p> | <p>N1 = 6</p> <p>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): subjects asked not to change diet</p> <p>Exercise Intervention(s): subjects asked not to change exercise</p> <p>Other Lifestyle Intervention(s): subjects asked not to change lifestyle</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)  | Other Interventions  |
|---------------------------|--|--|---|--|---|--|
| Napoli 1998 <sup>52</sup> | <p>N screened: NR<br/>N included/randomized: 220</p> <p>Age: 37.2<br/>%female: 36<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: hypercholesterolemia and normal concentrations of triglycerides,</p> <p>Exclusion Criteria: evidence of renal, liver, or endocrine diseases, type I, IIb, III, IV, V, hyperlipoproteinemia, recent MI or apoplexy (&lt;4 months), unstable angina pectoris, surgery within the previous 4 months, severe or mild heart failure, DM or fasting glycemia (blood glucose &gt;150mg/dl), chronic pancreatitis, porphyria, lupus erythematosus, alcoholism, patients receiving active treatment with fish oil preparations, corticosteroid, estrogens, androgens, quinidine, coumarinic derivatives, theophylline, barbituates, aluminum salts, laxatives, thiazitic diuretics and other hypolipidemic drugs and any who were hypersensitive to drugs, potentially pregnant, or breast feeding</p> <p>Brief Description: hypercholesterolemic patients with normal concentrations of triglycerides</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Primary care<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 84</p> <p>Treatment DurationCVD Drug(s): 84</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Pravastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 20-40mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 60<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 100mg</p> | <p>N1 = 52<br/>no treatment<br/>N2 = 52<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): American Heart Association Step I diet</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)   | Other Interventions   |
|---------------------------|---|--|---|--|--|---|
| Neil (2010) <sup>53</sup> | <p>N screened: NR<br/>N included/randomized:</p> <p>Age: 64 (SD 11.5)<br/>%female: 41.6<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs)<br/>CHD Risk Level: at high risk of CHD</p> <p>Inclusion Criteria: Type 2 diabetes for at least 3 months; 18 years of age or older; no known CVD events; not thought by their general practitioner to be at high enough CVD risk to require immediate lipid-lowering therapy</p> <p>Exclusion Criteria: Taking lipid lowering therapy; plasma triglycerides &gt; 8 mmol/L; impaired hepatic function (ALT &gt; 2 times upper limit of normal range); uncontrolled diabetes (HbA1c &gt; 10%); uncontrolled hypertension (bp &gt; 160/100 mm Hg); elevated creatine kinase (&gt; 3 times upper limit of normal)</p> <p>Brief Description: Patients with type 2 diabetes and no known CVD events.</p> | <p>Study Design: Parallel RCT<br/>Region: NR<br/>Setting: primary care<br/>Industry<br/>Funded: Yes (funded by Pfizer)</p> <p>Treatment Duration supplement(s): 120 days</p> <p>Treatment Duration<sub>CVD</sub><br/>Drug(s): similar to dietary treatment</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): Lipitor/ atorvastatin</p> <p>Drug Category: Antilipidemic (HMG Co-A Reductase Inhibitor)</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 20 mg/d<br/>Reason for taking CVD drug(s): cardiovascular indication</p> | <p>N: 163<br/>Supplement(s): omega-3 fatty acids<br/>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 2 g/day</p> | <p>N<sub>1</sub> = 169<br/>no treatment<br/>N<sub>2</sub> = None</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): None</p> <p>Exercise Intervention(s): None<br/>Other Lifestyle Intervention(s): None</p> <p><b>Note:</b> This study has four groups (double placebo; atorvastatin alone; omega-3 alone; and atorvastatin + omega-3. Only the atorvastatin alone and atorvastatin+omega-3 groups have been extracted.</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)           | Other Interventions  |
|---------------------------|--|---|---|---|----------------------------|--|
| Nordoy 2000 <sup>54</sup> | <p>N screened: NR<br/>N included/randomized: 41</p> <p>Age: 46.75<br/>%female: 29.2<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Type II diabetes (2)<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: combined hyperlipemia</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: patients with combined hyperlipemia</p> | <p>Study Design: Parallel RCT<br/>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 35</p> <p>Treatment DurationCVD Drug(s): 35</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s):<br/>Drug Category:<br/>Mode of Administration: Oral<br/>Mean Daily Dose:<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 21<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4000mg</p> | <p>N1 = 20<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                  | Population  | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)           | Other Interventions  |
|------------------------------|---|---|--|---|----------------------------|--|
| Nordøy<br>2003 <sup>55</sup> | <p>N screened: NR<br/>N included/randomized: 42</p> <p>Age: 49.8<br/>%female: 28.5<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Type II Diabetes (2)<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: patients with hyperlipemia</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: patients with hyperlipemia</p> | <p>Design: Parallel RCT<br/>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded:<br/>Unclear</p> <p>Treatment Duration supplement(s): 35</p> <p>Treatment DurationCVD Drug(s): 35</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): atorvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral</p> <p>Mean Daily Dose: 10mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 22<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 2g</p> | <p>N1 = 20<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): given dietary advice by a clinical dietician to adjust their macronutrient intake to comprise 30% (or less) of energy from fat, with no more than 10% of saturated fat, 55-60% from carbohydrate (preferably complex types) and 10-15% of energy from protein.</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                    | Population  | Study   | CVD Drug  | Dietary Supplements  | Control Group(s)           | Other Interventions  |
|--------------------------------|---|---|---|--|----------------------------|--|
| Paolisso<br>1995 <sup>56</sup> | <p>N screened: NR<br/>N included/randomized: 30</p> <p>Age: 73.8<br/>%female: 40<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): obese<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: elderly patients with CHD</p> | <p>Study Design: Crossover RCT<br/>Region: NR<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 120</p> <p>Treatment DurationCVD Drug(s): 120</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>nifedipine<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 88mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: NR<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 900mg</p> | <p>N1 = NR<br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                    | Population   | Study  | CVD Drug   | Dietary Supplements  | Control Group(s)          | Other Interventions  |
|--------------------------------|--|--|--|--|---------------------------|--|
| Paolisso<br>1992 <sup>57</sup> | <p>N screened: NR<br/>N included/randomized: 18</p> <p>Age: 64<br/>%female: 50<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: hypertensive patients receiving long term (&gt;1 year) thiazide treatment, (benign essential hypertension)</p> <p>Exclusion Criteria: renal impairment, papilloedema, family history of diabetes or drug use known to interfere with glucose metabolism for at least 4 weeks.</p> <p>Brief Description: hypertensive patients receiving thiazide treatment</p> | <p>Study Design: Parallel RCT<br/>Region: NR (likely Europe)<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 56</p> <p>Treatment DurationCVD Drug(s): 56</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): hydrochlorthiazide<br/>Drug Category: Diuretic:<br/>Thiazide/Thiazide-like<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 25mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 9<br/>Supplement(s): Magnesium<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 4500mg</p> | <p>N1 = 9<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)           | Other Interventions   |
|-----------------------------|--|---|---|---|----------------------------|---|
| Playford 2003 <sup>58</sup> | <p>N screened: NR<br/>N included/randomized: 40</p> <p>Age: 53.1<br/>%female: 30<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: Patients with type 2 diabetes and dyslipidaemia (fasting triglyceride &gt; 1.8mmol/l or HDL-cholesterol &lt; 1.0 mmol/l, totalcholesterol &lt; 6.5 mmol/l, total cholesterol/HDL-cholesterol ratio &gt;4</p> <p>Exclusion Criteria: age &gt; 75 years, BMI &gt; 40kg/m<sup>2</sup>, history of CV event, insulin therapy, smoking, macroalbuminuria, creatinemia (&gt; 150micromol/l), abnormal liver or muscle enzymes, use of antioxidants and lipid-regulators, hypertension (&gt;160/90 mmHg), habitual alcohol intake &gt; 3 standard drinks or treatment with angiotensin-converting-enzyme inhibitors and calcium antagonists.</p> <p>Brief Description: Diabetic subjects with dyslipidaemia</p> | <p>Study Design: Parallel RCT<br/>Region: Australia/New Zealand<br/>Setting: Not reported<br/>Industry<br/>Funded: No<br/>Treatment Duration supplement(s): 84</p> <p>Treatment DurationCVD Drug(s): 84</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): NR<br/>Fenofibrate<br/>Drug Category: Antilipidemic: Fibrate<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 200mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 20<br/>Supplement(s): Coenzyme Q10<br/>Form of Administration: NR<br/>Daily Dose: 200mg</p> | <p>N1 = 20<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): patients were on an isocaloric fat-modified diet for the 6 week run-in period</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Reyes 1984 <sup>59</sup>    | <p>N screened: NR<br/>N included/randomized: 21</p> <p>Age: 56.7<br/>%female: 80.9<br/>Ethnicity:</p>  | <p>Study Design: Parallel RCT<br/>Region: NR (likely Africa)<br/>Setting: NR<br/>Industry<br/>Funded:</p>   | <p>Generic Name(s): hydrochlorothiazide<br/>Drug Category: Diuretic:<br/>Thiazide/Thiazide-like<br/>Mode of</p>   | <p>N: 13<br/>Supplement(s): Magnesium<br/>Form of Administration: Capsule/Tablet</p>              | <p>N1 = 8<br/>Placebo</p>  | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise</p>   |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population  | Study   | CVD Drug  | Dietary Supplements                 | Control Group(s) | Other Interventions   |
|-------------------------|---|---|---|-------------------------------------|------------------|---|
|                         | <p>- Caucasian (100)</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: supine diastolic arterial pressures of 100 to 140 mmHg, recorded on at least two occasions separated by 7 days preceding the onset of therapy</p> <p>Exclusion Criteria: patients with one or more of the following: i) secondary or renal hypertension; ii) congestive cardiac failure; iii) a history or clinical evidence of cerebrovascular impairment, including retinal haemorrhages; iv) evidence of renal impairment defined as a serum creatinine level of more than 1.5 mg/dl v) hyper- or hypokalemia, arbitrarily defined by limits of 5.5 and 3.5 mol/l with a history or clinical evidence of gout vii) a history or clinical evidence of hepatic insufficiency viii) coronary insufficiency ix) diabetes mellitus x) rheumatic conditions requiring drug therapy xi) any severe systemic disease likely to interfere with objectives of the study xii) pregnant women xiii) lactating mothers xiv) patients considered uncooperative in terms of compliance.</p> <p>Brief Description: Caucasian ambulant patients with moderate to severe uncomplicated hypertension</p> | <p>Unclear</p> <p>Treatment Duration supplement(s): 21</p> <p>Treatment DurationCVD Drug(s): 21</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Administration: Oral</p> <p>Mean Daily Dose:50mg</p> <p>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>Daily Dose: 15.78 mmol MgCl2</p> |                  | <p>Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Roth 2009 <sup>60</sup> | N screened: 596   | Study Design:   | Generic Name(s):  |                                     | N1 = 82          | Non-CVD   |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population  | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)    | Other Interventions  |
|-------------|---|--|---|---|---------------------|--|
|             | <p>N included/randomized: 167</p> <p>Age: 52.04<br/>%female: 73.6<br/>Ethnicity:<br/>- Caucasian (88.6)<br/>- African-American (1.8)<br/>- Hispanic (7.2)<br/>- Other, not specified (6.6)</p> <p>Comorbidities (other than indication(s) for CVDs): DM, high BMI<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Hypertriglyceridemic men and women (fasting TG <math>\leq</math>500 - <math>\leq</math> 1300 mg/dL) aged 18-79 years, with BMI <math>\geq</math> 25 kg/m<sup>2</sup> and <math>\leq</math>43 kg/m<sup>2</sup></p> <p>Exclusion Criteria: use of warfarin, cyclic sex hormone tx, or other agents known to affect lipid levels during the run-in or tx, use of cyclosporine, systemic or high dose topical corticosteroids, androgens, phenytoin, isotretinoin, or thyroid hormones (except stable-dose replacement tx- 60 days prior to day 42. While on tx also excluded pts with sensitivity to seafood/fish, fibrates, EPA or DHA in addition to any history of pancreatitis, sig. renal, hepatic, biliary, or GI disease, type 1 DM, or uncontrolled type 2 DM, pregnant women, lactating, or childbearing potential; a medically approved method of contraception were also excluded</p> <p>Brief Description: subjects with very high</p> | <p>Parallel RCT<br/>Region: North America<br/>Setting: NR<br/>Industry<br/>Funded: Yes<br/>Treatment<br/>Duration<br/>supplement(s): 56</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 56</p> <p>Duration of<br/>Followup: 56</p> <p>Duration of<br/>Longest<br/>Followup: 56</p> | <p>fenofibrates<br/>Drug Category:<br/>Antilipidemic: Fibrate<br/>Mode of<br/>Administration: Oral<br/>Mean Daily<br/>Dose:130mg<br/>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> | <p>N: 81<br/>Supplement(s):<br/>Omega-3<br/>Form of<br/>Administration: NR<br/>Daily Dose:<br/>4000mg</p> | <p>No treatment</p> | <p>Medications: NR</p> <p>Dietary<br/>Intervention(s): a<br/>diet run in period;<br/>reinforced NCEP<br/>TLC diet during the<br/>tx period</p> <p>Exercise<br/>Intervention(s):<br/>maintaining correct<br/>physical activity</p> <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                | Population   | Study  | CVD Drug   | Dietary Supplements   | Control Group(s)                           | Other Interventions  |
|----------------------------|--|--|--|---|--|--|
|                            | TG levels (> or =500 mg/dL)  |  |  |   |  |  |
| Sconce 2007 <sup>61</sup>  | <p>N screened: NR<br/>N included/randomized: 70</p> <p>Age: NR<br/>%female: 50<br/>Ethnicity: Caucasian(100)</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: target international normalized ratio (INR) range of 2.0 to 3.0, had been taking warfarin for at least 9 months, and were defined as having unstable control</p> <p>Exclusion Criteria: Those patients whose instability was deemed to be due to poor adherence to warfarin therapy, changes in concurrent medication, comorbidity, or irregular and excessive alcohol consumption</p> <p>Brief Description: Patients with atrial fibrillation anticoagulated with warfarin for thromboembolic prophylaxis</p> | <p>Study Design: Parallel RCT</p> <p>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 180</p> <p>Treatment DurationCVD Drug(s): 180</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): warfarin<br/>Drug Category: anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR (various starting and ending dosages)<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 35<br/>Supplement(s): Vitamin K<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 0.15mg</p> | <p>N1 = 33<br/>Placebo</p>                 | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Steiner 1995 <sup>62</sup> | <p>N screened: NR<br/>N included/randomized: 100</p> <p>Age: 71<br/>%female: 58<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s))</p>  | <p>Study Design: Parallel RCT<br/>Region: NR (likely North America)<br/>Setting: Not reported<br/>Industry</p>   | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 325mg</p>   | <p>N: 52<br/>Supplement(s): Vitamin E<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 400IU</p>  | <p>N1 = 48<br/>Placebo (not described)</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p>  |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population   | Study   | CVD Drug  | Dietary Supplements | Control Group(s) | Other Interventions                            |
|-------------|--|---|---|---------------------|------------------|--|
|             | <p>for CVDs): Not reported<br/>                     CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: patients aged 18 y in whom any of the following conditions were diagnosed: 1) minor stroke, a focal ischemic cerebrovascular event that results in a less-than maximal neurologic deficit within the involved vascular distribution; 2) reversible ischemic neurologic deficit (RIND), a focal ischemic cerebrovascular event producing a neurologic deficit that persists for &gt; 24 h but &lt; 3 wk; 3) retinal ischemic event, an acute transient or permanent impairment of visual function caused by retinal ischemia; or 4) transient ischemic attack, a focal cerebrovascular event producing a neurologic deficit that resolves completely within 24 h of its onset. focal neurologic deficit had to occur within 8 wk of enrollment into the study, they had a performance status that allowed them to spend &gt; 50% of their waking hours out of bed, they had no known allergy or contraindication to the use of aspirin or a-tocopherol, had no history of primary or secondary hypercoagulable state, were not using anticoagulants or platelet-active drugs other than aspirin, had no disorder other than atherosclerotic cerebrovascular disease;had no evidence of intracranial hemorrhage and no concurrent medical or significant psychiatric disease</p> <p>Exclusion Criteria: NR</p> | <p>Funded:<br/>Unclear</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>730</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 730</p> <p>Duration of<br/>Followup: End<br/>of treatment<br/>period</p> <p>Duration of<br/>Longest<br/>Followup: End<br/>of treatment<br/>period</p> | <p>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> |                     |                  | <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population  | Study   | CVD Drug   | Dietary Supplements  | Control Group(s)   | Other Interventions  |
|---------------------------|---|---|--|--|--|--|
|                           | Brief Description: patients with transient ischemic attacks, minor strokes, or residual ischemic neurologic deficits  |   |  |  |  |  |
| Sutken 2006 <sup>63</sup> | <p>N screened: NR<br/>N included/randomized: 22</p> <p>Age: 29.5<br/>%female: 50<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: Hyperlipidemic subjects</p> <p>Exclusion Criteria: Acute illness or severe chronic disease, diabetes, hypertension, angina pectoris or previous MI or peripheral vascular disease, thyroid dysfunction, alcohol intake, smoking, hormonal treatment, lipid-lowering medication, or vitamin or iron supplementation in the last 6 months before admission.</p> <p>Brief Description: Young Hyperlipidemic</p> | <p>Study Design: Controlled clinical trial (CCT)</p> <p>Region: Middle East</p> <p>Setting: Speciality clinic</p> <p>Industry: Unclear</p> <p>Funded: Unclear</p> <p>Treatment Duration supplement(s): 30</p> <p>Treatment Duration CVD Drug(s): 30</p> <p>Duration of Followup: 30</p> <p>Duration of Longest Followup: NR</p> | <p>Generic Name(s): Gemfibrozil</p> <p>Drug Category: Antilipidemic: Fibrate</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 1200 mg</p> <p>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 12</p> <p>Supplement(s): Vitamin E</p> <p>Form of Administration: NR</p> <p>Daily Dose: 600 mg</p> | <p>N1 = 10</p> <p>No treatment</p> <p>N2 = 12</p> <p>Vitamin E</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year               | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)   | Other Interventions  |
|---------------------------|--|---|---|---|--|--|
| Sutken 2006 <sup>63</sup> | <p>N screened: NR<br/>N included/randomized: 45</p> <p>Age: 71.5<br/>%female: 46.7<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs: No</p> <p>CHD Risk Level: At low risk for CHD 90-1 risk factors)</p> <p>Inclusion Criteria: Hyperlipidemic subjects</p> <p>Exclusion Criteria: Acute illness or severe chronic disease, diabetes, hypertension, angina pectoris or previous MI or peripheral vascular disease, thyroid dysfunction, alcohol intake, smoking, hormonal treatment, lipid-lowering medication, or vitamin or iron supplementation in the last 6 months before admission.</p> <p>Brief Description: Elderly hyperlipidemic</p> | <p>Study Design:<br/>Controlled<br/>Clinical Trial</p> <p>Region: Middle East</p> <p>Setting:<br/>Specialty Clinic</p> <p>Industry<br/>Funded:<br/>Unclear</p> <p>Treatment<br/>Duration<br/>supplement(s):<br/>30</p> <p>Treatment<br/>DurationCVD<br/>Drug(s): 30</p> <p>Duration of<br/>Followup: 30</p> <p>Duration of<br/>Longest<br/>Followup: NR</p> | <p>Generic Name(s):<br/>Gemfibrozil<br/>Drug Category:<br/>Antilipidemic: Fibrate</p> <p>Mode of<br/>Administration: Oral<br/>Mean Daily Dose:<br/>1200 mg<br/>Reason for taking<br/>CVD drug(s):<br/>Cardiovascular<br/>indication</p> | <p>N: 20<br/>Supplement(s):<br/>Vitamin E<br/>Form of<br/>Administration: NR<br/>Daily Dose: 600<br/>mg</p> | <p>N1 = 23<br/><br/>No treatment<br/><br/>N2 = 22<br/><br/>Vitamin E</p> | <p>Non-CVD<br/>Medications: NR</p> <p>Dietary<br/>Intervention(s): No</p> <p>Exercise<br/>Intervention(s): No</p> <p>Other Lifestyle<br/>Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                     | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)          | Other Interventions  |
|---------------------------------|--|---|---|---|---------------------------|--|
| Svaneborg<br>2002 <sup>64</sup> | <p>N screened: NR<br/>N included/randomized: 14</p> <p>Age: 31<br/>%female: 0<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: healthy, nonsmoking, nonobese men</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: healthy, nonsmoking, nonobese men</p> | <p>Study Design: Parallel RCT<br/>Region: NR (likely Europe)<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear<br/>Treatment Duration supplement(s): 14</p> <p>Treatment DurationCVD Drug(s): NA</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Parenteral<br/>Mean Daily Dose: 100mg<br/>Reason for taking CVD drug(s): Aim was to test platelet function with ASA &amp; n-3s</p> | <p>N: 12<br/>Supplement(s): Fish oils/marine<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 10000mg</p> | <p>N1 = 6<br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |



**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population  | Study   | CVD Drug   | Dietary Supplements   | Control Group(s)                  | Other Interventions  |
|-----------------------------|---|---|--|---|-----------------------------------|--|
| Tankanow 2003 <sup>65</sup> | <p>N screened: 11<br/>N included/randomized: 11</p> <p>Age: 28<br/>%female: 50<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: age &gt; 18 years, serum creatinine &lt; 1.2 mg/dL, and bilirubin &lt; 1.5 mg/dL</p> <p>Exclusion Criteria: Individuals taking concurrent scheduled medications (excluding oral contraceptives), those with significant medical histories, and smokers and pregnant females</p> <p>Brief Description: Healthy subjects</p> | <p>Study Design: Crossover RCT</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Industry Funded: Unclear</p> <p>Treatment Duration supplement(s): 21</p> <p>Treatment DurationCVD Drug(s): 10</p> <p>Duration of Followup: 0.5</p> <p>Duration of Longest Followup: 3</p> | <p>Generic Name(s): Digoxin</p> <p>Drug Category: Inotropics</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: 0.25mg</p> <p>Reason for taking CVD drug(s): Pharmacokinetics and pharmacodynamic study</p> | <p>N: 8</p> <p>Supplement(s): Hawthorn</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 900mg</p>     | <p>N1 = 8</p> <p>No treatment</p> | <p>Non-CVD Medications: oral contraceptives not excluded</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |
| Watson 1999 <sup>66</sup>   | <p>N screened: NR<br/>N included/randomized: 30</p> <p>Age: 55<br/>%female: 13<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Not reported</p> <p>CHD Risk Level: At high risk for CHD</p>   | <p>Study Design: Crossover RCT</p> <p>Region: Australia/New Zealand</p> <p>Setting: Industry</p> <p>Funded: Unclear</p> <p>Treatment</p>  | <p>Generic Name(s): ACE inhibitors (no description)</p> <p>Drug Category: RAAS Antagonist: ACEI</p> <p>Mode of Administration: Oral</p> <p>Mean Daily Dose: NR</p> <p>Reason for taking</p>                          | <p>N: NR</p> <p>Supplement(s): Coenzyme Q10</p> <p>Form of Administration: Capsule/Tablet</p> <p>Daily Dose: 99mg</p> | <p>N1 = NR</p> <p>Placebo</p>     | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p>                               |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year | Population  | Study  | CVD Drug   | Dietary Supplements | Control Group(s) | Other Interventions |
|-------------|---|--|--|---------------------|------------------|---------------------|
|             | <p>Inclusion Criteria: between 18 and 75 years of age with ischemic or idiopathic dilated cardiomyopathy</p> <p>Exclusion Criteria: obstructive valvular heart disease, renal (serum creatinine &gt;0.18 mmol/liter-1) or hepatic (serum aspartate or alanine aminotransaminase &gt; upper limit of normal) impairment, a history of alcohol or drug abuse or an inadequate echocardiographic study, or if they were pregnant</p> <p>Brief Description: between 18 and 75 years of age with ischemic or idiopathic dilated cardiomyopathy</p> | <p>Duration supplement(s): 84</p> <p>Treatment DurationCVD Drug(s): 84</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>CVD drug(s): Cardiovascular indication</p> <p>Generic Name: Furosemide<br/>Drug Category: Diuretic: Loop<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name: digoxin, also hydralazine and/or nitrates<br/>Drug Category: Inotropics<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> |                     |                  |                     |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                  | Population  | Study  | CVD Drug  | Dietary Supplements   | Control Group(s)           | Other Interventions  |
|------------------------------|---|--|---|---|----------------------------|--|
| Wirell<br>1994 <sup>67</sup> | <p>N screened: NR<br/>N included/randomized: 40</p> <p>Age: 35.4<br/>%female: 23<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: mild to moderate essential hypertension</p> <p>Exclusion Criteria: Patients treated with drugs containing magnesium, ACE-inhibitors, Ca antagonists, or potassium and magnesium sparing diuretics; s-creatinine &gt;150 mmol L-1 or serum electrolyte disturbances (sodium and potassium) according to hospital normal values; Recent myocardial infarction less than 3 months before study start or cardiac failure class NYHA IV, AV block II or III; pregnancy, malignancies, diabetes mellitus, rheumatic diseases, collagenoses and patients unable to cooperate; Dlastolic blood pressure exceeding 110 mmHg and systolic blood pressure exceeding 190 mmHg</p> <p>Brief Description: Patients with mild to moderate essential hypertension</p> | <p>Study Design: Crossover RCT<br/>Region: Europe<br/>Setting: Speciality clinic<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 56</p> <p>Treatment DurationCVD Drug(s): 56</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): metoprolol<br/>Drug Category: b-blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name(s): atenolol<br/>Drug Category: b-blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> <p>Generic Name(s): pindolol &amp; propanolol<br/>Drug Category: b-blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: NR<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 19<br/>Supplement(s): Magnesium<br/>Form of Administration: Powder mixed with water<br/>Daily Dose: 365mg</p> | <p>N1 = 20<br/>Placebo</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)                     | Other Interventions   |
|-------------------------|---|--|---|--|--------------------------------------|---|
| Wolf 2006 <sup>68</sup> | <p>N screened: NR<br/>N included/randomized: 50</p> <p>Age: 27.2<br/>%female: 0<br/>Ethnicity:<br/>- Caucasian (98)<br/>- Asian (2)</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: normal laboratory values, had not been taking any medication within the last 3 weeks</p> <p>Exclusion Criteria: Intake of medication containing ASA, anticoagulants, NSAIDs, sulfipyrazone, ticlopidine and lipid-lowering agents</p> <p>Brief Description: healthy subjects</p> | <p>Study Design: Crossover RCT<br/>Region: Europe<br/>Setting: General community<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 7</p> <p>Treatment DurationCVD Drug(s): 7</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): ASA<br/>Drug Category: Antiplatelets<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 500mg<br/>Reason for taking CVD drug(s): to determine the influence of EBg761 on the effects of ASA on bleeding time, coagulation parameters and platelet activity</p> | <p>N: 50<br/>Supplement(s): Ginkgo biloba<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 240mg</p> | <p>N1 = 50<br/><br/>No treatment</p> | <p>Non-CVD Medications: paracetamol (15) and Sinupret (4)</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year                 | Population  | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)                | Other Interventions  |
|-----------------------------|---|---|---|---|---------------------------------|--|
| Yamamoto 1995 <sup>69</sup> | <p>N screened: NR<br/>N included/randomized: NR</p> <p>Age: 59.6<br/>%female: 22.7<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): No<br/>CHD Risk Level: At high risk for CHD</p> <p>Inclusion Criteria: variant angina, angiographically normal- appearing coronary artery after ISDM administration</p> <p>Exclusion Criteria: history of MI, DM, hypertension, heart failure or hyperlipidemia</p> <p>Brief Description: Participants with variant angina</p> | <p>Study Design: Parallel RCT<br/>Region: East Asia<br/>Setting: Primary care<br/>Industry<br/>Funded: Yes</p> <p>Treatment Duration supplement(s): 112</p> <p>Treatment DurationCVD Drug(s): 112</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): diltiazem<br/>Drug Category: Calcium channel blockers<br/>Mode of Administration: Oral<br/>Mean Daily Dose: 90-120mg<br/>Reason for taking CVD drug(s): Cardiovascular indication</p> | <p>N: 12<br/>Supplement(s): Omega-3<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 1800mg</p> | <p>N1 = 10<br/>No treatment</p> | <p>Non-CVD Medications: NR</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year              | Population  | Study  | CVD Drug  | Dietary Supplements  | Control Group(s)           | Other Interventions   |
|--------------------------|---|--|---|--|----------------------------|---|
| Young 2007 <sup>70</sup> | <p>N screened: NR<br/>N included/randomized: 44</p> <p>Age: 59<br/>%female: 50<br/>Ethnicity: NR</p> <p>Comorbidities (other than indication(s) for CVDs): Type II Diabetes (5)</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy</p> <p>Exclusion Criteria: acute myocardial infarction or cerebral vascular accident within 3 months, alanine aminotransferase or aspartate aminotransferase &gt;3 times the upper level of normal, calculated glomerular filtration rate &lt;45 ml/min, decompensated heart failure, warfarin treatment, and antioxidant vitamin supplementation.</p> <p>Brief Description: patients with self-reported myalgia who had been unable to continue taking adequate doses of statin therapy</p> | <p>Study Design: Parallel RCT<br/>Region:NR (likely Australia)<br/>Setting: Not reported<br/>Industry<br/>Funded: Unclear</p> <p>Treatment Duration supplement(s): 63</p> <p>Treatment DurationCVD Drug(s): 63</p> <p>Duration of Followup: End of treatment period</p> <p>Duration of Longest Followup: End of treatment period</p> | <p>Generic Name(s): simvastatin<br/>Drug Category: Antilipidemic: HMG Co-A Reductase Inhibitor<br/>Mode of Administration: Oral<br/>Mean Daily Dose: Starting 10mg, ending 40mg<br/>Reason for taking CVD drug(s): NR</p> | <p>N = 22<br/>Supplement(s): Coenzyme Q10<br/>Form of Administration: Capsule/Tablet<br/>Daily Dose: 200mg</p> | <p>N1 = 22<br/>Placebo</p> | <p>Non-CVD Medications: Ezetimibe (4)</p> <p>Dietary Intervention(s): No</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 57. General characteristics of all studies (continued)**

| Author Year             | Population   | Study   | CVD Drug  | Dietary Supplements   | Control Group(s)               | Other Interventions   |
|-------------------------|--|---|---|---|--------------------------------|---|
| Yuan 2004 <sup>71</sup> | <p>N screened: NR<br/>N included/randomized: 21</p> <p>Age: 27.84<br/>%female: 55<br/>Ethnicity:<br/>- Caucasian (10)<br/>- African-American (5)<br/>- Hispanic (3)<br/>- Asian (2)</p> <p>Comorbidities (other than indication(s) for CVDs: NR</p> <p>CHD Risk Level: At low risk for CHD (0-1 risk factors)</p> <p>Inclusion Criteria: NR</p> <p>Exclusion Criteria: NR</p> <p>Brief Description: Healthy patients</p> | <p>Study Design:<br/>Parallel RCT</p> <p>Region: North America</p> <p>Setting: Primary Care</p> <p>Industry<br/>Funded: No</p> <p>Treatment<br/>Duration<br/>supplement(s): 28</p> <p>Treatment<br/>Duration<br/>CVD Drug(s): 6</p> <p>Duration of<br/>Followup: End of treatment period</p> <p>Duration of<br/>Longest<br/>Followup: End of treatment period</p> | <p>Generic Name(s):<br/>Warfarin<br/>Drug Category:<br/>Anticoagulants<br/>Mode of Administration: Oral<br/>Mean Daily Dose:<br/>5mg<br/>Reason for taking<br/>CVD drug(s):<br/>Pharmacokinetics and pharmackodynamic study</p> | <p>N: 12<br/>Supplement(s):<br/>Ginseng<br/>Form of Administration:<br/>Capsule/Tablet<br/>Daily Dose:<br/>2000mg</p> | <p>N1 = 8<br/><br/>Placebo</p> | <p>Non-CVD Medications: NA</p> <p>Dietary Intervention(s):<br/>Patients were instructed to eat a balanced diet to maintain a consistent amount of vitamin K and to avoid drastic changes in dietary habits</p> <p>Exercise Intervention(s): No</p> <p>Other Lifestyle Intervention(s): No</p> |

**Evidence Table 58. Interventions listed in detail for all studies**

| Author Year                   | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition  | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported?   | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|-------------------------------|----------------------------|--|---|---------------------------------------|--|--|---|---|--|---|
| Abdul 2010 <sup>1</sup>       | Echinacea                  | E. angustifolia and E. purpurea                            | 600 mg of E. angustifolia roots and 675 mg of E. purpurea root; | No                                    | NR   | QLD, Australia   | No  | roots of E. angustifolia and E. purpurea  | NA   | Echinacea alkamide content in plasma                          |
| Aruna 2007 <sup>2</sup>       | Gingko biloba              | NR   | NR  | No                                    | NR   |  | No  | No  | NA   | No  |
| Avogaro 1974 <sup>3</sup>     | Niacin                     | nicotinic acid   | NR  | No                                    | NR   |  | No  | No  | NR   | No  |
| Balestrieri 1996 <sup>4</sup> | Fish oils/marine oils      | ethylester   | 85% n-3 fatty acids (EPA + DHA ratio 1:1)                       | No                                    | NR   | Esapent-Carlo Erba, Milano Italy                             | No  | No  | NR   | No  |
| Barbagallo 1999 <sup>5</sup>  | Vitamin E                  | NR   | NR  | No                                    | NR   |  | No  | No  | NR   | plasma vit E  |
| Bays 2009 <sup>7</sup>        | Omega-3 (EPA, DHA or both) | Lovaza   | NR  | No                                    | NR   | No   | No  | No  | NA   | No  |
| Bays 2010 <sup>6</sup>        | Omega-3 (EPA, DHA or both) | P-OM3 (omega-3-acid ethyl esters)                          | 465mg EHA;375mgDHA  | No                                    | NR   | No   | No  | No  | NA   | No  |
| Bender 1998 <sup>8</sup>      | Fish oils/marine oils      | MaxEPA   | NR  | No                                    | NR   |  | No  | No  | NR   | No  |
| Bordia 1998 <sup>9</sup>      | Garlic                     | NR   | NR  | No                                    | NR   |  | No  | Peeled garlic cloves were crushed, extracted in ethyl acetate, the solvent evaporated and the resultant oil dissolved in soy oil. The oil extract of garlic was encapsulated. Each capsule contained oil equivalent of 1g raw garlic. | NR   | No  |



**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                     | Supplement:                               | Latin or other names used in this study for the supplement | Supplement Composition  | Is purity of the supplement reported?   | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured?            | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|---------------------------------|---|--|---|---|--|---|---|---|--|---|
| Budoff 2004 <sup>10</sup>       | Garlic                                    | Aged Garlic Extract (AGE), Kyolic                          | NR  | No  | NR   |   | No  | No  | NR   | No  |
| Caso 2007 <sup>11</sup>         | Supp 1: Coenzyme Q10<br>Supp 2: Vitamin E | Supp 1: Q-Sorb softgel<br>Supp 2: NR                       | Supp 1: NA<br>Supp 2: NA  | Supp 1: No<br>Supp 2: No  | Supp 1: NR<br>Supp 2: NR                       | Supp 1: NY, USA<br>Supp 2: NY, USA                                      | Supp 1: No<br>Supp 2: No                                  | Supp 1: No<br>Supp 2: No                  | Supp 1: NA<br>Supp 2: NA                         | Supp 1: No<br>Supp 2: No                                      |
| Chan 2002 <sup>12</sup>         | Fish oils/marine oils                     | Omacor   | 45% EPA and 39% EHA   | No  | Yes  | Oslo, Norway  | No  | No  | NA   | measurements of plasma EPA and DHA levels                     |
| d'Arcangues 2004 <sup>13</sup>  | Vitamin E                                 | Evion  | NA  | tablets returned to the Merck laboratories for retesting at the end of the trial and their stability over the course of the study was confirmed | NR   | Germany   | No  | No  | NA   | No  |
| Davidson 1997 <sup>15</sup>     | Fish oils/marine oils                     | NR   | The Omega FA content of 7.2g of the marine oil supplements used was 3.6g EPA: DHA ratio = 1.5 | No  | NR   | SuperEPA 1200, Advanced Nutritional Technology, Inc., Dublin California | No  | No  | NR   | No  |
| Davidson, 2007 <sup>14</sup>    | Omega-3 (EPA, DHA or both)                | omega 3-acid ethyl esters (P-OM3)                          | 465mg EPA; 375mg DHA  | No  | NR   | New Jersey, USA   | No  | No  | NA   | No  |
| De, Caterina 2002 <sup>16</sup> | Vitamin E                                 | NA   | NA  | No  | NR   | Switzerland   | No  | No  | NA   | plasma vit E  |
| Dehmer 1988 <sup>17</sup>       | Omega-3 (EPA, DHA or both)                | MaxEPA   | 3.2g EPA 2.2g DHA in 18 capsules  | No  | NR   | Michigan  | No  | No  | NA   | No  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                    | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered?   | Are nutrient levels or biomarkers of the supplement reported?   |
|--------------------------------|----------------------------|--|--|---------------------------------------|--|--|---|---|--|---|
| Desideri 2003 <sup>18</sup>    | Vitamin E                  | alpha-tocopherol   | NR   | No                                    | NR   | Roche Molecular Biochemicals, Milan, Italy                   | No  | No  | NR   | Plasma Vit E concentrations were measured by HPLC according to the well-established method of Lee et al. Plasma vitamin E levels were expressed both in absolute concentrations and as the ratio of Vitamin E / (total cholesterol + triglycerides) |
| Di, Spirito 2008 <sup>19</sup> | Omega-3 (EPA, DHA or both) | P-OM3, Lovaza  | 465 mg of the ethyl ester of eicosapentaenoic acid and 375 mg of the ethyl ester of docosahexaenoic acid | No                                    | NR   | North Carolina US  | No  | No  | NA   | No  |
| Duffy 2001 <sup>20</sup>       | Vitamin E                  | NR   | NR   | No                                    | NR   | Victoria, Australia  | No  | No  | Acetylcholine for vasomotion study; Sodium nitroprusside to assess response to endothelial-independent vasodilator | tocopherol measured by high-performance liquid chromatography   |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                  | Supplement:           | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|------------------------------|-----------------------|--|--|---------------------------------------|--|--|---|---|--|---|
| Eritsland 1996 <sup>21</sup> | Fish oils/marine oils | Omacor   | Each soft gelatin capsule contains 1 g of fatty acids (51% eicosapentaenoic acid C20:5n-3 and 32% docosahexaenoic acid C22:6n-3 ethyl esters) and 3.7 mg $\alpha$ -tocopherol as an antioxidant. | No                                    | NR   | Pronova AS, Oslo, Norway                                     | No  | No  | NR   | No  |
| Eritsland 1996 <sup>21</sup> | Fish oils/marine oils | Omacor   | each capsule contained 1 gram fatty acids (51% EPA and 32% DHA) and 3.7 mg $\alpha$ -tocopherol  | No                                    | NR   | Pronova AS, Oslo, Norway                                     | No  | fish oil                                  | NR   | No  |
| Eritsland 1996 <sup>21</sup> | Fish oils/marine oils | n-3 fatty acids  | each capsule contained 1 gram fatty acids (51% EPA and 32% DHA) and 3.7 mg $\alpha$ -tocopherol  | No                                    | NR   | Norway   | No  | fish oil                                  | NR   | No  |
| Ferraro 2009 <sup>22</sup>   | Fish oils/marine oils | PUFA   | 85% EPA + DHA  | No                                    | NR   |  | No  | No  | NA   | No  |
| Gardner 2007 <sup>23</sup>   | Ginkgo biloba         | EGb 761  | 24% Ginkgo flavone glycosides and 6% terpene lactones  | No                                    | NR   | Springville, Utah by Nature's Way                            | No  | No  | NA   | No  |
| Garg 1995 <sup>24</sup>      | Ginkgo biloba         | Ginkgo Biloba Extract                                      | NR   | No                                    | NR   |  | No  | No  | NR   | No  |
| Glynn 2007 <sup>25</sup>     | Vitamin E             | $\alpha$ -tocopherol                                       | NR   | No                                    | NR   |  | No  | No  | NR   | No  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                   | Supplement:  | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|-------------------------------|--|--|--|---------------------------------------|--|--|---|---|--|---|
| Gosai 2008 <sup>26</sup>      | Omega-3 (EPA, DHA or both)                               | P-OM3  | 465 mg of the ethyl ester eicosapentaenoic acid and 375 mg of the ethyl ester docosahexaenoic acid   | No                                    | Yes  | North Carolina, US   | No  | No  | NA   | No  |
| Govil 1979 <sup>27</sup>      | Magnesium  | magnesium hydroxide solution                               | NA   | No                                    | NR   |  | No  | No  | NR   | serum magnesium   |
| Hansen 1993 <sup>29</sup>     | Fish oils/marine oils                                    | fish oil ethyl ester (K-85)                                | EPA to DHA ratio 1.90  | 94% n-3 fatty acids                   | NR   | Pronova A/S, Oslo, Norway)                                   | No  | No  | NR   | No  |
| Hajda, J <sup>28</sup> (2010) | Garlic extract   | GaliPure   | GarliPure®, 600mgcaplets from Natrol®, CA, USA containing gamma glutamylcysteines 12,000µg, 4800µg alliin, 3900µg sulfur and 3800µg thiosulfates resulting in a allicin yield 3600µg | No                                    | Yes  | Yes, USA   | No  | Yes                                       | NA   | No  |
| Howe 1994 <sup>30</sup>       | Fish oils/marine oils                                    | Lipitac Forte  | NR   | No                                    | NR   | Marker Pharma, Sydney Australia                              | No  | No  | NR   | No  |
| Isley 2007 <sup>31</sup>      | Supp 1: Omega-3 (EPA, DHA or both)<br><br>Supp 2: Niacin | Supp 1: Omacor<br><br>Supp 2: NR                           | Supp 1: 85% eicosapentaenoic (EPA) plus docosahexaenoic acids (DHA)<br><br>Supp 2: NA  | Supp 1: No<br><br>Supp 2: No          | Supp 1: NR<br><br>Supp 2: NR                   | Supp 1: Norway<br><br>Supp 2: NY, USA                        | Supp 1: No<br><br>Supp 2: No                              | Supp 1: No<br><br>Supp 2: No              | Supp 1: NA<br><br>Supp 2: NA                     | Supp 1: No<br><br>Supp 2: No                                  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year              | Supplement:                             | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported?  | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported?   | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|--------------------------|---|--|--|--|--|--|---|---|--|---|
| Jiang 2004 <sup>33</sup> | Ginseng                                 | Panax ginseng  | 8.93 mg ginsenosides as ginsenoside Rg1  | No   | NR   |  | No  | No  | NA   | No  |
| Jiang 2005 <sup>32</sup> | Supp 1: Gingko biloba<br>Supp 2: Ginger | Supp 1: Tavorin<br>Supp 2: NR                              | Supp 1: 2000mg of Ginkgo biloba leaf, 9.6 mg of ginkgo, avonglycosides, 2.4 mg of ginkgolides and bilobalide<br><br>Supp 2: each capsule containing extract equivalent to 0.4 g of ginger rhizome powder | Supp 1: No<br>Supp 2: No   | Supp 1: NR<br>Supp 2: NR                       | Supp 1: Germany<br>Supp 2: Australia                         | Supp 1: No<br>Supp 2: No                                  | Supp 1: ginkgo leaf, avonglycosides and ginkgolides and bilobalide<br><br>Supp 2: NR  | Supp 1: NA<br>Supp 2: NA                         | Supp 1: No<br>Supp 2: No                                      |
| Kaul 1992 <sup>34</sup>  | Fish oils/marine oils                   | Maxepa   | 1.8g EPA; 1.2g DHA   | No   | NR   | Hull, UK   | No  | No  | NA   | No  |
| Kim 2010 <sup>35</sup>   | Gingko biloba                           | NA   | 204% glycosidic flavonoids + 6% terpenoids   | No   | NR   | Korea  | No  | No  | NA   | No  |
| Lee 2008 <sup>36</sup>   | Ginseng                                 | P. ginseng   | NR   | The quality was tested according to the Korea Food & Drug Administration and hospital standards (ginsenoside Rb1>0.20%, Rg1>0.10%) | NR   | Korea  | No  | Root was air dried and crushed materials were added to distilled water, and extraction was performed by heating the solution for 4 hours at 100°C | NA   | No  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                      | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|----------------------------------|----------------------------|--|--|---------------------------------------|--|--|---|---|--|---|
| Liu 2003 <sup>37</sup>           | Fish oils/marine oils      | Eskimo-3   | 18% eicosapentaenoic acid (EPA, 20:5n-3), 12% docosahexaenoic acid (DHA, 22:6n-3) and a total of 38% of long-chain omega-3 fatty acids and is stabilized by a mixture of natural antioxidants, Pufanox, such as vitamins C and E and lecithin. | No                                    | NR   | Cardinova, Uppsala, Sweden                                   | No  | No  | NR   | No  |
| Lungershausen 1994 <sup>38</sup> | Fish oils/marine oils      | Omacor   | 1.9g EPA; 1.5g DHA   | No                                    | NR   | Oslo, Norway   | No  | No  | NR   | No  |
| Mabuchi 2007 <sup>39</sup>       | Coenzyme Q10               | NA   | NA   | No                                    | NR   | Kaneka Co., Osaka, Japan                                     | No  | No  | NA   | No  |
| Macan2006 <sup>40</sup>          | Garlic                     | Kyolic (Aged Garlic Extract)                               | NR   | No                                    | NR   | Wakunaga of America, Mission Viejo California                | No  | No  | NR   | No  |
| Maki 2008 <sup>41</sup>          | Omega-3 (EPA, DHA or both) | P-OM3  | NR   | No                                    | NR   | New Jersey   | No  | No  | NA   | No  |
| Manuel 2004 <sup>42</sup>        | Vitamin E                  | d-alpha-tocopherol   | NR   | No                                    | NR   | Omega Pharma, NV, Nazareth, Belgium                          | No  | No  | NR   | serum vit E   |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                   | Supplement:  | Latin or other names used in this study for the supplement | Supplement Composition                                 | Is purity of the supplement reported?  | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|-------------------------------|--|--|--|--|--|--|---|---|--|---|
| Mauro 2003 <sup>43</sup>      | Ginkgo biloba  | NR   | containing 24% ginkgo flavone glycosides               | Verification of the flavone content and a general fingerprint of the chemical constituents ethanolic, reversedphase high-performance liquid chromatography (HPLC) assay using UV detection according to a previously described procedure | NR   | California   | No  | leaf extract                              | NA   | No  |
| McDowell 1994 <sup>44</sup>   | Vitamin E  | RRR-alpha-tocopherol                                       | NR   | No   | NR   | Henkel Corporation, Cork, Ireland                            | No  | No  | NR   | serum alpha-tocopherol  |
| McKenney, 2006 <sup>45</sup>  | Omega-3 (EPA, DHA or both)   | Omacor   | NR   | No   | NR   | New Jersey, US   | No  | No  | NA   | No  |
| Meyer 2007 <sup>46</sup>      | Supp 1: Omega-3 (EPA, DHA or both)<br><br>Supp 2: Omega-3 (EPA, DHA or both) | Supp 1: DHA<br><br>Supp 2: DHA                             | Supp 1: 7% EPA, 27% DHA<br><br>Supp 2: 7% EPA, 27% DHA | Supp 1: No<br><br>Supp 2: No   | Supp 1: NR<br><br>Supp 2: NR                   | Supp 1: No<br><br>Supp 2: No                                 | Supp 1: No<br><br>Supp 2: No                              | Supp 1: No<br><br>Supp 2: No              | Supp 1: NA<br><br>Supp 2: NA                     | Supp 1: No<br><br>Supp 2: No                                  |
| Micheletta 2004 <sup>47</sup> | Vitamin E  | alpha-tocopherol   | NR   | No   | NR   |  | No  | No  | NA   | serum vit E   |
| Miyamoto 2004 <sup>48</sup>   | Vitamin E  | alpha-tocopherol acetate                                   | NR   | No   | NR   |  | No  | No  | NR   | No  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                       | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition   | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported?  |
|-----------------------------------|----------------------------|--|--|---------------------------------------|--|--|---|---|--|--|
| Mohammed Abdul 2008 <sup>49</sup> | Garlic                     | GarlipleX 2000   | equivalent to 3.71mg of allicin  | No                                    | NR   | Australia  | No  | garlic bulb                               | NA   | No   |
| Motoyama 1998 <sup>50</sup>       | Vitamin E                  | Alpha-tocopherol acetate                                   | NR   | No                                    | NR   |  | No  | No  | NR   | Measurement of flow-dependent vasodilation and blood sampling for assays of thiobarbituric acid reactive substances (TBARS) and alpha-tocopherol were performed before and 4 weeks after treatment |
| Mueller 1991 <sup>51</sup>        | Omega-3 (EPA, DHA or both) | Promega  | 8 g of omega-3 fatty acids and 3.5 g of eicosapentaenoic                           | No                                    | NR   | New Jersey, US   | No  | No  | NA   | No   |
| Napoli 1998 <sup>52</sup>         | Vitamin E                  | DL-alpha-tocopherol  | NR   | No                                    | NR   | Walgreen Co., Deerfield Illinois                             | No  | No  | NR   | No   |
| Neil, HAW                         | Omega-3 (EPA, DHA or both) | NR   | EPA=46%, DHA=38%   | No                                    | NR   | Yes  | No  | No  | NA   | No   |
| Nordoy 2000 <sup>54</sup>         | Omega-3 (EPA, DHA or both) | Omacor   | EHA=49%, DHA=39%   | No                                    | NR   |  | No  | No  | NR   | No   |
| Nordøy 2003 <sup>55</sup>         | Omega-3 (EPA, DHA or both) | Omacor   | ethyl esters of eicosapentaenoic acid (EPA) 45% and docosahexaenoic acid (DHA) 39% | No                                    | NR   | Pronova, A/S, Lysaker, Norway                                | No  | No  | NR   | No   |
| Paolisso 1992 <sup>57</sup>       | Magnesium                  | MAG2   | NR   | No                                    | NR   | Lyrca Synthelabo, Italy                                      | No  | No  | magnesium pidolate                               | erythrocyte magnesium  |
| Paolisso 1995 <sup>56</sup>       | Vitamin E                  | DL-a-tocopherol acetate/d                                  | NA   | No                                    | NR   | Milan, Italy   | No  | No  | NA   | No   |



**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                  | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition  | Is purity of the supplement reported? | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured?   | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported?   |
|------------------------------|----------------------------|--|---|---------------------------------------|--|--|---|---|--|---|
| Playford 2003 <sup>58</sup>  | Coenzyme Q10               | NR   | NR  | No                                    | NR   | Blackmores, Australia  | No  | No  | NR   | Serum CoQ was assayed by reverse-phase HPLC plasma fibrinogen by Clauss reaction and homocysteine by immunoassay. |
| Reyes 1984 <sup>59</sup>     | Magnesium                  | Slow Mag   | 2.63 mmol Mg2+  | No                                    | NR   |  | No  | No  | magnesium chloride                               | No  |
| Roth 2009 <sup>60</sup>      | Omega-3 (EPA, DHA or both) | prescription Omega-3                                       | NR  | No                                    | Yes  | Ovaza (Omacor)- US   | No  | No  | NA   | No  |
| Sconce 2007 <sup>61</sup>    | Vitamin K                  | phytomenadione   | 20:80 ethanol deionized water solution  | stability and quality control checks  | NR   | United Kingdom   | No  | No  | NA   | plasma vit K  |
| Steiner 1995 <sup>62</sup>   | Vitamin E                  | alpha-tocopherol   | NR  | No                                    | NR   |  | No  | No  | NR   | serum concentration of alpha-tocopherol   |
| Sutken 2006 <sup>63</sup>    | Vitamin E                  | NR   | NR  | No                                    | NR   |  | No  | No  | NR   | Vit E was measured in serum samples that were isolated and were determined according to the Hashim's method.      |
| Svaneborg 2002 <sup>64</sup> | Fish oils/marine oils      | NR   | NR  | No                                    | NR   | Pronova Biocare, Norway, delivered as Pikasol by Lube, Denmark | No  | No  | NR   | platelet levels of EPA & DHA  |
| Tankanow 2003 <sup>55</sup>  | Hawthorn                   | Crataegus  | one tablet contained 450 mg dry extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidines | No                                    | NR   | Germany  | No  | hawthorn leaves with flowers              | NA   | No  |

**Evidence Table 58. Interventions listed in detail for all studies (continued)**

| Author Year                 | Supplement:                | Latin or other names used in this study for the supplement | Supplement Composition              | Is purity of the supplement reported?   | Is the supplement licensed in the region used? | Does the paper report where the supplement was manufactured? | Have storage conditions for the supplement been reported? | Is the origin of the supplement reported? | What subtype of the supplement was administered? | Are nutrient levels or biomarkers of the supplement reported? |
|-----------------------------|----------------------------|--|-------------------------------------|---|--|--|---|---|--|---|
| Watson 1999 <sup>66</sup>   | Coenzyme Q10               | Coenzyme Q   | NR                                  | No  | NR   | Health World Limited, Brisbane, Australia                    | No  | No  | NR   | Plasma levels of Coenzyme Q                                   |
| Wirell 1994 <sup>67</sup>   | Magnesium                  | Magnesiocard   | NR                                  | No  | NR   | Tutzing Germany  | No  | No  | magnesium aspartate hydrochloride                | serum magnesium, also in urine                                |
| Wolf 2006 <sup>68</sup>     | Gingko biloba              | EGb761   | NA                                  | No  | NR   | Germany  | No  | dry extract from gingko biloba leaves     | NA   | No  |
| Yamamoto 1995 <sup>69</sup> | Omega-3 (EPA, DHA or both) | Epadel   | NR                                  | No  | NR   | Mochido Pharmacy, Japan                                      | No  | No  | NR   | plasma EPA levels   |
| Young 2007 <sup>70</sup>    | Coenzyme Q10               | Q-Gel  | NR                                  | No  | NR   |  | No  | No  | NR   | total plasma levels of CoQ10                                  |
| Yuan 2004 <sup>71</sup>     | Ginseng                    | Panax quinquefolius  | total ginsenoside content was 5.19% | The constituent split was as follows:<br>ginsenoside Rb1 , 1.93%; Rb2 , 0.20%; Rc, 0.61%; Rd, 0.42%; Re, 1.68%; and Rg1 , 0.35% | NR   | Wisconsin US   | No  | root of American ginseng                  | NA   | No  |

## Outcomes Tables Categorized by Key Question and Outcome

Evidence Table 59. KQ1—Dichotomous data—Mortality

| Author<br>Year<br><br>Study<br>design                  | Definition<br>of<br>outcome<br>(if<br>relevant) | CHD risk<br>category | CVD drug<br>(dose mg/d)               | Group 1:<br>Supplement<br>name (dose<br>g/d) | N1  | N1<br>with<br>event | Group 2:<br>Name | N2  | N2<br>with<br>event | Estimates<br>of Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---|----------------------|---------------------------------------|--|-----|---------------------|------------------|-----|---------------------|--------------------------------------|------------------------|--|
| <b>All cause<br/>mortality</b>                         |   |                      |                                       |  |     |                     |                  |     |                     |                                      |                        |  |
| Sconce<br>2007 <sup>61</sup><br><br>Parallel           | N/A   | Unclear              | Warfarin (3.3-<br>4.4)                | Vitamin K<br>(0.15)                          | 35  | 0                   | Placebo          | 33  | 1                   |                                      |                        | Medium   |
| Eritsland<br>1996 <sup>21</sup><br><br>Parallel        | N/A   | High                 | ASA (300)                             | Fish/marine<br>oils (4)                      | 143 | 5                   | No<br>treatment  | 148 | 4                   |                                      |                        | Medium   |
| Eritsland<br>1996 <sup>21</sup><br><br>Parallel        | N/A   | High                 | Warfarin (NR)                         | Fish/marine<br>oils (4)                      | 174 | 3                   | No<br>treatment  | 145 | 2                   |                                      |                        | Medium   |
| Garg<br>1995 <sup>24</sup><br><br>Parallel             | N/A   | High                 | ASA and/or<br>pentoxiphylline<br>(NR) | <i>Ginkgo biloba</i><br>(0.16)               | 29  | 0                   | Placebo          | 26  | 0                   |                                      |                        | High   |
| Roth<br>2009 <sup>60</sup><br><br>Parallel             | N/A   | Unclear              | Fenofibrates<br>(130)                 | Omega-3<br>(EPA, DHA or<br>both) (4)         | 84  | 0                   | Placebo          | 83  | 0                   |                                      |                        | Medium   |
| Di Spirito<br>2008 <sup>19</sup><br><br>Cross-<br>over | N/A   | Low<br>(healthy)     | Atorvastatin<br>(80)                  | Omega-3<br>(EPA, DHA or<br>both) (4)         | 50  | 0                   | No<br>treatment  | 50  | 0                   |                                      |                        | Medium   |

**Evidence Table 59. KQ1—Dichotomous data—Mortality**

| Author Year<br>Study design                      | Definition of outcome (if relevant) | CHD risk category | CVD drug (dose mg/d)  | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|-------------------|---|-------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Watson 1999 <sup>66</sup><br>Cross-over          | N/A                                 | High              | Mixed: ACE inhibitors + furosemide, digoxin, hydralazine and/or nitrates (NR) | Coenzyme Q10 (0.1)                  | 30 | 0             | Placebo       | 30 | 1             |                                |                     | Medium                                |
| <i>Vascular death – no outcome data</i>          |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |
| <i>Specific vascular death – no outcome data</i> |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |

**Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease)**

| Author Year<br>Study design                      | Definition of outcome (if relevant) | CHD risk category | CVD drug (dose mg/d)  | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|-------------------|---|-------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| <b>All myocardial infarction</b> (MI, acute MI)  |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |
| Wirell 1994 <sup>67</sup><br>Cross-over          | NR                                  | Unclear           | Beta Adrenergic Antagonists: metoprolol, atenolol, pindolol & propanolol (NR) | Magnesium (0.365)                   | 19 | 1             | Placebo       | 20 | 0             |                                |                     | Medium                                |
| <b>Nonfatal MI</b> (MI, acute MI)                |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |
| Kauli 1992 <sup>34</sup><br>Parallel             | Acute MI                            | High              | Calcium channel blocker, ASA (NR)   | Fish/marine oils                    | 58 | 4             | No treatment  | 49 | 2             |                                |                     | Low                                   |
| <b>Unstable angina</b> (see also Cont. data)     |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |
| <b>Acute coronary syndrome</b> - no outcome data |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |
| <b>(Re)stenosis</b> – see also Cont. data        |                                     |                   |   |                                     |    |               |               |    |               |                                |                     |                                       |

**Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease) (continued)**

| Author Year<br>Study design         | Definition of outcome (if relevant)   | CHD risk category | CVD drug (dose mg/d)              | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name       | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|---|-------------------|-----------------------------------|-------------------------------------|----|---------------|---------------------|----|---------------|--------------------------------|---|---------------------------------------|
| Kaul 1992 <sup>34</sup><br>Parallel | Angiographic restenosis: Patients with angina symptoms and/or positive exercise test who underwent repeat coronary angiography: loss of 50% of the gain in luminal diameter at angioplasty or recurrence of stenosis in only one of the two segments of vessel dilated – 6 months follow-up | High              | Calcium channel blocker, ASA (NR) | Fish/marine oils                    | 58 | 19            | No treatment        | 49 | 13            | -                              | 4 patients with clinical restenosis refused repeat angiography. | -                                     |
| Kaul 1992 <sup>34</sup><br>Parallel | Clinical restenosis: presence of positive exercise test, new since the early post angioplasty study with or without anginal symptoms – 6 months follow-up   | High              | Calcium channel blocker, ASA (NR) | Fish/marine oils                    | 58 | 22            | No treatment        | 49 | 14            | -                              | -   | -                                     |
|                                     | <i>Subgroup: male</i>   |                   |                                   | <i>Fish/marine oils</i>             | 50 | 18            | <i>No treatment</i> | 41 | 12            | -                              | -   | -                                     |
|                                     | <i>Subgroup: female</i>   |                   |                                   | <i>Fish/marine oils</i>             | 8  | 3             | <i>No treatment</i> | 8  | 1             | -                              | -   | -                                     |
| Kaul 1992 <sup>34</sup><br>Parallel | Progression of disease: the presence of a new luminal narrowing > 70% in the non-dilated vessel – 6 months follow-up  | High              | Calcium channel blocker, ASA (NR) | Fish/marine oils                    | 58 | 4             | No treatment        | 49 | 3             | -                              | -   | -                                     |

**Evidence Table 60. KQ1—Dichotomous data—Ischemic heart disease (coronary artery disease) (continued)**

| Author Year<br>Study design              | Definition of outcome (if relevant)  | CHD risk category | CVD drug (dose mg/d)   | Group 1: Supplement name (dose g/d) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|--|-------------------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---|---------------------------------------|
| Dehmer 1988 <sup>17</sup><br>Parallel    | Restenosis post-angioplasty (per patient): defined angiographically as recurrence of a lesion with more than 50% narrowing of the luminal diameter – 3 to 4 months follow-up | High              | ASA (325) + dipyridamole (225) + calcium channel blockers (NR) | Omega-3 (EPA, DHA, or both) (3.2)   | 43  | 8             | No treatment  | 39  | 18            | -                              | -   | -                                     |
| <b>Graft occlusion</b>                   |  |                   |  |                                     |     |               |               |     |               |                                |   |                                       |
| Eritsland 1996 <sup>21</sup><br>Parallel | occluded vein graft (>=1) per all patients   | High              | ASA (300)  | Fish/marine oils (4)                | 134 | 57            | Placebo       | 134 | 66            | -                              | N presented per arm are number free of event at baseline (Total N1 = 134; N2 = 140) | -                                     |
| Eritsland 1996 <sup>21</sup><br>Parallel | occluded vein graft (>=1) per all patients   | High              | Warfarin (NR)  | Fish/marine oils (4)                | 164 | 69            | Placebo       | 134 | 71            |                                | N presented per arm are number free of event at baseline (Total N1 = 168; N2 = 139) |                                       |

**Evidence Table 61. KQ1—Dichotomous data—Composite cardiovascular outcome**

| Author Year<br>Study design          | Definition of outcome (if relevant)   | CHD risk category           | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1            | N1 with event | Group 2: Name | N2   | N2 with event | Estimates of Group Differences                                | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---|-----------------------------|----------------------|-------------------------------------|---------------|---------------|---------------|------|---------------|---|---------------------|---------------------------------------|
| Glynn 2007 <sup>25</sup><br>Parallel | Combination of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes | Low and/or mod to high risk | ASA (100)            | Vitamin E (0.1)                     | 9966 included | 232           | Placebo       | 9968 | 245           | Crude risk ratio (95% CI): 0.95 (0.79, 1.13)<br>P-value: 0.55 |                     | Medium                                |



**Evidence Table 62. KQ1—Dichotomous data—Arrhythmia**

| Author Year<br>Study design                       | Definition of outcome (if relevant) | CHD risk category | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments         | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|-------------------|----------------------|-------------------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|-----------------------------|---------------------------------------|
| <i>Sudden Death</i> – no outcome data             |                                     |                   |                      |                                     |     |               |               |     |               |                                |                             |                                       |
| <i>Ventricular fibrillation</i> – no outcome data |                                     |                   |                      |                                     |     |               |               |     |               |                                |                             |                                       |
| <i>Ventricular tachycardia</i>                    |                                     |                   |                      |                                     |     |               |               |     |               |                                |                             |                                       |
| Davidson 2007 <sup>14</sup><br><br>Parallel       | Tachycardia                         | Unclear           | Simvastatin (40)     | Omega-3 (EPA, DHA, or both) (4)     | 122 | 1             | Placebo       | 132 | 0             | -                              | Also led to hospitalization | Medium                                |
| <i>Atrial fibrillation</i> – no outcome data      |                                     |                   |                      |                                     |     |               |               |     |               |                                |                             |                                       |
| <i>Heart block</i> – no outcome data              |                                     |                   |                      |                                     |     |               |               |     |               |                                |                             |                                       |

**Evidence Table 63. KQ1—Dichotomous data—Other heart disease**

| Author<br>Year<br><br>Study<br>design                      | Definition of<br>outcome (if<br>relevant) | CHD risk<br>category | CVD drug<br>(dose mg/d) | Group 1:<br>Supplement<br>name (dose<br>g/d) | N1  | N1<br>with<br>event | Group<br>2: Name | N2  | N2<br>with<br>event | Estimates<br>of Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---|----------------------|-------------------------|--|-----|---------------------|------------------|-----|---------------------|--------------------------------------|------------------------|--|
| <b><i>Congestive<br/>heart<br/>failure</i></b>             |   |                      |                         |  |     |                     |                  |     |                     |                                      |                        |  |
| Davidson<br>2007 <sup>14</sup><br><br>Parallel             | Exacerbation<br>of CHF after<br>8 weeks   | Unclear              | Simvastatin<br>(40)     | Omega-3<br>(EPA, DHA,<br>or both) (4)        | 122 | 1                   | Placebo          | 132 | 0                   | -                                    | -                      | -  |
| <b><i>Valvular<br/>disease</i></b> –<br>no outcome<br>data |   |                      |                         |  |     |                     |                  |     |                     |                                      |                        |  |

**Evidence Table 64. KQ1 - Dichotomous data—Cerebrovascular disease**

| Author Year<br>Study design  | Definition of outcome (if relevant)    | CHD risk category | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|----------------------|-------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| <b>All Stroke</b>  |  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
| Sconce 2007 <sup>61</sup><br>Parallel  | NR; 6 months follow-up                 | Unclear           | warfarin (3.3-4.4)   | Vitamin K (0.15)                    | 35 | 0             | Placebo       | 33 | 0             | -                              | -                   | Medium                                |
| Steiner 1995 <sup>62</sup><br>Parallel   | Fatal or non-fatal – 2 years follow-up | High              | ASA (325)            | Vitamin E (400 IU/d)                | 52 | 3             | Placebo       | 48 | 6             | -                              | -                   | Medium                                |
| <b>Hemorrhagic stroke</b>  |  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
| Steiner 1995 <sup>62</sup><br>Parallel   | 2 years follow-up                      | High              | ASA (325)            | Vitamin E (400 IU/d)                | 52 | 2             | Placebo       | 48 | 0             | -                              | -                   | Medium                                |
| <b>Ischemic stroke</b>   |  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
| Steiner 1995 <sup>62</sup><br>Parallel   | 2 years follow-up                      | High              | ASA (325)            | Vitamin E (400 IU/d)                | 52 | 1             | Placebo       | 48 | 6             | -                              | -                   | Medium                                |
| <b>Transient ischemia attack (TIA)</b>   |  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
| Steiner 1995 <sup>62</sup><br>Parallel   | Recurrent TIA - 2 years follow-up      | High              | ASA (325)            | Vitamin E (400 IU/d)                | 52 | 1             | Placebo       | 48 | 2             | -                              | -                   | -                                     |
| <b>Carotid artery disease (not measured by IMT or Doppler) – no outcome data</b> |  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |

**Evidence Table 65. KQ1—Dichotomous data—Peripheral arterial disease**

| Author Year<br>Study design | Definition of outcome (if relevant)                   | CHD risk category | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|---|-------------------|----------------------|-------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
|                             | <i>Limb thrombosis/leg ischemia – no outcome data</i> |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
|                             | <i>Claudication (pain walking) – no outcome data</i>  |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
|                             | <i>Mesenteric ischemia – no outcome data</i>          |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
|                             | <i>Abdominal aortic aneurysm - no outcome data</i>    |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |
|                             | <i>Ankle-brachial index – no outcome data</i>         |                   |                      |                                     |    |               |               |    |               |                                |                     |                                       |

**Evidence Table 66. KQ1—Dichotomous data—CVD surgery and procedures**

| Author Year<br>Study design                                    | Definition<br>of outcome<br>(if relevant)                                      | CHD risk<br>category | CVD drug<br>(dose mg/d)                          | Group 1:<br>Supplement<br>name (dose<br>g/d) | N1 | N1<br>with<br>event | Group 2:<br>Name | N2 | N2<br>with<br>event | Estimates<br>of Group<br>Differences | Additional<br>comments                  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|--|----------------------|--|--|----|---------------------|------------------|----|---------------------|--------------------------------------|---|--|
| <b>Coronary artery bypass graft</b>                            |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |
| Kaul 1992 <sup>34</sup><br>Parallel                            | Late CABG<br>– 6 months<br>follow-up   | High                 | Calcium<br>channel<br>blocker (NR)<br>+ ASA (NR) | Fish/marine<br>oils                          | 58 | 2                   | No<br>treatment  | 49 | 2                   | -                                    | -                                       | -  |
| <b>Percutaneous transluminal coronary angioplasty</b>          |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |
| Kaul 1992 <sup>34</sup><br>Parallel                            | Restenosis<br>documented<br>by repeat<br>angioplasty–<br>6 months<br>follow-up | High                 | Calcium<br>channel<br>blocker (NR)<br>+ ASA (NR) | Fish/marine<br>oils                          | 58 | 16                  | No<br>treatment  | 49 | 10                  | -                                    | Not<br>significant<br>between<br>groups | -  |
| <b>Stent – no outcome data</b>                                 |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |
| <b>Valve replacement – no outcome data</b>                     |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |
| <b>Carotid or peripheral vascularization - no outcome data</b> |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |
| <b>Amputation – no outcome data</b>                            |  |                      |  |  |    |                     |                  |    |                     |                                      |   |  |

**Evidence Table 67. KQ1—Dichotomous data—Hospitalization**

| Author Year                             | Definition of outcome (if relevant)   | CHD risk category | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------|-------------------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---------------------|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel | Hospitalization due to SAE (pneumonia, CHF, supraventricular tachycardia) – 8 weeks follow-up | Unclear           | simvastatin (40)     | Omega-3 (EPA, DHA, or both) (4)     | 122 | 3             | Placebo       | 132 | 0             | -                              | -                   | Medium                                |

**Evidence Table 68. KQ1—Dichotomous data—Adherence to cardiovascular drug**

| Author Year<br>Study design           | Definition of outcome (if relevant)  | CHD risk category | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|-------------------|----------------------|-------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Young 2007 <sup>70</sup><br>Parallel  | NR – 12 weeks follow-up  | Mod and high risk | simvastatin (10-40)  | Coenzyme Q10 (0.2)                  | 22 |               | Placebo       | 22 |               |                                | Both groups had 98% adherence to simvastatin  |                                       |
| Sconce 2007 <sup>61</sup><br>Parallel | Score of 1 or lower out of 10 in the Brief Medication Questionnaire – 6 months follow-up | Unclear           | warfarin (3.3-4.4)   | Vitamin K (0.15)                    | 35 | 35            | Placebo       | 33 | 33            | -                              | All participants were considered to have a 'high probable degree of adherence.  | -                                     |
| Napoli 1998 <sup>52</sup><br>Parallel | Pill counts – 3 months follow-up   | Unclear           | Pravastatin (20-40)  | Vitamin E (0.1)                     | -  | -             | -             | -  | -             | -                              | Report states "...almost all patients (98%) followed their treatments and diet carefully.' No individual group data reported. | -                                     |

**Evidence Table 68. KQ1—Dichotomous data—Adherence to cardiovascular drug (continued)**

| Author Year<br>Study design           | Definition of outcome (if relevant)                          | CHD risk category                                       | CVD drug (dose mg/d) | Group 1: Supplement name (dose g/d)  | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|---|----------------------|--------------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Bender 1998 <sup>8</sup><br>Parallel  | compliance rate (study drug) - %<br>- 4 weeks follow-up      | Unclear   | Warfarin (NR)        | Omega-3 (EPA, DHA, or both) (3 or 6) | 6  | -             | Placebo       | 5  | -             | -                              | Report states that compliance was >99.5%; no individual group data reported   | -                                     |
| Chan 2002 <sup>12</sup><br>Parallel   | Pill counts – 3 and 6 weeks follow-up                        | Moderate/moderately high risk for CHD (2+ risk factors) | atorvastatin (40)    | Fish/marine oils (4)                 | 11 | -             | Placebo       | 13 | -             | -                              | Report states that compliance was >95%; no individual group data reported   | -                                     |
| Liu 2003 <sup>37</sup><br>Parallel    | Pill counts – 12 weeks follow-up                             | Unclear   | simvastatin (10)     | Fish/marine oils (9.2)               | 19 | -             | No treatment  | 18 | -             | -                              | Report states that compliance was >95%; no individual group data reported   | -                                     |
| Maki 2008 <sup>41</sup><br>Cross-over | Pill counts and subject interview – 6 weeks follow-up/period | Low, Moderate and high risk                             | Simvastatin (20)     | Omega-3 (EPA, DHA, or both) (4)      | 39 | -             | Placebo       | 39 | -             | -                              | Report states: 'Compliance with simvastatin was 97% during POM3 treatment and 96% during placebo treatment (p = 0.448)' | -                                     |



**Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease)**

| Author Year<br>Study Design                  | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d) | Supplement/ Control | N                    | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means/ medians SD / P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------|---------------------|----------------------|---|---|--|---------------------|---------------------------------------|
| <i>Unstable angina (see also Dich. data)</i> |   |                   |                      |                     |                      |   |   |  |                     |                                       |
| Miyamoto 2004 <sup>48</sup><br>Parallel      | Number of anginal attacks recorded after before and after 1 month | High              | Diltiazem (100-200)  | Vitamin E (0.4)     | 20                   | Mean: 0.4<br>SE: 0.1  | P: <0.01  | P: NS  |                     | -                                     |
| Placebo                                      |   |                   |                      | 20                  | Mean: 0.6<br>SE: 0.1 | P: <0.01  |   |  |                     |                                       |
| Motoyama 1998 <sup>50</sup><br>Parallel      | Number of anginal attacks recorded after 1 month                  | High              | Diltiazem (200)      | Vitamin E (0.3)     | 30                   | Mean: 0.2<br>SD: 0.5  | Mean: -6.7  | Mean <sub>diff.</sub> : 0.7                              |                     | -                                     |
| Placebo                                      |   |                   |                      | 30                  | Mean: 0.9<br>SD: 1.1 | Mean: -5.9  |   |  |                     |                                       |

**Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease) (continued)**

| Author Year<br>Study Design                         | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d) | Supplement/ Control               | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD / P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------|-----------------------------------|----|---|---|--|---------------------|---------------------------------------|
| <i>(Re)stenosis</i><br>– see also <i>Dich. data</i> |   |                   |                      |                                   |    |   |   |  |                     |                                       |
| Yamamoto 1995 <sup>69</sup><br>Parallel             | Coronary artery diameter- nonspastic segments: angiographically normal site where acetylcholine injection did not provoke coronary vasospasm (diameter [mm], expressed as a % after admin of ISDN was reduced by < 50% after intracoronary admin of acetylcholine) – 4 months follow-up | High              | Diltiazem (90-120)   | Omega-3 (EPA, DHA, or both) (3.6) | 12 | Mean: 3.0<br>SE: 0.1  | -   | -  | -                   | -                                     |
|   |   |                   |                      | No treatment                      | 10 | Mean: 2.9<br>SE: 0.2  | -   |  |                     |                                       |
| Yamamoto 1995 <sup>69</sup><br>Parallel             | coronary artery diameter- spastic segments: spastic site = site of the most severe narrowing in the coronary vasospasm artery after injection of acetylcholine (mm) – 4 months follow-up  | High              | Diltiazem (90-120)   | Omega-3 (EPA, DHA, or both) (3.6) | 12 | Mean: 2.9<br>SE: 0.1  | -   | -  | -                   | -                                     |
|   |   |                   |                      | No treatment                      | 10 | Mean: 3.0<br>SE: 0.3  | -   |  |                     |                                       |

**Evidence Table 69. KQ1—Continuous data—Ischemic heart disease (coronary artery disease) (continued)**

| Author Year<br>Study Design           | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)   | Supplement/ Control               | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD / P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|-------------------|--|-----------------------------------|----|---|---|--|---------------------|---------------------------------------|
| Dehmer 1988 <sup>17</sup><br>Parallel | Luminal narrowing (%) after angioplasty – 3-4 months follow-up | High              | ASA (325) + dipyridamole (225) + calcium channel blockers (NR) | Omega-3 (EPA, DHA, or both) (3.2) | 43 | Mean: 25<br>SD: 15.1  | -   | -  | -                   | -                                     |
|                                       |  |                   |  | No treatment                      | 39 | Mean: 29<br>SD: 14  | -   |  |                     |                                       |

**Evidence Table 70. KQ1—Continuous data—Cerebrovascular disease**

| Author Year<br>Study Design        | Definition of outcome                                      | CHD Risk Category | CVD drug (dose mg/d)            | Supplement/ Control         | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|--|-------------------|---------------------------------|-----------------------------|----|---|--|---|---------------------|---------------------------------------|
| <i>Neurological recovery score</i> |  |                   |                                 |                             |    |   |  |   |                     |                                       |
| <sup>24</sup><br>Parallel          | Modified Mathew's score (scale: 0-100) – 4 weeks follow-up | High              | ASA and/or pentoxiphylline (NR) | <i>Ginkgo biloba</i> (0.16) | 29 | Mean: 77.79<br>SD: 14.73  | -  | -   | -                   | -                                     |
|                                    |  |                   |                                 | Placebo                     | 26 | Mean: 78.57<br>SD: 12.47  | -  |   |                     |                                       |

**Evidence Table 71. KQ1—Continuous data—Quality of life**

| Author Year<br>Study Design | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)  | Supplement/ Control  | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline / SD / P Value | Between group differences in Means/ medians SD / P Value | Additional comments                                      | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|-------------------|---|----------------------|----|---|--|--|--|---------------------------------------|
| <sup>66</sup><br>Cross-over | Minnesota Living with Heart Failure questionnaire – 12 weeks follow-up | High              | Mixed: ACE inhibitors + furosemide, digoxin, hydralazine and/or nitrates (NR) | Coenzyme Q10 (0.099) | 27 | Mean: 26.7<br>Median: 22<br>SD: 17.9  | Mean: -2.7   | P-value <sub>adj</sub> : 0.22                            | Between group difference adjusted for order of treatment | Medium                                |
|                             |  |                   |   | Placebo              | 27 | Mean: 26.5<br>Median: 22<br>SD: 18.7  | Mean: -2.9   |  |  |                                       |

**Evidence Table 72. KQ2—Continuous data—Bleeding time**

| Author Year<br>Study Design              | CHD Risk Category                      | CVD drug | Dose (mg/d) | Supplement/<br>Control       | N   | Definition of outcome  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results                         | Overall Risk of Bias (ROB) Assessment |
|--|--|----------|-------------|------------------------------|-----|--|--|--|--|--|---------------------------------------|
| Svaneborg 2002 <sup>64</sup><br>parallel | At low risk for CHD (0-1 risk factors) | ASA      | 100         | Omega-3 (EPA, DHA, or both). | 12  | BP cuff 40 mm Hg- incisions with parallel to the fold of the elbow | Median 9.6<br>Lower: 7.6<br>Upper: 11  | P: <0.05   | NR   | p value is for before the injection of ASA | medium                                |
|  |  |          |             | Placebo                      | 6   |  | Median 7.9<br>Lower: 6.3<br>Upper: 11.5  | P: <0.05   |  |  |                                       |
| Neil, HAW 2010 <sup>53</sup>             | At high risk for CHD                   | Statins  | 20          | Omega-3                      | 163 | Total Cholesterol (mmol/l)   | Mean: 3.4<br>SD: 0.7   | NR   | NR   | No significant differences between groups. | NA                                    |
|  | At high risk for CHD                   | Statins  | 20          | placebo                      | 169 |  | Mean: 3.4<br>SD: 0.7   | NR   |  |  |                                       |
| Neil, HAW 2010 <sup>53</sup>             | At high risk for CHD                   | Statins  | 20          | Omega-3                      | 163 | LDL-C (mmol/l)   | Mean: 1.7<br>SD: 0.5   | NR   | NR   | No significant differences between groups. | Low                                   |
|  |  |          |             | Placebo                      | 169 |  | Mean: 1.8<br>SD: 0.5   | NR   |  |  |                                       |
| Neil, HAW 2010 <sup>53</sup>             | At high risk for CHD                   | Statins  | 20          | Omega-3                      | 163 | HDL-C (mmol/L)   | Mean: 1.1<br>SD: 0.3   | NR   | NR   | No significant differences between groups. | Low                                   |
|  |  |          |             | Placebo                      | 169 |  | Mean: 1.1<br>SD: 0.2   | NR   |  |  |                                       |

**Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)**

| Author Year<br>Study Design          | CHD Risk Category    | CVD drug | Dose (mg/d) | Supplement/<br>Control | N   | Definition of outcome  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR,<br>95% CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change/<br>% change from<br>baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results                         | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|----------------------|----------|-------------|------------------------|-----|--|--|--|--|--|---------------------------------------|
| Neil, HAW 2010 <sup>53</sup>         | At high risk for CHD | Statins  | 20          | Omega-3                | 163 | Triglyceride (mmol/l)  | Median: 1.1<br>IQR, lower limit: 0.8<br>IQR, upper limit: 1.5  | NR   | NR   | No significant differences between groups. | Low                                   |
|                                      |                      |          |             | Placebo                | 169 |  | Median: 1.5<br>IQR, lower limit: 1.1<br>IQR, upper limit: 2.3  | NR   | NR   |  |                                       |
| Neil, HAW 2010 <sup>53</sup>         | At high risk for CHD | Statins  | 20          | Omega-3                | 163 | Systolic blood pressure (mmHg)   | Mean: 142<br>SD: 17  | NR   | NR   | No significant differences between groups. | Low                                   |
|                                      |                      |          |             | Placebo                | 169 |  | Mean: 143<br>SD: 21  | NR   | NR   |  |                                       |
| Neil, HAW 2010 <sup>53</sup>         | At high risk for CHD | Statins  | 20          | Omega-3                | 163 | Diastolic blood pressure   | Mean: 80<br>SD:11  | NR   | NR   | No significant differences between groups. | NA                                    |
|                                      |                      |          |             | Placebo                | 169 |  | Mean: 80<br>SD: 12   | NR   | NR   |  |                                       |
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate  | ASA      | 500         | ginkgo biloba          | 50  | Ivy method - bleeding time was the time between first and last extravasations and value was mean of three bleeding times | Mean: 6.3<br>SD: 3.1   | Mean: .21  | Mean: 1.01   | ratio of means presented with 90% CI       | low-medium                            |
|                                      |                      |          |             | Placebo                | 50  |  | Mean: 6.2<br>SD: 3.8   | Mean: 2.1  |  |  |                                       |

**Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)**

| Author Year<br>Study Design            | CHD Risk Category   | CVD drug    | Dose (mg/d)      | Supplement/ Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--|---------------------|-------------|------------------|---------------------|----|---|---|--|---|---|---------------------------------------|
| Hansen 1993 <sup>29</sup><br>crossover | Low and/or Moderate | lovastatin  | 40               | Fish/marine oils    | 14 | NR  | Mean: 390<br>Median<br>SD: 150<br>SE:<br>Lower:<br>Upper:                               | NR   | NR  | Reported in graphical form only.                                | medium                                |
|  |                     |             |                  | Placebo             | 14 |   | Mean: 330<br>Median<br>SD: 70<br>SE:<br>Lower:<br>Upper:                                | NR   |   |   |                                       |
| Kim 2010 <sup>35</sup><br>crossover    | Low and/or Moderate | Ticlopidine | 250- single dose | ginkgo biloba       | 24 | determined just before dosing and at 5, 12, and 48 hours after dosing. While applying 40 mm Hg of pressure on the upper arm, we made an incision using a bleeding-time measurement device (Surgicutt, International Technidyne Corp., Edison, New Jersey) on the volar surface of the forearm to measure the bleeding time. | Mean: 6.3<br>Median<br>SD: 2.3<br>SE:<br>Lower:<br>Upper:                               | Mean:1.1<br>% mean:<br>Median:<br>SD:<br>P:      | NR  | Range of mean: ginkgo group 3-11.5; To treatment group 2.5-8.5. | medium                                |
|  |                     |             |                  | No treatment        | 24 |   | Mean: 5.3<br>Median<br>SD: 1.7<br>SE:<br>Lower:<br>Upper:                               | Mean:0.9<br>Median:<br>SD:<br>P:<br><0.05        |   |   |                                       |



**Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)**

| Author Year<br>Study Design          | CHD Risk Category                      | CVD drug          | Dose (mg/d)                                      | Supplement/Control | N  | Definition of outcome  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|-------------------|--|--------------------|----|--|---|--|---|---|---------------------------------------|
| Aruna 2007 <sup>2</sup><br>crossover | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol); 75 to 150 (clopidogrel) | ginkgo biloba      | 10 | measured 0 and 6 h after drug administration by Ivy's method | Mean: 211<br>Median<br>SD: 70<br>SE: 25<br>Lower:<br>Upper:                             | NR   | NR  | 95% CI of mean for individual group data: ginkgo group: 153.00-270.00; No treatment group: 118.00-182.00. | medium                                |
|                                      |  |                   |  | No treatment       | 10 |  | Mean: 150<br>Median<br>SD: 42<br>SE: 14<br>Lower:<br>Upper:                             | NR   |   |   |                                       |
| Aruna 2007 <sup>2</sup><br>crossover | At low risk for CHD (0-1 risk factors) | Clopidogrel 75 mg | 105 to 200 (cilostazol); 75 to 150 (clopidogrel) | ginkgo biloba      | 10 | measured 0 and 6 h after drug administration by Ivy's method | Mean: 148<br>Median<br>SD: 78<br>SE: 28<br>Lower:<br>Upper:                             | Mean: % mean:<br>Median:<br>SD:<br>P:            | Mean:<br>Median:<br>SD:<br>P:                           | 95% CI of mean for individual group data: ginkgo group: 83.00-213.00; No treatment group: 91.00-190.00.   | medium                                |
|                                      |  |                   |  | No treatment       | 10 |  | Mean: 141<br>Median<br>SD: 59<br>SE: 21   | NR   |   |   |                                       |

**Evidence Table 72. KQ2—Continuous data—Bleeding time (continued)**

| Author<br>Year<br><br>Study<br>Design      | CHD Risk<br>Category      | CVD drug | Dose (mg/d)          | Supplement/<br>Control | N  | Definition of outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower<br>limit (IQR,<br>95% CI)<br>Upper<br>Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---------------------------|----------|----------------------|------------------------|----|---|--|--|---|-----------------------|--|
| Mueller<br>1991 <sup>51</sup><br>crossover | Low<br>and/or<br>Moderate | aspirin  | 325 - single<br>dose | Fish/marine<br>oils    | 12 | measured using a<br>Simplate II system. By<br>blinded operator. | Mean: 680<br>Median<br>SD: 302.6<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>18.6<br>Median:<br>SD:<br>P:                   | NR  |                       | medium   |
|  |                           |          |                      | Placebo                | 12 |   | Mean:<br>633.8<br>Median<br>SD: 339.8  | Mean:<br>% mean:<br>14.5   |   |                       |  |

**Evidence Table 73. KQ2—Continuous data—Clotting time**

| Author<br>Year<br><br>Study<br>Design         | CHD Risk<br>Category | CVD<br>drug | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------|-------------|------|------------------------|----|-----------------------------|---|---|---|-----------------------|--|
| Gardner<br>2007 <sup>23</sup><br><br>Parallel | moderate<br>to high  | ASA         | 325  | ginkgo<br>biloba       | 29 | NR                          | NR  | Mean: 1.5<br>SD:17  | NR  |                       | low  |
|   |                      |             |      | Placebo                | 26 |                             | NR  | Mean: 6.5<br>SD:<br>16.7  |   |                       |  |

**Evidence Table 74. KQ2—Continuous data—Coronary artery calcification**

| Author Year Study Design           | CHD Risk Category    | CVD drug          | Dose    | Supplement/ Control | N  | Definition of outcome  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD / P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|----------------------|-------------------|---------|---------------------|----|--|---|---|--|--------------------|---------------------------------------|
| Budoff 2004 <sup>10</sup> parallel | At high risk for CHD | statins + aspirin | 10 - 40 | Garlic              | 9  | volume calcim score; volumetric score by the method of isotropic interpolation | Mean: Median SD: SE: Lower: Upper:  | Mean: 45.2 % mean: Median: SD: 57.2 P:          | Mean: Median: SD: P: 0.0445                              |                    | medium                                |
|                                    |                      |                   |         | Placebo             | 10 |  | Mean: Median SD: SE: Lower: Upper:  |   |  |                    |                                       |
| Budoff 2004 <sup>10</sup> parallel | At high risk for CHD | statins + aspirin | 10 - 40 | Garlic              | 9  | % change (volume of calcium)   | Mean: Median SD: SE: Lower: Upper:  | Mean: % mean: 7.5 Median: SD: 9.40 P:           | Mean: Median: SD: P: 0.064                               |                    | medium                                |
|                                    |                      |                   |         | Placebo             | 10 |  | Mean: Median SD: SE: Lower: Upper:  |   |  |                    |                                       |

**Evidence Table 74. KQ2—Continuous data—Coronary artery calcification (continued)**

| Author Year Study Design           | CHD Risk Category    | CVD drug          | Dose    | Supplement/ Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means/ medians SD / P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|----------------------|-------------------|---------|---------------------|----|---|---|---|--|--------------------|---------------------------------------|
| Budoff 2004 <sup>10</sup> parallel | At high risk for CHD | statins + aspirin | 10 - 40 | Garlic              | 9  | Agatston calcium score; as described by Agatston et al. by multiplying the lesion area by a coefficient based on the peak density within that plaque. The total Agatston score was determined by summing the scores obtained for each lesion. | Mean: Median SD: SE: Lower: Upper:  | Mean: 71.1 % mean: Median: SD: 95.8 P:              | Mean: Median: SD: P: 0.1401                              |                    | medium                                |
|                                    |                      |                   |         | Placebo             | 10 |   | Mean: Median SD: SE: Lower: Upper:  | Mean: 151.6 Median: SD: 126.5                       |  |                    |                                       |
| Budoff 2004 <sup>10</sup> parallel | At high risk for CHD | statins + aspirin | 10 - 40 | Garlic              | 9  | % change of Agatston score  | NR  | Mean: 38 % mean: 11.5                               | Mean: Median: SD: P: 0.2628                              |                    | medium                                |
|                                    |                      |                   |         | Placebo             | 10 |   | NR  | Mean: % mean: 21.1 SD: 18.90P:                      |  |                    |                                       |

**Evidence Table 75. KQ2—Continuous data—C-reactive protein**

| Author Year<br>Study Design                | CHD Risk Category | CVD drug     | Dose | Supplement/<br>Control | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR,<br>95% CI)<br>Upper Limit (IQR,<br>95% CI) | Mean change/ % change from baseline/<br>SD/<br>P Value   | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|--------------|------|------------------------|----|-----------------------|---|--|--|--|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br><br>parallel | Unclear           | atorvastatin | 1    | Coenzyme Q10.          | 24 | NR                    | Mean: 799<br>Median<br>SD: 1209<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean: -46.8<br>Median:<br>SD:<br>0.5408<br>P: | Mean:<br>Median:<br>SD:<br>P:                                    | There's no significant differences between groups (p=0.5943). Several other continuous outcomes, such as alkaline phosphatase, LDH, CoQ10/ total cholesterol and CoQ10/LDL were not extracted. | medium                                |
|  |                   |              |      | Placebo                | 25 |                       | Mean:777<br>Median<br>SD: 1038<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -14.6<br>Median:<br>SD:<br>P:<br>0.8743 |  |  |                                       |

**Evidence Table 75. KQ2—Continuous data—C-reactive protein (continued)**

| Author Year<br>Study Design           | CHD Risk Category  | CVD drug          | Dose  | Supplement/<br>Control | N  | Definition of outcome               | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value         | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|-------------------|-------|------------------------|----|-------------------------------------|---|--|---|--------------------|---------------------------------------|
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD                                       | statins + aspirin | 10-40 | Garlic                 | 9  | measured after 12 hr fast at 800 hr | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:-<br>0.1<br>% mean:<br>Median:<br>SD:<br>0.22<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.8464                 |                    | medium                                |
|                                       |  |                   |       | Placebo                | 10 |                                     | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:-<br>0.13<br>Median:<br>SD:<br>0.27<br>P:           |   |                    |                                       |
| Chan 2002 <sup>12</sup><br>parallel   | At moderate/moderately high risk for CHD (2+ risk factors) | atorvastatin      | 40    | Fish/marine oils.      | 11 | 12 hr fasting at 800hr              | Mean:<br>1.14<br>Median<br>SD: 1.97<br>SE:<br>Lower:<br>0.6<br>Upper:<br>2.4            | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                 | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|                                       |  |                   |       | Placebo                | 13 |                                     | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>1.1<br>Upper:4                               | Mean:<br>Median:<br>SD:<br>P:                            |   |                    |                                       |

**Evidence Table 75. KQ2—Continuous data—C-reactive protein (continued)**

| Author Year<br>Study Design             | CHD Risk Category                      | CVD drug                 | Dose                              | Supplement/<br>Control             | N | Definition of outcome     | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|--|--------------------------|-----------------------------------|------------------------------------|---|---------------------------|---|--|---|---|---------------------------------------|
| Desideri 2003 <sup>18</sup><br>parallel | At low risk for CHD (0-1 risk factors) | Simvastatin, Bezafibrate | simvastatin: 40; Bezafibrate: 800 | Vitamin E.                         |   | Measured after 12 hr fast | Mean: 1.5<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:                               | Mean: % mean:<br>Median:<br>SD:<br>P:<br><0.05   | Mean:<br>Median:<br>SD:<br>P:                           | I assumed no losses to follow-up although I did not see this explicitly stated. Baseline data also given. | medium                                |
|   |  |                          |                                   | No treatment (aside from CVD drug) |   |                           | Mean: 1.9<br>Median<br>SD: 0.3<br>SE:<br>Lower:<br>Upper:                               | Mean:<br>Median:<br>SD:<br>P:<br><0.05           |   |   |                                       |
|   |  |                          |                                   |                                    |   |                           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |



**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP)**

| Author Year Study Design            | CHD Risk Category   | CVD drug  | Dose | Supplement/ Control                | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|---------------------|---|------|------------------------------------|----|-----------------------|---|--|---|---|---------------------------------------|
| Ferraro 2009 <sup>22</sup> parallel | Unclear             | ramipril  | 10   | Omega-3 (EPA, DHA, or both).       | 15 | NR                    | Mean: 73.5<br>Median<br>SD: 20.3  | NR   | NR  |   | medium                                |
|                                     |                     |   |      | No treatment (aside from CVD drug) | 15 |                       | Mean:76.7<br>Median<br>SD: 9.0  | NR   |   |   |                                       |
| Meyer 2007 <sup>46</sup> parallel   | Unclear             | simvastatin 13, atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin | 81   | Fish/marine oils.                  | 13 | Supine in clinic      | NR  | NR   | NR  | Report states that no changes were noted in DBP across groups and results are not shown | medium                                |
|                                     |                     |   |      | Fish/marine oils.                  | 13 |                       | NR  | NR   |   |   |                                       |
|                                     |                     |   |      | Placebo                            | 14 |                       |   |  |   |   |                                       |
| Sutken 2006 <sup>63</sup> parallel  | Low and/or Moderate | Gemfibrozil   | 1200 | Vitamin E.                         | 22 | NR                    | Mean: 84<br>Median<br>SD:<br>SE: 4<br>Lower:<br>Upper:                                  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         |   |   | high                                  |
|                                     |                     |   |      | No treatment (aside from CVD drug) | 23 |                       | Mean:80<br>Median<br>SD:<br>SE:6.4<br>Lower:<br>Upper:                                  | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design                 | CHD<br>Risk<br>Category   | CVD drug    | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome                            | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---------------------------|-------------|------|--|----|---|---|--|---|--|--|
| Sutken 2006 <sup>63</sup><br>parallel       | Low<br>and/or<br>Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 12 | NR  | Mean: 80<br>Median<br>SD:<br>SE:3.9<br>Lower:<br>Upper:   | NR   | NR  |  | high   |
|   |                           |             |      | No treatment<br>(aside from<br>CVD drug) | 10 |   | Mean:81<br>Median<br>SD:<br>SE:4.2<br>Lower:<br>Upper:  | NR   |   |  |  |
| Macan 2006 <sup>40</sup><br>parallel        | Low<br>and/or<br>Moderate | Warfarin    | NR   | Garlic.                                  | 22 | NR  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.5<br>% mean:<br>Median:<br>SD: 11.8<br>P:                  | Mean:<br>Median:<br>SD:<br>P: 0.829                                       |  | medium   |
|   |                           |             |      | Placebo                                  | 26 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.3<br>Median:<br>SD: 13.7<br>P:                              |   |  |  |
| Barbagallo<br>1999 <sup>5</sup><br>parallel | Unclear                   | furosemide  | 25   | Vitamin E.                               | 12 | overnight fast,<br>supine at rest,<br>empty bladder | Mean:82<br>Median<br>SD: 4<br>SE:<br>Lower:<br>Upper:   | Mean:-8<br>% mean:<br>Median:<br>SD:<br>P:<br><0.005               | Mean:<br>Median:<br>SD:<br>P:   | calculation of mean<br>change from baseline<br>questionably as it won't<br>be useable (SD cannot<br>be inferred, I don't<br>think.). | medium   |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design         | CHD<br>Risk<br>Category | CVD drug  | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|-------------------------------------|-------------------------|-----------|------|--|----|--------------------------|---|--|---|---|--|
|                                     |                         |           |      | No treatment<br>(aside from<br>CVD drug) | 12 |                          | Mean:84<br>Median<br>SD: 6<br>SE:<br>Lower:<br>Upper:   | Mean:-9<br>Median:<br>SD:<br>P:<br><0.005                          |   |   |  |
| Howe 1994 <sup>30</sup><br>parallel | Unclear                 | Captopril | 61   | Fish/marine<br>oils.                     | 14 | NR                       | Mean: 77<br>Median<br>SD:<br>SE:2<br>Lower:<br>Upper:   | Mean:3.1<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   | outcomes in this study<br>are reported as the<br>average of three<br>measurment during the<br>treatment period. | medium   |
|                                     |                         |           |      | Placebo                                  | 14 |                          | Mean:79<br>Median<br>SD:<br>SE:2<br>Lower:<br>Upper:  | Mean:2.3<br>Median:<br>SD:<br>P:                                   |   |   |  |
|                                     |                         |           |      | Fish/marine<br>oils.                     | 14 |                          | Mean:79<br>Median<br>SD: 2<br>SE:<br>Lower:<br>Upper:   | Mean:4.0<br>Median:<br>SD:<br>1.1<br>P:                            |   |   |  |
|                                     |                         |           |      | Placebo                                  | 14 |                          | Mean:77<br>Median<br>SD: 2<br>SE:<br>Lower:<br>Upper:   | Mean:4.4<br>Median:<br>SD:<br>1.7<br>P:                            |   |   |  |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design                | CHD<br>Risk<br>Category   | CVD drug            | Dose | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---------------------------|---------------------|------|------------------------|----|---|---|--|---|--|--|
| Paolisso<br>1992 <sup>57</sup><br>parallel | Unclear                   | hydrochlorothiazide | 25   | Magnesium.             | 9  | supine, fasted (12 h) and at rest for 30 minutes - measured over 60 minutes, mean of last 10 minutes of measurement included. | Mean: 95<br>Median<br>SD:<br>SE:3<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    |  | medium   |
|  |                           |                     |      | Placebo                | 9  |   | Mean:89<br>Median<br>SD:<br>SE:5<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                      |   |  |  |
| Nordøy 2003 <sup>55</sup><br>parallel      | Mod and<br>high risk      | atorvastatin        | 10   | Fish/marine oils.      | 22 | NR  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-2.8<br>% mean:<br>Median:<br>SD:<br>7.2<br>P:<br><0.05       | Mean:<br>Median:<br>SD:<br>P:<br>0.92                                     |  | medium   |
|  |                           |                     |      | Placebo                | 20 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-3.0<br>Median:<br>SD:<br>8.1<br>P:                           |   |  |  |
| Reyes 1984 <sup>59</sup><br>parallel       | Low<br>and/or<br>Moderate | hydrochlorothiazide | 50   | Magnesium.             | 13 | Supine diastolic  | Mean: 104.4<br>Median<br>SD:<br>SE:3.9<br>Lower:<br>Upper:  | Mean:-6<br>% mean:<br>Median:<br>SD:<br>P:<br><0.05                | Mean:<br>Median:<br>SD:<br>P:   | Data for % change measured from graph and verified with numerical data in abstract | medium   |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design           | CHD<br>Risk<br>Category    | CVD drug  | Dose   | Supplement/<br>Control             | N  | Definition of<br>outcome          | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------------|---|--|------------------------------------|----|-----------------------------------|---|--|---|---|--|
|                                       |                            |   |  | Placebo                            | 8  |                                   | Mean:1.5<br>Median<br>SD:<br>SE:4.2<br>Lower:<br>Upper:   | Mean:<br>% mean: -<br>3.4<br>Median:<br>SD:<br>P:<br><0.05         |   |   |  |
| Reyes 1984 <sup>59</sup><br>parallel  | Low<br>and/or<br>Moderate  | hydrochlorothiazide                                 | 50   | Magnesium.                         | 13 | Erect diastolic<br>blood pressure | Mean: 106<br>Median<br>SD:<br>SE:2<br>Lower:<br>Upper:  | Mean:-5<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   | Data extracted from<br>bar charts - method of<br>extraction verified for<br>other variables that<br>had corresponding<br>numerical summary. In<br>this case for final mean<br>and SEM 1.9 cm = 40<br>mmHg and results<br>rounded to nearest<br>whole mmHg. For %<br>change from time of<br>randomization 1.1 cm<br>= 2.5% and results<br>rounded to nearest<br>0.5% | medium   |
|                                       |                            |   |  | Placebo                            | 8  |                                   | Mean: 105<br>Median<br>SD:<br>SE:4<br>Lower:<br>Upper:  | Mean:-3<br>% mean:<br>Median:<br>SD:<br>P:                         |   |   |  |
| Dehmer 1988 <sup>17</sup><br>parallel | At high<br>risk for<br>CHD | aspirin +<br>Dipyridamole + ca<br>channel blockers) | ASA: 325;<br>dipyridamole:<br>225; Ca<br>blocker: NR | Omega-3<br>(EPA, DHA,<br>or both). | 43 | NR                                | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design                 | CHD<br>Risk<br>Category    | CVD drug   | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------------|------------|------|--|----|--------------------------|---|--|---|---|--|
|   |                            |            |      | No treatment<br>(aside from<br>CVD drug) | 39 |                          | Mean:36<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                      |   |   |  |
| Wolf 2006 <sup>58</sup><br>crossover        | Low<br>and/or<br>Moderate  | ASA        | 500  | ginkgo biloba                            | NR | NR                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:   | Study states that:<br>Laboratory findings in<br>all subjects were<br>unremarkable and did<br>not indicate any<br>differences between<br>the treatment groups.<br>Similarly, no<br>noteworthy changes of<br>vital sign variables<br>occurred during the<br>study | low-medium                                     |
|   |                            |            |      |  | NR |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                      |   |   |  |
| Paolisso<br>1995 <sup>56</sup><br>crossover | At high<br>risk for<br>CHD | nifedipine | 88   | Vitamin E                                | 30 | NR                       | Mean: 85<br>Median<br>SD:<br>SE:0.7<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |
|   |                            |            |      | Placebo                                  | 30 |                          | Mean:86<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                      |   |   |  |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design                      | CHD<br>Risk<br>Category | CVD drug   | Dose | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|-------------------------|------------|------|------------------------|----|---|---|--|---|---|--|
| Lungershausen<br>1994 <sup>38</sup><br>crossover | Unclear                 | b-blockers | NR   | Fish/marine<br>oils    | 25 | Clinical diastolic<br>BP - Resting for 5<br>min, empty<br>bladder, fasted<br>and no exercise for<br>2 hours; average<br>of 3 or 4 readings<br>after discarding<br>initial reading;<br>measured using<br>automated<br>oscillometric<br>monitor | Mean: 72.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    | Data of mean<br>measured from<br>histogram (10 mmHg =<br>2.2 cm). Measure of<br>dispersion not stated.<br>This study is at risk of<br>selective outcome<br>reporting; p-values for<br>crude difference also<br>don't make sense in<br>context of graph. I<br>would approach this<br>data with e | medium   |
|  |                         |            |      | Placebo                | 25 |   | Mean:75.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                      |   |   |  |
| Lungershausen<br>1994 <sup>38</sup><br>crossover | Unclear                 | b-blockers | NR   | Fish/marine<br>oils    | 25 | Ambulatory<br>diastolic BP -<br>Measured over<br>next 24 hours<br>using Spacelab<br>90207 instrument,<br>same time of day;<br>taken at 20 min<br>intervals during<br>wake and every 1<br>hour during sleep.                                   | Mean: 76<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:2.3<br>% mean:<br>Median:<br>SD:<br>SD:<br>0.8<br>P:          | Mean:<br>Median:<br>SD:<br>P:<br><0.01                                    | Data of mean<br>measured from<br>histogram (10 mmHg =<br>2.2 cm). Measure of<br>dispersion not stated.<br>Data of mean<br>difference in text. This<br>study is at risk of<br>selective outcome<br>reporting; p-values for<br>crude difference also<br>don't make sense in<br>context of graph.  | medium   |
|  |                         |            |      | Placebo                | 25 |   | Mean:78<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>SD:<br>1<br>P:                          |   |   |  |

**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design             | CHD<br>Risk<br>Category   | CVD drug   | Dose               | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---------------------------|--|--------------------|------------------------|----|---|---|--|---|--------------------|--|
| Mueller 1991 <sup>51</sup><br>crossover | Low<br>and/or<br>Moderate | aspirin  | 325-single<br>dose | Fish/marine<br>oils    | 12 | before and 90<br>minutes after a<br>single oral 325-mg<br>dose of aspirin.<br>Done by blinded<br>operator | Mean: 77.5<br>Median<br>SD: 11.7<br>SE:<br>Lower:<br>Upper:   | Mean:-2<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |
|   |                           |  |                    | Placebo                | 12 |   | Mean:74.08<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                      |   |                    |  |
| Maki 2008 <sup>41</sup><br>crossover    | Low<br>and/or<br>Moderate | simvastatin  | 20                 | Omega-3                | 39 | At rest, seated   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -<br>3.3<br>Median:<br>SD:<br>P:                  | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |
|   |                           |  |                    | Placebo                | 40 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                      |   |                    |  |
| Wirell 1994 <sup>67</sup><br>Crossover  | Unclear                   | metoprolol, atenolol,<br>pindolol &<br>propranolol | NR                 | magnesium              | 39 | standing  | Mean:<br>100.84<br>Median<br>SD: 9.48   | NR   | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |
|   |                           |  |                    | Placebo                | 39 |   | Mean:102.49   | NR   |   |                    |  |



**Evidence Table 76. KQ2—Continuous data—Diastolic blood pressure (DBP) (continued)**

| Author Year<br>Study Design            | CHD<br>Risk<br>Category | CVD drug   | Dose | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|-------------------------|--|------|------------------------|----|--------------------------|---|--|---|--------------------|--|
| Wirell 1994 <sup>67</sup><br>Crossover | Unclear                 | metoprolol, atenolol,<br>pindolol &<br>propranolol | NR   | magnesium              | 39 | supine                   | Mean: 93.03<br>Median<br>SD: 9.37<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | NR  |                    | medium   |
|  |                         |  |      | Placebo                | 39 |                          | Mean:95.68  | NR   |   |                    |  |
|  |                         |  |      |                        |    |                          | NR  | NR   |   |                    |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C)**

| Author Year<br>Study Design        | CHD Risk<br>Category | CVD drug     | Dose  | Supplement/<br>Control          | N   | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/<br>% change<br>from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|------------------------------------|----------------------|--------------|-------|---------------------------------|-----|-----------------------------|---|---|---|-----------------------|--|
| Bays 2010 <sup>6</sup><br>parallel | Unclear              | atorvastatin | 10-40 | Omega-3 (EPA,<br>DHA, or both). | 122 |                             | Mean:<br>Median<br>39.8<br>SD: 34<br>SE:48<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                            | Mean:2.4<br>Median:<br>SD:<br>P:<0.001                                    |                       | medium   |
|                                    |                      |              |       | Placebo                         | 121 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                       |   |                       |  |
| Bays 2010 <sup>6</sup><br>parallel | Unclear              | atorvastatin | 10-40 | Omega-3 (EPA,<br>DHA, or both). | 122 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                            | Mean:6.3<br>Median:<br>SD:<br>P:0.001                                     |                       | medium   |
|                                    |                      |              |       | Placebo                         | 121 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                       |   |                       |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category | CVD drug              | Dose  | Supplement/<br>Control             | N   | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|-------------------|-----------------------|-------|------------------------------------|-----|-----------------------------|---|--|---|--|--|
| Mabuchi<br>2007 <sup>39</sup><br>parallel  | Unclear           | atorvastatin          | 1     | Coenzyme<br>Q10.                   | 24  |                             | Mean: 1.74<br>Median<br>SD: 0.42<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br>0.0033               | Mean:<br>Median:<br>SD:<br>P:   | "...no<br>significant<br>differences<br>between the<br>groups" | medium   |
|  |                   |                       |       | Placebo                            | 25  |                             | Mean:1.61<br>Median<br>SD: 0.34<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br>0.0583                          |   |  |  |
| Young 2007 <sup>70</sup><br>parallel       | Mod and high risk | simvastatin<br>statin | 10-40 | Coenzyme<br>Q10.                   | 22  |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:<br>0.65                                     | No<br>difference in<br>groups<br>(p=0.65)                      | medium   |
|  |                   |                       |       | Placebo                            | 22  |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                    |   |  |  |
| Davidson<br>2007 <sup>14</sup><br>parallel | Unclear           | simvastatin<br>statin | 40    | Omega-3<br>(EPA, DHA,<br>or both). | 122 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:<br><0.001                                   |  | medium   |
|  |                   |                       |       | Placebo                            | 132 |                             | Mean:   | Mean:  |   |  |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control    | N  | Definition<br>of<br>outcome                                | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---------------------|-------------|------|---------------------------|----|--|---|--|---|-----------------------|--|
|                                       |                     |             |      |                           |    |  | Mean<br>SD:<br>SE:<br>Lower:<br>Upper:  | % mean:<br>-1.10<br>Median:<br>SD:<br>P:                         |   |                       |  |
| Meyer 2007 <sup>46</sup><br>parallel  | Unclear             | simvastatin | 81   | Fish/marine<br>oils.      | 13 |  | Mean: 1.16<br>Median<br>SD:<br>SE:0.09<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |                     |             |      | Fish/marine<br>oils. 8g/d | 13 | Mean: 1.21<br>Median<br>SD:<br>SE:0.05<br>Lower:<br>Upper: | Mean:<br>% mean:<br>Median:<br>SD:<br>P:  |  |   |                       |  |
|                                       |                     |             |      | Placebo                   | 14 | Mean:1.11<br>Median<br>SD:<br>SE:0.10<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:   |  |   |                       |  |
| Sutken 2006 <sup>63</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                | 22 |  | Mean: 0.82<br>Median<br>SD:<br>SE:0.04<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.05                | Mean:<br>Median:<br>SD:<br>P:   |                       | high   |
|                                       |                     |             |      | Placebo                   | 23 | Mean:0.82<br>Median  | Mean:<br>Median:  |  |   |                       |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug     | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome                               | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------|--------------|------|------------------------|----|---|---|--|---|--|--|
|                                       |                      |              |      |                        |    |   | SD:<br>SE:0.04<br>Lower:<br>Upper:  | SD:<br>P:<br><0.05   |   |  |  |
| Sutken 2006 <sup>63</sup><br>parallel | Low and/or Moderate  | Gemfibrozil  | 1200 | Vitamin E.             | 12 |   | Mean: 1.57<br>Median<br>SD:<br>SE:0.04<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01                | Mean:<br>Median:<br>SD:<br>P:   |  | high   |
|                                       |                      |              |      | Placebo                | 10 | Mean:1.41<br>Median<br>SD:<br>SE:0.08<br>Lower:<br>Upper: | Mean:<br>Median:<br>SD:<br>P:<br><0.01  |  |   |  |  |
| Macan 2006 <sup>40</sup><br>parallel  | Low and/or Moderate  | Warfarin     | NR   | Garlic.                | 22 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.9<br>% mean:<br>Median:<br>SD:<br>7.9<br>P:               | Mean:<br>Median:<br>SD:<br>P:<br>0.038                                    | Other<br>continous<br>outcome<br>assessed in<br>this study:<br>hemoglobin<br>(weight also<br>but I stated<br>this in<br>another<br>comment as<br>well) | medium   |
|                                       |                      |              |      | Placebo                | 26 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:         | Mean:-1.6<br>Median:<br>SD:<br>6.7<br>P:  |  |   |  |  |
| Manuel                                | At high risk for CHD | Atorvastatin | 20   | Vitamin E.             | 11 |   | Mean:   | Mean:  | Mean:   | Data not   | medium   |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category    | CVD drug    | Dose | Supplement/<br>Control                                   | N  | Definition<br>of<br>outcome                               | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|-------------|------|--|----|---|---|--|---|---|--|
| 2004 <sup>42</sup><br>parallel             |                      |             |      |  |    |   | Mean<br>SD:<br>SE:<br>Lower:<br>Upper:  | % mean:<br>Median:<br>SD:<br>P:                                  | Median:<br>SD:<br>P:  | presented in<br>paper - only<br>provides<br>baseline<br>data per<br>group and<br>states that<br>this outcome<br>'did not<br>change in<br>either group'. |  |
|  |                      |             |      | Placebo  | 11 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:         | Mean:<br>Median:<br>SD:<br>P:   |  |   |   |  |
| Playford<br>2003 <sup>58</sup><br>parallel | At high risk for CHD | Fenofibrate | 200  | Coenzyme<br>Q10.<br>200 mg plus<br>200 mg<br>fenofibrate | 18 |   | Mean: 1.07<br>Median<br>SD: 0.05<br>SE:<br>Lower:<br>Upper:   | Mean:0.14<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:0.04<br>(group 1 vs.<br>group 2<br>Median:<br>SD:<br>P:0.385         |   | low-medium                                     |
|  |                      |             |      | No treatment<br>(aside from<br>CVD drug)                 | 17 | Mean:1.11<br>Median<br>SD:<br>SE:0.04<br>Lower:<br>Upper: | Mean:0.17<br>Median:<br>SD:<br>P:   |  |   |   |  |
|  |                      |             |      | Coenzyme<br>Q10.<br>200 mg<br>CoQ10 only                 | 20 | Mean:0.98<br>Median<br>SD:<br>SE:0.04<br>Lower:<br>Upper: | Mean:0.03<br>Median:<br>SD:<br>P:   |  |   |   |  |
|  |                      |             |      | Placebo  | 18 | Mean:0.98<br>Median                                       | Mean:-0.05<br>Median:   |  |   |   |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                 | CHD Risk Category                         | CVD drug              | Dose  | Supplement/<br>Control                                   | N  | Definition<br>of<br>outcome                                    | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results                         | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---|-----------------------|-------|--|----|--|---|--|---|---|--|
|   |   |                       |       |  |    |  | SD:<br>SE:0.04<br>Lower:<br>Upper:  | SD:<br>P:  |   |   |  |
| Svaneborg<br>2002 <sup>64</sup><br>parallel | At low risk for CHD<br>(0-1 risk factors) | ASA                   | 100   | Omega-3<br>(EPA, DHA,<br>or both).                       | 12 |  | Mean:<br>Median<br>1.18<br>SD: 0.73<br>SE:1.38<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   | placebo=<br>corn oil<br>containing<br>omega-6 | medium   |
|   |   |                       |       | Placebo  | 6  | Mean:1.05<br>Median<br>SD:<br>SE:<br>Lower: 0.88<br>Upper:1.45 | Mean:<br>Median:<br>SD:<br>P:   |  |   |   |  |
| Duffy 2001 <sup>20</sup><br>parallel        | Low and/or Moderate                       | simvastatin<br>statin | 10-40 | Vitamin E<br>1000 IU<br>vitmain E<br>plus<br>simvastatin | 6  |  | Mean: 1.4<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:   | Mean:-0.1<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |
|   |   |                       |       | No treatment<br>(aside from<br>CVD drug)                 | 7  | Mean:1.3<br>Median<br>SD: 0.3<br>SE:<br>Lower:<br>Upper:       | Mean:0<br>Median:<br>SD:<br>P:  |  |   |   |  |
|   |   |                       |       | 1000IU<br>Vitamin E                                      | 6  | Mean:1.4<br>Median   | Mean:0.1<br>Median:   |  |   |   |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category | CVD drug    | Dose  | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|-------------------|-------------|-------|--|----|-----------------------------|---|--|---|--|--|
|                                       |                   |             |       |  |    |                             | SD: 0.3<br>SE:<br>Lower:<br>Upper:  | SD:<br>P:  |   |  |  |
|                                       |                   |             |       | Placebo                                  | 7  |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean-0.1<br>Median:<br>SD:<br>P:                                 |   |  |  |
| Napoli 1998 <sup>52</sup><br>parallel | Unclear           | Pravastatin | 20-40 | Vitamin E.                               | 52 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: 9<br>Median:<br>SD:<br>3%<br>P:<br><0.05        | Mean:<br>Median:<br>SD:<br>P:   | Data not<br>extracted but<br>also<br>available for<br>VLDL-C,<br>IDL-C, ApoB,<br>Apo AI, Apo<br>All. Further,<br>data not<br>reported for<br>routine<br>laboratory<br>tests and<br>adverse<br>effects. For<br>these<br>outcomes it<br>is reported<br>that "no<br>differences<br>in routine | medium   |
|                                       |                   |             |       | No treatment<br>(aside from<br>CVD drug) | 56 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:10<br>Median:<br>SD:<br>4%<br>P:<br><0.05        |   |  |  |



**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design          | CHD Risk Category    | CVD drug | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--------------------------------------|----------------------|----------|------|------------------------|----|-----------------------------|---|--|---|---|--|
|                                      |                      |          |      |                        |    |                             |   |  |   | laboratory tests and adverse effects were registered during the study (data not shown); in particular, there were no differences between the values recorded in each individual after treatment compared with baseline values, and no differences between the treatment groups. |  |
| Bordia 1998 <sup>9</sup><br>parallel | At high risk for CHD | Nitrates | NR   | Garlic.                | 30 |                             | Mean: 49.5<br>Median<br>SD:<br>SE:1.6   | Mean:9<br>% mean22.3:<br>Median:<br>SD:                          | Mean:<br>Median:<br>SD:<br>P:   |   | high   |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category    | CVD drug    | Dose   | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|-------------|--------|--|----|-----------------------------|---|--|---|-----------------------|--|
|  |                      |             |        |  |    |                             | Lower:<br>Upper:  | P:<br><0.05  |   |                       |  |
|  |                      |             |        | Placebo                                  | 30 |                             | Mean:41.1<br>Median<br>SD:<br>SE:2.8<br>Lower:<br>Upper:  | Mean:0.1<br>Median:<br>SD:<br>P:                                 |   |                       |  |
| Davidson<br>1997 <sup>15</sup><br>parallel | Unclear              | Simvastatin | 10     | Fish/marine<br>oils                      | 9  |                             | Mean: 44.8<br>Median<br>SD:<br>SE:3.5<br>Lower:<br>Upper:   | Mean:4.5<br>% mean: 10.4<br>Median:<br>SD:<br>P:<br><0.05        | Mean:<br>Median:<br>SD:<br>P:   |                       | Medium   |
|  |                      |             |        | No treatment<br>(aside from<br>CVD drug) | 10 |                             | Mean:45.1<br>Median<br>SD:<br>SE:2.9<br>Lower:<br>Upper:  | Mean:2.7<br>% mean 7.2<br>Median:<br>SD:<br>P:<br><0.05          |   |                       |  |
| Yamamoto<br>1995 <sup>69</sup><br>parallel | At high risk for CHD | diltiazem   | 90-120 | Omega-3<br>(EPA, DHA,<br>or both).       | 12 |                             | Mean: 45<br>Median<br>SD:<br>SE:9<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|  |                      |             |        | No treatment<br>(aside from              | 10 |                             | Mean:47<br>Median   | Mean:<br>Median:   |   |                       |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category    | CVD drug                        | Dose  | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|---------------------------------|---|--|----|-----------------------------|---|--|---|-----------------------|--|
|  |                      |                                 |   | CVD drug)                                |    |                             | SD:<br>SE:12<br>Lower:<br>Upper:  | SD:<br>P:  |   |                       |  |
| McDowell<br>1994 <sup>44</sup><br>parallel | Unclear              | Simvastatin                     | 20  | Vitamin E.                               | 8  |                             | Mean: 1.3<br>Median<br>SD: 0.3<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|  |                      |                                 |   | Placebo                                  | 8  |                             | Mean:1.3<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                    |   |                       |  |
| Kaul 1992 <sup>34</sup><br>parallel        | At high risk for CHD | Calcium channel<br>blocker, ASA | ASA: 150;<br>heparin: 1000<br>U/d; ca blockers:<br>NR | Fish/marine<br>oils.                     | 58 |                             | Mean: 37<br>Median<br>SD: 10.5<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |                       | low-medium                                     |
|  |                      |                                 |   | No treatment<br>(aside from<br>CVD drug) | 49 |                             | Mean:37<br>Median<br>SD: 10.5<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                    |   |                       |  |
| Nordøy<br>2003 <sup>55</sup><br>parallel   | Mod and high risk    | atorvastatin                    | 10  | Fish/marine<br>oils.                     | 22 |                             | Mean:<br>Median<br>SD:  | Mean:0.07<br>% mean:<br>Median:                                  | Mean:<br>Median:<br>SD:   |                       | medium   |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design          | CHD Risk Category | CVD drug                | Dose | Supplement/<br>Control             | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results                   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--------------------------------------|-------------------|-------------------------|------|------------------------------------|----|-----------------------------|---|--|---|---|--|
|                                      |                   |                         |      |                                    |    |                             | SE:<br>Lower:<br>Upper:   | SD:<br>0.08<br>P:  | P:<br>0.03  |   |  |
|                                      |                   |                         |      | Placebo                            | 20 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.01<br>Median:<br>SD:<br>0.09<br>P:                        |   |   |  |
| Roth 2009 <sup>60</sup><br>parallel  | Unclear           | fenofibrates by<br>100% | 130  | Omega-3<br>(EPA, DHA,<br>or both). | 81 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median :<br>-1.9<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:   | Not<br>significant<br>between<br>groups | medium   |
|                                      |                   |                         |      | Placebo                            | 82 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                    |   |   |  |
| Isley 2007 <sup>31</sup><br>parallel | Unclear           | niacin                  | 325  | Omega-3                            | 7  |                             | Mean: 49<br>Median<br>SD: 5<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:33<br>Median:<br>SD:<br>P:                       | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |
|                                      |                   |                         |      | Placebo                            | 8  |                             | Mean:48<br>Median<br>SD: 14<br>SE:  | Mean:<br>% mean: 18<br>Median:<br>SD:                            |   |   |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category  | CVD drug          | Dose  | Supplement/<br>Control | N  | Definition<br>of<br>outcome                                 | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|--|-------------------|-------|------------------------|----|---|---|--|---|-----------------------|--|
|                                       |  |                   |       |                        |    |   | Lower:<br>Upper:  | P:   |   |                       |  |
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD                                       | statins + aspirin | 10-40 | Garlic                 | 9  |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:3<br>% mean:<br>Median:<br>SD:<br>10.6<br>P:                | Mean:<br>Median:<br>SD:<br>P:<br>0.4611                                   |                       | medium   |
|                                       |  |                   |       | Placebo                | 10 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:           | Mean:-1.3<br>Median:<br>SD:<br>13.8<br>P:   |  |   |                       |  |
| Chan 2002 <sup>12</sup><br>parallel   | At moderate/moderately high risk for CHD (2+ risk factors) | atorvastatin      | 40    | Fish/marine oils.      | 11 |   | Mean: 1.25<br>Median<br>SD:<br>SE:0.09<br>Lower:<br>Upper:  | Mean:<br>% mean: 13.5<br>Median:<br>SD:<br>3.80%<br>P:           | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |  |                   |       | Placebo                | 13 | Mean: 1.04<br>Median<br>SD:<br>SE: 0.05<br>Lower:<br>Upper: | Mean:<br>% mean:4.5<br>Median:<br>SD:<br>P:   |  |   |                       |  |
| Liu 2003 <sup>37</sup><br>parallel    | Unclear  | simvastatin       | 10    | Fish/marine oils.      | 19 |   | Mean: 1.53<br>Median<br>SD: 0.36<br>SE:<br>Lower:   | Mean:0.11<br>% mean:<br>Median:<br>SD:<br>0.21                   | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category                         | CVD drug   | Dose   | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---|--|--|--|----|-----------------------------|---|--|---|---|--|
|  |   |  |  | No treatment<br>(aside from<br>CVD drug) | 18 |                             | Upper:<br>Mean:1.77<br>Median<br>SD: 0.54<br>SE:<br>Lower:<br>Upper:7.1   | P:<br>Mean:0.12<br>Median:<br>SD:<br>0.2<br>P:                   |   |   |  |
| Dehmer<br>1988 <sup>17</sup><br>parallel   | At high risk for CHD                      | aspirin +<br>Dipyridamole +<br>ca channel<br>blockers) | ASA: 325;<br>dipyridamole:<br>225; Ca blocker:<br>NR | Omega-3<br>(EPA, DHA,<br>or both).       | 43 |                             | Mean: 36<br>Median<br>SD: 8.7<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:7.4<br>Median:<br>SD:<br>P:                      | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |
|  |   |  |  | No treatment<br>(aside from<br>CVD drug) | 39 |                             | Mean:36<br>Median<br>SD: 9.4<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                    |   |   |  |
| Desideri<br>2003 <sup>18</sup><br>parallel | At low risk for CHD<br>(0-1 risk factors) | Simvastatinstatin,<br>Bezafibrate                      | simvastatinstatin:<br>40; Bezafibrate:<br>800        | Vitamin E.                               |    |                             | Mean: 1.2<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   | I assumed<br>no losses to<br>follow-up<br>although I<br>did not see<br>this<br>explicitly<br>stated | medium   |
|  |   |  |  | No treatment<br>(aside from<br>CVD drug) |    |                             | Mean:1.1<br>Median<br>SD: 0.1<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                    |   |   |  |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                    | CHD Risk Category    | CVD drug              | Dose  | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome                              | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|-----------------------|-------|--|----|--|---|--|---|--|--|
| Wolf 2006 <sup>68</sup><br>crossover           | Low and/or Moderate  | ASA                   | 500   | ginkgo biloba                            |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   | Study states<br>that:<br>Laboratory<br>findings in all<br>subjects<br>were un-<br>remarkable<br>and did not<br>indicate any<br>differences<br>between the<br>treatment<br>groups.    | low-medium                                     |
|  |                      |                       |       |  |    | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:        | Mean:<br>Median:<br>SD:<br>P:   |  |   |  |  |
| De Caterina<br>2002 <sup>16</sup><br>crossover | At high risk for CHD | simvastatin<br>statin | 10-40 | Vitamin E                                |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   | Values are<br>presented in<br>graphs, but<br>difficult to<br>read.<br>Statement<br>that "Neither<br>LDL<br>cholesterol<br>nor<br>triglycerides<br>were<br>affected by<br>Vitamin E." | high   |
|  |                      |                       |       | No treatment<br>(aside from<br>CVD drug) |    | Mean:54<br>Median<br>SD: 15.3<br>SE:<br>Lower:<br>Upper: | Mean:2.2<br>Median:<br>SD:<br>P:  |  |   |  |  |
| Balestrieri<br>1996 <sup>4</sup><br>crossover  | Low and/or Moderate  | Simvastatin<br>statin | 10-40 | Fish/marine<br>oils                      | 14 |  | Mean: 53<br>Median<br>SD: 21<br>SE:   | Mean:2<br>% mean:<br>Median:<br>SD:                              | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |

**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                 | CHD Risk Category    | CVD drug   | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------|------------|------|------------------------|----|-----------------------------|---|--|---|-----------------------|--|
|   |                      |            |      |                        |    |                             | Lower:<br>Upper:  | P:   |   |                       |  |
|   |                      |            |      | Placebo                | 14 |                             | Mean:52<br>Median<br>SD: 18<br>SE:<br>Lower:<br>Upper:  | Mean:2<br>Median:<br>SD:<br>P:                                   |   |                       |  |
| Paolisso<br>1995 <sup>56</sup><br>crossover | At high risk for CHD | nifedipine | 88   | Vitamin E              | 30 |                             | Mean: 0.89<br>Median<br>SD:<br>SE:0.04<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    |                       | medium   |
|   |                      |            |      | Placebo                | 30 |                             | Mean:0.78<br>Median<br>SD: 0.07<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                    |   |                       |  |
| Hansen1993 <sup>29</sup><br>crossover       | Low and/or Moderate  | lovastatin | 40   | Fish/marine<br>oils    | 14 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: 6<br>Median:<br>SD:<br>P:                       | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|   |                      |            |      | Placebo                | 14 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:   | Mean:<br>% mean:14<br>Median:<br>SD:<br>P:                       |   |                       |  |



**Evidence Table 77. KQ2—Continuous data—High-density lipoprotein cholesterol (HDL-C) (continued)**

| Author Year<br>Study Design                | CHD Risk Category   | CVD drug    | Dose            | Supplement/<br>Control | N  | Definition<br>of<br>outcome                                 | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---------------------|-------------|-----------------|------------------------|----|---|---|--|---|--|--|
|  |                     |             |                 |                        |    |   | Upper:  |  |   |  |  |
| Mueller<br>1991 <sup>51</sup><br>crossover | Low and/or Moderate | aspirin     | 325-single dose | Fish/marine<br>oils    | 12 |   | Mean:46.17<br>Median<br>SD: 11.56<br>SE:<br>Lower:<br>Upper:  | Mean:3.34<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                     |             |                 | Placebo                | 12 | Mean:44.25<br>Median<br>SD: 9.17<br>SE:<br>Lower:<br>Upper: | Mean:1.42<br>Median:<br>SD:<br>P:   |  |   |  |  |
| Maki 2008 <sup>41</sup><br>crossover       | Low and/or Moderate | simvastatin | 20              | Omega-3                | 39 |   | Mean:<br>Median 45<br>SD:<br>SE:<br>Lower: 27<br>Upper:106  | Mean:<br>% mean:<br>Median:<br>16.4%<br>SD:<br>P:                | Mean:<br>Median: 7.2<br>SD:<br>P:<br>0.001                                | The IQRs<br>reported are<br>actually<br>ranges (low-<br>high). | medium   |
|  |                     |             |                 | Placebo                | 39 | Mean:<br>Median 41<br>SD:<br>SE:<br>Lower: 29<br>Upper:93   | Mean:<br>Median:10.6%<br>SD:<br>P:  |  |   |  |  |

**Evidence Table 78. KQ2—Continuous data—INR**

| Author Year<br>Study Design | CHD Risk Category | CVD drug | Dose          | Supplement/ Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value          | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|-------------------|----------|---------------|---------------------|----|---|---|---|---|--|---------------------------------------|
| Sconce 2007 <sup>61</sup>   | Unclear           | wafarin  | varying doses | Vitamin K           | 35 | Standard deviation of INR ( This is actually the standard deviation of the INR over a 6 month period after beginning treatment with Vit K compared to 6 months prior to treatment with vit K) | Mean: 0.47<br>Median<br>SD: 0.18<br>SE:<br>Lower:<br>Upper:                             | Mean:-0.24<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001   | Mean:<br>Median:<br>SD:<br>P:                           | Some data (<1% in each arm) omitted from analysis due to known confounding factors | medium                                |
|                             |                   |          |               | Placebo             | 33 |   | Mean:0.59<br>Median<br>SD: 0.15<br>SE:<br>Lower:<br>Upper:                              | Mean:-0.11<br>Median:<br>SD:<br>0.18<br>P:<br><0.001      |   |  |                                       |
| Sconce 2007 <sup>61</sup>   | Unclear           | wafarin  | varying doses | Vitamin K           | 35 | % of time in target INR range (within 0.5 U); within 0.5 U  | Mean: 87<br>Median<br>SD: 14<br>SE:<br>Lower:<br>Upper:                                 | Mean:28<br>% mean:<br>Median:<br>SD:<br>20<br>P:<br><0.01 | Mean:<br>Median:<br>SD:<br>P:                           |  | medium                                |
|                             |                   |          |               | Placebo             | 33 |   | Mean:78<br>Median<br>SD: 17<br>SE:<br>Lower:<br>Upper:                                  | Mean:15<br>Median:<br>SD:<br>20<br>P:<br><0.01            |   |  |                                       |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design | CHD Risk Category    | CVD drug | Dose | Supplement/<br>Control                   | N  | Definition of outcome                                     | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|-----------------------------|----------------------|----------|------|--|----|---|---|---|---|-----------------------|--|
| Lee 2008 <sup>36</sup>      | At high risk for CHD | wafarin  | 3.5  | Ginseng.                                 | 12 | Peak INR  | Mean: 1.16<br>Median<br>SD: 0.09<br>SE:<br>Lower:<br>Upper:   | Mean:0.15<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01           | Mean:0.01<br>Median:<br>SD:<br>P:   |                       | medium   |
|                             |                      |          |      | No treatment<br>(aside from<br>CVD drug) | 13 |   | Mean:1.15<br>Median<br>SD: 0.07<br>SE:<br>Lower:<br>Upper:  | Mean:0.13<br>Median:<br>SD:<br>P:<br><0.01                      |   |                       |  |
| Lee 2008 <sup>36</sup>      | At high risk for CHD | wafarin  | 3.5  | Ginseng.                                 | 12 | Peak INR  | Mean: 2.25<br>Median<br>SD: 0.38<br>SE:<br>Lower:<br>Upper:   | Mean:1.24<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01           | Mean:0.11<br>Median:<br>SD:<br>P:   |                       | medium   |
|                             |                      |          |      | No treatment<br>(aside from<br>CVD drug) | 13 |   | Mean:2.14<br>Median<br>SD: 0.38<br>SE:<br>Lower:<br>Upper:  | Mean:1.12<br>Median:<br>SD:<br>P:<br><0.01                      |   |                       |  |
| Lee 2008 <sup>36</sup>      | At high risk for CHD | wafarin  | 3.5  | Ginseng                                  | 12 | AUC <sub>INR</sub><br>Measured as area<br>under the curve | Mean: 7.55<br>Median<br>SD: 0.41<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:0.04<br>Median:<br>SD:<br>P:   |                       | medium   |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design | CHD Risk Category           | CVD drug      | Dose | Supplement/<br>Control                   | N  | Definition of outcome                                  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|-----------------------------|---------------|------|--|----|--|---|---|---|--------------------|---------------------------------------|
|                             |                             |               |      | No treatment<br>(aside from<br>CVD drug) | 13 |  | Mean:7.52<br>Median<br>SD: 0.31<br>SE:<br>Lower:<br>Upper:  | Mean:<br>SD:<br>P:  |   |                    |                                       |
| Lee 2008 <sup>36</sup>      | At high risk for CHD        | phenprocoumon | 3.5  | Ginseng.                                 | 12 | AUC <sub>INR</sub><br>Measured as area under the curve | Mean: 22.18<br>Median<br>SD: 1.85<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:0.49<br>Median:<br>SD:<br>P:   |                    | medium                                |
|                             |                             |               |      | No treatment<br>(aside from<br>CVD drug) | 13 |  | Mean:21.69<br>Median<br>SD: 1.54<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |                    |                                       |
| Macan 2006 <sup>40</sup>    | Low and/or mod to high risk | Warfarin      | NR   | Garlic.                                  | 22 | NR - assessed after 12 hr fast                         | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0<br>% mean:<br>Median:<br>SD:<br>P:<br>0.579              |   |                    | medium                                |
|                             |                             |               |      | Placebo                                  | 26 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.2<br>Median:<br>SD:<br>0.09<br>P:                        |   |                    |                                       |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design | CHD Risk Category   | CVD drug | Dose | Supplement/<br>Control | N  | Definition of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between group differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|---------------------|----------|------|------------------------|----|---|---|--|---|--------------------|---------------------------------------|
| Yuan 2004 <sup>71</sup>     | Low and/or Moderate | Warfarin | 5.00 | Ginseng                | 12 | peak INR  | Mean:<br>Median<br>SD:<br>SE:<br>Lower: -2.41<br>Upper:0.02   | Mean:<br>% mean:<br>Median: :-<br>0.16<br>SD:<br>P:          | Mean:<br>Median<br>SD:<br>P:<br>0.019                               |                    | low                                   |
|                             |                     |          |      | Placebo                | 8  |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower: -2.41<br>Upper:-0.07  | Mean:-0.02<br>Median:<br>SD:<br>P:                           |   |                    |                                       |
| Yuan 2004 <sup>71</sup>     | Low and/or Moderate | Warfarin | 5.00 | Ginseng                | 12 | AUC <sub>INR</sub>  | Mean:<br>Median<br>SD:<br>SE:<br>Lower: -6.36<br>Upper:0.36   | Mean:<br>% mean:<br>Median:-<br>0.46<br>SD:<br>P:            | Mean:<br>Median:<br>SD:<br>P:                                       |                    | low                                   |
|                             |                     |          |      | Placebo                | 8  |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower: -0.51<br>Upper:0.72   | Mean:-0.09<br>Median:<br>SD:<br>P:                           |   |                    |                                       |
| Wolf 2006 <sup>68</sup>     | Unclear             | Warfarin | NR   | Omega-3                | 6  | no numeric data reported- data could not be obtained from the graph with an acceptable degree | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:<br>Median:<br>SD:<br>P:                                       |                    | high                                  |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design | CHD Risk Category                      | CVD drug | Dose             | Supplement/<br>Control | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between group differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|----------|------------------|------------------------|----|-----------------------|---|--|---|---|---------------------------------------|
|                             |  |          |                  | Placebo                | 5  | of accuracy           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                |   |   |                                       |
| Jiang 2004 <sup>33</sup>    | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Ginseng                | 12 | AUC(0-168)            | Mean: 111.1<br>Median<br>SD: 43.1<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:1.01 (Ginseng+ no treatment)                                   | 95% CI of mean for individual group data: Ginseng group: 83.9-138.7; St. Johns Wort group: 68.8-107.8; No treatment group: 79.6-142.3 | medium                                |
|                             |  |          |                  | St. John's             | 12 |                       | Mean:88.3<br>Median<br>SD: 30.7<br>SE:<br>Lower:<br>Upper:  | Mean:0.79<br>Median:<br>SD:<br>P:                            |   |   |                                       |
|                             |  |          |                  | No treatment           | 12 |                       | Mean: 111<br>Median<br>SD: 49.3<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                |   |   |                                       |
| Jiang 2005 <sup>32</sup>    | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Gingko Biloba          | 12 | AUC(0-168)            | Mean: 121<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:0.93 (gingko biloba + no treatment)<br>Median:<br>SD:          | 95% CI of mean for individual group data: ginkgo group: 77-165; Ginger  | medium                                |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design       | CHD Risk Category                      | CVD drug | Dose             | Supplement/<br>Control | N  | Definition of outcome  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean change/ % change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|-----------------------------------|--|----------|------------------|------------------------|----|--|---|--|--|---|---------------------------------------|
|                                   |  |          |                  | Ginger                 | 12 |  | Mean:125<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                          | P:   | group: 91-160;<br>No treatment group: 90-158                                      |                                       |
|                                   |  |          |                  | No treatment           | 12 |  | Mean:124<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                          |  |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup> | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Garlic                 | 12 | INR <sub>max</sub> measured at each blood sampling time before and after warfarin dosing using a BFT II analyser | Mean: 2.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:               | Mean: 0.95<br>Median:<br>SD:<br>P:                               | Post treatment mean 95% CI: Garlic group 2.10-2.80; No treatment group 2.30-3.00. | medium                                |
|                                   |  |          |                  | No treatment           | 12 |  | Mean: 2.6<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                          |  |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup> | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Garlic                 | 12 | AUC <sub>INR</sub> measured at each blood sampling time before and after warfarin dosing using a                 | Mean: 100.3<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:               | Mean:0.98<br>Median:<br>SD:<br>P:                                | Post treatment mean 95% CI: Garlic group 70.90-129.80; No treatment group 72.10-  | medium                                |

**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author Year<br>Study Design | CHD Risk Category                      | CVD drug | Dose             | Supplement/<br>Control | N  | Definition of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean change/ % change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|----------|------------------|------------------------|----|---|---|--|--|--|---------------------------------------|
|                             |  |          |                  | No treatment           | 12 | BFT II analyser   | Mean:96<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                          |  | 119.80.  |                                       |
| Abdul 2010 <sup>1</sup>     | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Echinacea              | 11 | INR max samples were collected into sodium citrate - measured using a BFT II analyzer <sup>TM</sup> (Dade Behring Diagnostics Pty Ltd, Lane Cove, NSW, Australia) as previously reported (reference provided) | Mean: 1.8<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | NR   | Mean:1.04<br>Median:<br>SD:<br>P:                                | Post treatment mean 95% CI: Echinacea group 1.60-2.00; No treatment group 1.50-1.90. | medium                                |
|                             |  |          |                  | No treatment           | 11 |   | Mean:1.7<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | NR   |  |  |                                       |
| Abdul 2010 <sup>1</sup>     | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Echinacea              | 11 | AUC <sub>INR</sub> samples were collected into sodium citrate -   | Mean: 55.2  | NR   | Mean:1.09<br>Median:<br>SD:<br>P:                                | Post treatment mean 95% CI: Echinacea group 42.80-                                   | medium                                |
|                             |  |          |                  | No treatment           | 11 |   | NR  | NR   |  |  |                                       |



**Evidence Table 78. KQ2—Continuous data—INR (continued)**

| Author<br>Year<br><br>Study<br>Design | CHD Risk<br>Category | CVD drug | Dose | Supplement/<br>Control | N | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results                            | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------|----------|------|------------------------|---|---|---|--|---|--|--|
|                                       |                      |          |      |                        |   | measured using a<br>BFT II analyzer™<br>(Dade Behring<br>Diagnostics Pty<br>Ltd, Lane Cove,<br>NSW, Australia) as<br>previously reported<br>(reference<br>provided) | NR  | NR   |   | 67.60; No<br>treatment<br>group 38.30-<br>67.20. |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C)**

| Author Year<br>Study Design        | CHD Risk Category | CVD drug     | Dose  | Supplement/<br>Control             | N   | Definition of<br>outcome                      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|------------------------------------|-------------------|--------------|-------|------------------------------------|-----|---|---|---|---|-----------------------|--|
| Bays 2010 <sup>6</sup><br>parallel | Unclear           | atorvastatin | 10-40 | Omega-3<br>(EPA, DHA,<br>or both). | 122 | at week 8, end<br>of 10 mg/d<br>atorvastatin  | Mean:<br>Median 97<br>SD:<br>SE:<br>Lower: 82<br>Upper: 118   | Mean:<br>% mean:<br>Median:-<br>29.3%<br>SD:<br>P:              | Mean:<br>Median:2.2%<br>SD:<br>P:2.4                                      |                       | medium   |
|                                    |                   |              |       | Placebo                            | 121 |   | Mean:<br>Median 98<br>SD:<br>SE:<br>Lower: 81<br>Upper:111  | Mean:<br>Median:-<br>31.5%<br>SD:<br>P:                         |   |                       |  |
| Bays 2010 <sup>6</sup><br>parallel | Unclear           | atorvastatin | 10-40 | Omega-3<br>(EPA, DHA,<br>or both). | 122 | at week 16, end<br>of 40 mg/d<br>atorvastatin | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:0.3%<br>SD:<br>P:0.64                                     |                       | medium   |
|                                    |                   |              |       | Placebo                            | 121 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug              | Dose  | Supplement/<br>Control             | N   | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value  | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------|-----------------------|-------|------------------------------------|-----|--------------------------|---|--|---|---|--|
| Mabuchi<br>2007 <sup>39</sup>           | Unclear           | atorvastatin          | 1     | Coenzyme<br>Q10.                   | 24  |                          | Mean: 2.68<br>Median<br>SD: 0.55<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -43<br>Median:<br>SD:<br>P:<br><0.001           | Mean:<br>Median:<br>SD:<br>P:   | "...there<br>were no<br>differences<br>between<br>the groups" | medium   |
|   |                   |                       |       | Placebo                            | 25  |                          | Mean:2.47<br>Median<br>SD: 0.49<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:-49<br>Median:<br>SD:<br>P:<br><0.0001           |   |   |  |
| Young 2007 <sup>70</sup><br>parallel    | Mod and high risk | simvastatin<br>statin | 10-40 | Coenzyme<br>Q10.                   | 22  |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:-1.7%<br>SD:<br>P:<br>>0.001          | Mean:<br>Median:<br>SD:<br>P:<br>0.53                                     | No<br>difference<br>in groups<br>(p=0.53)                     | medium   |
|   |                   |                       |       | Placebo                            | 22  |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:-1.3%<br>SD:<br>P:<br>>0.001                     |   |   |  |
| Davidson<br>2007 <sup>14</sup> parallel | Unclear           | simvastatin<br>statin | 40    | Omega-3<br>(EPA, DHA,<br>or both). | 122 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: 3.4<br>Median:0.7<br>SD:<br>SD:<br>18.50%<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.53                                     |   | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design | CHD Risk Category | CVD drug  | Dose          | Supplement/<br>Control | N   | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|-----------------------------|-------------------|---|---------------|------------------------|-----|---|---|---|---|---|--|
|                             |                   |   |               | Placebo                | 132 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:-1.9%<br>SD:<br>12.40%<br>P:                    |   |   |  |
| Caso 2007 <sup>11</sup>     | Unclear           | Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)                 | varying doses | Coenzyme Q10.          | 18  | fasting plasma  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:-2.8<br>SD:<br>P:                    | Mean:<br>Median:<br>SD:<br>P:   | No final outcome data presented. Study reports baseline data and that the values did not change during the intervention period. Mean +/- SEM - Baseline CoQ10: 96 +/- 3; Baseline Vit E: 115 +/- 13 | low  |
|                             |                   |   |               | Vit E                  | 14  |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |   |  |
| Meyer 2007 <sup>46</sup>    | Unclear           | simvastatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin<br>81 | 81            | Fish/marine oils       | 13  | For all participants at 6 months: Blood plasma LDL-C under overnight fasted condition | Mean: 2.4<br>Median<br>SD:<br>SE:0.21<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   | also measured in a subset of participants with higher   | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug  | Dose | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---------------------|---|------|------------------------|----|---|---|---|---|--|--|
|                                       |                     |   |      | Fish/marine<br>oils    | 13 |   | Mean:2.35<br>Median<br>SD:<br>SE:0.21<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   | TC<br>baseline<br>levels (will<br>be<br>extracted<br>separately) |  |
|                                       |                     |   |      | Placebo                | 14 |   | Mean:2.49<br>Median<br>SD:<br>SE:0.22<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |  |  |
| Meyer 2007 <sup>46</sup>              | Unclear             | simvastatin, 13 atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin<br>81 | 81   | Fish/marine<br>oils    | 13 | Blood plasma LDL-C in subjects with baseline Total cholesterol levels >= 3.8 mmol/L as reduction is total cholesterol was associated with baseline values | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   | Data<br>presented<br>in bar<br>graph with<br>Means and<br>SEs    | medium   |
|                                       |                     |   |      | Fish/marine<br>oils    | 13 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |  |  |
|                                       |                     |   |      | Placebo                | 14 |   |   |   |   |  |  |
| Sutken 2006 <sup>83</sup><br>parallel | Low and/or Moderate | Gemfibrozil   | 1200 | Vitamin E.             | 22 | Serum for elderly sub-group   | Mean: 5.99<br>Median<br>SD:<br>SE:1.22<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01               | Mean:<br>Median:<br>SD:<br>P:   |  | high   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome          | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---------------------|-------------|------|--|----|-----------------------------------|---|---|---|-----------------------|--|
|                                       |                     |             |      | No treatment<br>(aside from<br>CVD drug) | 23 |                                   | Mean:5.81<br>Median<br>SD:<br>SE:1.3<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br><0.05                          |   |                       |  |
| Sutken 2006 <sup>83</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 22 | Serum<br>for younger<br>sub-group | Mean: 4.61<br>Median<br>SD:<br>SE:0.12<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   |                       | high   |
|                                       |                     |             |      | No treatment<br>(aside from<br>CVD drug) | 23 |                                   | Mean:4.72<br>Median<br>SD:<br>SE:0.1<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |
| Macan 2006 <sup>40</sup><br>parallel  | Low and/or Moderate | Warfarin    | NR   | Garlic.                                  | 22 | 12 hour fasting<br>blood sample   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.6<br>% mean:<br>Median:<br>SD:<br>25.8<br>P:             | Mean:<br>Median:<br>SD:<br>P:<br>0.626                                    |                       | medium   |
|                                       |                     |             |      | Placebo                                  | 26 |                                   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-1.6<br>Median:<br>SD:<br>30<br>P:                         |   |                       |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug     | Dose | Supplement/<br>Control  | N  | Definition of<br>outcome      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------|--------------|------|---|----|-------------------------------|---|---|---|--|--|
| Manuel 2004 <sup>42</sup><br>parallel | At high risk for CHD | Atorvastatin | 20   | Vitamin E.  | 11 | serum, fasting                | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001              | Mean:<br>Median:<br>SD:<br>P:   | Data not<br>presented<br>in paper -<br>only<br>combined<br>data for<br>both groups<br>across time<br>and for<br>groups<br>separately<br>at baseline<br>only.<br>Report<br>states that<br>changes<br>were 'same<br>in both<br>groups (the<br>between-<br>group<br>comparison<br>of change<br>over time<br>was not<br>significant) | medium   |
|                                       |                      |              |      | Placebo   | 11 |                               | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:<br><0.001                         |   |  |  |
| Playford<br>2003 <sup>58</sup>        | At high risk for CHD | Fenofibrate  | 200  | Coenzyme<br>Q10: 200 mg<br>COQ10 plus<br>200mg<br>fenofibrate | 18 | measured after<br>14 hr fast; | Mean: 3.0<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:-0.1<br>% mean:<br>Median:<br>SD:<br>P:                    | Mean:0.4<br>Median:<br>SD:<br>P:<br>0.353 or<br>0.014                     |  | low-medium                                     |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design                 | CHD Risk Category                         | CVD drug | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results                         | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---|----------|------|--|----|--------------------------|---|---|---|---|--|
|   |   |          |      | No treatment<br>(aside from<br>CVD drug) | 17 |                          | Mean:2.9<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:-0.4<br>Median:<br>SD:<br>P:                               |   |   |  |
|   |   |          |      | 200 mg<br>CoQ10 only                     | 20 |                          | Mean:3.4<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:-0.2<br>Median:<br>SD:<br>P:                               |   |   |  |
|   |   |          |      | Placebo                                  | 18 |                          | Mean:3.2<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean: 0<br>Median:<br>SD:<br>P:                                 |   |   |  |
| Svaneborg<br>2002 <sup>64</sup><br>parallel | At low risk for CHD<br>(0-1 risk factors) | ASA      | 100  | Omega-3<br>(EPA, DHA,<br>or both).       | 12 |                          | Mean:<br>Median 2.55<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   | placebo=<br>corn oil<br>containing<br>omega-6 | medium   |
|   |   |          |      | Placebo                                  | 6  |                          | Mean:<br>Median 2.95<br>SD:<br>SE:<br>Lower:2.15<br>Upper:3.8   | Mean:<br>Median:<br>SD:<br>P:                                   |   |   |  |



**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug    | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---------------------|-------------|-------|--|----|--|---|---|---|-----------------------|--|
| Duffy 2001 <sup>20</sup><br>parallel  | Low and/or Moderate | simvastatin | 10-40 | Vitamin E.                               | 6  |  | Mean: 2.6<br>Median<br>SD: 0.7<br>SE:<br>Lower:<br>Upper:   | Mean:-1.5<br>% mean:<br>Median:<br>SD:<br>P:<br>0.02            | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |                     |             |       | No treatment<br>(aside from<br>CVD drug) | 7  |  | Mean:3.3<br>Median<br>SD: 0.6<br>SE:<br>Lower:<br>Upper:  | Mean:-2.1<br>Median:<br>SD:<br>P:<br>0.01                       |   |                       |  |
|                                       |                     |             |       | 1000IU<br>Vitamin E                      | 6  |  | Mean:4.9<br>Median<br>SD: 2.3<br>SE:<br>Lower:<br>Upper:  | Mean:0.2<br>Median:<br>SD:<br>P:                                |   |                       |  |
|                                       |                     |             |       | Placebo                                  | 7  |  | Mean:4.3<br>Median<br>SD: 0.9<br>SE:<br>Lower:<br>Upper:  | Mean:-0.6<br>Median:<br>SD:<br>P:<br>0.02                       |   |                       |  |
| Napoli 1998 <sup>52</sup><br>parallel | Unclear             | Pravastatin | 20-40 | Vitamin E.                               | 52 | 12-14 hr fasting<br>determined<br>enzymatically<br>by Boehringer<br>test kit | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -34<br>Median:<br>SD:<br>P:<br><0.05           | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    |                       | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose   | Supplement/<br>Control                   | N  | Definition of<br>outcome            | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------|-------------|--------|--|----|-------------------------------------|---|---|---|-----------------------|--|
|   |                      |             |        | No treatment<br>(aside from<br>CVD drug) | 56 |                                     | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:<br><0.05                          |   |                       |  |
| Yamamoto<br>1995 <sup>69</sup> parallel | At high risk for CHD | diltiazem   | 90-120 | Omega-3<br>(EPA, DHA,<br>or both).       | 12 |                                     | Mean: 118<br>Median<br>SD:<br>SE:36<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|   |                      |             |        | No treatment<br>(aside from<br>CVD drug) | 10 |                                     | Mean:118<br>Median<br>SD:<br>SE:24<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |
| McDowell<br>1994 <sup>44</sup> parallel | Unclear              | Simvastatin | 20     | Vitamin E.                               | 8  | overnight<br>fasting<br>measurement | Mean: 4.1<br>Median<br>SD: 1.0<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|   |                      |             |        | Placebo                                  | 8  |                                     | Mean:4.8<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug                        | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results    | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------|---------------------------------|---|--|----|---|---|---|---|--------------------------|--|
| Kaul 1992 <sup>34</sup><br>parallel   | At high risk for CHD | Calcium channel<br>blocker, ASA | ASA: 150;<br>heparin: 1000<br>U/d; ca blockers:<br>NR | Fish/marine<br>oils.                     | 58 |   | Mean: 132<br>Median<br>SD: 31.7<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   |                          | low-medium                                     |
|                                       |                      |                                 |   | No treatment<br>(aside from<br>CVD drug) | 49 |   | Mean:131<br>Median<br>SD: 30.1<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |                          |  |
| Nordøy 2003 <sup>55</sup><br>parallel | Mod and high risk    | atorvastatin                    | 10  | Fish/marine<br>oils.                     | 22 | Blood sample<br>taken after 12<br>hr fasting,<br>within 6 days of<br>end of study | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.12<br>% mean:<br>Median:<br>SD:<br>0.51<br>P:           | Mean:<br>Median:<br>SD:<br>P:<br>0.28                                     |                          | medium   |
|                                       |                      |                                 |   | Placebo                                  | 20 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.27<br>Median:<br>SD:<br>0.37<br>P:                      |   |                          |  |
| Roth 2009 <sup>60</sup><br>parallel   | Unclear              | fenofibrates by<br>100%         | 130   | Omega-3<br>(EPA, DHA,<br>or both).       | 81 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:48.2%<br>SD:<br>P:                   | Mean:<br>Median:<br>SD:<br>P:<br>9.0 or 0.03                              | Significant<br>p = 0.030 | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug          | Dose  | Supplement/<br>Control | N  | Definition of<br>outcome     | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|----------------------|-------------------|-------|------------------------|----|------------------------------|---|---|---|-----------------------|--|
|                                       |                      |                   |       | Placebo                | 82 |                              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:39%<br>SD:<br>P:                                |   |                       |  |
| Isley 2007 <sup>31</sup><br>parallel  | Unclear              | niacin            | 325   | Omega-3                | 7  |                              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: 11<br>Median:<br>SD:<br>P:                     | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |                      |                   |       | Placebo                | 8  |                              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean -4<br>Median:<br>SD:<br>P:                      |   |                       |  |
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD | statins + aspirin | 10-40 | Garlic                 | 9  | Measured after<br>12 hr fast | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-3.2<br>% mean:<br>Median:<br>SD:<br>16.2<br>P:            | Mean:<br>Median:<br>SD:<br>P:<br>0.0932                                   |                       | medium   |
|                                       |                      |                   |       | Placebo                | 10 |                              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:21.9<br>Median:<br>SD:<br>39.4<br>P:                       |   |                       |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug  | Dose   | Supplement/<br>Control                   | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---|---|--|--|----|--|---|---|---|-----------------------|--|
| Chan 2002 <sup>12</sup><br>parallel   | At<br>moderate/moderately<br>high risk for CHD (2+<br>risk factors) | atorvastatin  | 40   | Fish/marine<br>oils.                     | 11 | collected after<br>an overnight<br>fast (14 h) in a<br>semirecumbent<br>position for all<br>biochemical<br>measurements. | Mean: 2.15<br>Median<br>SD:<br>SE:0.19<br>Lower:<br>Upper:  | Mean:<br>% mean:-42.5<br>Median:<br>SD:<br>3.50%<br>P:          | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |   |   |  | Placebo                                  | 13 |  | Mean:1.84<br>Median<br>SD:<br>SE:0.12<br>Lower:<br>Upper:   | Mean:<br>% mean:-54<br>Median:<br>SD:<br>P:                     |   |                       |  |
| Liu 2003 <sup>37</sup><br>parallel    | Unclear   | simvastatin   | 10   | Fish/marine<br>oils.                     | 19 | Fasting blood<br>samples   | Mean: 3.21<br>Median<br>SD: 1.15<br>SE:<br>Lower:<br>Upper:   | Mean:-1.29<br>% mean: -28.7<br>Median:<br>SD:<br>1.05<br>P:     | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|                                       |   |   |  | No treatment<br>(aside from<br>CVD drug) | 18 |  | Mean:3.05<br>Median<br>SD:0.7<br>SE:<br>Lower:<br>Upper:-31.6   | Mean:-1.41<br>Median:<br>SD:<br>0.76<br>P:                      |   |                       |  |
| Dehmer<br>1988 <sup>17</sup> parallel | At high risk for CHD  | aspirin +<br>Dipyridamole + ca<br>channel blockers) | ASA: 325;<br>dipyridamole:<br>225; Ca blocker:<br>NR | Omega-3<br>(EPA, DHA,<br>or both).       | 43 | Fasting blood<br>samples;<br>standard<br>automated<br>techniques   | Mean: 140<br>Median<br>SD: 54.3<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design             | CHD Risk Category                         | CVD drug                           | Dose   | Supplement/<br>Control                   | N  | Definition of<br>outcome          | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians/<br>SD/<br>P Value | Summary<br>of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---|------------------------------------|--|--|----|-----------------------------------|---|---|--|---|--|
|   |   |                                    |  | No treatment<br>(aside from<br>CVD drug) | 39 |                                   | Mean:221<br>Median<br>SD: 127.7<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                   |  |   |  |
| Desideri<br>2003 <sup>18</sup> parallel | At low risk for CHD<br>(0-1 risk factors) | Simvastatin,statin,<br>Bezafibrate | simvastatin:statin:<br>40; Bezafibrate:<br>800 | Vitamin E.                               |    | 12 hr fasting at<br>800hr - serum | Mean: 3.9<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001             | Mean:<br>Median:<br>SD:<br>P:  | I assumed<br>no losses<br>to follow-up<br>although I<br>did not see<br>this<br>explicitly<br>stated   | medium   |
|   |   |                                    |  | No treatment<br>(aside from<br>CVD drug) |    |                                   | Mean:4.1<br>Median<br>SD: 0.9<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br><0.0001                        |  |   |  |
| Wolf 2006 <sup>68</sup><br>crossover    | Low and/or Moderate                       | ASA                                | 500  | ginkgo biloba                            | 50 |                                   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:  | Study<br>states that:<br>Laboratory<br>findings in<br>all subjects<br>were un-<br>remarkable<br>and did not<br>indicate<br>any<br>differences<br>between<br>the<br>treatment<br>groups. | low-medium                                     |
|   |   |                                    |  | Placebo                                  | 50 |                                   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |  |   |  |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design                    | CHD Risk Category    | CVD drug          | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|-------------------|-------|--|----|---|---|---|---|--|--|
| De Caterina<br>2002 <sup>16</sup><br>crossover | At high risk for CHD | simvastatinstatin | 10-40 | Vitamin E                                |    | at 1 mo after<br>treatment<br>started - like a<br>parallel RCT<br>(treatment<br>lasted two<br>months) | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:   | Values are<br>presented<br>in graphs,<br>but difficult<br>to read. | High   |
|  |                      |                   |       | No treatment<br>(aside from<br>CVD drug) |    |   | Mean:<br>Median:<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                   |   |  |  |
| Balestrieri<br>1996 <sup>4</sup><br>crossover  | Low and/or Moderate  | Simvastatinstatin | 10-40 | Fish/marine<br>oils                      | 14 | 12 hour fast,<br>anti-tubectal<br>vein  | Mean: 228<br>Median<br>SD: 50<br>SE:<br>Lower:<br>Upper:  | Mean:0<br>% mean:<br>Median:<br>SD:<br>P:                       | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                      |                   |       | Placebo                                  | 14 |   | Mean:227<br>Median<br>SD: 52<br>SE:<br>Lower:<br>Upper:   | Mean:-5<br>Median:<br>SD:<br>P:                                 |   |  |  |
| Paolisso<br>1995 <sup>56</sup><br>crossover    | At high risk for CHD | nifedipine        | 88    | Vitamin E                                | 30 | Fasting;<br>at 2 months at<br>end of<br>treatment   | Mean: 4.94<br>Median<br>SD:<br>SE:0.34<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    |  | medium   |

**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design             | CHD Risk Category   | CVD drug   | Dose              | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---------------------|------------|-------------------|------------------------|----|--------------------------|---|---|---|-----------------------|--|
|   |                     |            |                   | Placebo                | 30 |                          | Mean:5.97<br>Median<br>SD:<br>SE:0.22<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |
| Hansen1993 <sup>29</sup><br>crossover   | Low and/or Moderate | lovastatin | 40                | Fish/marine<br>oils    | 14 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -39<br>Median:<br>SD:<br>P:                    | Mean:<br>Median:<br>SD:<br>P:   |                       | medium   |
|   |                     |            |                   | Placebo                | 14 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -37<br>Median:<br>SD:<br>P:                    |   |                       |  |
| Mueller 1991 <sup>51</sup><br>crossover | Low and/or Moderate | aspirin    | 325 - single dose | Fish/marine<br>oils    | 12 | Fasting                  | Mean:<br>135.58<br>Median<br>SD: 34.94<br>SE:<br>Lower:<br>Upper:   | Mean:-1<br>% mean:<br>Median:<br>SD:<br>P:<br><0.06             | Mean:-15<br>Median:<br>SD:<br>P:  |                       | medium   |
|   |                     |            |                   | Placebo                | 12 |                          | Mean:121.58<br>Median<br>SD: 33.81<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                   |   |                       |  |



**Evidence Table 79. KQ2—Continuous data—Low-density lipoprotein cholesterol (LDL-C) (continued)**

| Author Year<br>Study Design          | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--------------------------------------|---------------------|-------------|------|------------------------|----|----------------------------|---|---|---|-----------------------|--|
| Maki 2008 <sup>41</sup><br>crossover | Low and/or Moderate | simvastatin | 20   | Omega-3                | 39 | Least square<br>mean (SEM) | Mean: 103<br>Median<br>SD:<br>SE:5.2<br>Lower:<br>Upper:  | Mean:<br>% mean:-37.2<br>Median:<br>SD:<br>P:<br>0.433          | Mean:1.3<br>Median:<br>SD:<br>P:<br>0.433                                 |                       | medium   |
|                                      |                     |             |      | Placebo                | 40 |                            | Mean:98<br>Median<br>SD:<br>SE:5.<br>3<br>Lower:<br>Upper:  |   |   |                       |  |

**Evidence Table 80. KQ2—Continuous data—Non-HDL-C**

| Author Year<br>Study Design     | CHD Risk Category | CVD drug     | Dose  | Supplement/. Control         | N   | Definition of outcome  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------|-------------------|--------------|-------|------------------------------|-----|--|---|--|---|---|---------------------------------------|
| Bays 2010 <sup>6</sup> parallel | Unclear           | atorvastatin | 10-40 | Omega-3 (EPA, DHA, or both). | 122 | The follow up was at the end of 10 mg atorvastatin at week 8 | Mean: Median 133 SD: SE: Lower: 114.5 Upper:153.5                                       | Mean: % mean: Median:-40.2 SD: P:                | Mean: Median: SD: P: <0.001                             | there are 90% CIs reported instead of 95% CI  | medium                                |
|                                 |                   |              |       | Placebo                      | 121 |  | Mean: Median 142.5 SD: SE: Lower:123.5 Upper:162.5                                      | Mean: Median:-33.7 SD: P:                        |   |   |                                       |
| Bays 2010 <sup>6</sup> parallel | Unclear           | atorvastatin | 10-40 | Omega-3 (EPA, DHA, or both). | 122 | At week 16, end of 40 mg atorvastatin                        | Mean: Median SD: SE: Lower: Upper:  | Mean: % mean: Median: -50 SD: P:                 | Mean: Median: SD: P: <0.001                             | The 95% CIs reported are actually 90% CIs. The difference in % medians reported for individual group data were read from a graph. | medium                                |
|                                 |                   |              |       | Placebo                      | 121 |  | Mean: Median SD: SE: Lower: Upper:  | Mean: Median:-45 SD: P:                          |   |   |                                       |

**Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose | Supplement/. Control                         | N   | Definition of outcome      | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value         | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|------|--|-----|----------------------------|---|--|---|--------------------|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>parallel | Unclear              | simvastatin | 40   | Omega-3 (EPA, DHA, or both).                 | 122 |                            | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:-<br>9<br>SD:<br>P:           | Mean:<br>Median:<br>SD:<br>P:<br><0.001                 |                    | medium                                |
|   |                      |             |      | Placebo                                      | 132 |                            | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean -<br>1.5<br>Median:-<br>2.2<br>SD:<br>P: |   |                    |                                       |
|   |                      |             |      |  |     |                            | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>Median:<br>SD:<br>P:                            |   |                    |                                       |
| Playford 2003 <sup>58</sup><br>parallel | At high risk for CHD | Fenofibrate | 200  | Coenzyme Q10. 200 mg plus 200 mg fenofibrate | 18  | measured after 14 hr fast; | Mean: 3.7<br>Median<br>SD: 0.2<br>SE:<br>Lower:<br>Upper:                               | Mean:-<br>0.6<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:0.1<br>Median:<br>SD:<br>P:0.496                   |                    | low-medium                            |

**Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)**

| Author Year<br>Study Design                | CHD Risk Category | CVD drug    | Dose | Supplement/.<br>Control                  | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/<br>%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|-------------------|-------------|------|--|----|--------------------------|---|---|---|-----------------------|--|
|  |                   |             |      | No treatment<br>(aside from<br>CVD drug) | 17 |                          | Mean: 3.6<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:-<br>0.8<br>% mean:<br>Median:<br>SD:<br>P:                      |   |                       |  |
|  |                   |             |      | Coenzyme<br>Q10.<br>200 mg<br>CoQ10 only | 20 |                          | Mean: 4.3<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:0<br>% mean:<br>Median:<br>SD:<br>P:                             |   |                       |  |
|  |                   |             |      | Placebo                                  | 18 |                          | Mean:4.4<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:0.1<br>Median:<br>SD:<br>P:                                      |   |                       |  |
| Davidson<br>1997 <sup>15</sup><br>parallel | Unclear           | Simvastatin | 10   | Fish/marine<br>oils.                     | 9  | fasting blood<br>sample  | Mean:<br>170.4<br>Median<br>SD:<br>SE:15.8<br>Lower:<br>Upper:  | Mean:-<br>61.9<br>% mean:<br>-24.8%<br>Median:<br>SD:<br>P:<br><0.001 | Mean:5.6<br>Median:<br>SD:<br>P:  |                       | Medium   |

**Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)**

| Author Year<br>Study Design      | CHD Risk Category | CVD drug             | Dose | Supplement/. Control               | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value            | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|----------------------------------|-------------------|----------------------|------|------------------------------------|----|-----------------------|---|---|---|--------------------|---------------------------------------|
|                                  |                   |                      |      | No treatment (aside from CVD drug) | 10 |                       | Mean: 164.8<br>Median<br>SD:<br>SE:6.8<br>Lower:<br>Upper:                              | Mean:- 57.9<br>% mean: -25.8<br>Median:<br>SD:<br>P: <0.001 |   |                    |                                       |
|                                  |                   |                      |      | 7.2 g/day marine oil               | 10 |                       | Mean:226.4<br>Median<br>SD:<br>SE:10.2<br>Lower:<br>Upper:                              | Mean:- 9.8<br>% mean: -3.5%<br>Median:<br>SD:<br>P:         |   |                    |                                       |
| Roth 2009 <sup>60</sup> parallel | Unclear           | fenofibrates by 100% | 130  | Omega-3 (EPA, DHA, or both).       | 81 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:- 8.2<br>SD:<br>P:               | Mean:<br>Median:<br>SD:<br>P: 0.767                     |                    | medium                                |
|                                  |                   |                      |      | Placebo                            | 82 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>Median:- 7<br>SD:<br>P:                            |   |                    |                                       |

**Evidence Table 80. KQ2—Continuous data—Non-HDL-C (continued)**

| Author Year<br>Study Design          | CHD Risk Category  | CVD drug     | Dose | Supplement/.<br>Control | N  | Definition of outcome  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value      | Between group differences in Means/ medians SD/ P Value | Summary of Results                                | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|--------------|------|-------------------------|----|--|---|---|---|---|---------------------------------------|
| Chan 2002 <sup>12</sup>              | At moderate/moderately high risk for CHD (2+ risk factors) | atorvastatin | 40   | Fish/marine oils.       | 11 | collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements. | Mean: 2.72<br>Median<br>SD:<br>SE:0.22<br>Lower:<br>Upper:                                    | Mean:<br>% mean:<br>-48<br>Median:<br>SD:<br>3%<br>P: | Mean:<br>Median:<br>SD:<br>P:                           |   | medium                                |
|                                      |  |              |      | Placebo                 | 13 |  | Mean:2.58<br>Median<br>SD:<br>SE:0.11<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>-43<br>Median:<br>SD:<br>P:       |   |   |                                       |
| Maki 2008 <sup>41</sup><br>crossover | Low and/or Moderate  | simvastatin  | 20   | Omega-3                 | 39 | 10-14 hour fast; Centers for Disease Control and Prevention lipid standardization program              | Mean:<br>Median 133<br>SD:<br>SE:<br>Lower: 70<br>Upper:288                                   | Mean:<br>% mean:<br>Median:-<br>40<br>SD:<br>P:       | Mean:<br>Median:<br>SD:<br>P:<br><0.001                 | The IQRs reported are actually ranges (low-high). | medium                                |
|                                      |  |              |      | Placebo                 | 40 |  | Mean:<br>Median 139<br>SD:<br>SE:<br>Lower: 45<br>Upper:260                                   | Mean:<br>Median:-<br>34.3<br>SD:<br>P:                |   |   |                                       |
|                                      |  |              |      |                         |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                         |   |   |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability**

| Author Year<br>Study Design                | CHD Risk Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition of outcome                             | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results               | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|----------|------|------------------------|----|---|---|---|--|----------------------------------|---------------------------------------|
| Gardner 2007 <sup>23</sup><br><br>Parallel | moderate to high  | ASA      | 325  | ginkgo biloba          | 29 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:1.3<br>Median:<br>SD:<br>6.00%<br>P:      | Mean:<br>Median:<br>SD:<br>P:                                    | No difference in groups (p=0.2)  | low                                   |
|  |                   |          |      | Placebo                | 26 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>% mean:-2.7<br>Median:<br>SD:<br>10.00%<br>P:  |   |  |                                  |                                       |
| Gardner 2007 <sup>23</sup><br><br>Parallel | moderate to high  | ASA      | 325  | ginkgo biloba          | 29 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:-1.3<br>Median:<br>SD:<br>12.00%<br>P:    | Mean:<br>Median:<br>SD:<br>P:                                    | No difference in groups (p=0.15) | low                                   |
|  |                   |          |      | Placebo                | 26 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>% mean4.2<br>Median:<br>SD:<br>12.60%<br>P:  |   |  |                                  |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design            | CHD Risk Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition of outcome                             | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value  | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results              | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|----------|------|------------------------|----|---|---|--|--|---------------------------------|---------------------------------------|
| Gardner 2007 <sup>23</sup><br>Parallel | moderate to high  | ASA      | 325  | ginkgo biloba          | 29 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-4.1<br>Median:<br>SD:<br>14.90%<br>P: | Mean:<br>Median:<br>SD:<br>P:                                    | No difference in groups (p=0.7) | low                                   |
|  |                   |          |      | Placebo                | 26 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>% mean -<br>6<br>Median:<br>SD:<br>19.60%<br>P:  |  |  |                                 |                                       |
| Gardner 2007 <sup>23</sup><br>Parallel | moderate to high  | ASA      | 325  | ginkgo biloba          | 29 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-1.5<br>Median:<br>SD:<br>18.70%<br>P: | Mean:<br>Median:<br>SD:<br>P:                                    | No difference in groups (p=0.3) | low-medium                            |
|  |                   |          |      | Placebo                | 26 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>% mean -<br>6.3<br>Median:<br>SD:<br>18.70%<br>P:  |  |  |                                 |                                       |



**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design            | CHD Risk Category    | CVD drug    | Dose             | Supplement/ Control | N  | Definition of outcome             | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value          | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--|----------------------|-------------|------------------|---------------------|----|-----------------------------------|---|---|---|--|---------------------------------------|
| Steiner 1995 <sup>62</sup><br>Parallel | At high risk for CHD | ASA         | 325              | Vitamin E           | 25 | platelet adhesion to collagen III | Mean: 2.7<br>Median<br>SD: 0.4<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>40<br>Median:<br>SD:<br>P:<br><0.0001 | Mean:<br>Median:<br>SD:<br>P:                           | please ensure about the unit. the difference is reported for change from baseline in the vit E group only. | medium                                |
|  |                      |             |                  | Placebo             | 48 |                                   | Mean:4.4<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>Median:<br>SD:<br>P:                             |   |  |                                       |
| Kim 2010 <sup>35</sup><br>crossover    | Low and/or Moderate  | Ticlopidine | 250- single dose | ginkgo biloba       | 24 | 5µl of 10 µM ADP                  | Mean: 63<br>Median<br>SD: 18.9<br>SE:<br>Lower:<br>Upper:                                     | Mean:-<br>3.6<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           | Mean ratio of ginkgo/No treatment: 1.02  | medium<br>medium                      |
|  |                      |             |                  | No treatment        | 24 |                                   | Mean:64.8<br>Median<br>SD: 19.7<br>SE:<br>Lower:<br>Upper:                                    | Mean:-<br>3.5<br>Median:<br>SD:<br>P:                     |   |  |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design         | CHD Risk Category                      | CVD drug    | Dose             | Supplement/ Control | N  | Definition of outcome                         | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|--|-------------|------------------|---------------------|----|---|---|--|---|--|---------------------------------------|
| Kim 2010 <sup>35</sup><br>crossover | Low and/or Moderate                    | Ticlopidine | 250- single dose | ginkgo biloba       | 24 | 1 µL of 2 µg/mL collagen                      | Mean: 80.4<br>Median<br>SD: 11.2<br>SE:<br>Lower:<br>Upper:                                   | Mean:3.5 % mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | Mean ratio of ginkgo/No treatment: 1.03  | medium                                |
|                                     |  |             |                  | No treatment        | 24 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |
| Jiang 2004 <sup>33</sup>            | At low risk for CHD (0-1 risk factors) | Warfarin    | 25 - single dose | Ginseng             | 12 | Arachidonic acid 10 ml of 50 mM concentration | Mean: 7.1<br>Median<br>SD: 1.4<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:1<br>Median:<br>SD:<br>P:                          | 95% CI of mean for individual group data: Ginseng group: 6-7.8; St. Johns Wort: 6.5-8.2; No treatment group: 5.6-9.1 | medium                                |
|                                     |  |             |                  | St. John's          | 12 |   | Mean: 7.5<br>Median<br>SD: 1.1<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         |   |  |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design          | CHD Risk Category                      | CVD drug          | Dose   | Supplement/ Control | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|-------------------|--|---------------------|----|-----------------------|---|--|---|---|---------------------------------------|
|                                      |  |                   |  | No treatment        | 12 |                       | Mean:7.7<br>Median<br>SD: 2.2<br>SE:<br>Lower:<br>Upper:                                | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |
| Jiang 2005 <sup>32</sup>             | At low risk for CHD (0-1 risk factors) | Warfarin          | 25 - single dose                                 | Ginkgo Biloba       | 12 | Arachidonic acid      | Mean: 8.4<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:1.14<br>Median:<br>SD:<br>P:                       | 95% CI of mean for individual group data: ginkgo group: 7.60-9.20; Ginger group: 7.50-8.70; No treatment group: 6.50-8.40 | medium                                |
|                                      |  |                   |  | Ginger              | 12 |                       | Mean: 8.1<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         |   |   |                                       |
|                                      |  |                   |  | No treatment        | 12 |                       | Mean:7.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                    | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |
| Aruna 2007 <sup>2</sup><br>crossover | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol); 75 to 150 (clopidogrel) | ginkgo biloba       | 10 | 2.5µl of 10µM ADP     | Mean: 77<br>Median<br>SD: 20<br>SE:7<br>Lower:<br>Upper:                                | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | 95% CI of mean for individual group data: ginkgo group: 39.00-73.00;  | medium                                |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design          | CHD Risk Category                      | CVD drug          | Dose  | Supplement/ Control | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|-------------------|---|---------------------|----|-----------------------|---|--|---|---|---------------------------------------|
|                                      |  |                   |   | No treatment        | 10 |                       | Mean:59<br>Median<br>SD: 13<br>SE:10<br>Lower:<br>Upper:                                      | Mean:<br>Median:<br>SD:<br>P:                    |   | No treatment group: 36.00-82.00   |                                       |
| Aruna 2007 <sup>2</sup><br>crossover | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol);<br>75 to 150 (clopidogrel) | ginkgo biloba       | 10 | 2.5µl of 10µM ADP     | Mean: 56<br>Median<br>SD: 19<br>SE:7<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | 95% CI of mean for individual group data:<br>ginkgo group: 61.00-92.00;<br>No treatment group: 41.00-79.00.                                 | medium                                |
|                                      |  |                   |   | No treatment        | 10 |                       | Mean:60<br>Median<br>SD: 23<br>SE:8<br>Lower:<br>Upper:                                       | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |
| Aruna 2007 <sup>2</sup><br>crossover | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol);<br>75 to 150 (clopidogrel) | ginkgo biloba       | 10 | 2.5µl of 5µM ADP      | Mean: 57<br>Median<br>SD: 22<br>SE:8<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | 95% CI of mean for individual group data:<br>ginkgo group: 39.00-75.00<br>p-value <0.05;<br>No treatment group: 23.00-72.00, p-value <0.05. | medium                                |
|                                      |  |                   |   | No treatment        | 10 |                       | Mean:47<br>Median<br>SD:32<br>SE:11<br>Lower:<br>Upper:                                       | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design                    | CHD Risk Category                      | CVD drug          | Dose   | Supplement/ Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|--|---------------------|----|---|---|--|---|--|---------------------------------------|
| Aruna 2007 <sup>2</sup><br>crossover           | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol); 75 to 150 (clopidogrel) | ginkgo biloba       | 10 | 2.5µl of 5µM ADP  | Mean: 49<br>Median<br>SD: 21<br>SE:8<br>Lower:<br>Upper:                                | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | 95% CI of mean for individual group data: ginkgo group: 31.00-67.00, p-value <0.05; No treatment group: 30.00-73.00, p-value < 0.05. | medium                                |
|  |  |                   |  | No treatment        | 10 |   | Mean:52<br>Median<br>SD: 26<br>SE:9<br>Lower:<br>Upper:                                 | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |
| Mohammed Abdul 2008 <sup>49</sup><br>Crossover | At low risk for CHD (0-1 risk factors) | Warfarin          | 25 - single dose                                 | Garlic              | 12 | assessed on blood samples (within 3 h of blood collection) collected 24 h | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | "...2 weeks of pretreatment with garlic...had no effect on platelet  | medium                                |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design              | CHD Risk Category   | CVD drug    | Dose | Supplement/ Control | N  | Definition of outcome  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|--|---------------------|-------------|------|---------------------|----|--|---|--|---|--------------------|---------------------------------------|
|  |                     |             |      | No treatment        | 12 | prior to warfarin administration ( 24 h) in each treatment period using a whole blood aggregometer (Chrono-par; Chrono-log Corp., Havertown, Pennsylvania, USA; Edward Keller Australia Pty Ltd, Hallam, VIC, Australia). Method described further but not extracted | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                    |   | aggregation."      |                                       |
| McKenney 2006 <sup>45</sup><br>Crossover | Low and/or Moderate | simvastatin | 80   | Omega-3             | 24 | ADP  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-3.4<br>Median:<br>SD:<br>P: | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design              | CHD Risk Category                      | CVD drug    | Dose             | Supplement/ Control | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------|------------------|---------------------|----|-----------------------|---|--|---|--|---------------------------------------|
|  |  |             |                  | No treatment        | 23 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean -<br>4.5<br>Median:<br>SD:<br>P: |   |  |                                       |
| McKenney 2006 <sup>45</sup><br>Crossover | Low and/or Moderate                    | simvastatin | 80               | Omega-3             | 24 | Collagen              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:-<br>5.1<br>Median:<br>SD:<br>P: | Mean:<br>Median:<br>SD:<br>P:                           |  | medium                                |
|  |  |             |                  | No treatment        | 23 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean -<br>6<br>Median:<br>SD:<br>P:   |   |  |                                       |
| Abdul 2010 <sup>1</sup>                  | At low risk for CHD (0-1 risk factors) | Warfarin    | 25 - single dose | Echinacea           | 11 | 10µM ADP              | Mean: 7.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:0.84<br>Median:<br>SD:<br>P:                       | Post treatment mean 95% CI: Echinacea group 4.1-10.8; No treatment group 5.5-10. | medium                                |
|  |  |             |                  | No treatment        | 11 |                       | Mean:7.8<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design | CHD Risk Category                      | CVD drug | Dose             | Supplement/<br>Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|----------|------------------|------------------------|----|-------------------------|---|--|---|--|---------------------------------------|
| Abdul 2010 <sup>1</sup>     | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Echinacea              | 11 | Arachidonic acid 0.5mM  | Mean: 12.1<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:1.06<br>Median:<br>SD:<br>P:                       | Post treatment mean 95% CI: Echinacea group 9.3-15; No treatment group 9.6-12.5.     | medium                                |
|                             |  |          |                  | No treatment           | 11 |                         | Mean:11<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |
| Abdul 2010 <sup>1</sup>     | At low risk for CHD (0-1 risk factors) | Warfarin | 25 - single dose | Echinacea              | 11 | Collagen-induced 2µg/ml | Mean:15.8<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                    | Mean:1<br>Median:<br>SD:<br>P:                          | Post treatment mean 95% CI: Echinacea group 12.2-19.5; No treatment group 11.5-14.6. | medium                                |
|                             |  |          |                  | No treatment           | 11 |                         | Mean:13<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |



**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design          | CHD Risk Category   | CVD drug | Dose | Supplement/<br>Control | N  | Definition of outcome                                  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results                   | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---------------------|----------|------|------------------------|----|--|---|---|--|--------------------------------------|---------------------------------------|
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba          | 50 | Collagen-induced at 7 days after treatment             | Mean: 81<br>Median<br>SD: 8.6<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>-5.6<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                                    | ratio of means presented with 90% CI | medium                                |
|                                      |                     |          |      | Placebo                | 50 |  | Mean:81<br>Median<br>SD: 12.7<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>-3.5<br>Median:<br>SD:<br>P:          |  |                                      |                                       |
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba          | 50 | Adenosine diphosphate-induced at day 7 after treatment | Mean:<br>44.8<br>Median<br>SD: 18.1<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>-26.9<br>Median:<br>SD:<br>P:         | Mean:0.95<br>Median:<br>SD:<br>P:                                | ratio of means reported with 90% CI  | low-medium                            |
|                                      |                     |          |      | Placebo                | 50 |  | Mean:47.2<br>Median<br>SD: 15.1<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>-25.4<br>Median:<br>SD:<br>P:         |  |                                      |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design          | CHD Risk Category   | CVD drug | Dose | Supplement/<br>Control | N  | Definition of outcome                         | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---------------------|----------|------|------------------------|----|---|---|---|--|--|---------------------------------------|
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba          | 50 | Arachidonate-induced at day 7 after treatment | Mean: 2.2<br>Median<br>SD: 2.1<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-76<br>Median:<br>SD:<br>P:           | Mean:0.65<br>Median:<br>SD:<br>P:                                | ratio of means reported with 90% CI; 100 put in as top of 90% CI but actually infinity | low-medium                            |
|                                      |                     |          |      | Placebo                | 50 |   | Mean:3.4<br>Median<br>SD: 10.4<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:-<br>75.1<br>Median:<br>SD:<br>P:         |  |  |                                       |
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba          | 50 | Ristocetin-induced at 7 days, after treatment | Mean: 90<br>Median<br>SD: 10.5<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-6.5<br>Median:<br>SD:<br>P:          | Mean:0.98<br>Median:<br>SD:<br>P:                                | ratio of means reported with 90% CI  | low-medium                            |
|                                      |                     |          |      | Placebo                | 50 |   | Mean:92.2<br>Median<br>SD: 12.3<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:-<br>4.1<br>Median:<br>SD:<br>P:          |  |  |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author Year<br>Study Design          | CHD Risk Category   | CVD drug | Dose | Supplement/ Control | N  | Definition of outcome                                       | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results                  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---------------------|----------|------|---------------------|----|---|---|--|---|-------------------------------------|---------------------------------------|
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba       | 50 | Epinephrine-induced at 7 days after treatment               | Mean: 13.7<br>Median<br>SD: 7.7<br>SE:<br>Lower:<br>Upper:                                    | Mean:-7.1<br>% mean:<br>Median:<br>SD:<br>P:     | Mean:0.99<br>Median:<br>SD:<br>P:                       | ratio of means reported with 90% CI | low-medium                            |
|                                      |                     |          |      | Placebo             | 50 |   | Mean:13.8<br>Median<br>SD: 6.8<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:-6.5<br>Median:<br>SD:<br>P:     |   |                                     |                                       |
| Wolf 2006 <sup>68</sup><br>crossover | Low and/or Moderate | ASA      | 500  | ginkgo biloba       | 50 | Platelet-activating factor-induced at day 7 after treatment | Mean: 4.8<br>Median<br>SD: 3.7<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:-22.3<br>Median:<br>SD:<br>P:    | Mean:0.69<br>Median:<br>SD:<br>P:                       | ratio of means reported with 90% CI | low-medium                            |
|                                      |                     |          |      | Placebo             | 50 |   | Mean:6.9<br>Median<br>SD: 11.5<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:-23.2<br>Median:<br>SD:<br>P:    |   |                                     |                                       |

**Evidence Table 81. KQ2—Continuous data—Platelet aggregability (continued)**

| Author<br>Year<br><br>Study<br>Design | CHD Risk<br>Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower<br>limit (IQR,<br>95% CI)<br>Upper<br>Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk of Bias<br>(ROB) Assessment |
|---------------------------------------|----------------------|----------|------|------------------------|----|--------------------------|--|---|---|-----------------------|--|
|                                       |                      |          |      | Placebo                | 50 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                              |   |                       |  |

**Evidence Table 82. KQ2—Continuous data—Platelet count**

| Author Year<br>Study Design          | CHD Risk Category    | CVD drug | Dose | Supplement/ Control                | N  | Definition of outcome           | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value    | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|----------------------|----------|------|------------------------------------|----|---------------------------------|---|---|---|--|---------------------------------------|
| Lee 2008 <sup>36</sup>               | At high risk for CHD | wafarin  | 3.5  | Ginseng.                           | 12 |                                 | Mean: 265.5<br>Median<br>SD: 66.35<br>SE:<br>Lower:<br>Upper:                                 | Mean:0.8<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | "There were no statistically significant differences between the ginseng group and control group." | medium                                |
|                                      |                      |          |      | No treatment (aside from CVD drug) | 13 |                                 | Mean:278.3<br>Median<br>SD: 88.67<br>SE:<br>Lower:<br>Upper:                                  | Mean:11.6<br>Median:<br>SD:<br>P:                   |   |  |                                       |
| Macan 2006 <sup>40</sup><br>parallel | Low and/or Moderate  | Warfarin | NR   | Garlic.                            | 22 | 12 hr fasting blood measurement | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.1<br>% mean:<br>Median:<br>SD:<br>72.1<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.887                  |  | medium                                |
|                                      |                      |          |      | Placebo                            | 26 |                                 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.4<br>Median:<br>SD:<br>35.4<br>P:            |   |  |                                       |

**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design              | CHD Risk Category                      | CVD drug    | Dose  | Supplement/ Control          | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------|-------|------------------------------|----|-----------------------|---|--|---|---|---------------------------------------|
| Svaneborg 2002 <sup>64</sup><br>parallel | At low risk for CHD (0-1 risk factors) | ASA         | 100   | Omega-3 (EPA, DHA, or both). | 12 |                       | Mean:<br>Median 198<br>SD:<br>SE:<br>Lower: 156<br>Upper:240                                  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           |   | medium                                |
|  |  |             |       | Placebo                      | 6  |                       | Mean:<br>Median 201<br>SD:<br>SE:<br>Lower: 169<br>Upper:254                                  | Mean:<br>Median:<br>SD:<br>P:                    |   |   |                                       |
| Nordøy 2000 <sup>54</sup><br>Parallel    | Low and/or mod to high risk            | simvastatin | 20    | Omega-3 (EPA, DHA, or both). | 21 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:9<br>% mean:<br>Median:<br>SD:<br>7<br>P:   | Mean:<br>Median:<br>SD:<br>P:                           | Crude difference between groups in mean change from baseline (omega-3 vs. placebo): 6 (p=0.5) | medium                                |
|  |  |             |       | Placebo                      | 20 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:3<br>Median:<br>SD:<br>6<br>P:              |   |   |                                       |
| Napoli 1998 <sup>52</sup><br>parallel    | Unclear                                | Pravastatin | 20-40 | Vitamin E.                   | 52 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | "..no differences in routine laboratory tests or adverse                                      | medium                                |

**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug          | Dose   | Supplement/ Control                | N  | Definition of outcome     | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value    | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|-------------------|--------|------------------------------------|----|---------------------------|---|---|---|---|---------------------------------------|
|                                       |                      |                   |        | No treatment (aside from CVD drug) | 56 |                           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                       |   | events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.” |                                       |
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD | statins + aspirin | 10 -40 | Garlic                             | 9  | Measured after 12 hr fast | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:3.2<br>% mean:<br>Median:<br>SD:<br>17.4<br>P: | Mean:<br>Median:<br>SD:<br>P: 0.9269                    |   | medium                                |

**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug                                      | Dose  | Supplement/<br>Control             | N  | Definition of outcome                                | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|---|---|------------------------------------|----|--|---|--|---|--|---------------------------------------|
|                                       |                      |   |   | Placebo                            | 10 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:1.8<br>Median:<br>SD:<br>42.6<br>P:         |   |  |                                       |
| Dehmer 1988 <sup>17</sup><br>parallel | At high risk for CHD | aspirin + Dipyridamole + ca channel blockers) | ASA: 325; dipyridamole: 225; Ca blocker: NR | Omega-3 (EPA, DHA, or both).       | 43 | Fasting blood samples; standard automated techniques | Mean: 259<br>Median<br>SD: 55<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           |  | medium                                |
|                                       |                      |   |   | No treatment (aside from CVD drug) | 39 |  | Mean:287<br>Median<br>SD: 73<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>Median:<br>SD:<br>P:                    |   |  |                                       |
| Wolf 2006 <sup>68</sup><br>crossover  | Low and/or Moderate  | ASA   | 500   | ginkgo biloba                      | 50 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           | Study data are in forest plot with point estimates and 90% CIs | low-medium                            |



**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design            | CHD Risk Category   | CVD drug   | Dose | Supplement/<br>Control | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|--|---------------------|------------|------|------------------------|----|-----------------------|---|---|--|--|---------------------------------------|
|  |                     |            |      | Placebo                | 50 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                             |  | for the ratio acetylsalicylic acid (ASA) + EGb 761@/ASA - difficult to extract (can certainly do this with a ruler..but have not yet.. - can say that point estimate is close to 1 (between 1 an |                                       |
| Hansen 1993 <sup>29</sup><br>crossover | Low and/or Moderate | lovastatin | 40   | Fish/marine oils       | 14 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>17<br>Median:<br>SD:<br>P:            | Mean:<br>Median:<br>SD:<br>P:                                    |  | medium                                |
|  |                     |            |      | Placebo                | 14 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>20<br>Median:<br>SD:<br>P:            |  |  |                                       |

**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design              | CHD Risk Category                      | CVD drug          | Dose   | Supplement/. Control | N  | Definition of outcome                        | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value          | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|--|----------------------|----|--|---|---|---|---|---------------------------------------|
| Aruna 2007 <sup>2</sup><br>crossover     | At low risk for CHD (0-1 risk factors) | Cilostazol 100 mg | 104 to 200 (cilostazol); 75 to 150 (clopidogrel) | ginkgo biloba        | 10 | measured 0 and 6 h after drug administration | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                  | Mean:<br>Median:<br>SD:<br>P:                           | "There were no significant changes in...platelet count in any of the treatment groups." | medium                                |
|  |  |                   |  | No treatment         | 10 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                             |   |   |                                       |
| McKenney 2006 <sup>45</sup><br>Crossover | Low and/or Moderate                    | simvastatin       | 80   | Omega-3              | 24 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>6.92<br>% mean:<br>Median:<br>SD:<br>55.6<br>P: | Mean:<br>Median:<br>SD:<br>P:                           |   | medium                                |
|  |  |                   |  | No treatment         | 23 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.9<br>Median:<br>SD:<br>53.4<br>P:                  |   |   |                                       |

**Evidence Table 82. KQ2—Continuous data—Platelet count (continued)**

| Author Year<br>Study Design             | CHD Risk Category   | CVD drug | Dose              | Supplement/<br>Control | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value   | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---|---------------------|----------|-------------------|------------------------|----|-----------------------|---|---|--|--------------------|---------------------------------------|
| Mueller 1991 <sup>51</sup><br>crossover | Low and/or Moderate | aspirin  | 325 - single dose | Fish/marine oils       | 12 | Fasting               | Mean:<br>251.83<br>Median<br>SD: 52.51<br>SE:<br>Lower:<br>Upper:                                   | Mean:-<br>36.34<br>% mean:<br>Median:<br>SD:<br>P:<br><0.05 | Mean:<br>Median:<br>SD:<br>P:                                    |                    | medium                                |
|   |                     |          |                   | Placebo                | 12 |                       | Mean:<br>253.67<br>Median<br>SD: 51.46<br>SE:<br>Lower:<br>Upper:                                   | Mean:-<br>34.5<br>Median:<br>SD:<br>P:                      |  |                    |                                       |

**Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT)**

| Author Year<br>Study Design | CHD Risk<br>Category       | CVD drug | Dose | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome                                      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk of Bias<br>(ROB) Assessment |
|-----------------------------|----------------------------|----------|------|--|----|--|---|---|---|-----------------------|--|
| Lee 2008 <sup>36</sup>      | At high<br>risk for<br>CHD | wafarin  | 3.5  | Ginseng.                                 | 12 | Peak PT<br>After 2 mg<br>warfarin<br>phase<br>(after 1<br>week)  | Mean: 14.75<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:   | Mean:1.59<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001            | Mean:0.08<br>Median:<br>SD:<br>P:   |                       | medium                                   |
|                             |                            |          |      | No treatment<br>(aside from<br>CVD drug) | 13 |  | Mean:14.67<br>Median<br>SD: 0.71<br>SE:<br>Lower:<br>Upper:   | Mean:1.41<br>Median:<br>SD:<br>P:<br><0.001                       |   |                       |  |
| Lee 2008 <sup>36</sup>      | At high<br>risk for<br>CHD | wafarin  | 3.5  | Ginseng.                                 | 12 | Peak PT<br>After 5 mg<br>warfarin<br>phase<br>(after 2<br>weeks) | Mean: 24.23<br>Median<br>SD: 3.25<br>SE:<br>Lower:<br>Upper:  | Mean:11.07<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001           | Mean:0.8<br>Median:<br>SD:<br>P:  |                       | medium                                   |
|                             |                            |          |      | No treatment<br>(aside from<br>CVD drug) | 13 |  | Mean:23.42<br>Median<br>SD: 3.2<br>SE:<br>Lower:<br>Upper:  | Mean:10.16<br>Median:<br>SD:<br>P:<br><0.001                      |   |                       |  |

**Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)**

| Author Year<br>Study Design           | CHD Risk<br>Category       | CVD drug    | Dose      | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results   | Overall Risk of Bias<br>(ROB) Assessment |
|---------------------------------------|----------------------------|-------------|-----------|--|----|--|---|---|---|---|--|
| Lee 2008 <sup>36</sup>                | At high<br>risk for<br>CHD | wafarin     | 3.5       | Ginseng.                                 | 12 | Measured<br>as area<br>under the<br>curve<br>After 5 mg<br>warfarin                                | Mean: 97.33<br>Median<br>SD: 4.03<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:0.34<br>Median:<br>SD:<br>P:   |   | medium                                   |
|                                       |                            |             |           | No treatment<br>(aside from<br>CVD drug) | 13 | phase<br>(after 2<br>weeks)  | Mean:96.99<br>Median<br>SD: 3.16<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |   |  |
| Lee 2008 <sup>36</sup>                | At high<br>risk for<br>CHD | wafarin     | 3.5       | Ginseng.                                 | 12 | Measured<br>as area<br>under the<br>curve<br>After 5 mg<br>warfarin<br>phase<br>(after 2<br>weeks) | Mean:<br>142.67<br>Median<br>SD: 14.24<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:3.55<br>Median:<br>SD:<br>P:   |   |  |
|                                       |                            |             |           | No treatment<br>(aside from<br>CVD drug) | 13 | phase<br>(after 2<br>weeks)  | Mean:139.12<br>Median<br>SD: 12.88<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |   |  |
| Napoli 1998 <sup>52</sup><br>parallel | Unclear                    | Pravastatin | 20-<br>40 | Vitamin E.                               | 52 | NR   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | "..no<br>differences<br>in routine<br>laboratory<br>tests or<br>adverse | medium                                   |

**Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)**

| Author Year<br>Study Design              | CHD Risk<br>Category      | CVD drug    | Dose | Supplement/<br>Control                   | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results   | Overall Risk of Bias<br>(ROB) Assessment |
|--|---------------------------|-------------|------|--|----|-----------------------------|---|---|---|---|--|
|  |                           |             |      | No treatment<br>(aside from<br>CVD drug) | 56 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   | events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.” |  |
| McKenney 2006 <sup>45</sup><br>Crossover | Low<br>and/or<br>Moderate | simvastatin | 80   | Omega-3                                  | 24 | partial PT                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.1<br>% mean:<br>Median:<br>SD:<br>0.3<br>P:                | Mean:<br>Median:<br>SD:<br>P:   |   | medium                                   |

**Evidence Table 83. KQ2—Continuous data—Prothrombin time (PT) (continued)**

| Author Year<br>Study Design | CHD Risk<br>Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk of Bias<br>(ROB) Assessment |
|-----------------------------|----------------------|----------|------|------------------------|----|-----------------------------|---|---|---|-----------------------|--|
|                             |                      |          |      | No treatment           | 23 |                             | NR  | Mean:0.2<br>SD:0.3  |   |                       |  |

**Evidence Table 84. KQ2—Continuous data—Proteinuria**

| Author Year<br>Study Design            | CHD<br>Risk<br>Category | CVD<br>drug | Dose | Supplement/.<br>Control                  | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/<br>%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk of Bias<br>(ROB) Assessment |
|--|-------------------------|-------------|------|--|----|--|---|---|---|-----------------------|--|
| Ferraro 2009 <sup>22</sup><br>parallel | Unclear                 | ramipril    | 10   | Omega-3<br>(EPA, DHA,<br>or both).       | 15 | UPE (urinary<br>protein<br>excursion)<br>baseline was<br>considered a<br>mean of the<br>positive<br>measurements<br>obtained before<br>the final period. | Mean: 367<br>Median<br>SD: 520<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -<br>77.9<br>Median:<br>SD:<br>P:<br>P:              | Mean:-61.6<br>Median:<br>SD:<br>P:<0.01                                   |                       | medium                                   |
|  |                         |             |      | No treatment<br>(aside from<br>CVD drug) | 15 |  | Mean:1353<br>Median<br>SD: 1304   | Mean:<br>% mean: -<br>11.3  |   |                       |  |



**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP)**

| Author Year<br>Study Design            | CHD Risk Category | CVD drug   | Dose | Supplement/Control                 | N  | Definition of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|--|------|------------------------------------|----|-----------------------|---|---|--|---|---------------------------------------|
| Ferraro 2009 <sup>22</sup><br>parallel | Unclear           | ramipril   | 10   | Omega-3 (EPA, DHA, or both).       | 15 |                       | Mean: 123<br>Median<br>SD: 23<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>Median:<br>SD:<br>P:        | Mean:<br>Median:<br>SD:<br>P:                          |   | medium                                |
|  |                   |  |      | No treatment (aside from CVD drug) | 15 |                       | Mean:123<br>Median<br>SD: 19.9<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>Median:<br>SD:<br>P:                   |  |   |                                       |
| Meyer 2007 <sup>46</sup>               | Unclear           | simvastatin 13, atorvastatin, 4 pravastatin, 2 cerivastatin and 2 fluvastatin 81 | 81   | Fish/marine oils                   | 13 | Supine in clinic      | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:        | Mean:<br>Median:<br>SD:<br>P:                          | Report states that no changes were noted in SBP across groups and results are not shown | medium                                |
|  |                   |  |      | Fish/marine oils                   | 13 |                       |   |   |  |   |                                       |
|  |                   |  |      | Placebo                            | 14 |                       | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                   |  |   |                                       |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design           | CHD Risk<br>Category      | CVD drug    | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome                                | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|---------------------------|-------------|------|--|----|---|---|---|---|---|--|
| Sutken 2006 <sup>63</sup><br>parallel | Low<br>and/or<br>Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 22 | Data for elderly<br>sub-group                           | Mean: 132<br>Median<br>SD:<br>SE:8<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | Other continuous<br>outcomes also<br>measured in this study:<br>BMI, Height , Weight,<br>Glutathione - whole<br>blood, Malondialdehyde<br>- plasma, Vitamin E,<br>Erythrocyte GPx and<br>SOD activities | high   |
|                                       |                           |             |      | No treatment<br>(aside from<br>CVD drug) | 23 | Mean:125<br>Median<br>SD:<br>SE:6.7<br>Lower:<br>Upper: | Mean:<br>Median:<br>SD:<br>P:   |   |   |   |  |
| Sutken 2006 <sup>63</sup><br>parallel | Low<br>and/or<br>Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 22 | For young sub-<br>group                                 | Mean: 125<br>Median<br>SD:<br>SE:5<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |   | high   |
|                                       |                           |             |      | No treatment<br>(aside from<br>CVD drug) | 23 | Mean:128<br>Median<br>SD:<br>SE:7.7<br>Lower:<br>Upper: | Mean:<br>Median:<br>SD:<br>P:   |   |   |   |  |
| Macan 2006 <sup>40</sup><br>parallel  | Low<br>and/or<br>Moderate | Warfarin    | NR   | Garlic.                                  | 22 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.9<br>% mean:<br>Median:<br>SD:<br>P:0.697                  | Mean:<br>Median:<br>SD:<br>P:<br>0.697                                    | This study also<br>assesses the<br>continuous outcome:<br>weight  | medium   |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design             | CHD Risk<br>Category       | CVD drug    | Dose | Supplement/<br>Control                                   | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------------|-------------|------|--|----|--|---|---|---|--------------------|--|
|   |                            |             |      | Placebo  | 26 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.7<br>Median:<br>SD:<br>19.7<br>P:                          |   |                    |  |
| Playford 2003 <sup>58</sup><br>parallel | At high<br>risk for<br>CHD | Fenofibrate | 200  | Coenzyme<br>Q10.<br>200 mg plus<br>200 mg<br>fenofibrate | 18 | measured after 14<br>hr fast;<br>measured after<br>resting in supine<br>for 10 minutes, at<br>2 minute intervals<br>for 10 minutes | Mean: 127.4<br>Median<br>SD:<br>SE:3.8<br>Lower:<br>Upper:  | Mean:-4.4<br>% mean:<br>Median:<br>SD:<br>P:                      | Mean:3.4<br>Median:<br>SD:<br>P:0.033                                     |                    | low-medium                                     |
|   |                            |             |      | No treatment<br>(aside from<br>CVD drug)                 | 17 |  | Mean:130.8<br>Median<br>SD:<br>SE:4.3<br>Lower:<br>Upper:   | Mean:0.4<br>Median:<br>SD:<br>P:                                  |   |                    |  |
|   |                            |             |      | Coenzyme<br>Q10.<br>200 mg<br>CoQ10 only                 | 20 |  | Mean:124.8<br>Median<br>SD:<br>SE:3.4<br>Lower:<br>Upper:   | Mean:-4<br>Median:<br>SD:<br>P:                                   |   |                    |  |
|   |                            |             |      | Placebo  | 18 |  | Mean:137.8<br>Median<br>SD:<br>SE:4<br>Lower:<br>Upper:   | Mean:1.2<br>Median:<br>SD:<br>P:                                  |   |                    |  |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design                 | CHD Risk<br>Category | CVD drug   | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome                      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------|------------|------|--|----|---|---|---|---|--|--|
| Barbagallo<br>1999 <sup>5</sup><br>parallel | Unclear              | furosemide | 25   | Vitamin E.                               | 12 | supine, overnight<br>fasted, empty<br>bladder | Mean: 132<br>Median<br>SD: 6<br>SE:<br>Lower:<br>Upper:   | Mean:26<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001              | Mean:3<br>Median:<br>SD:<br>P:  | calculation of mean<br>change from baseline<br>questionably as it won't<br>be useable (SD cannot<br>be inferred, I don't<br>think.). | medium   |
|   |                      |            |      | No treatment<br>(aside from<br>CVD drug) | 12 |   | Mean:135<br>Median<br>SD: 5<br>SE:<br>Lower:<br>Upper:  | Mean:22<br>Median:<br>SD:<br>P:<br><0.001                         |   |  |  |
| Howe 1994 <sup>30</sup><br>parallel         | Unclear              | Captopril  | 61   | Fish/marine<br>oils.                     | 14 |   | Mean: 139<br>Median<br>SD:<br>SE:6<br>Lower:<br>Upper:  | Mean:4.3<br>% mean:<br>Median:<br>SD:<br>P:                       | Mean:4.2<br>Median:<br>SD:<br>P:0.05                                      |  | medium   |
|   |                      |            |      | Placebo                                  | 14 |   | Mean:140<br>Median<br>SD:<br>SE:4<br>Lower:<br>Upper:   | Mean:5.3<br>Median:<br>SD:<br>P:                                  |   |  |  |
|   |                      |            |      | Fish/marine<br>oils.                     | 14 |   | Mean:138<br>Median<br>SD:<br>SE:4<br>Lower:<br>Upper:   | Mean:7.7<br>Median:<br>SD:<br>1.8<br>P:                           |   |  |  |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design                | CHD Risk<br>Category | CVD drug           | Dose | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|--------------------|------|------------------------|----|---|---|---|---|--------------------|--|
|  |                      |                    |      | Placebo                | 14 |   | Mean:135<br>Median<br>SD:<br>SE:5<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Paolisso<br>1992 <sup>57</sup><br>parallel | Unclear              | hydrochlorthiazide | 25   | Magnesium.             | 9  | supine, fasted (12 h) and at rest for 30 minutes - measured over 60 minutes, mean of last 10 minutes of measurement included. | Mean: 171<br>Median<br>SD:<br>SE:8<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:<br><0.04                                    |                    | medium   |
|  |                      |                    |      | Placebo                | 9  |   | Mean:159<br>Median<br>SD:<br>SE:4<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Nordøy 2003 <sup>55</sup><br>parallel      | Mod and<br>high risk | atorvastatin       | 10   | Fish/marine oils.      | 22 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-5.5<br>% mean:<br>Median:<br>SD:<br>11.3<br>P:              | Mean:<br>Median:<br>SD:<br>P:<br>0.03                                     |                    | medium   |
|  |                      |                    |      | Placebo                | 20 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:3<br>Median:<br>SD:<br>12.8<br>P:                            |   |                    |  |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design          | CHD Risk<br>Category      | CVD drug            | Dose | Supplement/<br>Control | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value  | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--------------------------------------|---------------------------|---------------------|------|------------------------|----|--|---|--|---|---|--|
| Reyes 1984 <sup>59</sup><br>parallel | Low<br>and/or<br>Moderate | hydrochlorothiazide | 50   | Magnesium.             | 13 | Patients rested<br>supine for 10<br>minutes prior to<br>measurement - an<br>average of 3<br>measurements<br>rounded to<br>nearest 10 mmHg<br>- 900-1100hr<br>readings        | Mean: 145.4<br>Median<br>SD:<br>SE:3.3<br>Lower:<br>Upper:  | Mean:<br>% mean: -<br>7<br>Median:<br>SD:<br><0.02<br>P:<br><0.005 | Mean:<br>Median:<br>SD:<br>P:   | Percent change data<br>taken from graph -<br>2.5% = 1.1 cm, rounded<br>to the nearest 0.5%  | medium   |
|                                      |                           |                     |      | Placebo                | 8  |  | Mean:147.5<br>Median<br>SD:<br>SE:3.7<br>Lower:<br>Upper:   | Mean:<br>% mean:-8<br>Median:<br>SD:<br>P:                         |   |   |  |
| Reyes 1984 <sup>59</sup><br>parallel | Low<br>and/or<br>Moderate | hydrochlorothiazide | 50   | Magnesium.             | 13 | Erect systolic<br>blood pressure<br>Patients rested<br>erect for 10<br>minutes prior to<br>measurement - an<br>average of 3<br>measurements<br>rounded to<br>nearest 10 mmHg | Mean: 145<br>Median<br>SD:<br>SE:2<br>Lower:<br>Upper:  | Mean:<br>% mean: -<br>7<br>Median:<br>SD:<br><0.01<br>P:<br><0.01  | Mean:<br>Median:<br>SD:<br>P:   | Data extracted from bar<br>charts - method of<br>extraction verified for<br>other variables that had<br>corresponding<br>numerical summary. In<br>this case for final mean<br>and SEM 1.9 cm = 40<br>mmHg and results<br>rounded to nearest<br>whole mmHg. For %<br>change from time of<br>randomization 1.1 cm =<br>2.5% and results<br>rounded to nearest<br>0.5% | medium   |
|                                      |                           |                     |      | Placebo                | 8  |  | Mean:145<br>Median<br>SD:<br>SE:2<br>Lower:<br>Upper:   | Mean:<br>% mean:-<br>6.5<br>Median:<br>SD:<br>P:                   |   |   |  |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design                 | CHD Risk<br>Category       | CVD drug  | Dose   | Supplement/<br>Control                   | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------------|---|--|--|----|--------------------------|---|---|---|--|--|
| Dehmer 1988 <sup>17</sup><br>parallel       | At high<br>risk for<br>CHD | aspirin +<br>Dipyridamole + ca<br>channel blockers) | ASA: 325;<br>dipyridamole:<br>225; Ca<br>blocker: NR | Omega-3<br>(EPA, DHA,<br>or both).       | 43 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:6<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|   |                            |   |  | No treatment<br>(aside from<br>CVD drug) | 39 |                          | Mean:36<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Wolf 2006 <sup>68</sup><br>crossover        | Low<br>and/or<br>Moderate  | ASA   | 500  | ginkgo biloba                            | NR |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | Study states that:<br>Laboratory findings in<br>all subjects were un-<br>remarkable and did not<br>indicate any differences<br>between the treatment<br>groups. Similarly, no<br>noteworthy changes of<br>vital sign variables<br>occurred during the<br>study | low-medium                                     |
|   |                            |   |  |  | NR |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Paolisso<br>1995 <sup>56</sup><br>crossover | At high<br>risk for<br>CHD | nifedipine  | 88   | Vitamin E                                | 30 |                          | Mean: 147<br>Median<br>SD:<br>SE:6.3<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design                      | CHD Risk<br>Category | CVD drug   | Dose | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|------------|------|------------------------|----|---|---|---|---|--|--|
|  |                      |            |      | Placebo                | 30 |   | Mean:149<br>Median<br>SD:<br>SE:6.1<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Lungershausen<br>1994 <sup>38</sup><br>crossover | Unclear              | b-blockers | NR   | Fish/marine<br>oils    | 25 | Clinical systolic<br>BP (no exercise or<br>eating for 2hr<br>before, empty<br>bladder, resting<br>for 5 minutes);<br>taken by<br>averaging 3 or 4<br>consecutive<br>readings after<br>discarding initial<br>reading | Mean: 127<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | Data of mean<br>measured from<br>histogram (10 mmHg =<br>2.2 cm). Measure of<br>dispersion not stated.<br>This study is at risk of<br>selective outcome<br>reporting; p-values for<br>crude difference also<br>don't make sense in<br>context  | medium   |
|  |                      |            |      | Placebo                | 25 |   | Mean:131<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Lungershausen<br>1994 <sup>38</sup><br>crossover | Unclear              | b-blockers | NR   | Fish/marine<br>oils    | 25 | Ambulatory<br>systolic BP -<br>Measured over<br>next 24 hours<br>using Spacelab<br>90207 instrument,<br>same time of day;<br>taken at 20 min<br>intervals during<br>wake and every 1<br>hour during sleep.          | Mean: 128<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:2.5<br>% mean:<br>Median:<br>SD: 1<br>P:                     | Mean:<br>Median:<br>SD:<br>P: <0.05                                       | Data of mean<br>measured from<br>histogram (10 mmHg =<br>2.2 cm). Measure of<br>dispersion not stated.<br>Data of mean difference<br>in text. This study is at<br>risk of selective<br>outcome reporting; p-<br>values for crude<br>difference | medium   |
|  |                      |            |      | Placebo                | 25 |   | Mean:131<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:3.3<br>Median:<br>SD: 1.8<br>P:                              |   |  |  |



**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design             | CHD Risk<br>Category                            | CVD drug          | Dose  | Supplement/<br>Control | N  | Definition of<br>outcome  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---|-------------------|---|------------------------|----|---|---|---|---|---|--|
| Aruna 2007 <sup>2</sup><br>crossover    | At low risk<br>for CHD<br>(0-1 risk<br>factors) | Clopidogrel 75 mg | 105 to 200<br>(cilostazol);<br>75 to 150<br>(clopidogrel) | ginkgo biloba          | 10 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | "There was no<br>significant change in<br>systolic BP in any of the<br>groups..." | medium   |
|   |   |                   |   | No treatment           | 10 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |   |  |
| Mueller 1991 <sup>51</sup><br>crossover | Low<br>and/or<br>Moderate                       | aspirin           | 325 - single<br>dose                                      | Fish/marine<br>oils    | 12 | before and 90<br>minutes after a<br>single oral 325-mg<br>dose of aspirin.<br>Done by blinded<br>operator | Mean: 117<br>Median<br>SD: 12.47<br>SE:<br>Lower:<br>Upper:   | Mean:-0.6<br>% mean:<br>Median:<br>SD:<br>P:                      | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |
|   |   |                   |   | Placebo                | 12 |   | Mean:117.08<br>Median<br>SD: 11.54<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>0.52<br>Median:<br>SD:<br>P:                            |   |   |  |
| Maki 2008 <sup>41</sup><br>crossover    | Low<br>and/or<br>Moderate                       | simvastatin       | 20  | Omega-3                | 39 | At rest, seated   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |   | medium   |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design            | CHD Risk<br>Category | CVD drug   | Dose | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|--|------|------------------------|----|--------------------------|---|---|---|--------------------|--|
|  |                      |  |      | Placebo                | 40 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>0.3<br>Median:<br>SD:<br>P:                   |   |                    |  |
| Wirell 1994 <sup>67</sup><br>Crossover | Unclear              | metoprolol,<br>atenolol, pindolol &<br>propranolol | NR   | magnesium              | 39 | standing                 | Mean:<br>141.62<br>Median<br>SD: 18.4<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |
|  |                      |  |      | Placebo                | 39 |                          | Mean:145.96<br>Median<br>SD: 23.62<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Wirell 1994 <sup>67</sup><br>Crossover | Unclear              | metoprolol,<br>atenolol, pindolol &<br>propranolol | NR   | magnesium              | 39 | supine                   | Mean:<br>145.05<br>Median<br>SD: 18.2<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |

**Evidence Table 85. KQ2—Continuous data—Systolic blood pressure (SBP) (continued)**

| Author Year<br>Study Design | CHD Risk<br>Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|-----------------------------|----------------------|----------|------|------------------------|----|--------------------------|---|---|---|--------------------|--|
|                             |                      |          |      | Placebo                | 39 |                          | Mean:149.31<br>Median<br>SD: 18.61<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
|                             |                      |          |      |                        |    |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |

**Evidence Table 86. KQ2—Continuous data—TD: HDL-C**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug     | Dose  | Supplement/ Control          | N   | Definition of outcome                                  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|-------------------|--------------|-------|------------------------------|-----|--|---|--|---|---|---------------------------------------|
| Bays 2010 <sup>6</sup><br>parallel      | Unclear           | atorvastatin | 10-40 | Omega-3 (EPA, DHA, or both). | 122 | TC: HDL-C ratio at week 8, end of 10 mg/d atorvastatin | Mean: Median 4.3 SD: SE: Lower: 3.5 Upper:5.2   | Mean: % mean: Median:-38.3 SD: P:                | Mean: Median:-3.8% SD: P:0.001                          |   | medium                                |
|   |                   |              |       | Placebo                      | 121 |  | Mean: Median 4.7 SD: SE: Lower: 3.9 Upper:5.7   |  |   |   |                                       |
| Davidson 2007 <sup>14</sup><br>parallel | Unclear           | simvastatin  | 40    | Omega-3 (EPA, DHA, or both). | 122 | TC: HDL-C ratio  | Mean: Median SD: SE: Lower: Upper:  | Mean: % mean: -8 Median:-9.6 SD: P:              | Mean: Median:-3.8 SD: P:0.001                           | *TC:HDL-C ratio was significantly lower in omega group compared withthe placebo group (p = 0.012) | medium                                |
|   |                   |              |       | Placebo                      | 132 |  | Mean: Median SD: SE: Lower: Upper:  |  |   |   |                                       |

**Evidence Table 86. KQ2—Continuous data—TD: HDL-C (continued)**

| Author Year<br>Study Design          | CHD Risk Category | CVD drug             | Dose | Supplement/ Control                | N  | Definition of outcome               | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results             | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------|----------------------|------|------------------------------------|----|-------------------------------------|---|--|---|--------------------------------|---------------------------------------|
| Davidson 1997 <sup>15</sup> parallel | Unclear           | Simvastatin          | 10   | Fish/marine oils.                  | 9  | TC/HDL-C ratio fasting blood sample | Mean: 5.06<br>Median<br>SD:<br>SE:0.46<br>Lower:<br>Upper:                              | Mean:<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:<br>Median:<br>SD:<br>P:                           |                                | medium                                |
|                                      |                   |                      |      | No treatment (aside from CVD drug) | 10 |                                     | Mean:4.77<br>Median<br>SD:<br>SE:0.24<br>Lower:<br>Upper:                               | Mean:<br>% mean: -25.6<br>Median:<br>SD:<br>P:   |   |                                |                                       |
| Roth 2009 <sup>60</sup> parallel     | Unclear           | fenofibrates by 100% | 130  | Omega-3 (EPA, DHA, or both).       | 81 | TC/HDL-C ratio                      | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:-4.8<br>SD:<br>P:     | Mean:<br>Median:<br>SD:<br>P:                           | Not significant between groups | medium                                |
|                                      |                   |                      |      | Placebo                            | 82 |                                     | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>Median:-8.3<br>SD:<br>P:                |   |                                |                                       |

**Evidence Table 86. KQ2—Continuous data—TD: HDL-C (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug          | Dose    | Supplement/<br>Control | N  | Definition of outcome             | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|-------------------|---------|------------------------|----|-----------------------------------|---|---|--|--------------------|---------------------------------------|
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD | statins + aspirin | 10 - 40 | Garlic                 | 9  | TC: HDL Measured after 12 hr fast | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>0.15<br>% mean:<br>Median:<br>SD:<br>1.04<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.0763                          |                    | medium                                |
|                                       |                      |                   |         | Placebo                | 10 |                                   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.79<br>Median:<br>SD:<br>1.13<br>P:                 |  |                    |                                       |
| Maki 2008 <sup>41</sup><br>crossover  | Low and/or Moderate  | simvastatin       | 20      | Omega-3                | 39 | Least square mean (SEM)           | Mean: 4.1<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:<br>% mean: -<br>39<br>Median:<br>SD:<br>P:          | Mean:-6.5<br>Median:<br>SD:<br>P:<br><0.001                      |                    | medium                                |
|                                       |                      |                   |         | Placebo                | 40 |                                   | Mean:4.5<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:<br>% mean: -<br>33<br>Median:<br>SD:<br>P:          |  |                    |                                       |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol**

| Author Year<br>Study Design               | CHD Risk Category | CVD drug     | Dose  | Supplement/<br>Control             | N   | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------|--------------|-------|------------------------------------|-----|--------------------------|---|---|---|--|--|
| Bays 2010 <sup>6</sup><br>parallel        | Unclear           | atorvastatin | 10-40 | Omega-3<br>(EPA, DHA, or<br>both). | 122 |                          | Mean:<br>Median 172.5<br>SD:<br>SE:<br>Lower:157.5<br>Upper:194.5   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:-4.1;<br>-2.7<br>SD:<br>P:<br><0.001                      |  | medium   |
|   |                   |              |       | Placebo                            | 121 |                          | Mean:<br>Median 181.5<br>SD:<br>SE:<br>Lower:164.5<br>Upper:206   | Mean:<br>Median:-<br>27.4<br>SD:<br>P:                            |   |  |  |
| Bays 2010 <sup>6</sup><br>parallel        | Unclear           | atorvastatin | 10-40 | Omega-3<br>(EPA, DHA, or<br>both). | 122 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:<br><0.001                                   |  | medium   |
|   |                   |              |       | Placebo                            | 121 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Mabuchi<br>2007 <sup>39</sup><br>parallel | Unclear           | atorvastatin | 1     | Coenzyme<br>Q10.                   | 24  |                          | Mean: 4.99<br>Median<br>SD: 0.68<br>SE:<br>Lower:<br>Upper:   | Mean:-30<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001            | Mean:<br>Median:<br>SD:<br>P:   | "There were no<br>significant differences<br>between the 2 groups".<br>NOTE: For all outcomes,<br>data is also presented for<br>followup 4 weeks after<br>end of treatment (none of<br>this data was extracted). | medium   |
|   |                   |              |       | Placebo                            | 25  |                          | Mean:4.68<br>Median<br>SD: 0.68<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean: -<br>36<br>Median:<br>SD:<br>P:<br><0.0001       |   |  |  |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug  | Dose          | Supplement/<br>Control | N  | Definition of<br>outcome                | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------|---|---------------|------------------------|----|---|---|---|---|---|--|
| Young<br>2007 <sup>70</sup><br>parallel | Mod and high risk | simvastatin<br>statin   | 10-40         | Coenzyme<br>Q10.       | 22 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001                | Mean:<br>Median:<br>SD:<br>P:<br>0.57                                     | No difference in groups<br>(p=0.57).  | medium   |
|   |                   |   |               | Placebo                | 22 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:-<br>1.6%<br>SD:<br>P:<br><0.001                  |   |   |  |
| Caso<br>2007 <sup>11</sup>              | Unclear           | Simvastatin<br>statin (22);<br>Atorvastatin<br>(7); Pravastatin<br>(2);<br>Lovastatin (1)                 | varying doses | Coenzyme<br>Q10.       | 18 | Fasting plasma                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | No final outcome data<br>presented. Study reports<br>baseline data and that the<br>values did not change<br>during the intervention<br>period. Mean +/- SEM -<br>Baseline CoQ10: 183 +/-<br>10; Baseline Vit E: 189<br>+/- 14                         | low  |
|   |                   |   |               | Vit E                  | 14 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |   |  |
| Meyer<br>2007 <sup>46</sup>             | Unclear           | simvastatin<br>statin, 13<br>atorvastatin, 4<br>pravastatin, 2<br>cerivastatin and 2<br>fluvastatin<br>81 | 81            | Fish/marine<br>oils    | 13 | Blood plasma TC<br>after overnight fast | Mean: 4.43<br>Median<br>SD:<br>SE:0.23<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | significant correlation<br>between dosage of fish<br>oil and extent of<br>cholesterol reduction (r =<br>-0.344, P < 0.05); The<br>reduction of plasma total<br>cholesterol correlated<br>with initial cholesterol<br>levels (r = -0.44, P <<br>0.05). | medium   |
|   |                   |   |               | Fish/marine<br>oils    | 13 |   | Mean:4.18<br>Median<br>SD:<br>SE:0.23<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |   |  |



**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design              | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome                        | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---------------------|-------------|------|--|----|---|---|---|---|--------------------|--|
|  |                     |             |      | Placebo                                  | 14 |   | Mean:4.47<br>Median<br>SD:<br>SE:0.21<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Sutken<br>2006 <sup>63</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 22 | serum<br>for elderly sub-group                  | Mean: 7.3<br>Median<br>SD:<br>SE:1.07<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |                    | high   |
|  |                     |             |      | No treatment<br>(aside from<br>CVD drug) | 23 |   | Mean:7.1<br>Median<br>SD:<br>SE:2.3<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Sutken<br>2006 <sup>63</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                               | 12 | Serum<br>For younger sub-<br>group              | Mean: 6.58<br>Median<br>SD:<br>SE:0.18<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |                    | high   |
|  |                     |             |      | No treatment<br>(aside from<br>CVD drug) | 10 |   | Mean:6.55<br>Median<br>SD:<br>SE:0.07<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Macan<br>2006 <sup>40</sup><br>parallel  | Low and/or Moderate | Warfarin    | NR   | Garlic.                                  | 22 | NR - other than 12<br>hr fasting<br>measurement | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:8.4<br>% mean:<br>Median:<br>SD:<br>P:<br>28.0               | Mean:<br>Median:<br>SD:<br>P:<br>0.128                                    |                    | medium   |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design              | CHD Risk Category    | CVD drug     | Dose | Supplement/<br>Control | N  | Definition of<br>outcome                    | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|--------------|------|------------------------|----|---|---|---|---|--|--|
|  |                      |              |      | Placebo                | 26 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-4.1<br>Median:<br>SD:<br>27.6<br>P:                         |   |  |  |
| Manuel<br>2004 <sup>42</sup><br>parallel | At high risk for CHD | Atorvastatin | 20   | Vitamin E.             | 11 | serum, fasting                              | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001               | Mean:<br>Median:<br>SD:<br>P:   | Data not presented in<br>paper - only combined<br>data for both groups<br>across time  | medium   |
|  |                      |              |      | Placebo                | 11 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:<br><0.0001                          |   |  |  |
| Manuel<br>2004 <sup>42</sup><br>parallel | At high risk for CHD | Atorvastatin | 20   | Vitamin E.             | 11 | total cholesterol in<br>non-HDL subfraction | Mean: 2.57<br>Median<br>SD: 0.81<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001                | Mean:<br>Median:<br>SD:<br>P:   | Other outcomes reported<br>but not extracted for this<br>study: serum tocopherol,<br>TBARS - Copper-induced<br>production of<br>thiobarbituric reactive<br>substances in LDL and<br>VLDL sub-fractions (lag-<br>time, propagation phase<br>and saturation phase),<br>Plasma malondialdehyde,<br>Blood count,<br>Creatinephosphokinase,<br>Oxidant-antioxidant<br>balance (concentrations<br>of Vit A and E in serum),<br>non-HDL-fraction of Vit E,<br>non-HDL fraction of Vit A,<br>7 bands in LDL<br>subfraction | medium   |
|  |                      |              |      | Placebo                | 11 |   | Mean:2.69<br>Median<br>SD: 1.11<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br><0.001                           |   |  |  |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                      | CHD Risk Category    | CVD drug           | Dose | Supplement/<br>Control                   | N | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|--------------------|------|--|---|--|---|---|---|--|--|
| Micheletta<br>2004 <sup>47</sup><br><br>Parallel | At high risk for CHD | ASA or ticlopidine | NR   | Vitamin E.                               | 8 | Total cholesterol in<br>atherosclerotic<br>plaque tissue<br>excised during<br>endarterectomy | Mean: 34.8<br>Median<br>SD: 24.5<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | This study also assesses<br>TG and TC (relevant but<br>with no data to extract,<br>only noted that there<br>were no differences<br>between baseline and<br>follow-up - to fill out<br>separate form after) and<br>the following non-relevant<br>outcomes: Plasma<br>alphatocopherol, 7-beta<br>hydroxycholesterol, 7-<br>ketocholesterol | medium   |
|  |                      |                    |      | No treatment<br>(aside from<br>CVD drug) | 8 |  | Mean:40.6<br>Median<br>SD: 28.7<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Micheletta<br>2004 <sup>47</sup><br><br>Parallel | At high risk for CHD | ASA or ticlopidine | NR   | Vitamin E.                               | 8 | Plasma - 12hr fast at<br>800-900hr   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          |   | Total cholesterol outcome<br>data reported. Study<br>states only baseline data<br>and that 'no changes of<br>cholesterol and<br>triglyceride<br>concentrations were<br>observed at the end of<br>follow-up. Baseline<br>values for total<br>cholesterol given for both<br>groups together... (mean<br>+/- SD): 5.9 +/- 1.2               | medium   |
|  |                      |                    |      | No treatment<br>(aside from<br>CVD drug) | 8 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                 | CHD Risk Category                          | CVD drug    | Dose | Supplement/<br>Control                                   | N  | Definition of<br>outcome      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|--|-------------|------|--|----|-------------------------------|---|---|---|--|--|
| Playford<br>2003 <sup>58</sup><br>parallel  | At high risk for CHD                       | Fenofibrate | 200  | Coenzyme<br>Q10.<br>200 mg plus<br>200 mg<br>fenofibrate | 18 | measured after 14 hr<br>fast; | Mean: 4.7<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:-0.5<br>% mean:<br>Median:<br>SD:<br>P:                      | Mean:<br>Median:<br>SD:<br>P:<br>0.455 or<br>0.001                        |  | low-medium                                     |
|   |  |             |      | No treatment<br>(aside from<br>CVD drug)                 | 17 |                               | Mean: 4.7<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:-0.8<br>% mean:<br>Median:<br>SD:<br>P:                      |   |  |  |
|   |  |             |      | Coenzyme<br>Q10.<br>200 mg<br>CoQ10 only                 | 20 |                               | Mean: 5.3<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:0<br>% mean:<br>Median:<br>SD:<br>P:                         |   |  |  |
|   |  |             |      | Placebo  | 18 |                               | Mean:5.4<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:0.1<br>Median:<br>SD:<br>P:                                  |   |  |  |
| Svaneborg<br>2002 <sup>64</sup><br>parallel | At low risk for CHD (0-<br>1 risk factors) | ASA         | 100  | Omega-3<br>(EPA, DHA, or<br>both).                       | 12 |                               | Mean:<br>Median 3.85<br>SD:<br>SE:<br>Lower:3.25<br>Upper:5.2   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | baseline is 14 days prior<br>to the second IV dose of<br>ASA.--- vs. placebo (corn<br>oil containing 61%<br>omega-6) | medium   |
|   |  |             |      | Placebo  | 6  |                               | Mean:<br>Median 4.65<br>SD:<br>SE:<br>Lower:3.57<br>Upper:6.08  | Mean:<br>Median:<br>SD:<br>P:<br><0.05                            |   |  |  |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design              | CHD Risk Category              | CVD drug              | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|--------------------------------|-----------------------|-------|--|----|--------------------------|---|---|---|--|--|
| Duffy<br>2001 <sup>20</sup><br>parallel  | Low and/or Moderate            | simvastatin<br>statin | 10-40 | Vitamin E.                               | 6  |                          | Mean: 4.7<br>Median<br>SD: 0.9<br>SE:<br>Lower:<br>Upper:   | Mean:-1.6<br>% mean:<br>Median:<br>SD:<br>P:<br>0.01              | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                                |                       |       | No treatment<br>(aside from<br>CVD drug) | 7  |                          | Mean:5.1<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:  | Mean:-2.2<br>Median:<br>SD:<br>P:<br>0.01                         |   |  |  |
|  |                                |                       |       | 1000IU<br>Vitamin E                      | 6  |                          | Mean:6.8<br>Median<br>SD: 1.7<br>SE:<br>Lower:<br>Upper:  | Mean:0<br>Median:<br>SD:<br>P:                                    |   |  |  |
|  |                                |                       |       | Placebo                                  | 7  |                          | Mean:6.4<br>Median<br>SD: 1<br>SE:<br>Lower:<br>Upper:  | Mean:0.6<br>Median:<br>SD:<br>P:<br>0.01                          |   |  |  |
| Nordøy<br>2000 <sup>54</sup><br>Parallel | Low and/or mod to<br>high risk | simvastatin<br>statin | 20    | Omega-3<br>(EPA, DHA, or<br>both).       | 21 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | "Simvastatin and w-3 FA<br>compared with<br>simvastatin and placebo<br>reduced seum<br>concentrations of total<br>cholesterol (p=0.05). No<br>data provided. | medium   |
|  |                                |                       |       | Placebo                                  | 20 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose   | Supplement/<br>Control             | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value                  | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|--------|------------------------------------|----|---|---|--|---|--------------------|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>parallel   | Unclear              | Pravastatin | 20-40  | Vitamin E.                         | 52 | Fasting 12-14 hrs; determined enzymatically using Boehringer test kit | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-25<br>% mean:<br>Median:<br>SD:<br>P:0.05                  | Mean:<br>0.225<br>Median:<br>SD:<br>P:<br><0.05         |                    | medium                                |
|   |                      |             |        | No treatment (aside from CVD drug) | 56 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-26<br>Median:<br>SD:<br>5%<br>P:<br><0.05   |   |                    |                                       |
| Bordia 1998 <sup>9</sup><br>parallel    | At high risk for CHD | Nitrates    | NR     | Garlic.                            | 30 |   | Mean: 220.5<br>Median<br>SD:<br>SE:7<br>Lower:<br>Upper:                                      | Mean:-32.4<br>% mean: -<br>12.8<br>Median:<br>SD:<br>P:<br><0.01 | Mean:28.2<br>Median:<br>SD:<br>P:                       |                    | high                                  |
|   |                      |             |        | Placebo                            | 30 |   | Mean:248.7<br>Median<br>SD:<br>SE:7.2<br>Lower:<br>Upper:                                     | Mean:-4.6<br>Median:<br>SD:<br>P:                                |   |                    |                                       |
| Yamamoto 1995 <sup>69</sup><br>parallel | At high risk for CHD | diltiazem   | 90-120 | Omega-3 (EPA, DHA, or both).       | 12 |   | Mean: 185<br>Median<br>SD:<br>SE:37<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                | CHD Risk Category    | CVD drug                        | Dose   | Supplement/<br>Control                   | N  | Definition of<br>outcome                      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|---------------------------------|--|--|----|---|---|---|---|--|--|
|  |                      |                                 |  | No treatment<br>(aside from<br>CVD drug) | 10 |   | Mean:180<br>Median<br>SD:<br>SE:24<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| McDowell<br>1994 <sup>44</sup><br>parallel | Unclear              | Simvastatin                     | 20   | Vitamin E.                               | 8  | overnight fast                                | Mean: 5.9<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | Other continuous<br>outcomes not extracted:<br>Vascular forearm<br>bloodflow response to 3<br>agents (possibly to come<br>back to after discussion<br>with Michelle Turek); Apo<br>A1; Apo B; serum alpha-<br>tocopherol; serum<br>probucol; serum TBARS | medium   |
|  |                      |                                 |  | Placebo                                  | 8  |   | Mean:6.5<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Paolisso<br>1992 <sup>57</sup><br>parallel | Unclear              | hydrochlorthiazide              | 25   | Magnesium.                               | 9  | plasma<br>measurement after<br>overnight fast | Mean: 6.28<br>Median<br>SD:<br>SE:0.21<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                      |                                 |  | Placebo                                  | 9  |   | Mean:6.31<br>Median<br>SD:<br>SE:0.18<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Kaul 1992 <sup>34</sup><br>parallel        | At high risk for CHD | Calcium channel<br>blocker, ASA | ASA: 150;<br>heparin: 1000 U/d;<br>ca blockers: NR | Fish/marine<br>oils.                     | 58 |   | Mean: 224<br>Median<br>SD: 39.8<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |  | low-medium                                     |

Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)

| Author Year<br>Study Design              | CHD Risk Category | CVD drug                | Dose | Supplement/<br>Control                   | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|-------------------|-------------------------|------|--|----|--|---|---|---|--------------------|--|
|  |                   |                         |      | No treatment<br>(aside from<br>CVD drug) | 49 |  | Mean:215<br>Median<br>SD: 40.2<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Nordøy<br>2003 <sup>55</sup><br>parallel | Mod and high risk | atorvastatin            | 10   | Fish/marine<br>oils.                     | 22 | Blood sample taken<br>after 12 hr fasting,<br>within 6 days of end<br>of study                           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.07<br>% mean:<br>Median:<br>SD:<br>P:<br>0.42             | Mean:2.9<br>Median:-16.9<br>SD:<br>P:<br>0.13                             |                    | medium   |
|  |                   |                         |      | Placebo                                  | 20 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.36<br>Median:<br>SD:<br>P:<br>0.74                        |   |                    |  |
| Roth 2009 <sup>60</sup><br>parallel      | Unclear           | fenofibrates by<br>100% | 130  | Omega-3<br>(EPA, DHA, or<br>both).       |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:2.9  |                    | medium   |
|  |                   |                         |      | Placebo                                  |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:-<br>5.1<br>SD:<br>P:                             |   |                    |  |
| Isley 2007 <sup>31</sup><br>parallel     | Unclear           | niacin                  | 325  | Omega-3                                  |    | measured<br>enzymatically on a<br>Cobas Fara II<br>(Roche) using<br>enzymatic reagents<br>and procedures | Mean: 194<br>Median<br>SD: 29<br>SE:<br>Lower:<br>Upper:  | Mean:-5<br>% mean:<br>Median:<br>SD:<br>P:                        | Mean:-16.9<br>Median:<br>SD:<br>P:<0.001                                  |                    | medium   |



**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design              | CHD Risk Category  | CVD drug          | Dose  | Supplement/<br>Control | N | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|--|-------------------|-------|------------------------|---|--|---|---|---|--------------------|--|
|  |  |                   |       | Placebo                |   | standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention/National Institutes of Health. | Mean:185<br>Median<br>SD: 18<br>SE:<br>Lower:<br>Upper:   | Mean:12.8<br>% mean:-6<br>Median:<br>SD:<br>P:                    |   |                    |  |
| Budoff<br>2004 <sup>10</sup><br>parallel | At high risk for CHD                                       | statins + aspirin | 10-40 | Garlic                 |   | Measured after 12 hr fast  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:7<br>% mean:<br>Median:<br>SD:<br>21.8<br>P:                 | Mean:<br>Median:<br>SD:<br>P:<br>0.6065                                   |                    | medium   |
|  |  |                   |       | Placebo                |   |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>25.9<br>P:                             |   |                    |  |
| Chan<br>2002 <sup>12</sup><br>parallel   | At moderate/moderately high risk for CHD (2+ risk factors) | atorvastatin      | 40    | Fish/marine oils.      |   | collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements.                             | Mean: 3.9<br>Median<br>SD:<br>SE:0.27<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |
|  |  |                   |       | Placebo                |   |  | Mean:3.6<br>Median<br>SD:<br>SE:0.12<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                     |   |                    |  |
| Liu 2003 <sup>37</sup><br>parallel       | Unclear  | simvastatin       | 10    | Fish/marine oils.      |   | Fasting blood samples  | Mean: 5.13<br>Median<br>SD: 0.95<br>SE:<br>Lower:<br>Upper:   | Mean:-1.56<br>% mean:-<br>23.3<br>Median:<br>SD:<br>0.95<br>P:    | Mean:<br>Median:<br>SD:<br>P:   |                    | medium   |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                | CHD Risk Category                          | CVD drug  | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome                                      | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|--|---|---|--|----|---|---|---|---|--|--|
|  |  |   |   | No treatment<br>(aside from<br>CVD drug) |    |   | Mean:5.56<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:   | Mean:-1.48<br>Median:<br>SD:<br>0.8<br>P:                         |   |  |  |
| Dehmer<br>1988 <sup>17</sup><br>parallel   | At high risk for CHD                       | aspirin +<br>Dipyridamole + ca<br>channel blockers) | ASA: 325;<br>dipyridamole: 225;<br>Ca blocker: NR | Omega-3<br>(EPA, DHA, or<br>both).       |    | Fasting blood<br>samples; standard<br>automated<br>techniques | Mean: 236<br>Median<br>SD: 50.3<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |  |   |   | No treatment<br>(aside from<br>CVD drug) |    |   | Mean:217<br>Median<br>SD: 42.9<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Desideri<br>2003 <sup>18</sup><br>parallel | At low risk for CHD (0-<br>1 risk factors) | Simvastatinstatin,<br>Bezafibrate                   | simvastatinstatin:<br>40; Bezafibrate:<br>800     | Vitamin E.                               |    | 12 hr fasting at<br>800hr – serum;                            | Mean: 5.8<br>Median<br>SD: 0.7<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001               | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |  |   |   | No treatment<br>(aside from<br>CVD drug) |    |   | Mean:5.6<br>Median<br>SD: 0.6<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br><0.0001                          |   |  |  |
| Wolf 2006 <sup>68</sup><br>crossover       | Low and/or Moderate                        | ASA   | 500   | ginkgo biloba                            | 50 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   | Study states that:<br>Laboratory findings in all<br>subjects were un-<br>remarkable and did not<br>indicate any differences<br>between the treatment | low-medium                                     |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                    | CHD Risk Category    | CVD drug    | Dose  | Supplement/<br>Control                   | N  | Definition of<br>outcome                         | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------|-------------|-------|--|----|--|---|---|---|--|--|
|  |                      |             |       | Placebo                                  | 50 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   | groups.  |  |
| De Caterina<br>2002 <sup>16</sup><br>crossover | At high risk for CHD | simvastatin | 10-40 | Vitamin E                                |    | 20% reduction in TC<br>for each patient          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>%<br>mean:26.5<br>Median:<br>SD:<br>P:                   | Mean:<br>Median:<br>SD:<br>P:   | Values are presented in<br>graphs, but difficult to<br>read. | high   |
|  |                      |             |       | No treatment<br>(aside from<br>CVD drug) |    |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   |   |   |  |  |
| Balestrieri<br>1996 <sup>4</sup><br>crossover  | Low and/or Moderate  | Simvastatin | 10-40 | Fish/marine<br>oils                      | 14 | 12 hour fast, anti-<br>tubectal vein             | Mean: 300<br>Median<br>SD: 49<br>SE:<br>Lower:<br>Upper:  | Mean:2<br>% mean:<br>Median:<br>SD:<br>P:                         | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                      |             |       | Placebo                                  | 14 |  | Mean:302<br>Median<br>SD: 44<br>SE:<br>Lower:<br>Upper:   |   |   |  |  |
| Paolisso<br>1995 <sup>56</sup><br>crossover    | At high risk for CHD | nifedipine  | 88    | Vitamin E                                | 30 | Fasting;<br>at 2 months after<br>treatment start | Mean: 6.03<br>Median<br>SD:<br>SE:0.09<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br>P:                    | Mean:<br>Median:<br>SD:<br>P:<br><0.05                                    |  | medium   |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design               | CHD Risk Category   | CVD drug    | Dose     | Supplement/<br>Control                   | N  | Definition of<br>outcome    | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results              | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|---------------------|-------------|----------|--|----|-----------------------------|---|---|---|---------------------------------|--|
|   |                     |             |          | Placebo                                  | 30 |                             | Mean:6.96<br>Median<br>SD:<br>SE:0.11<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |                                 |  |
| Hansen<br>1993 <sup>29</sup><br>crossover | Low and/or Moderate | lovastatin  | 40       | Fish/marine<br>oils                      | 14 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:-<br>31<br>Median:<br>SD:<br>P:                   | Mean:<br>Median:<br>SD:<br>P:   |                                 | medium   |
|   |                     |             |          | Placebo                                  | 14 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean: -<br>27<br>Median:<br>SD:<br>P:                  |   |                                 |  |
| Avogaro<br>1974 <sup>3</sup><br>Crossover | Unclear             | propranolol | 20 or 60 | Niacin                                   | 10 | at end of 1 mo<br>treatment | Mean: 316.2<br>Median<br>SD:<br>SE:12.1<br>Lower:<br>Upper:   | Mean:-30<br>% mean:<br>Median:<br>SD:<br>P:                       | Mean:-10.8<br>Median:<br>SD:<br>P:  | Type II<br>hyperlipoproteinemia | high   |
|   |                     |             |          | No treatment<br>(aside from<br>CVD drug) | 10 |                             | Mean:327<br>Median<br>SD:<br>SE:50.29<br>Lower:<br>Upper:   | Mean:-19.2<br>Median:<br>SD:<br>P:                                |   |                                 |  |
| Avogaro<br>1974 <sup>3</sup><br>Crossover | Unclear             | propranolol | 20 or 60 | Niacin                                   | 10 | at end of 1 mo<br>treatment | Mean: 241.67<br>Median<br>SD:<br>SE:41.79<br>Lower:<br>Upper:   | Mean:-12.5<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:-5.83<br>Median:<br>SD:<br>P:  | Type IV<br>hyperlipoproteinemia | high   |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author Year<br>Study Design                | CHD Risk Category   | CVD drug    | Dose              | Supplement/<br>Control                   | N  | Definition of<br>outcome   | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results                                       | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|---------------------|-------------|-------------------|--|----|--|---|---|---|--|--|
|  |                     |             |                   | No treatment<br>(aside from<br>CVD drug) | 10 |  | Mean:247.5<br>Median<br>SD:<br>SE:37.38<br>Lower:<br>Upper:   | Mean:-6.67<br>Median:<br>SD:<br>P:                                |   |  |  |
| Mueller<br>1991 <sup>51</sup><br>crossover | Low and/or Moderate | aspirin     | 325 - single dose | Fish/marine<br>oils                      | 12 | Fasting  | Mean: 198.75<br>Median<br>SD: 34.45<br>SE:<br>Lower:<br>Upper:  | Mean:-3.92<br>% mean:<br>Median:<br>SD:<br>P:                     | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |
|  |                     |             |                   | Placebo                                  | 12 |  | Mean:188.83<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                     |   |  |  |
| Maki 2008 <sup>41</sup><br>crossover       | Low and/or Moderate | simvastatin | 20                | Omega-3                                  | 39 | 10-14 hour fast;<br>Centers for Disease<br>Control and<br>Prevention lipid<br>standardization<br>program | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:<br>0.006                                    | The IQRs reported are<br>actually ranges (low-<br>high). | medium   |
|  |                     |             |                   | Placebo                                  | 40 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>13.84<br>Median:<br>SD:<br>P:                           |   |  |  |
| Maki 2008 <sup>41</sup><br>crossover       | Low and/or Moderate | simvastatin | 20                | Omega-3                                  | 39 | Hour fast  | Mean:37.25<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          | Mean:<br>Median:<br>SD:<br>P:   |  | medium   |

**Evidence Table 87. KQ2—Continuous data—Total cholesterol (continued)**

| Author<br>Year<br><br>Study<br>Design | CHD Risk Category | CVD drug | Dose | Supplement/<br>Control | N  | Definition of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---------------------------------------|-------------------|----------|------|------------------------|----|--------------------------|---|---|---|--------------------|--|
|                                       |                   |          |      | Placebo                | 40 |                          | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                          |   |                    |  |

**Evidence Table 88. KQ2—Continuous data—Triglycerides**

| Author Year<br>Study Design        | CHD Risk Category | CVD drug     | Dose  | Supplement/ Control          | N   | Definition of outcome                   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|-------------------|--------------|-------|------------------------------|-----|---|---|---|--|--------------------|---------------------------------------|
| Bays 2010 <sup>6</sup><br>parallel | Unclear           | atorvastatin | 10-40 | Omega-3 (EPA, DHA, or both). | 122 | at week 8, end of 10 mg/d atorvastatin  | Mean:<br>Median 184.5<br>SD:<br>SE:<br>Lower: 154.5<br>Upper:232                              | Mean:<br>% mean: -45.4<br>Median:<br>SD:<br>P:    | Mean:<br>Median:-18.6(-19.2)<br>SD:<br>P:<0.001        |                    | medium                                |
|                                    |                   |              |       | Placebo                      | 121 |   | Mean:<br>Median 233.5<br>SD:<br>SE:<br>Lower: 186.5<br>Upper:325r:                            | Mean:<br>Median:-26.9<br>SD:<br>P:                |  |                    |                                       |
| Bays 2010 <sup>6</sup><br>parallel | Unclear           | atorvastatin | 10-40 | Omega-3 (EPA, DHA, or both). | 122 | at week 16, end of 40 mg/d atorvastatin | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:-19.1<br>SD:<br>P:<0.001               |                    | medium                                |
|                                    |                   |              |       | Placebo                      | 121 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                     |  |                    |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design            | CHD Risk Category | CVD drug     | Dose | Supplement/<br>Control             | N  | Definition of outcome                                       | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results                                  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|--------------|------|------------------------------------|----|---|---|---|--|---|---------------------------------------|
| Ferraro 2009 <sup>22</sup><br>parallel | Unclear           | ramipril     | 10   | Omega-3 (EPA, DHA, or both).       | 15 |   | Mean: 145.7<br>Median<br>SD: 143.4<br>SE:<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:                                    |   | medium                                |
|  |                   |              |      | No treatment (aside from CVD drug) | 15 | Mean:184.3<br>Median<br>SD:167.3<br>SE:<br>Lower:<br>Upper: | Mean:<br>Median:<br>SD:<br>P:   |   |  |   |                                       |
| Mabuchi 2007 <sup>39</sup>             | Unclear           | atorvastatin | 1    | Coenzyme Q10.                      | 24 |   | Mean: 1.13<br>Median<br>SD: 0.46<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001     | Mean:<br>Median:<br>SD:<br>P:                                    | "...no significant differences between the groups." | medium                                |
|  |                   |              |      | Placebo                            | 25 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:           | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.0001   |   |  |   |                                       |



**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug    | Dose  | Supplement/<br>Control       | N   | Definition of outcome                             | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value            | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results               | Overall Risk of Bias (ROB) Assessment |
|---|-------------------|-------------|-------|------------------------------|-----|---|---|--|--|----------------------------------|---------------------------------------|
| Young 2007 <sup>70</sup><br>parallel    | Mod and high risk | simvastatin | 10-40 | Coenzyme Q10.                | 22  |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:-<br>0.4<br>SD:<br>P:                   | Mean:<br>Median<br>SD:<br>P:<br>0.90                             | No difference in groups (p=0.90) | medium                                |
|   |                   |             |       | Placebo                      | 22  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>Median:-<br>0.3<br>SD:<br>P:<br><0.05  |  |  |                                  |                                       |
| Davidson 2007 <sup>14</sup><br>parallel | Unclear           | simvastatin | 40    | Omega-3 (EPA, DHA, or both). | 122 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-28.2<br>Median:-<br>29.5<br>SD:<br>18.7<br>P: | Mean:<br>Median:<br>SD:<br>P:<br><0.001                          |                                  | medium                                |
|   |                   |             |       | Placebo                      | 132 | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper: | Mean:<br>%mean: -<br>3.5<br>Median:-<br>6.3<br>SD:<br>22.1<br>P:                                    |  |  |                                  |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design          | CHD Risk Category | CVD drug  | Dose          | Supplement/Control | N  | Definition of outcome                | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------|---|---------------|--------------------|----|--------------------------------------|---|---|---|---|---------------------------------------|
| Caso 2007 <sup>11</sup>              | Unclear           | Simvastatin (22); Atorvastatin (7); Pravastatin (2); Lovastatin (1)                 | varying doses | Coenzyme Q10.      | 18 | fasting plasma measurement           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           | No final outcome data presented. Study reports baseline data and that the values did not change during the intervention period. Mean +/- SEM - Baseline CoQ10: 196 +/- 30; Baseline Vit E: 155 +/- 18<br>ata analysis performed on log-transformed data as data were not normally distributed | low                                   |
|                                      |                   |   |               | Vit E              | 14 |                                      | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                     |   |   |                                       |
| Meyer 2007 <sup>46</sup><br>parallel | Unclear           | simvastatin (13), atorvastatin (4), pravastatin (2), cerivastatin and 2 fluvastatin | 81            | Fish/marine oils.  | 13 | Blood plasma TG after overnight fast | Mean:<br>1.9*2<br>Median<br>SD:<br>SE:0.27<br>Lower:<br>Upper:                                | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           |   | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control             | N  | Definition of outcome       | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|---------------------|-------------|------|------------------------------------|----|-----------------------------|---|---|--|--------------------|---------------------------------------|
|                                       |                     |             |      | Fish/marine oils.                  | 13 |                             | Mean: 1.72<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                |  |                    |                                       |
|                                       |                     |             |      | Placebo                            | 14 |                             | Mean:2.05<br>Median<br>SD:<br>SE:0.2<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                           |  |                    |                                       |
| Sutken 2006 <sup>63</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                         | 22 | serum for elderly sub-group | Mean: 2.23<br>Median<br>SD:<br>SE:0.07<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001      | Mean:<br>Median:<br>SD:<br>P:                                    |                    | high                                  |
|                                       |                     |             |      | No treatment (aside from CVD drug) | 23 |                             | Mean:2.5<br>Median<br>SD:<br>SE:1.7<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:<br><0.001                 |  |                    |                                       |
| Sutken 2006 <sup>63</sup><br>parallel | Low and/or Moderate | Gemfibrozil | 1200 | Vitamin E.                         | 12 | serum for younger sub-group | Mean: 1.88<br>Median<br>SD:<br>SE:0.07<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001      | Mean:<br>Median:<br>SD:<br>P:                                    |                    | high                                  |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug     | Dose | Supplement/<br>Control             | N  | Definition of outcome      | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|--------------|------|------------------------------------|----|----------------------------|---|---|--|--|---------------------------------------|
|                                       |                      |              |      | No treatment (aside from CVD drug) | 10 |                            | Mean:1.97<br>Median<br>SD:<br>SE:0.18<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:<br><0.001                 |  |  |                                       |
| Macan 2006 <sup>40</sup><br>parallel  | Low and/or Moderate  | Warfarin     | NR   | Garlic.                            | 22 | 12 hr fasting blood sample | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:27.9<br>% mean:<br>Median:<br>SD:<br>115.3<br>P:   | Mean:<br>Median:<br>SD:<br>P:<br>0.279                           |  | medium                                |
|                                       |                      |              |      | Placebo                            | 26 |                            | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-4<br>Median:<br>SD:<br>59.4<br>P:                 |  |  |                                       |
| Manuel 2004 <sup>42</sup><br>parallel | At high risk for CHD | Atorvastatin | 20   | Vitamin E.                         | 11 | serum, fasting             | Mean: 0.59<br>Median<br>SD: 0.24<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br>~0.005      | Mean:<br>Median:<br>SD:<br>P:                                    | Data not presented in paper - only combined data for both groups across time | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design               | CHD Risk Category    | CVD drug           | Dose | Supplement/<br>Control | N  | Definition of outcome                     | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|--------------------|------|------------------------|----|---|---|---|--|---|---------------------------------------|
|   |                      |                    |      | Placebo                | 11 |   | Mean:0.75<br>Median<br>SD: 0.37<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:<br>~0.005                 |  | and for groups separately at baseline only. Report states that changes were 'same in both groups (the between-group comparison of change over time was not significant) |                                       |
| Manuel 2004 <sup>42</sup><br>parallel     | At high risk for CHD | Atorvastatin       | 20   | Vitamin E.             | 11 | Triglycerides in non-HDL fraction         | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:                                    |   | medium                                |
|   |                      |                    |      | Placebo                | 11 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                           |  |   |                                       |
| Micheletta 2004 <sup>47</sup><br>Parallel | At high risk for CHD | ASA or ticlopidine | NR   | Vitamin E.             | 8  | fasting plasma (12 hr) taken at 800-900hr | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:                                    | This is not likely usable data and should likely be excluded or authors   | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose | Supplement/<br>Control                                | N  | Definition of outcome         | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|------|---|----|-------------------------------|---|---|---|---|---------------------------------------|
|   |                      |             |      | No treatment (aside from CVD drug)                    | 8  |                               | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                     |   | contacted...Tri glyceride outcome data reported. Study states only baseline data and that 'no changes of cholesterol and triglyceride concentrations were observed at the end of follow-up. Baseline values for triglyceride given for both groups together... (mean +/- SD): 1.55 +/-0.9 |                                       |
| Playford 2003 <sup>58</sup><br>parallel | At high risk for CHD | Fenofibrate | 200  | Coenzyme Q10.<br>200 mg plus<br>200 mg<br>fenofibrate | 18 | measured after<br>14 hr fast; | Mean: 1.4<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>1.2<br>% mean:<br>Median:<br>SD:<br>P:  | Mean:0.1<br>Median:<br>SD:<br>P:<br>0.369 or .001       |   | low-medium                            |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category                      | CVD drug | Dose | Supplement/<br>Control             | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|----------|------|------------------------------------|----|-----------------------|---|---|--|--------------------|---------------------------------------|
|                                       |  |          |      | No treatment (aside from CVD drug) | 17 |                       | Mean:1.3<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:-1.1<br>Median:<br>SD:<br>P:                       |  |                    |                                       |
|                                       |  |          |      | Coenzyme Q10. 200 mg CoQ10 only    | 20 |                       | Mean: 1.9<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-0.1<br>% mean:<br>Median:<br>SD:<br>P:            |  |                    |                                       |
|                                       |  |          |      | Placebo                            | 18 |                       | Mean: 2.4<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.1<br>% mean:<br>Median:<br>SD:<br>P:             |  |                    |                                       |
| Svaneborg 2002 <sup>64</sup> parallel | At low risk for CHD (0-1 risk factors) | ASA      | 100  | Omega-3 (EPA, DHA, or both).       | 12 | used TG PAP           | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.05       | Mean:<br>Median:<br>SD:<br>P: 0.05                               |                    | medium                                |
|                                       |  |          |      | Placebo                            | 6  |                       | Mean:<br>Median 0.9<br>SD:<br>SE:<br>Lower: 0.65<br>Upper:2.42                                      | Mean:<br>Median:<br>SD:<br>P:                           |  |                    |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category           | CVD drug    | Dose  | Supplement/<br>Control             | N  | Definition of outcome  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-----------------------------|-------------|-------|------------------------------------|----|--|---|---|--|--------------------|---------------------------------------|
| Duffy 2001 <sup>20</sup><br>parallel  | Low and/or Moderate         | simvastatin | 10-40 | Vitamin E.                         | 6  |  | Mean: 1.4<br>Median<br>SD: 0.7<br>SE:<br>Lower:<br>Upper:   | Mean:-0.4<br>% mean:<br>Median:<br>SD:<br>P:            | Mean:<br>Median:<br>SD:<br>P:                                    |                    | medium                                |
|                                       |                             |             |       | No treatment (aside from CVD drug) | 7  |  | Mean: 1.2<br>Median<br>SD: 0.5<br>SE:<br>Lower:<br>Upper:   | Mean:-0.1<br>% mean:<br>Median:<br>SD:<br>P:            |  |                    |                                       |
|                                       |                             |             |       | 1000IU Vitamin E                   | 6  |  | Mean: 1.8<br>Median<br>SD: 1.6<br>SE:<br>Lower:<br>Upper:   | Mean:0.2<br>% mean:<br>Median:<br>SD:<br>P:             |  |                    |                                       |
|                                       |                             |             |       | Placebo                            | 7  |  | Mean:1.4<br>Median<br>SD: 0.6<br>SE:<br>Lower:<br>Upper:  | Mean:0.6<br>Median:<br>SD:<br>P:                        |  |                    |                                       |
| Nordøy 2000 <sup>54</sup><br>Parallel | Low and/or mod to high risk | simvastatin | 20    | Omega-3 (EPA, DHA, or both).       | 21 | Measured area under the curve, integrated incremental (AUCi) | Mean: 8.8<br>Median<br>SD: 4.7<br>SE:<br>Lower:<br>Upper:   | Mean:-5.8<br>% mean:<br>Median:<br>SD:<br>P:<br><0.05   | Mean:<br>Median:<br>SD:<br>P:                                    |                    | medium                                |



**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design               | CHD Risk Category           | CVD drug    | Dose | Supplement/<br>Control       | N  | Definition of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|-----------------------------|-------------|------|------------------------------|----|---|---|---|--|---|---------------------------------------|
|   |                             |             |      | Placebo                      | 20 |   | Mean:15.2<br>Median<br>SD: 9.6<br>SE:<br>Lower:<br>Upper:   | Mean:4.5<br>Median:<br>SD:<br>P:<br><0.05               |  |   |                                       |
| Nordøy 2000 <sup>54</sup><br><br>Parallel | Low and/or mod to high risk | simvastatin | 20   | Omega-3 (EPA, DHA, or both). | 21 | Measured as area under the curve, intergrated absolute (AUC)  | Mean: 23.9<br>Median<br>SD: 9.1<br>SE:<br>Lower:<br>Upper:  | Mean:-23<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01    | Mean:<br>Median:<br>SD:<br>P:                                    | Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -10.3 (p=0.003) | medium                                |
|   |                             |             |      | Placebo                      | 20 |   | Mean:36.8<br>Median<br>SD: 18.4<br>SE:<br>Lower:<br>Upper:  | Mean:-9<br>Median:<br>SD:<br>P:                         |  |   |                                       |
| Nordøy 2000 <sup>54</sup><br><br>Parallel | Low and/or mod to high risk | simvastatin | 20   | Omega-3 (EPA, DHA, or both)  | 21 | Measured as triglyceride response: defined as average of the 2 highest postprandial triglyceride concentrations | Mean: 1.77<br>Median<br>SD: 0.8<br>SE:<br>Lower:<br>Upper:  | Mean:-1.37<br>% mean:<br>Median:<br>SD:<br>P:<br><0.001 |  | Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -14.1 (p=0.087) | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category | CVD drug    | Dose  | Supplement/<br>Control             | N  | Definition of outcome  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value        | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-------------------|-------------|-------|------------------------------------|----|--|---|--|--|---|---------------------------------------|
|                                       |                   |             |       | Placebo                            | 20 | minus the baseline concentration                                     | Mean: 2.8<br>Median<br>SD: 1.56<br>SE:<br>Lower:<br>Upper:  | Mean:0.6<br>% mean:<br>Median:<br>SD:<br>P:                    |  | Crude difference between groups in mean change from baseline (omega-3 vs. placebo): -1.96 (p=0.001) |                                       |
| Napoli 1998 <sup>52</sup><br>parallel | Unclear           | Pravastatin | 20-40 | Vitamin E                          | 52 | 12 -14 hr fasting determined enzymatically using Boehringer test kit | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-15<br>Median:<br>SD:<br>4%<br>P:<br><0.05 | Mean:0.013<br>Median:<br>SD:<br>P:<br><0.05                      |   | medium                                |
|                                       |                   |             |       | No treatment (aside from CVD drug) | 56 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>-16<br>Median:<br>SD:<br>4%<br>P:<br><0.05 |  |   |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose | Supplement/<br>Control             | N  | Definition of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value   | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|------|------------------------------------|----|-----------------------|---|---|--|--------------------|---------------------------------------|
| Bordia 1998 <sup>9</sup><br>parallel    | At high risk for CHD | Nitrates    | NR   | Garlic.                            | 30 |                       | Mean: 110.2<br>Median<br>SD:<br>SE:4.2<br>Lower:<br>Upper:  | Mean:-19.8<br>% mean: -15.2<br>Median:<br>SD:<br>P: <0.01 | Mean:10.3<br>Median:<br>SD:<br>P:                                |                    | high                                  |
|   |                      |             |      | Placebo                            | 30 |                       | Mean:120.5<br>Median<br>SD:<br>SE:7.5<br>Lower:<br>Upper:   | Mean:-4.5<br>Median:<br>SD:<br>P:                         |  |                    |                                       |
| Davidson 1997 <sup>15</sup><br>parallel | Unclear              | Simvastatin | 10   | Fish/marine oils.                  | 9  | fasting blood sample  | Mean: 190.6<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean: % mean:-28.8<br>Median:<br>SD:<br>P: <0.01          | Mean:74.5<br>Median:<br>SD:<br>P:                                |                    | Medium                                |
|   |                      |             |      | No treatment (aside from CVD drug) | 10 |                       | Mean:265.1<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean: % mean:-18.5<br>Median:<br>SD:<br>P: <0.05          |  |                    |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug    | Dose   | Supplement/<br>Control             | N  | Definition of outcome         | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value          | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|--------|------------------------------------|----|-------------------------------|---|--|---|--------------------|---------------------------------------|
|   |                      |             |        | Marine Oil                         | 10 |                               | Mean:211.5<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>-25.3<br>Median:<br>SD:<br>P:<br><0.01 |   |                    |                                       |
| Yamamoto 1995 <sup>69</sup><br>parallel | At high risk for CHD | diltiazem   | 90-120 | Omega-3 (EPA, DHA, or both).       | 12 |                               | Mean: 105<br>Median<br>SD:<br>SE:56<br>Lower:<br>Upper:                                       | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                   | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|   |                      |             |        | No treatment (aside from CVD drug) | 10 |                               | Mean:73<br>Median<br>SD:<br>SE:35<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                              |   |                    |                                       |
| McDowell 1994 <sup>44</sup><br>parallel | Unclear              | Simvastatin | 20     | Vitamin E.                         | 8  | overnight fasting measurement | Mean:1.7<br>Median<br>SD: 1.2<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                   | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|   |                      |             |        | Placebo                            | 8  |                               | Mean:1.2<br>Median<br>SD: 0.6<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>Median:<br>SD:<br>P:                              |   |                    |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug           | Dose | Supplement/<br>Control | N  | Definition of outcome                  | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|-------------------|--------------------|------|------------------------|----|--|---|---|--|---|---------------------------------------|
| Howe 1994 <sup>30</sup><br>parallel     | Unclear           | Captopril          | 61   | Fish/marine oils.      | 14 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.4<br>% mean:<br>Median:<br>SD:<br>P:             | Mean:<br>Median:<br>SD:<br>P:<br><0.05                           | the study stated that plasma total cholesterol were unaffected by intervention. no further data provided. | medium                                |
|   |                   |                    |      | Placebo                | 14 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.1<br>2<br>% mean:<br>Median:<br>SD:<br>P:        |  |   |                                       |
|   |                   |                    |      | Fish/marine oils.      | 14 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                |  |   |                                       |
|   |                   |                    |      | Placebo                | 14 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                           |  |   |                                       |
| Paolisso 1992 <sup>57</sup><br>parallel | Unclear           | hydrochlorthiazide | 25   | Magnesium.             | 9  | fasting (overnight) plasma measurement | Mean: 2.33<br>Median<br>SD:<br>SE:0.38<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:                                    | Many other outcomes assessed but not extracted - if not noted elsewhere,                                  | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug                     | Dose   | Supplement/<br>Control             | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results       | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|------------------------------|--|------------------------------------|----|---|---|---|---|--------------------------|---------------------------------------|
|                                       |                      |                              |  | Placebo                            | 9  |   | Mean:2.31<br>Median<br>SD:<br>SE:0.41<br>Lower:<br>Upper:                                     | Mean:<br>Median:<br>SD:<br>P:                     |   | look to JMT's excel file |                                       |
| Kaul 1992 <sup>34</sup><br>parallel   | At high risk for CHD | Calcium channel blocker, ASA | ASA: 150; heparin: 1000 U/d; ca blockers: NR | Fish/marine oils.                  | 58 |   | Mean: 161<br>Median<br>SD: 95.5<br>SE:<br>Lower:<br>Upper:                                    | Mean:<br>% mean:<br>Median:<br>SD:<br>P:<br><0.01 | Mean:<br>Median:<br>SD:<br>P:                           |                          | low-medium                            |
|                                       |                      |                              |  | No treatment (aside from CVD drug) | 49 |   | Mean: 215<br>Median<br>SD: 113.5<br>SE:<br>Lower:<br>Upper:                                   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          |   |                          |                                       |
| Nordøy 2003 <sup>55</sup><br>parallel | Mod and high risk    | atorvastatin                 | 10   | Fish/marine oils.                  | 22 | Blood sample taken after 12 hr fasting, within 6 days of end of study | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>0.04<br>% mean:<br>Median:<br>SD:<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.59                   |                          | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design          | CHD Risk Category | CVD drug             | Dose | Supplement/<br>Control       | N  | Definition of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------|----------------------|------|------------------------------|----|---|---|---|--|--------------------|---------------------------------------|
|                                      |                   |                      |      | Placebo                      | 20 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:0.2<br>6<br>Median:<br>SD:<br>1.71<br>P:           |  |                    |                                       |
| Roth 2009 <sup>60</sup><br>parallel  | Unclear           | fenofibrates by 100% | 130  | Omega-3 (EPA, DHA, or both). | 81 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:-<br>60.8<br>SD:<br>P:       | Mean:7<br>Median:<br>SD:<br>P:0.059                              | P = 0.059          | medium                                |
|                                      |                   |                      |      | Placebo                      | 82 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:-<br>53.8<br>SD:<br>P:                  |  |                    |                                       |
| Isley 2007 <sup>31</sup><br>parallel | Unclear           | niacin               | 325  | Omega-3                      | 7  | measured enzymatically on a Cobas Fara II (Roche) using enzymatic | Mean: 128<br>Median<br>SD: 72<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>-52<br>Median<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                                    |                    | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug          | Dose  | Supplement/<br>Control | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value       | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|-------------------|-------|------------------------|----|---|---|---|---|--------------------|---------------------------------------|
|                                       |                      |                   |       | Placebo                | 8  | reagents and procedures standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention/ National Institutes of Health. | Mean:222<br>Median<br>SD: 102<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>% mean:-17<br>Median<br>SD:<br>P:              |   |                    |                                       |
| Budoff 2004 <sup>10</sup><br>parallel | At high risk for CHD | statins + aspirin | 10-40 | Garlic                 | 9  | Measured after 12 hr fast   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>8.3<br>% mean:<br>Median:<br>SD:<br>42.6<br>P: | Mean:<br>Median:<br>SD:<br>P:<br>0.55                   |                    | medium                                |
|                                       |                      |                   |       | Placebo                | 10 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:29.5<br>Median:<br>SD:<br>95.7<br>P:               |   |                    |                                       |



**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design         | CHD Risk Category   | CVD drug     | Dose | Supplement/<br>Control             | N  | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value                             | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|---|--------------|------|------------------------------------|----|---|---|---|---|--------------------|---------------------------------------|
| Chan 2002 <sup>12</sup><br>parallel | At moderate/ moderately high risk for CHD (2+ risk factors) | atorvastatin | 40   | Fish/marine oils.                  | 11 | collected after an overnight fast (14 h) in a semirecumbent position for all biochemical measurements | Mean: 1.2<br>Median<br>SD:<br>SE:0.17<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>-43<br>Median:<br>SD:<br>3%<br>P:                         | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|                                     |   |              |      | Placebo                            | 13 |   | Mean:1.4<br>Median<br>SD:<br>SE:0.12<br>Lower:<br>Upper:                                      | Mean:<br>% mean:<br>-26<br>Median:<br>SD:<br>P:                               |   |                    |                                       |
| Liu 2003 <sup>37</sup><br>parallel  | Unclear   | simvastatin  | 10   | Fish/marine oils.                  | 19 | Fasting blood samples   | Mean: 1.21<br>Median<br>SD: 0.46<br>SE:<br>Lower:<br>Upper:                                   | Mean:-<br>0.55<br>% mean:-<br>31.2<br>Median:<br>SD:<br>0.58<br>P:<br><0.0001 | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|                                     |   |              |      | No treatment (aside from CVD drug) | 18 |   | Mean:1.4<br>Median<br>SD: 0.75<br>SE:<br>Lower:<br>Upper:                                     | Mean:-<br>0.14<br>Median:<br>SD:<br>0.63<br>P:<br><0.0001                     |   |                    |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category                      | CVD drug                                      | Dose  | Supplement/<br>Control             | N  | Definition of outcome                                | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD / P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|--|---|---|------------------------------------|----|--|---|---|---|---|---------------------------------------|
| Dehmer 1988 <sup>17</sup><br>parallel   | At high risk for CHD                   | aspirin + Dipyridamole + ca channel blockers) | ASA: 325; dipyridamole: 225; Ca blocker: NR | Omega-3 (EPA, DHA, or both).       | 43 | Fasting blood samples; standard automated techniques | Mean: 158<br>Median<br>SD: 42.9<br>SE:<br>Lower:<br>Upper:                                    | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           |   | medium                                |
|   |  |   |   | No treatment (aside from CVD drug) | 39 |  | Mean:137<br>Median<br>SD: 36.8<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>Median:<br>SD:<br>P:                     |   |   |                                       |
| Desideri 2003 <sup>18</sup><br>parallel | At low risk for CHD (0-1 risk factors) | Simvastatin, Bezafibrate                      | simvastatin: 40; Bezafibrate: 800           | Vitamin E.                         |    | 12 hr fasting at 800hr - serum                       | Mean: 1.1<br>Median<br>SD: 0.1<br>SE:<br>Lower:<br>Upper:                                     | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           | I have assumed no losses to follow-up although I did not see this explicitly stated | medium                                |
|   |  |   |   | No treatment (aside from CVD drug) |    |  | Mean:1.1<br>Median<br>SD: 0.1<br>SE:<br>Lower:<br>Upper:                                      | Mean:<br>Median:<br>SD:<br>P:                     |   |   |                                       |
| Wolf 2006 <sup>68</sup><br>crossover    | Low and/or Moderate                    | ASA   | 500   | ginkgo biloba                      | 50 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:          | Mean:<br>Median:<br>SD:<br>P:                           | Study states that: Laboratory findings in all subjects were un-remarkable           | low-medium                            |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design                 | CHD Risk Category    | CVD drug    | Dose  | Supplement/<br>Control             | N  | Definition of outcome            | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results  | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|-------------|-------|------------------------------------|----|----------------------------------|---|---|--|---|---------------------------------------|
|   |                      |             |       | Placebo                            | 50 |                                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                           |  | and did not indicate any differences between the treatment groups.  |                                       |
| De Caterina 2002 <sup>16</sup><br>crossover | At high risk for CHD | simvastatin | 10-40 | Vitamin E                          | NR |                                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:                                    | Values are presented in graphs, but difficult to read. Statement that "Neither LDL cholesterol nor triglycerides were affected by Vitamin E." | high                                  |
|   |                      |             |       | No treatment (aside from CVD drug) | NR |                                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:28.5<br>% mean:<br>Median:<br>SD:<br>P:            |  |   |                                       |
| Balestrieri 1996 <sup>4</sup><br>crossover  | Low and/or Moderate  | Simvastatin | 10-40 | Fish/marine oils                   | 14 | 12 hour fast, anti-tubercal vein | Mean: 90<br>Median<br>SD: 26<br>SE:<br>Lower:<br>Upper:   | Mean:-7<br>% mean:<br>Median:<br>SD:<br>P:              | Mean:<br>Median:<br>SD:<br>P:                                    |   | medium                                |
|   |                      |             |       | Placebo                            | 14 |                                  |   | Mean:111<br>Median<br>SD: 58<br>SE:<br>Lower:<br>Upper: |  |   |                                       |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design              | CHD Risk Category    | CVD drug    | Dose     | Supplement/<br>Control | N  | Definition of outcome            | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results           | Overall Risk of Bias (ROB) Assessment |
|--|----------------------|-------------|----------|------------------------|----|----------------------------------|---|---|--|------------------------------|---------------------------------------|
| Paolisso 1995 <sup>56</sup><br>crossover | At high risk for CHD | nifedipine  | 88       | Vitamin E              | 30 | Fasting at end of 2 mo treatment | Mean: 1.07<br>Median<br>SD:<br>SE:0.03<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:<br><0.05                           |                              | medium                                |
|  |                      |             |          | Placebo                | 30 |                                  | Mean:1.34<br>Median<br>SD:<br>SE:0.06<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                           |  |                              |                                       |
| Hansen1993 <sup>29</sup><br>crossover    | Low and/or Moderate  | lovastatin  | 40       | Fish/marine oils       | 14 |                                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-41<br>% mean:<br>Median:<br>SD:<br>P:             | Mean:<br>Median:<br>SD:<br>P:                                    |                              | medium                                |
|  |                      |             |          | Placebo                | 14 |                                  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:-18<br>Median:<br>SD:<br>P:                        |  |                              |                                       |
| Avogaro 1974 <sup>3</sup><br>Crossover   | Unclear              | propranolol | 20 or 60 | Niacin                 | 10 | at end of 1 mo treatment         | Mean:<br>122.4<br>Median<br>SD:<br>SE:34.26<br>Lower:<br>Upper:                                     | Mean:-<br>12.6<br>% mean:<br>Median:<br>SD:<br>P:       | Mean:-8.4<br>Median:<br>SD:<br>P:                                | Type II hyperlipoproteinemia | high                                  |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design             | CHD Risk Category   | CVD drug    | Dose              | Supplement/<br>Control             | N  | Definition of outcome    | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results           | Overall Risk of Bias (ROB) Assessment |
|---|---------------------|-------------|-------------------|------------------------------------|----|--------------------------|---|---|--|------------------------------|---------------------------------------|
|   |                     |             |                   | No treatment (aside from CVD drug) | 10 |                          | Mean:130.8<br>Median<br>SD:<br>S E:36.92<br>Lower:<br>Upper:  | Mean:-4.2<br>Median:<br>SD:<br>P:                       |  |                              |                                       |
| Avogaro 1974 <sup>3</sup><br>Crossover  | Unclear             | propranolol | 20 or 60          | Niacin                             | 10 | at end of 1 mo treatment | Mean: 240<br>Median<br>SD:<br>SE:150.02<br>Lower:<br>Upper:   | Mean:-119.83<br>% mean:<br>Median:<br>SD:<br>P:         | Mean:-49.83<br>Median:<br>SD:<br>P:                              | Type IV hyperlipoproteinemia | high                                  |
|   |                     |             |                   | No treatment (aside from CVD drug) | 10 |                          | Mean:289.8<br>3<br>Median<br>SD:<br>SE150.9:<br>Lower:<br>Upper:                                    | Mean:-70<br>Median:<br>SD:<br>P:                        |  |                              |                                       |
| Mueller 1991 <sup>51</sup><br>crossover | Low and/or Moderate | aspirin     | 325 - single dose | Fish/marine oils                   | 12 | Fasting                  | Mean:<br>82.58<br>Median<br>SD: 40.98<br>SE:<br>Lower:<br>Upper:                                    | Mean:-31.5<br>% mean:<br>Median:<br>SD:<br>P:           | Mean:<br>Median:<br>SD:<br>P:                                    |                              | medium                                |

**Evidence Table 88. KQ2—Continuous data—Triglycerides (continued)**

| Author Year<br>Study Design          | CHD Risk Category   | CVD drug    | Dose | Supplement/<br>Control | N  | Definition of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD / P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Summary of Results                                | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---------------------|-------------|------|------------------------|----|---|---|---|--|---|---------------------------------------|
|                                      |                     |             |      | Placebo                | 12 |   | Mean:112.5<br>Median<br>S67.37D:<br>SE:<br>Lower:<br>Upper:   | Mean:-<br>1.58<br>Median:<br>SD:<br>P:                  |  |   |                                       |
| Maki 2008 <sup>41</sup><br>crossover | Low and/or Moderate | simvastatin | 20   | Omega-3                | 39 | 10-14 hour fast; Centers for Disease Control and Prevention lipid standardization program | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                | Mean:<br>Median:<br>SD:<br>P:<br><0.001                          | The IQRs reported are actually ranges (low-high). | medium                                |
|                                      |                     |             |      | Placebo                | 40 |   | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                           |  |   |                                       |

**Evidence Table 89. KQ2—Continuous data—Activated partial thromboplastin time (aPTT)**

| Author Year<br>Study Design                 | CHD Risk<br>Category      | CVD drug    | Dose | Supplement/<br>Control | N  | Definition<br>of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/%<br>change from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk<br>of Bias (ROB)<br>Assessment |
|---|---------------------------|-------------|------|------------------------|----|-----------------------------|---|--|---|-----------------------|---|
| Wolf 2006 <sup>68</sup><br>crossover        | Low<br>and/or<br>Moderate | ASA         | 500  | ginkgo biloba          | 50 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                       | Mean:<br>Median:<br>SD:<br>P:   |                       | medium                                      |
|   |                           |             |      | Placebo                | 50 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean:<br>Median:<br>SD:<br>P:                                  |   |                       |   |
| McKenney<br>2006 <sup>45</sup><br>Crossover | Low<br>and/or<br>Moderate | simvastatin | 80   | Omega-3                | 24 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean: -0.3<br>% mean:<br>Median:<br>SD: 1.2<br>P:              | Mean:<br>Median:<br>SD:<br>P:   |                       | medium                                      |
|   |                           |             |      | No<br>treatment        | 23 |                             | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:   | Mean: -0.4<br>Median:<br>SD: 1.2<br>P:                         |   |                       |   |

**Evidence Table 90. KQ2—Continuous data—Ejection fraction**

| Author Year<br>Study Design | CHD Risk Category    | CVD drug   | Dose | Supplement/. Control | N  | Definition of outcome  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Summary of Results | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|----------------------|--|------|----------------------|----|------------------------|---|---|---|--------------------|---------------------------------------|
| 36585                       | At high risk for CHD | ACE inhibitors (no description); furosemide; digoxin, also hydralazine and/or nitrates | NR   | Coenzyme Q10         | 27 | at 12 wks of treatment | Mean: 31<br>Median<br>SD: 9<br>SE:<br>Lower:<br>Upper:  | Mean:5<br>% mean:<br>Median:<br>SD:<br>P:       | Mean:<br>Median:<br>SD:<br>P:                           |                    | medium                                |
|                             |                      |  |      | Placebo              | 27 |                        | Mean:31<br>Median<br>SD: 9<br>SE:<br>Lower:<br>Upper:   | Mean:5<br>Median:<br>SD:<br>P:                  |   |                    |                                       |



**Evidence Table 91. KQ2—Continuous data—Lipoprotein A**

| Author Year<br>Study Design                | CHD Risk<br>Category      | CVD drug              | Dose      | Supplement/<br>Control | N  | Definition<br>of<br>outcome                | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower<br>limit (IQR,<br>95% CI)<br>Upper<br>Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD /<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary<br>of Results | Overall Risk of Bias<br>(ROB) Assessment |
|--|---------------------------|-----------------------|-----------|------------------------|----|--|--|--|---|-----------------------|--|
| Balestrieri 1996 <sup>4</sup><br>crossover | Low<br>and/or<br>Moderate | Simvastatin<br>statin | 10-<br>40 | Fish/marine<br>oils    | 14 | 12 hour<br>fast, anti-<br>tubectal<br>vein | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>% mean:<br>Median:<br>SD:<br>P:                           | Mean:<br>Median:<br>SD:<br>P:   |                       | medium                                   |
|  |                           |                       |           | Placebo                | 14 |  | Mean:<br>Median<br>SD:<br>SE:<br>Lower:<br>Upper:  | Mean:<br>Median:<br>SD:<br>P:                                      |   |                       |  |

**Evidence Table 92. KQ2—Continuous data—PR interval**

| Author Year<br>Study Design    | CHD<br>Risk<br>Category                            | CVD<br>drug | Dose | Supplement/<br>Control                   | N | Definition of<br>outcome            | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper<br>Limit (IQR,<br>95% CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Summary of<br>Results | Overall Risk of Bias<br>(ROB) Assessment |
|--------------------------------|--|-------------|------|--|---|-------------------------------------|---|---|---|-----------------------|--|
| Tankanow<br>2003 <sup>65</sup> | At low<br>risk for<br>CHD (0-1<br>risk<br>factors) | digoxin     | 0.25 | Hawthorn                                 | 8 | PR Interval<br>(ECG<br>measurement) | Mean: 152<br>Median<br>SD: 14<br>SE:<br>Lower:<br>Upper:  | Mean:1<br>% mean:<br>Median:<br>SD:13<br>P:                       | Mean:<br>Median:<br>SD:<br>P:   |                       | medium                                   |
|                                |  |             |      | No treatment<br>(aside from<br>CVD drug) | 8 |                                     | Mean:156<br>Median<br>SD: 24<br>SE:<br>Lower:<br>Upper:   | Mean:6.5<br>Median:<br>SD:11<br>P:                                |   |                       |  |

**Evidence Table 93. KQ2—Dichotomous outcomes**

| Author Year<br>Study Design                    | Definition of outcome (if relevant)  | CHD Risk Category                      | CVD drug (dose)               | Group 1: Name (supplement)   | N1  | N1 with event | Group 2: Name                      | N2  | N2 with event | Estimates of Group Differences     | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|--|-------------------------------|------------------------------|-----|---------------|------------------------------------|-----|---------------|------------------------------------|---|---------------------------------------|
| Bays 2010 <sup>6</sup><br>parallel             | Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). <160 mg/dL, <130 mg/dL, or <100 mg/dL | Unclear                                | Atorvastatin (10-40mg/d)      | Omega-3 (EPA, DHA, or both). | 105 | 90            | Placebo                            | 106 | 97            | NR                                 | p value =0.20   | Medium                                |
| Bays 2010 <sup>6</sup><br>parallel             | non-HDL-C. <190 mg/dL, <160 mg/dL, or <130 mg/dL   | Unclear                                | Atorvastatin (10-40mg/d)      | Omega-3 (EPA, DHA, or both). | 106 | 94            | Placebo                            | 107 | 94            | NR                                 | p value >0.99   | Medium                                |
| Ferraro 2009 <sup>22</sup><br>parallel         | Proteinuria reduction; % of patients achieving reduction of $\geq$ 50% from baseline                       | Unclear                                | ramipril (10mg/d)             | Omega-3 (EPA, DHA, or both). | 15  | 12            | No treatment (aside from CVD drug) | 15  | 3             | 4 (4.1; adjusted event risk ratio) | 5 (33.3%) of ptas in tx group vs. 0 in control showed a completed negativization of proteinuria (p=0.042) | Medium                                |
| Mohammed Abdul 2008 <sup>49</sup><br>Crossover | International normalized ratio (INR) (above/below threshold). Indicate threshold. INR > 4                  | At low risk for CHD (0-1 risk factors) | Warfarin (26mg - single dose) | Garlic                       | 12  | 0             | No treatment (aside from CVD drug) | 12  | 0             | NR                                 |   | Medium                                |

**Evidence Table 93. KQ2—Dichotomous outcomes (continued)**

| Author Year<br>Study Design              | Definition of outcome (if relevant)   | CHD Risk Category   | CVD drug (dose)                     | Group 1: Name (supplement)                      | N1 | N1 with event | Group 2: Name                      | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|---|---------------------|-------------------------------------|---|----|---------------|------------------------------------|----|---------------|--------------------------------|--|---------------------------------------|
| Sconce 2007 <sup>61</sup><br>Parallel    | INR; Number achieving improved control of anticoagulation   | Unclear             | Warfarin (3.8-4.4 vs. 3.3-3.4 mg/d) | Vitamin K. Other details if needed (e.g. dose). | 35 | 33            | Placebo                            | 33 | 24            | NR                             | Some data (<1% in each arm) omitted from analysis due to known confounding factors | Medium                                |
| Sconce 2007 <sup>61</sup><br>Parallel    | INR; Number reaching target for stable anticoagulation (SD of INR values below 0.5)   | Unclear             | Warfarin (3.8-4.4 vs. 3.3-3.4 mg/d) | Vitamin K. Other details if needed (e.g. dose). | 35 | 19            | Placebo                            | 33 | 7             | NR                             | Some data (<1% in each arm) omitted from analysis due to known confounding factors | Medium                                |
| McKenney 2006 <sup>45</sup><br>Crossover | Platelet aggregability (above/below threshold). Indicate outcome and threshold. adenosine diphosphate, collagen; threshold not reported | Low and/or Moderate | Simvastatin (20mg/d)                | Omega-3 (EPA, DHA, or both)                     | NR | 0             | No treatment (aside from CVD drug) | NR | 0             | NR                             |  | Medium                                |
| Bender 1998 <sup>8</sup><br>Parallel     | Hypertension (HTN), new or worsening (e.g. need for change in therapy)  | Unclear             | warfarin (NR)                       | Omega-3 (EPA, DHA, or both).                    | 6  | 0             | Placebo                            | 5  | 0             | NR                             |  | High                                  |
| Bender 1998 <sup>8</sup><br>Parallel     | Hypotension   | Unclear             | warfarin (NR)                       | Omega-3 (EPA, DHA, or both).                    | 6  | 0             | Placebo                            | 5  | 0             | NR                             |  | High                                  |

**Evidence Table 93. KQ2—Dichotomous outcomes (continued)**

| Author Year<br>Study Design         | Definition of outcome (if relevant)                                    | CHD Risk Category | CVD drug (dose)         | Group 1: Name (supplement)   | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|--|-------------------|-------------------------|------------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Roth 2009 <sup>60</sup><br>parallel | Hypertension (HTN), new or worsening (e.g. need for change in therapy) | Unclear           | fenofibrates (130 mg/d) | Omega-3 (EPA, DHA, or both). | 84 | 2             | Placebo       | 83 | 2             | NR                             |                     | Medium                                |

**Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT)**

| Author Year<br>Study Design                | CHD Risk<br>Category                           | CVD drug     | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N   | Definition of<br>outcome/ Unit of<br>outcome                    | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Additional<br>Comments   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|--|--------------|-----------------------|------------------------|-----|---|---|--|---|--|--|
| Lee 2008 <sup>36</sup><br>Parallel         | At high<br>risk for<br>CHD                     | Warfarin     | 3.5                   | Ginseng                | 12  | NR<br>Unit: U/L   | Mean: 22.09<br>SD: 7.19   | Mean:0.18  | NR  | There were no<br>statistically<br>significant<br>differences<br>between the two<br>groups. | N/A  |
|  |  |              |                       | No treatment           | 13  |   | Mean:23.15<br>SD: 5.61  | Mean:1.8   |   |  |  |
| Mabuchi<br>2007 <sup>39</sup><br>Parallel  | Unclear  | Atorvastatin | 10                    | CoQ10                  | 24  | NR<br>Unit: IU/L  | Mean: 31.6<br>SD: 26.1  | Mean:18.4<br>P: 0.0219   | NR  | There were no<br>significant<br>differences<br>between the two<br>groups.                  | Medium   |
|  |  |              |                       | Placebo                | 25  |   | Mean:32.6<br>SD: 14.9   | Mean:21.6<br>P:0.0147  |   |  |  |
| Davidson<br>2007 <sup>14</sup><br>Parallel | Unclear  | Simvastatin  | 40                    | Omega 3                | 122 | NR<br>Unit: U/L   | NR  | Mean:5.7   | Mean:6.4<br>P: <0.001   | N/A  | Medium   |
|  |  |              |                       | Placebo                | 132 |   | NR  | Mean: -0.7   |   |  |  |
| Nordøy<br>2000 <sup>54</sup><br>Parallel   | Mixed:<br>Low<br>and/or<br>mod to<br>high risk | Simvastatin  | 20                    | Omega 3                |     | laboratory tests<br>performed for liver<br>function<br>Unit: NR | NR  | NR   | NR  | No significant<br>changes were<br>observed in serum<br>ALT                                 | Medium   |
|  |  |              |                       | Placebo                |     |   | NR  | NR   |   |  |  |

**Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT) (continued)**

| Author Year<br>Study Design              | CHD Risk<br>Category       | CVD drug             | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N  | Definition of<br>outcome/ Unit of<br>outcome                  | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Additional<br>Comments   | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|--|----------------------------|----------------------|-----------------------|------------------------|----|---|---|---|---|--|--|
| Napoli<br>1998 <sup>52</sup><br>Parallel | Unclear                    | Pravastatin          | 20-40                 | Vitamin E              |    | alanine<br>aminotransferase<br><br>Unit: NR                   | NR  | NR  | NR  | No differences in routine laboratory tests or adverse events were registered during the study. In particular, there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium   |
|  |                            |                      |                       | No treatment           |    |   | NR  | NR  |   |  |  |
| Budoff<br>2004 <sup>10</sup><br>Parallel | At high<br>risk for<br>CHD | Statins +<br>aspirin | 10-40                 | Garlic                 | 9  | Measured after 12<br>hr fast<br><br>Unit: mg/dl               | NR  | Mean:0.11<br>SD:7.25  | P:0.5876  | N/A  | Medium   |
|  |                            |                      |                       | Placebo                | 10 |   | NR  | Mean: -2.6<br>SD:13   |   |  |  |
| Lui<br>2003 <sup>37</sup><br>Parallel    | Unclear                    | Simvastatin          | 10                    | Omega3                 | 19 | Narratively<br>reported for post<br>treatment<br><br>Unit: NR | NR:   | NR  | NR  | N/A  | Medium   |
|  |                            |                      |                       | Control                | 18 |   | NR  | NR  |   |  |  |

**Evidence Table 94. KQ3—Continuous Alanine transaminase (ALT) (continued)**

| Author Year<br>Study Design             | CHD Risk<br>Category                | CVD drug | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N | Definition of<br>outcome/ Unit of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Additional<br>Comments  | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------------------------|----------|-----------------------|------------------------|---|--|---|---|---|---|--|
| Wolf<br>2008 <sup>68</sup><br>Crossover | Mixed:<br>Low<br>and/or<br>Moderate | ASA      | 500                   | Ginkgo biloba          |   | NR<br><br>Unit: NR                           | NR  | NR  | NR  | Study states that:<br>Laboratory findings<br>in all subjects were<br>un-remarkable and<br>did not indicate any<br>differences<br>between the<br>treatment groups. | Medium   |
|   |                                     |          |                       |                        |   |  | NR  | NR  |   |   |  |



**Evidence Table 95. KQ3—Continuous—Alkaline phosphatase**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug     | CVD Dose (mg/d) | Supplement/ Control  | N  | Definition of outcome/<br>Unit of outcome | Post treatment Mean/<br>(Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/<br>% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians SD/<br>P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|--------------|-----------------|----------------------|----|---|--|---|---|---|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br>Parallel  | Unclear              | Atorvastatin | 10              | Co Q10               | 24 | NR<br>Unit: IU/L                          | Mean: 256<br>SD: 76  | NR  | P: 0.3409   | There's no significant differences between groups (p=0.5943). | Medium                                |
|   |                      |              |                 | Placebo              | 25 |   | Mean:235<br>SD: 58   | NR  |   |   |                                       |
| Playford 2003 <sup>58</sup><br>Parallel | At high risk for CHD | Fenofibrate  | 200             | Co Q10 + Fenofibrate | 18 | NR<br>Unit: U/L                           | Mean: 52.5<br>Lower: 44.0<br>Upper: 62.6   | NR  | NR  | N/A   | Low-medium                            |
|   |                      |              |                 | No Treatment         | 17 |   | Mean:58.5<br>Lower: 52.7<br>Upper:65.1   | NR  |   |   |                                       |
|   |                      |              |                 | CoQ 10               | 20 |   | NR   | NR  |   |   |                                       |
|   |                      |              |                 | Placebo              | 18 |   | NR   | NR  |   |   |                                       |

**Evidence Table 95. KQ3—Continuous—Alkaline phosphatase (continued)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug          | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|-------------------|-----------------|---------------------|----|--|---|--|---|--|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>Parallel | Unclear              | Pravastatin       | 20-40           | Vitamin E           |    | NR<br>Unit: NR                         | NR  | NR   | NR  | No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
|                                       |                      |                   |                 | No Treatment        |    |  | NR  | NR   |   |  |                                       |
| Budoff 2004 <sup>10</sup><br>Parallel | At high risk for CHD | Statins + aspirin | 10-40           | Garlic              | 9  | NR<br>Unit: mg/dl                      | NR  | Mean:4<br>Median:<br>SD:12.1                     | P: 0.1452   | N/A  | Medium                                |
|                                       |                      |                   |                 | Placebo             | 10 |  | NR  | Mean:-<br>10.1<br>SD:25.2                        |   |  |                                       |

**Evidence Table 95. KQ3—Continuous—Alkaline phosphatase (continued)**

| Author Year<br>Study Design          | CHD Risk Category          | CVD drug | CVD Dose (mg/d) | Supplement/ Control | N | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|----------------------------|----------|-----------------|---------------------|---|--|---|--|---|--|---------------------------------------|
| Wolf 2008 <sup>68</sup><br>Crossover | Mixed: Low and/or Moderate | ASA      | 500             | Gingko biloba       |   | NR<br>Unit: NR                         | NR  | NR   | NR  | Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups. | Low-medium                            |
|                                      |                            |          |                 |                     |   |  | NR  | NR   |   |  |                                       |

**Evidence Table 96. KQ 3—Continuous Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome—Hemoglobin**

| Author Year<br>Study Design           | CHD Risk Category | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/<br>Unit of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95% CI)<br>Upper Limit<br>(IQR, 95% CI) | Mean change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-------------------|-------------|-----------------|---------------------|----|---|---|--|--|--|---------------------------------------|
| Macan 2006 <sup>40</sup><br>Parallel  | Unclear           | Warfarin    | NR              | Garlic              | 22 | NR<br>Unit: g/dl                          | NR  | Mean:-0.2<br>SD:0.6  | NR   | p-value for comparison of changes of mean from baseline between two groups: 0.210  | Medium                                |
|                                       |                   |             |                 | Placebo             | 26 |   | NR  | Mean:0.0<br>SD:0.8   |  |  |                                       |
| Napoli 1998 <sup>52</sup><br>Parallel | Unclear           | Pravastatin | 20-40           | Vitamin E           |    | NR<br>Unit: NR                            | NR  | NR   | NR   | No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
|                                       |                   |             |                 | No Treatment        |    |   | NR  | NR   |  |  |                                       |

**Evidence Table 96. KQ 3—Continuous Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome—Hemoglobin (continued)**

| Author Year<br>Study Design            | CHD Risk Category          | CVD drug   | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/<br>Unit of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--|----------------------------|------------|-----------------|---------------------|----|---|---|---|--|--|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel     | At high risk for CHD       | Warfarin   | 3.5             | Ginseng             | 12 | NR<br>Unit: g/dl                          | Mean: 13.1<br>SD: 1.03  | Mean: -0.25   | NR   | There were no statistically significant differences between the ginseng group and control group.   | N/A                                   |
|  |                            |            |                 | No Treatment        | 13 |   | Mean:14.05<br>SD: 1.41  | Mean:-0.26  |  |  |                                       |
| Wolf 2008 <sup>68</sup><br>Crossover   | Mixed: Low and/or Moderate | ASA        | 500             | Gingko biloba       |    | NR<br>Unit: NR                            | NR  | NR  | NR   | Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups. | Low-medium                            |
|  |                            |            |                 |                     |    |   | NR  | NR  |  |  |                                       |
| Hansen 1993 <sup>29</sup><br>Crossover | Mixed: Low and/or Moderate | Lovastatin | 40              | Omega-3             | 14 | NR<br>Unit: % change                      | NR  | % Mean: 0<br>SD: 1<br>P: NS                           | NR   | N/A  | Medium                                |
|  |                            |            |                 | No treatment        | 14 |   | NR  | % Mean: 0<br>SD: 1<br>P: NS                           |  |  |                                       |

**Evidence Table 97. KQ 3—Continuous Aspartate aminotransferase (AST)**

| Author Year<br>Study Design             | CHD Risk Category                  | CVD drug          | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome                    | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|---|------------------------------------|-------------------|-----------------|---------------------|----|---|---|---|---|--|---------------------------------------|
| Nordøy 2000 <sup>54</sup><br>Parallel   | Mixed: Low and/or mod to high risk | Simvastatin       | 20              | Omega-3             |    | laboratory tests performed for liver function<br>Unit: NR | NR  | NR  | NR  | no significant changes were observed in serum AST                            | Medium                                |
|   |                                    |                   |                 | Placebo             |    |   | NR  | NR  |   |  |                                       |
| Napoli 1998 <sup>52</sup><br>Parallel   | Unclear                            | Pravastatin       | 20-40           | Vitamin E           |    | NR<br>Unit: NR  | NR  | NR  | NR  |  | Medium                                |
|   |                                    |                   |                 | No Treatment        |    |   | NR  | NR  |   |  |                                       |
| McDowell 1994 <sup>44</sup><br>Parallel | Unclear                            | Simvastatin       | 20              | Vitamin E           | 8  | Serum levels<br>Unit: NR                                  | NR  | NR  | NR  | report states 'there was no change in serum levels of aspartate transaminase | Medium                                |
|   |                                    |                   |                 | Placebo             | 8  |   | NR  | NR  |   |  |                                       |
| Budoff 2004 <sup>10</sup><br>Parallel   | At high risk for CHD               | Statins + aspirin | 10-40           | Garlic              | 9  | Measured after 12 hr fast<br>Unit: mg/dl                  | NR  | Mean:1.89<br>SD:7.85                            | P: 0.262  | N/A  | Medium                                |
|   |                                    |                   |                 | Placebo             | 10 |   | NR  | Mean:-4.6<br>SD:15                              |   |  |                                       |
| Lui 2003 <sup>37</sup><br>Parallel      | Unclear                            | Simvastatin       | 10              | Omega-3             | 19 | narratively reported for post treatment<br>Unit: U/L      | NR  | NR  | NR  | N/A  | Medium                                |
|   |                                    |                   |                 | No Treatment        | 18 |   | NR  | NR  |   |  |                                       |

**Evidence Table 97. KQ 3—Continuous Aspartate aminotransferase (AST) (continued)**

| Author Year<br>Study Design             | CHD Risk Category          | CVD drug     | CVD Dose (mg/d) | Supplement/ Control | N   | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|---|----------------------------|--------------|-----------------|---------------------|-----|--|---|---|---|--|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel      | At high risk for CHD       | Warfarin     | 3.5             | Ginseng             | 12  | NR<br>Unit: U/L                        | Mean: 24.45<br>SD: 7.10   | Mean:-1.10                                      | NR  | There were no statistically significant differences between the two groups.  | N/A                                   |
|   |                            |              |                 | No Treatment        | 13  |  | Mean:26.88<br>SD: 7.8   | Mean:1.69                                       |   |  |                                       |
| Mabuchi 2007 <sup>39</sup><br>Parallel  | Unclear                    | Atorvastatin | 10              | Co Q10              | 24  | NR<br>Unit: IU/L                       | Mean: 28.8<br>SD: 13.4  | % mean: 12.5<br>P:0.0205                        | NR  | There were no significant differences between the two groups.  | Medium                                |
|   |                            |              |                 | Placebo             | 25  |  | Mean:27.9<br>SD: 7.4  | % mean: 10.7<br>P:0.0184                        |   |  |                                       |
| Davidson 2007 <sup>14</sup><br>Parallel | Unclear                    | Simvastatin  | 40              | Omega-3             | 122 | NR<br>Unit: U/L                        | NR  | Mean:1.9  | Mean: 1.7<br>P: <0.032                                  | N/A  | Medium                                |
|   |                            |              |                 | Placebo             | 132 |  | NR  | Mean:0.2  |   |  |                                       |
| Wolf 2008 <sup>68</sup><br>Crossover    | Mixed: Low and/or Moderate | ASA          | 500             | Gingko biloba       |     | NR<br>Unit: NR                         | NR  | NR  | NR  | Study states that: Laboratory findings in all subjects were un-remarkable and did not indicate any differences between the treatment groups. | Low-medium                            |
|   |                            |              |                 |                     |     |  | NR  | NR  |   |  |                                       |

**Evidence Table 98. KQ 3—Continuous Blood urea nitrogen (BUN)**

| Author Year<br>Study Design           | CHD Risk Category    | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome / Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|----------------------|-------------|-----------------|---------------------|----|---|---|---|---|---|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel    | At high risk for CHD | Warfarin    | 3.5             | Ginseng             | 12 | NR<br>Unit: mg/dl                       | Mean:9.45<br>SD: 5.16   | Mean:-2.28                                      | NR  | There were no statistically significant differences between the two groups.   | N/A                                   |
|                                       |                      |             |                 | No Treatment        | 13 |   | Mean:13.46<br>SD: 4.44  | Mean:0.46                                       |   |   |                                       |
| Napoli 1998 <sup>52</sup><br>Parallel | Unclear              | Pravastatin | 20-40           | Vitamin E           |    | NR<br>Unit: NR                          | NR  | NR  | NR  | No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
|                                       |                      |             |                 | No Treatment        |    |   | NR  | NR  |   |   |                                       |



**Evidence Table 99. KQ 3—Continuous CK or CPK**

| Author Year<br>Study Design            | CHD Risk Category        | CVD drug   | CVD Dose (mg/d) | Supplement/ Control                  | N  | Definition of outcome / Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--|--------------------------|--|-----------------|--------------------------------------|----|---|---|--|---|--|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br>Parallel | Unclear                  | Atorvastatin   | 10              | Co Q10                               | 24 | NR<br>Unit: IU/L                        | Mean: 145<br>SD: 73   | %<br>mean:14.2<br>P:0.2423                       | NR  | There's no significant difference between groups (p=1182)                        | Medium                                |
|  |                          |  |                 | Placebo                              | 25 |   | Mean:192<br>SD: 196   | %<br>mean:23.9<br>P:0.1081                       |   |  |                                       |
| Young 2007 <sup>70</sup><br>Parallel   | Mixed: Mod and high risk | Simvastatin  | 10-40           | Co Q10                               | 22 | NR<br>Unit: U/L                         | NR  | NR   | P:0.85  | No difference in groups (p=0.85)   | Medium                                |
|  |                          |  |                 | Co Q10                               | 22 |   | NR  | NR   |   |  |                                       |
| Caso 2007 <sup>11</sup><br>Parallel    | Unclear                  | Simvastatin (22);<br>Atorvastatin (7);<br>Pravastatin (2);<br>Lovastatin (1) | Varying Doses   | Co Q10                               | 18 | Fasting<br>Unit: U/L                    | Mean: 157<br>SE:23  | NR   | NR  | The report states 'there was no change in serum levels of aspartate transaminase | Low                                   |
|  |                          |  |                 | Other dietary supplement – Vitamin E | 14 |   | Mean:103<br>SE:14   | NR   |   |  |                                       |

**Evidence Table 99. KQ 3—Continuous CK or CPK (continued)**

| Author Year Study Design           | CHD Risk Category    | CVD drug     | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome / Unit of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|----------------------|--------------|-----------------|---------------------|----|---|---|--|---|---|---------------------------------------|
| Manuel 2004 <sup>42</sup> Parallel | At high risk for CHD | Atorvastatin | 20              | Vitamin E           | 11 | NR<br>Unit: U/L                         | NR  | Mean:1.89<br>SD:7.85                             | NR  | Creatine phosphokinase tended to increase in both groups and to the same extent (from 132 ± 69 U/L before treatment to 136 ± 70 U/L after 3 months and 171 ± 113 U/L after 6 months, P = 0.07 when comparing inclusion and 6 months). | Medium                                |
|                                    |                      |              |                 | Placebo             | 11 |   | NR  | Mean:-4.6<br>SD:15                               |   |   |                                       |

**Evidence Table 99. KQ 3—Continuous CK or CPK (continued)**

| Author Year Study Design             | CHD Risk Category | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome / Unit of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------|-------------|-----------------|---------------------|----|---|---|--|---|--|---------------------------------------|
| Napoli 1998 <sup>52</sup> Parallel   | Unclear           | Pravastatin | 20-40           | Vitamin E           | 19 | NR<br>Unit: NR                          | NR  | NR   | NR  | ..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
|                                      |                   |             |                 | No Treatment        |    |   | NR  | NR   |   |  |                                       |
| McDowell 1994 <sup>44</sup> Parallel | Unclear           | Simvastatin | 20              | Vitamin E           | 8  | NR<br>Unit: NR                          | Mean: 24.45<br>SD: 7.10   | Mean:-1.10                                       | NR  | Study reports: "There was no change in serum levels of...creatinine kinase   | Medium                                |
|                                      |                   |             |                 | Placebo             | 8  |   | Mean:26.88<br>SD: 7.8   | Mean:1.69  |   |  |                                       |

**Evidence Table 99. KQ 3—Continuous CK or CPK (continued)**

| Author Year Study Design        | CHD Risk Category | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome / Unit of outcome             | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|---------------------------------|-------------------|-------------|-----------------|---------------------|----|---|---|--|---|---------------------|---------------------------------------|
| Lui 2003 <sup>37</sup> Parallel | Unclear           | Simvastatin | 10              | Omega-3             | 19 | narratively reported for post treatment<br>Unit: NR | Mean: 28.8<br>SD: 13.4  | % mean: 12.5<br>P:0.0205                         | NR  | N/A                 | Medium                                |
|                                 |                   |             |                 | No Treatment        | 18 |   | Mean:27.9<br>SD: 7.4  | % mean: 10.7<br>P:0.0184                         |   |                     |                                       |

**Evidence Table 100.KQ 3—Continuous Creatinine**

| Author Year<br>Study Design           | CHD Risk Category                  | CVD drug            | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome / Unit of outcome  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD / P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|------------------------------------|---------------------|-----------------|---------------------|----|--|---|---|--|---|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel    | At high risk for CHD               | Warfarin            | 3.5             | Ginseng             | 12 | NR<br>Unit: mg/dl                        | Mean: 0.74<br>SD: 0.19  | Mean:-0.04                                      | NR:  | There were no statistically significant differences between the ginseng group and control group.  | N/A                                   |
|                                       |                                    |                     |                 | No Treatment        | 13 |  | Mean:0.86<br>SD: 0.21   | Mean:-0.01<br>SD:0.8                            |  |   |                                       |
| Nordøy 2000 <sup>54</sup><br>Parallel | Mixed: Low and/or mod to high risk | Simvastatin         | 20              | Omega-3             |    | NR<br>Unit: NR                           | NR  | NR  | NR   | no significant changes were observed in serum creatinine levels   | Medium                                |
|                                       |                                    |                     |                 | Placebo             |    |  | NR  | NR  |  |   |                                       |
| Napoli 1998 <sup>52</sup><br>Parallel | Unclear                            | Pravastatin         | 20-40           | Vitamin E           |    | NR<br>Unit: NR                           | NR  | NR  | NR   | No differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.” | Medium                                |
|                                       |                                    |                     |                 | No Treatment        |    |  | NR  | NR  |  |   |                                       |
| Reyes 1984 <sup>59</sup><br>Parallel  | Mixed: Low and/or Moderate         | Hydrochlorothiazide | 50              | Magnesium           | 13 | NR<br>Unit: NR                           | NR  | P: NS   | NR   | Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'.   | Medium                                |
|                                       |                                    |                     |                 | Placebo             | 8  |  | NR  | P: NS   |  |   |                                       |
| Budoff 2004 <sup>10</sup><br>Parallel | At high risk for CHD               | Statins + aspirin   | 10-40           | Garlic              | 9  | Measured after 12 hr fast<br>Unit: mg/dl | NR  | Mean: 0<br>SD: 0                                | P:0.9152   | N/A   | Medium                                |
|                                       |                                    |                     |                 | Placebo             | 10 |  | NR  | Mean: 0.01<br>SD: 0.14                          |  |   |                                       |

**Evidence Table 100.KQ 3—Continuous Creatinine (continued)**

| Author Year<br>Study Design                 | CHD Risk Category             | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N | Definition of outcome / Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD / P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------|-------------|-----------------|---------------------|---|---|---|---|--|---|---------------------------------------|
| Wolf 2008 <sup>68</sup><br>Crossover        | Mixed:<br>Low and/or Moderate | ASA         | 500             | Ginkgo biloba       |   | NR<br>Unit: NR                          | NR  | NR  | NR   | Study states that: Laboratory findings in all subjects were unremarkable and did not indicate any differences between the treatment groups. | Low-medium                            |
|   |                               |             |                 |                     |   |   | NR  | NR  |  |   |                                       |
| De Caterina 2002 <sup>16</sup><br>Crossover | At high risk for CHD          | Simvastatin | 10-40           | Vitamin E           |   | NR<br>Unit: pg/mg                       | Mean: 237<br>SD: 122  | NR  | NR   | N/A   | High                                  |
|   |                               |             |                 | No treatment        |   |   | Mean: 240<br>SD: 124  | NR  |  |   |                                       |

**Evidence Table 101. KQ 3—Continuous Fasting blood glucose**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug     | CVD Dose (mg/d) | Supplement/ Control  | N   | Definition of outcome/ Unit of outcome  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments                   | Overall Risk of Bias (ROB) Assessment |           |
|---|----------------------|--------------|-----------------|----------------------|-----|---|---|---|---|---------------------------------------|---------------------------------------|-----------|
| Bays 2010 <sup>6</sup><br>Parallel      | Unclear              | Atorvastatin | 10-40           | Omega-3              | 122 | NR  | NR  | Mean: 6.18<br>SD:24.29                          | NR  | N/A                                   | Medium                                |           |
|   |                      |              |                 | Placebo              | 121 | Unit: mg/dL   | NR  | Mean:4.39<br>SD: 18.67                          |   |                                       |                                       |           |
| Mabuchi 2007 <sup>39</sup><br>Parallel  | Unclear              | Atorvastatin | 10              | Co-Q10               | 24  | NR  | NR  | NR  | NR  | no significant changes in both groups | Medium                                |           |
|   |                      |              |                 | Placebo              |     | Unit: NR  | NR  | NR  |   |                                       |                                       |           |
| Neil 2010 <sup>53</sup><br>Parallel     | High                 | Atorvastatin | 20              | Omega-3              | 163 | HbA <sub>1c</sub> %   | Mean: 7.3<br>SD: 1.2  | NR  | NR  | No significant changes between groups | Low                                   |           |
|   |                      |              |                 | Placebo              | 169 |   | Mean: 7.4<br>SD: 1.2  | NR  | NR  |                                       |                                       |           |
| Davidson 2007 <sup>14</sup><br>Parallel | Unclear              | Simvastatin  | 40              | Omega-3              | 122 | NR  | NR  | Mean:5.5  | P: 0.002  | N/A                                   | Medium                                |           |
|   |                      |              |                 | Placebo              | 132 |   | Unit: mg/dL   | NR  |   |                                       |                                       | Mean:-0.1 |
| Macan 2006 <sup>40</sup><br>Parallel    | Unclear              | Warfarin     | NR              | Garlic               | 22  | Blood draw after 12 hour fast. Samples centrifuged and serum separated<br>Unit: mg/dL | NR  | Mean:7.4<br>SD:34.9                             | P: 0.788  | N/A                                   | Medium                                |           |
|   |                      |              |                 | Placebo              | 26  |   | NR  | Mean:9.9<br>SD:29.6                             |   |                                       |                                       |           |
| Playford 2003 <sup>58</sup><br>Parallel | At high risk for CHD | Fenofibrate  | 200             | Co-Q10 + Fenofibrate | 18  | NR  | NR  | NR  | NR  | N/A                                   | Low-medium                            |           |
|   |                      |              |                 | No Treatment         | 17  |   | NR  | NR  |   |                                       |                                       |           |
|   |                      |              |                 | Co-Q10               | 20  |   | Unit: NR  | NR  |   |                                       |                                       | NR        |
|   |                      |              |                 | Placebo              | 18  |   | NR  | NR  |   |                                       |                                       |           |

**Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)**

| Author Year<br>Study Design              | CHD Risk Category                   | CVD drug    | CVD Dose (mg/d) | Supplement/ Control     | N  | Definition of outcome/ Unit of outcome                                | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|-------------|-----------------|-------------------------|----|---|---|---|---|--|---------------------------------------|
| Duffy 2001 <sup>20</sup><br>Parallel     | Mixed - Low and/or Moderate         | Simvastatin | 10-40           | Vitamin E + Simvastatin | 6  | NR<br>Unit: mmol/L  | Mean: 5.2<br>SD: 0.6  | Mean:0.3  | NR  | N/A  | Medium                                |
|  |                                     |             |                 | No Treatment            | 7  |   | Mean:4.9<br>SD: 0.5   | Mean:0  |   |  |                                       |
|  |                                     |             |                 | Vitamin E               | 6  |   | Mean:5.7<br>SD: 2.1   | Mean:0.2  |   |  |                                       |
|  |                                     |             |                 | Placebo                 | 7  |   | Mean:4.6<br>SD: 0.4   | Mean:- 0.2                                      |   |  |                                       |
| Nordøy 2000 <sup>54</sup><br>Parallel    | Mixed - Low and/or mod to high risk | Simvastatin | 20              | Omega-3                 | 15 | Measured in a fasted state 4 and 8 hours after meal<br>Unit: mmol/h/L | Mean: 42.3<br>SD: 5.0   | Mean:1.1<br>P: NS                               | NR  | Crude difference between groups in mean change from baseline (omega-2 vs. placebo): -3.2 (p=0.312)   | Medium                                |
|  |                                     |             |                 | Placebo                 | 15 |   | Mean: 48.2<br>SD: 10.2  | Mean:4.2<br>P: NS                               |   |  |                                       |
| Barbagallo 1999 <sup>5</sup><br>Parallel | Unclear                             | Flurosemide | 25              | Vitamin E               | 12 | fasting plasma glucose<br>Unit: mmol/L                                | Mean: 4.9<br>SD: 0.5  | P: NS   | P: NS   | Outcomes addressed in study but not extracted: Body fat, Fasting plasma insulin, Vitamin E, Blood (e.g. red blood cell) Mg, Plasma glutathione, Total Glutathione, GSH, GSSG | Medium                                |
|  |                                     |             |                 | Placebo                 | 12 |   | Mean:5.0<br>SD: 0.3   | P: NS   |   |  |                                       |



**Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug            | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|---------------------|-----------------|---------------------|----|--|---|---|---|---|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>Parallel   | Unclear              | Pravastatin         | 20-40           | Vitamin E           |    | NR<br>Unit: NR                         | NR:   | NR  | NR:   | no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
|   |                      |                     |                 | No Treatment        |    |  | NR  | NR  |   |   |                                       |
| Bordia 1998 <sup>9</sup><br>Parallel    | At high risk for CHD | Nitrates            | NR              | Garlic              | 30 | fasting blood sugar                    | Mean: 100.8 SE:2.5  | Mean:4 P: NS                                    | NR  | N/A   | High                                  |
|   |                      |                     |                 | Placebo             |    | Unit: mg/dL                            | NR  | NR  |   |   |                                       |
| Paolissa 1992 <sup>57</sup><br>Parallel | Unclear              | Hydrochlorothiazide | 25              | ??                  |    | Fasting plasma glucose                 | NR  | NR  | NR  | N/A   | Medium                                |
|   |                      |                     |                 | Placebo             |    | Unit: NR                               | NR  | NR  |   |   |                                       |

**Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)**

| Author Year<br>Study Design           | CHD Risk Category           | CVD drug            | CVD Dose (mg/d) | Supplement/<br>Control | N  | Definition of outcome/<br>Unit of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Additional Comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-----------------------------|---------------------|-----------------|------------------------|----|---|---|---|--|---|---------------------------------------|
| Nordøy 2003 <sup>55</sup><br>Parallel | Mixed - Mod and high risk   | Atorvastatin        | 10              | Omega-3                | 22 | Blood sample taken after 12 hr fasting, within 6 days of end of study<br><br>Unit: mmol/L | NR  | Mean: 0.1<br>SD: 0.5                                  | P:0.23   | N/A   | Low                                   |
|                                       |                             |                     |                 | Placebo                | 20 |   | NR  | Mean: 0.1<br>SD: 0.7                                  |  |   |                                       |
| Reyes 1984 <sup>59</sup><br>Parallel  | Mixed - Low and/or Moderate | Hydrochlorothiazide | 50              | Magnesium              | 13 | measured between 900-1100hrs<br><br>Unit: NR  | NR  | P: NS   | NR   | Blood glucose measured. Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'. | Medium                                |
|                                       |                             |                     |                 | Placebo                | 8  |   | NR  | P: NS   |  |   |                                       |
| Budoff 2004 <sup>10</sup><br>Parallel | At high risk for CHD        | Statins + aspirin   | 10-40           | Garlic                 | 9  | Measured after 12 hr fast<br><br>Unit: mg/dL  | NR  | Mean:14.3<br>SD: 55.1                                 | P: 0.9666  | N/A   | Medium                                |
|                                       |                             |                     |                 | Placebo                | 10 |   | NR  | Mean:13.3<br>SD:50.8                                  |  |   |                                       |

**Evidence Table 101. KQ 3—Continuous Fasting blood glucose (continued)**

| Author Year<br>Study Design          | CHD Risk Category  | CVD drug     | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome              | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|--------------|-----------------|---------------------|----|---|---|---|---|---------------------|---------------------------------------|
| Chan 2002 <sup>12</sup><br>Parallel  | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin | 40              | Omega-3             | 11 | narratively reported for post treatment<br>Unit: NR | NR  | NR  | NR  | N/A                 | Medium                                |
|                                      |  |              |                 | No Treatment        | 13 |   | NR  | NR  |   |                     |                                       |
| Lui 2003 <sup>37</sup><br>Parallel   | Unclear  | Simvastatin  | 10              | Omega-3             | 19 | narratively reported for post treatment<br>Unit: NR | NR  | NR  | NR  | N/A                 | Medium                                |
|                                      |  |              |                 | No Treatment        | 18 |   | NR  | NR  |   |                     |                                       |
| Maki 2008 <sup>41</sup><br>Crossover | Mixed: Low, Moderate and high risk                         | Simvastatin  | 20              | Omega-3             | 39 | NR<br>Unit: mg/dl                                   | NR  | Median: 5                                       | NR  | N/A                 | Medium                                |
|                                      |  |              |                 | No treatment        | 39 |   | NR  | Median: 1                                       |   |                     |                                       |

**Evidence Table 102. KQ 3—Continuous Fasting plasma glucose**

| Author<br>Year<br><br>Study<br>Design       | CHD<br>Risk<br>Category    | CVD drug   | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N  | Definition<br>of<br>outcome/<br>Unit of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians/<br>SD/<br>P Value | Additional<br>Comments | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|----------------------------|------------|-----------------------|------------------------|----|--|---|--|--|------------------------|--|
| Paolissa<br>1995 <sup>56</sup><br>Crossover | At high<br>risk for<br>CHD | Nifedipine | 88                    | Vitamin E              | 30 | NR   | Mean:5.7<br>SE: 0.6   | NR   | NR   | N/A                    | Medium   |
|   |                            |            |                       | Placebo                | 30 | Unit:<br>mmol/L                                    | Mean:5.7<br>SE: 0.4   | NR   |  |                        |  |

**Evidence Table 103. KQ 3—Continuous Glomerular filtration rate**

| Author<br>Year<br>Study<br>Design         | CHD<br>Risk<br>Category | CVD<br>drug | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N  | Definition<br>of<br>outcome /<br>Unit of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/%<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians<br>SD/<br>P Value | Additional<br>Comments | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------------|-------------|-----------------------|------------------------|----|---|---|---|---|------------------------|--|
| Ferraro<br>2009 <sup>22</sup><br>Parallel | Unclear                 | Ramipril    | 10                    | Omega-3                | 15 | Estimated<br>GFR                                    | Mean: 93.9<br>SD: 35.4  | NR  | NR  | N/A                    | Medium   |
|   |                         |             |                       | No Treatment           | 15 | Unit:<br>ml/min                                     | Mean:67.7<br>SD: 35.0   | NR  |   |                        |  |

**Evidence Table 104. KQ 3—Continuous Glycosylated hemoglobin (HbA1c)**

| Author Year<br>Study Design             | CHD Risk Category    | CVD drug     | CVD Dose (mg/d) | Supplement/ Control  | N   | Definition of outcome/<br>Unit of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value     | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|---|----------------------|--------------|-----------------|----------------------|-----|---|---|---|--|---------------------|---------------------------------------|
| Manuel 2004 <sup>42</sup><br>Parallel   | At high risk for CHD | Atorvastatin | 20              | Vitamin E            | 11  | Fasting, measured using a HPLC cation exchange column<br><br>Unit: measured as percentage | NR  | P: NS   | P: NS  | N/A                 | Medium                                |
|   |                      |              |                 | Placebo              | 11  |   | NR  | P: NS   |  |                     |                                       |
| Playford 2003 <sup>58</sup><br>Parallel | At high risk for CHD | Fenofibrate  | 200             | Co-Q10 + Fenofibrate | 18  | Measured after 14 hr fast;<br><br>Unit: measured as percentage                            | Mean: 7.2<br>SE:0.2   | Mean:-0.3   | Mean:0.2<br>P:0.032<br><br>Crude difference in means: 0.2<br>P:0.832 | N/A                 | Low-medium                            |
|   |                      |              |                 | No Treatment         | 17  |   | Mean:7.4<br>SE:0.4  | Mean:0.3  |  |                     |                                       |
|   |                      |              |                 | Co-Q10               | 20  |   | Mean: 7.0<br>SE:0.3   | Mean:0.1  |  |                     |                                       |
|   |                      |              |                 | Placebo              | 18  |   | Mean:6.6<br>SE:0.2  | Mean:0.3  |  |                     |                                       |
| Bays 2010 <sup>6</sup><br>Parallel      | Unclear              | Atorvastatin | 10-40           | Omega-3              | 122 | NR<br><br>Unit: measured as percentage  | NR  | Mean: 0.18<br>SD: 0.45                                | NR   | N/A                 | Medium                                |
|   |                      |              |                 | Placebo              | 121 |   | NR  | Mean: 0.10<br>SD: 0.33                                |  |                     |                                       |

**Evidence Table 10. KQ 3—Continuous Hematocrit**

| Author Year<br>Study Design            | CHD Risk Category          | CVD drug   | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/Unit of outcome  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD / P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--|----------------------------|------------|-----------------|---------------------|----|--|---|--|---|--|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel     | At high risk for CHD       | Warfarin   | 3.5             | Ginseng             | 12 | Average rating of the interference items of Pain Inventory questionnaire<br>Unit: measured as percentage | Mean: 39.36<br>SD: 3.03   | Mean: -0.06                                      | NR  | There were no statistically significant differences between the ginseng group and control group. | N/A                                   |
|  |                            |            |                 | No Treatment        | 13 |  | Mean: 42.11<br>SD: 4.12   | Mean: -0.54                                      |   |  |                                       |
| Hansen 1993 <sup>29</sup><br>Crossover | Mixed: Low and/or Moderate | Lovastatin | 40              | Omega-3             | 14 | NR<br>Unit: % change   | NR  | % Mean: 7<br>SD: 3<br>P: <0.001                  | NR  | N/A  | Medium                                |
|  |                            |            |                 | No Treatment        | 14 |  | NR  | % Mean: 5<br>SD: 3<br>P: <0.01                   |   |  |                                       |

**Evidence Table 106. KQ 3 Continuous Leukopenia: WBC count**

| Author Year<br>Study Design             | CHD Risk Category          | CVD drug          | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|---|----------------------------|-------------------|-----------------|---------------------|----|--|---|---|---|--|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>Parallel   | Unclear                    | Pravastatin       | 20-40           | Vitamin E           |    | NR<br>Unit: NR                         | NR  | NR  | NR  | No differences in routine laboratory tests or adverse events were registered during the study. In particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
|   |                            |                   |                 | No Treatment        |    |  | NR  | NR  |   |  |                                       |
| Budoff 2004 <sup>10</sup><br>Parallel   | At high risk for CHD       | Statins + aspirin | 10-40           | Garlic              | 9  | Measured after 12 hr fast<br>Unit: NR  | NR  | Mean: -0.2<br>SD: 1.9                           | P:0.396   | N/A  | Medium                                |
|   |                            |                   |                 | Placebo             | 10 |  | NR  | Mean: -0.95<br>SD: 1.85                         |   |  |                                       |
| Wolf 2008 <sup>68</sup><br>Crossover    | Mixed: Low and/or Moderate | ASA               | 500             | Gingko biloba       |    | NR<br>Unit: NR                         | NR  | NR  | NR  | Study states that: Laboratory findings in all subjects were unremarkable and did not indicate any differences between the treatment groups.  | Low-medium                            |
|   |                            |                   |                 |                     |    |  | NR  | NR  |   |  |                                       |
| Hansen 1993 <sup>29</sup><br>Crossover  | Mixed: Low and/or Moderate | Lovastatin        | 40              | Omega-3             | 14 | NR<br>Unit: % change                   | NR  | % Mean: 49<br>SD: 29<br>P: <0.001               | NR  | N/A  | Medium                                |
|   |                            |                   |                 | No treatment        | 14 |  | NR  | % Mean: 50<br>SD: 31<br>P: <0.001               |   |  |                                       |
| Mueller 1991 <sup>51</sup><br>Crossover | Mixed: Low and/or Moderate | Aspriin           | 325             | Omega-3             | 12 | NR<br>Unit: x 103/mm3                  | Mean:5.36<br>SD:1.44  | Mean: -1.02                                     | NR  |  | Medium                                |
|   |                            |                   |                 | Placebo             | 12 |  | Mean:5.68<br>SD:1.61  | P: <0.05  |   |  |                                       |



**Evidence Table 107. KQ 3—Continuous Myalgia**

| Author Year<br>Study Design          | CHD Risk Category         | CVD drug   | CVD Dose (mg/d) | Supplement/ Control                  | N  | Definition of outcome/<br>Unit of outcome   | Post treatment Mean/<br>(Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value        | Between group differences in Means/<br>medians SD/<br>P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---------------------------|--|-----------------|--------------------------------------|----|---|--|--|---|--|---------------------------------------|
| Young 2007 <sup>70</sup><br>Parallel | Mixed - Mod and high risk | Simvastatin  | 10-40           | Co Q10                               | 22 | Patients documented the number of sites affected by myalgia and rated the intensity of pain on the scale.<br><br>Unit: Visual analogue scale with intensity of pain rated from 0 to 100mm | NR   | Median:6.0<br>P:0.001  | NR  | No difference in groups (p=0.63). An adjusted analysis has also been presented for individual group data (myalgia score adjusted for no. of affected sites). | Medium                                |
|                                      |                           |  |                 | Placebo                              | 21 |   | NR   | Median:2.3<br>P:0.001  |   |  |                                       |
| Caso 2007 <sup>11</sup><br>Parallel  | Unclear                   | Simvastatin (22);<br>Atorvastatin (7);<br>Pravastatin (2);<br>Lovastatin (1) | Varying Doses   | Co Q10                               | 18 | Pain severity score: averaging scores of the 4 pain intensity items of Brief Pain Inventory questionnaire<br><br>Unit: Score on questionnaire   | Mean: 2.97<br>SE:0.48  | Mean: -2.03<br>SE: 0.44<br>P: <0.001<br>% mean: 40<br>SE: 11 | P: 0.001  | N/A  | Low                                   |
|                                      |                           |  |                 | Other dietary supplement – Vitamin E | 14 |   | Mean:4.73<br>SE:0.68   | Mean: 0.34<br>SE: 0.33<br>P: NS<br>% mean: 9<br>SE: 14       |   |  |                                       |

**Evidence Table 107. KQ 3—Continuous Myalgia (continued)**

| Author Year<br>Study Design         | CHD Risk Category | CVD drug   | CVD Dose (mg/d) | Supplement/ Control                  | N  | Definition of outcome/<br>Unit of outcome   | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|-------------------|--|-----------------|--------------------------------------|----|---|---|---|--|---------------------|---------------------------------------|
| Caso 2007 <sup>11</sup><br>Parallel | Unclear           | Simvastatin (22);<br>Atorvastatin (7);<br>Pravastatin (2);<br>Lovastatin (1) | Varying Doses   | Co Q10                               | 18 | averaging ratings of the 7 interference items of Brief Pain Inventory questionnaire<br><br>Unit: Score on questionnaire | Mean: 2.82<br>SE:0.61   | P: <0.02<br>% mean: 38<br>SE: 14                      | NR   | N/A                 | Low                                   |
|                                     |                   |  |                 | Other dietary supplement – Vitamin E | 14 |   | Mean:4.25<br>SE:0.70  | P: NS   |  |                     |                                       |

**Evidence Table 108. KQ 3—Continuous Myoglobin**

| Author Year<br>Study Design            | CHD Risk Category | CVD drug     | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/<br>Unit of outcome | Post treatment Mean/<br>(Median)<br>SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/<br>SD/<br>P Value | Between group differences in Means/<br>medians<br>SD/<br>P Value | Additional Comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------|--------------|-----------------|---------------------|----|---|---|---|--|--|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br>Parallel | Unclear           | Atorvastatin | 10              | Co-Q10              | 24 | NR<br>Unit: ng/ml                         | Mean: 59.7<br>SD: 28.3  | % mean:<br>17.5<br>P:0.0713                           | NR   | There's no significant differences between groups (p=0.1453) | Medium                                |
|  |                   |              |                 | Placebo             | 25 |   | Mean: 66.9<br>SD: 39.4  | % mean:<br>0.75<br>P:0.7405                           |  |  |                                       |

**Evidence Table 109. KQ 3—Continuous QT interval**

| Author Year<br>Study Design             | CHD Risk Category | CVD drug    | CVD Dose (mg/d) | Supplement/ Control | N | Definition of outcome   | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|---|-------------------|-------------|-----------------|---------------------|---|---|---|--|---|---------------------|---------------------------------------|
| McDowell 1994 <sup>44</sup><br>Parallel | Unclear           | Simvastatin | 20              | Vitamin E           | 8 | At rest using Siemens Minograf 470 which computes QT interval corrected to a heart rate of 60/min using formula - QTc = QT + 1.75(HR-60)<br><br>Unit: m/sec | Mean: 413<br>SD: 22   | P: NS  | NR  | N/A                 | Medium                                |
|   |                   |             |                 | Placebo             | 8 |   | Mean: 399<br>SD: 16   | P: NS  |   |                     |                                       |

**Evidence Table 110. KQ 3—Continuous RBC count**

| Author<br>Year<br><br>Study<br>Design     | CHD<br>Risk<br>Category             | CVD drug   | CVD<br>Dose<br>(mg/d) | Supplement/<br>Control | N  | Definition<br>of<br>outcome/<br>Unit of<br>outcome | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean<br>change/ %<br>change<br>from<br>baseline/<br>SD/<br>P Value | Between<br>group<br>differences<br>in Means/<br>medians/<br>SD/<br>P Value | Additional<br>Comments | Overall Risk<br>of Bias<br>(ROB)<br>Assessment |
|---|-------------------------------------|------------|-----------------------|------------------------|----|--|---|--|--|------------------------|--|
| Hansen<br>1993 <sup>29</sup><br>Crossover | Mixed:<br>Low<br>and/or<br>Moderate | Lovastatin | 40                    | Omega-3                | 14 | NR   | NR  | % Mean: 8<br>SD: 4<br>P: <0.001                                    | NR   | N/A                    | Medium   |
|   |                                     |            |                       | No treatment           | 14 | Unit: %<br>change                                  | NR  | % Mean: 5<br>SD: 2<br>P: <0.001                                    |  |                        |  |

**Evidence Table 111. KQ 3—Continuous Serum potassium**

| Author Year<br>Study Design            | CHD Risk Category    | CVD drug                                    | CVD Dose (mg/d) | Supplement/ Control | N  | Definition of outcome/ Unit of outcome | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional Comments | Overall Risk of Bias (ROB) Assessment |
|--|----------------------|---|-----------------|---------------------|----|--|---|---|---|---------------------|---------------------------------------|
| Budoff 2004 <sup>10</sup><br>Parallel  | At high risk for CHD | Statins + aspirin                           | 10-40           | Garlic              | 9  | Unit: mg/dl                            | NR  | Mean: -0.01<br>SD: 1.15                         | P:0.7464  | N/A                 | Medium                                |
|  |                      |   |                 | Placebo             | 10 |  | NR  | Mean: -0.15<br>SD: 0.64                         |   |                     |                                       |
| Wirell 1994 <sup>67</sup><br>Crossover | Unclear              | metoprolol, atenolol, pindolol & propanolol | NR              | Magnesium           | 39 | NR<br>mmol/L                           | Mean: 4<br>SD: 0.3  | NR  | P: 0.045<br>Crude difference                            | N/A                 | Medium                                |
|  |                      |   |                 | Placebo             | 39 |  | Mean: 3.9<br>SD: 0.3  | NR  |   |                     |                                       |

**Evidence Table 112. KQ3—Dichotomous outcomes—Abnormal ECG**

| Author Year Study Design                   | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Reyes 1984 <sup>59</sup><br>Parallel       | N/A                                 | Mixed:<br>Low and/or<br>Moderate       | Hydrochlorothiazide (50)        | Magnesium                  | 13 | NR            | Placebo       | 8  | NR            | NR                             | Results state only that 'no statistically significant changes affected the electrocardiogram or the plasma variables studied during the trial'. Methods do not state which electrocardiographic measurements were taken. | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel    | N/A                                 | At high risk for CHD                   | Fenofibrate (200)               | Co-Q10                     | 18 | NR            | No Treatment  | 17 | NR            | NR                             |  | Low-medium                            |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)               | Omega-3                    | 50 |               | No Treatment  | 50 |               | NR                             | No treatment related trends regarding ECG or other clinical or laboratory markers were found (no specific data)  | Medium                                |
| McKenney 2006 <sup>45</sup><br>Crossover   | N/A                                 | Mixed:<br>Low and/or<br>Moderate       | Simvastatin (80)                | Omega-3                    | 24 |               | No Treatment  | 24 |               | NR                             |  | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed:<br>Low and/or<br>Moderate       | Ticlopidine (250 – single dose) | Gonkgo Biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             |  | Medium                                |

**Evidence Table 113. KQ3—Dichotomous outcomes—Adverse event other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event)**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|----------------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| McDowell 1994 <sup>44</sup><br>Parallel | N/A                                 | Unclear                    | Simvastatin (20)     | Vitamin E                  | 8  | 0             | Placebo       | 8  | 0             | NR                             | It is unclear if this was measured actively or in a standard manner - it is not reported for these two groups, only for the third, non-relevant group and no indication that this was actively sought. | Medium                                |
| Wolf 2006 <sup>68</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | ASA (500)            | Ginkgo biloba              | 50 | 50            | Placebo       | 50 | 49            | NR                             |  | Low-medium                            |
| Wolf 2006 <sup>68</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | ASA (500)            | Ginkgo biloba              | 50 | 49            | Placebo       | 50 | 48            | NR                             |  | Low-medium                            |
| Wolf 2006 <sup>68</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | ASA (500)            | Ginkgo biloba              | 50 | 19            | Placebo       | 50 | 19            | NR                             |  | Low-medium                            |
| Wolf 2006 <sup>68</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | ASA (500)            | Ginkgo biloba              | 50 | 17            | Placebo       | 50 | 20            | NR                             |  | Low-medium                            |
| Hansen 1993 <sup>29</sup><br>Crossover  | N/A                                 | Mixed: Low and/or Moderate | Lovastatin (40)      | Omega-3                    | 14 | 0             | No Treatment  | 14 | 0             | NR                             |  | Medium                                |



**Evidence Table 114. KQ3—Dichotomous outcomes—Adverse events general**

| Author Year<br>Study Design            | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|----------------------------|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Watson 1999 <sup>66</sup><br>Crossover | N/A                                 | At high risk for CHD       | ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR) | Co-Q10                     |    | 0             | Placebo       | 0  | 0             | NR                             |                     | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | Ticlopidine (250 – single dose)   | Ginkgo biloba              | 24 | 7             | No Treatment  | 24 | 7             | NR                             |                     | Medium                                |

**Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised)**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category        | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|--------------------------|----------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Bays 2010 <sup>6</sup><br>Parallel      |                                     | Unclear                  | Atorvastatin (10-40) | Omega-3                    |     | NR            | Placebo       |     | NR            | NR                             |  | Medium                                |
| Young 2007 <sup>70</sup><br>Parallel    | > 3 times the upper level of normal | Mixed: Mod and high risk | Simvastatin (10-40)  | Co-Q10                     | 22  | 1             | Placebo       | 22  | 1             | NR                             | Exclusion criteria included: alanine aminotransferase or aspartate aminotransferase > 3 times the upper level of normal and results state: "Liver... function, ...[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | mild elevation of ALT               | Unclear                  | Simvastatin (40)     | Omega-3                    | 122 | 0             | Placebo       | 132 | 0             | NR                             | p=NS   | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | ALT >3.0 x ULN                      | Unclear                  | Simvastatin (40)     | Omega-3                    | 122 | 2             | Placebo       | 132 | 1             |                                | Study reports: no cases of clinically significant increases in hepatic transaminase levels (>3.0 x ULN) in either group.   | Medium                                |

**Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised) (continued)**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category  | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|--|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Duffy 2001 <sup>20</sup><br>Parallel    |                                     | Mixed: Mod and high risk.                                  | Simvastatin (10-40)  | Vitamin E                  | 6  | 0             | No Treatment  | 7  | 0             |                                |  | Medium                                |
| Napoli 1998 <sup>52</sup><br>Parallel   | NR                                  | Unclear  | Pravastatin (20-40)  | Vitamin E                  |    | 0             | No Treatment  |    | 0             |                                | "..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
| Chan 2002 <sup>12</sup><br>Parallel     |                                     | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)    | Omega-3                    | 11 | 0             | No Treatment  | 13 | 0             |                                |  | Medium                                |
| Liu 2003 <sup>37</sup><br>Parallel      | tested for liver function           | Unclear  | Simvastatin (10)     | Omega-3                    | 19 | 0             | No Treatment  | 18 | 0             |                                |  | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel |                                     | At high risk for CHD                                       | Fenofibrate (200)    | Co-Q10                     | 18 | 0             | No Treatment  | 17 | 0             |                                |  | Low-medium                            |

**Evidence Table 115. KQ3—Dichotomous—Alanine transaminase (ALT) (raised) (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant)                      | CHD Risk Category                      | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|--|--|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Gosai 2008 <sup>26</sup><br>Crossover      | reference range<br>males: 0-46 U/L;<br>females: 0-36 U/L | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)   | Omega-3                    | 48 | 1             | No Treatment  | 48 | 4             |                                | N/A                 | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A  | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)   | Omega-3                    | 50 | 14            | No Treatment  | 50 | 13            |                                | N/A                 | Medium                                |
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A  | Mixed:<br>Low and/or mod to high risk  | Simvastatin (10-40)   | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                | N/A                 | Medium                                |
| Paolissa 1992 <sup>56</sup><br>Crossover   | N/A  | At high risk for CHD                   | Nifedipine (88)   | Vitamin E                  |    | 0             | Placebo       |    | 0             |                                | N/A                 | Medium                                |
| Watson 1999 <sup>66</sup><br>Crossover     | N/A  | At high risk for CHD                   | ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR) | Co-Q10                     |    | 0             | Placebo       | 0  | 0             | NR                             | N/A                 | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A  | Mixed:<br>Low and/or Moderate          | Ticlopidine (250 – single dose)   | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A                 | Medium                                |

**Evidence Table 11. KQ3- Dichotomous – Alkaline phosphatase**

| Author Year<br>Study Design           | Definition of outcome (if relevant) | CHD Risk Category  | CVD drug (dose mg/d)           | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-------------------------------------|--|--------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>Parallel | NA                                  | Unclear  | Pravastatin (20-40)            | Vitamin E                  |    | 0             | No Treatment  |    | 0             |                                | No differences in routine laboratory tests or adverse events were registered during the study. In particular, there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
| Chan 2002 <sup>12</sup><br>Parallel   | NA                                  | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)              | Omega-3                    | 11 | 0             | No Treatment  | 13 | 0             |                                |  | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover   | N/A                                 | Mixed: Low and/or Moderate                                 | Ticlopidine (250 –single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A  | Medium                                |

**Evidence Table 117. KQ3—Dichotomous—Anemia**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                  | CVD drug (dose mg/d)           | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|------------------------------------|--------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A                                 | Mixed: Low and/or mod to high risk | Simvastatin (10-40)            | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             | NR                             | N/A                 | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed: Low and/or Moderate         | Ticlopidine (250 –single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A                 | Medium                                |

**Evidence Table 118. KQ3—Dichotomous—Any adverse event**

| Author<br>Year<br><br>Study<br>Design   | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category                           | CVD drug<br>(dose<br>mg/d) | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group<br>2:<br>Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias (ROB)<br>Assessment |
|---|---|--|----------------------------|----------------------------------|----|---------------------|---------------------|----|---------------------|--------------------------------------|------------------------|---|
| Maki<br>2008 <sup>41</sup><br>Crossover | N/A                                       | Mixed:<br>Low,<br>Moderate<br>and high<br>risk | Simvastatin<br>(20)        | Omega-3                          |    | 18                  | Placebo             |    | 17                  | NR                                   | N/A                    | Medium                                      |

**Evidence Table 119. KQ3—Dichotomous—Asparatate aminotransaminase (AST) raised**

| Author Year<br>Study Design         | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|-------------------------------------|----------------------------|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Crossover | N/A                                 | Mixed: Low and/or Moderate | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A                 | Medium                                |



**Evidence Table 120. KQ3—Dichotomous—Asparatate aminotransferase (AST) raised**

| Author Year<br>Study Design             | Definition of outcome (if relevant)   | CHD Risk Category  | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|---|--|----------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel | > 3.0 x ULN   | Unclear  | Simvastatin (40)     | Omega-3                    | 122 | 0             | Placebo       | 132 | 0             | NR                             |  | Medium                                |
| Napoli 1998 <sup>52</sup><br>Parallel   | Data imputed- there were no differences between baseline and post treatment values. | Unclear  | Pravastatin (20-40)  | Vitamin E                  |     | 0             | No Treatment  |     | 0             |                                | No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
| Chan 2002 <sup>12</sup><br>Parallel     | thresholds not specified  | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)    | Omega-3                    | 11  | 0             | No Treatment  | 13  | 0             |                                |  | Medium                                |
| Liu 2003 <sup>37</sup><br>Parallel      | thresholds not specified  | Unclear  | Simvastatin (10)     | Omega-3                    | 19  | 0             | No Treatment  | 18  | 0             |                                |  | Medium                                |

**Evidence Table 120. KQ3—Dichotomous—Aspartate aminotransferase (AST) raised (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant)                | CHD Risk Category                      | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|--|--|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Young 2007 <sup>70</sup><br>Parallel       | > 3 times the upper level of normal                | Mixed: Mod and high risk               | Simvastatin (10-40)   | Co-Q10                     | 22 | 0             | Placebo       | 22 | 0             | NR                             | Exclusion criteria included: alanine aminotransferase or aspartate aminotransferase > 3 times the upper level of normal and results state: "Liver... function, ...[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm | Medium                                |
| Gosai 2008 <sup>26</sup><br>Crossover      | reference range males: 0-46 U/L; females: 0-36 U/L | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)   | Omega-3                    | 48 | 0             | No Treatment  | 48 | 2             |                                | N/A  | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A  | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)   | Omega-3                    | 50 | 9             | No Treatment  | 50 | 13            |                                | N/A  | Medium                                |
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A  | Mixed: Low and/or mod to high risk     | Simvastatin (10-40)   | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                | N/A  | Medium                                |
| Paolissa 1992 <sup>56</sup><br>Crossover   | N/A  | At high risk for CHD                   | Nifedipine (88)   | Vitamin E                  |    | 0             | Placebo       |    | 0             |                                | N/A  | Medium                                |
| Watson 1999 <sup>66</sup><br>Crossover     | N/A  | At high risk for CHD                   | ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR) | Co-Q10                     |    | 0             | Placebo       |    | 0             | NR                             | N/A  | Medium                                |

**Evidence Table 121. KQ3—Dichotomous—Bleeding**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category        | CVD drug (dose mg/d)           | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences    | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|--------------------------|--------------------------------|----------------------------|----|---------------|---------------|----|---------------|-----------------------------------|---|---------------------------------------|
| Ferraro 2009 <sup>22</sup><br>Parallel  | Bleeding: Erythrocyturi a Class1    | Unclear                  | Ramipril (10)                  | Omega-3                    | 15 | 5             | No Treatment  | 15 | 0             |                                   | 2 vs. 10 at baseline were at level 1 erythrocyturia.              | Medium                                |
| Ferraro 2009 <sup>22</sup><br>Parallel  | Bleeding: CE (erythrocyturi a 2     | Unclear                  | Ramipril (10)                  | Omega-3                    | 15 | -4            | No Treatment  | 15 | 0             |                                   |   | Medium                                |
| Ferraro 2009 <sup>22</sup><br>Parallel  | Bleeding: CE (erythrocyturi a 3     | Unclear                  | Ramipril (10)                  | Omega-3                    | 15 | -1            | No Treatment  | 15 | 0             |                                   |   | Medium                                |
| Lee 2008 <sup>36</sup><br>Parallel      |                                     | At high risk for CHD     | Warfarin (3.5)                 | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                   | No events occurred. No data reported.                             | Medium                                |
| Gardner 2007 <sup>23</sup><br>Parallel  | Nosebleed and/or unusual bleeding   | Mixed : Moderate to high | ASA (325)                      | Gingko baloba              | 30 | 5             | Placebo       | 30 | 4             |                                   |   | Low                                   |
| Whitlock 2007 <sup>72</sup><br>Parallel |                                     | At high risk for CHD     | Warfarin (2)                   | Vitamin K                  | 12 | 0             | Placebo       | 16 | 0             |                                   |   |                                       |
| Sconce 2007 <sup>61</sup><br>Parallel   |                                     | Unclear                  | Warfarin (3.8-4.4 vs. 3.3-3.4) | Vitamin K                  | 35 | 0             | Placebo       | 33 | 0             |                                   |   | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel    | Incidence of hemorrhager            | Unclear                  | Warfarin (NR)                  | Garlic                     | 22 | 0             | Placebo       | 26 | 0             | P: 1.000 (Crude event risk ratio) | N included is unclear: Unclear (66 enrolled, 52 randomized total) | Medium                                |

**Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)**

| Author Year<br>Study Design          | Definition of outcome (if relevant)         | CHD Risk Category | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|---|-------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Macan 2006 <sup>40</sup><br>Parallel | Epitaxis                                    | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Other dichotomous outcomes assessed in this study (not specifically relevant): change in warfarin dosage | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel | Clinically relevant bleeding: Hemoptysis    | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                |  | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel | Clinically relevant bleeding: bloody stools | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Total included per arm is unclear (66 enrolled, 52 randomized total)                                     | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel | hemorrhage into organs                      | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Total included per arm is unclear (66 enrolled, 52 randomized total)                                     | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel | Clinically relevant bleeding: hemarthrosis  | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Total included per arm is unclear (66 enrolled, 52 randomized total)                                     | Medium                                |

**Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)**

| Author Year<br>Study Design            | Definition of outcome (if relevant)     | CHD Risk Category    | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|---|----------------------|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Macan 2006 <sup>40</sup><br>Parallel   | Clinically relevant bleeding: hematomas | Unclear              | Warfarin (NR)   | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Total included per arm is unclear (66 enrolled, 52 randomized total)   | Medium                                |
| Macan 2006 <sup>40</sup><br>Parallel   | Clinically relevant bleeding?: bruising | Unclear              | Warfarin (NR)   | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                | Total included per arm is unclear (66 enrolled, 52 randomized total)   | Medium                                |
| Steiner 1995 <sup>62</sup><br>Parallel | Hemorrhagic event                       | At high risk for CHD | ASA (325)   | Vitamin E                  | 52 | 3             | Placebo       | 48 | 3             |                                |  | Low-medium                            |
| Kaul 1992 <sup>34</sup><br>Parallel    | bleeding complications (non-specific)   | At high risk for CHD | Calcium channel blocker, ASA (NR)                                 | Omega-3                    | 58 | 0             | No Treatment  | 49 | 0             |                                |  | Low-medium                            |
| Bender 1998 <sup>8</sup><br>Parallel   | Bleeding                                | Unclear              | Warfarin (NR)   | Omega-3                    | 6  | 0             | No Treatment  | 5  | 0             |                                |  | High                                  |
| Bender 1998 <sup>8</sup><br>Parallel   | minor bruising                          | Unclear              | Warfarin (NR)   | Omega-3                    | 6  |               | No Treatment  | 5  |               |                                | numeric data is not separated by groups. One episode of bruising occurred but no group designation reported. | High                                  |
| Dehmer 1988 <sup>17</sup><br>Parallel  | bleeding complications                  | At high risk for CHD | Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR) | Omega-3                    | 43 | 0             | No Treatment  | 39 | 0             |                                |  | Medium                                |

**Evidence Table 121. KQ3—Dichotomous—Bleeding (continued)**

| Author Year<br>Study Design              | Definition of outcome (if relevant)      | CHD Risk Category          | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|--|----------------------------|---|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---------------------|---------------------------------------|
| Dehmer 1988 <sup>17</sup><br>Parallel    | serious passive hematoams                | At high risk for CHD       | Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR) | Omega-3                    | 43  | 3             | No Treatment  | 39  | 1             |                                |                     | Medium                                |
| Eritsland 1996 <sup>21</sup><br>Parallel | bleeding complications (major and minor) | At high risk for CHD       | Warfarin (NR)   | Omega-3                    | 174 | 2             | No Treatment  | 145 | 2             |                                |                     | Medium                                |
| Eritsland 1996 <sup>21</sup><br>Parallel | bleeding complications (major and minor) | At high risk for CHD       | Aspirin (300)   | Omega-3                    | 143 | 3             | No Treatment  | 148 | 2             |                                |                     | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover  | N/A                                      | Mixed: Low and/or Moderate | ASA (325 – single dose)   | Omega-3                    |     | 0             | Placebo       |     | 0             |                                |                     | Medium                                |

**Evidence Table 122.KQ3—Dichotomous—Bloating**

| Author<br>Year<br><br>Study<br>Design      | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category                | CVD<br>drug<br>(dose<br>mg/d)    | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group<br>2: Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk of<br>Bias (ROB)<br>Assessment |
|--|---|-------------------------------------|----------------------------------|----------------------------------|----|---------------------|------------------|----|---------------------|--------------------------------------|------------------------|---|
| Mueller<br>1991 <sup>51</sup><br>Crossover | N/A                                       | Mixed:<br>Low<br>and/or<br>Moderate | ASA<br>(325 –<br>single<br>dose) | Omega-3                          |    | 2                   | Placebo          |    | 0                   |                                      |                        | Medium                                      |

**Evidence Table 123. KQ3—Dichotomous—Blood urea nitrogen (BUN) (raised)**

| Author Year<br>Study Design            | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|----------------------------|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Watson 1999 <sup>66</sup><br>Crossover | N/A                                 | At high risk for CHD       | ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR) | Co-Q10                     |    | 0             | Placebo       |    | 0             | NR                             | N/A                 | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate | Ticlopidine (250 –single dose)  | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A                 | Medium                                |



**Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK**

| Author Year<br>Study Design             | Definition of outcome (if relevant)                            | CHD Risk Category          | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|---|--|----------------------------|----------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Bays 2010 <sup>6</sup><br>Parallel      | Creatine kinase greater than 3 times the upper limit of normal | Unclear                    | Atorvastatin (10-40) | Omega-3                    |     | 3             | Placebo       |     | 3             | NR                             |                                       | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | AE-myopathy  | Unclear                    | Simvastatin (40)     | Omega-3                    | 122 | 0             | Placebo       | 132 | 0             |                                | described as no AEs involved myopathy | Medium                                |
| Duffy 2001 <sup>20</sup><br>Parallel    | Threshold not specified  | Mixed: Low and/or moderate | Simvastatin (10-40)  | Vitamin E                  | 6   | 0             | No Treatment  | 7   | 0             |                                |                                       | Medium                                |

**Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK (continued)**

| Author Year<br>Study Design             | Definition of outcome (if relevant)   | CHD Risk Category  | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|---|--|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Napoli 1998 <sup>52</sup><br>Parallel   | Data imputed- there were no differences between baseline and post treatment values. | Unclear  | Pravastatin (20-40)  | Vitamin E                  |    | 0             | No Treatment  |    | 0             |                                | "..no differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups." | Medium                                |
| Chan 2002 <sup>12</sup><br>Parallel     | thresholds not specified  | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)    | Omega-3                    | 11 | 0             | No Treatment  | 13 |               |                                |  | Medium                                |
| Liu 2003 <sup>37</sup><br>Parallel      | thresholds not specified  | Unclear  | Simvastatin (10)     | Omega-3                    | 19 | 0             | No Treatment  | 18 |               |                                |  | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel | NR  | At high risk for CHD                                       | Fenofibrate (200)    | Co-Q10                     | 18 | 0             | No Treatment  | 17 |               |                                |  | Low-medium                            |

**Evidence Table 124. KQ3—Dichotomous—Parallel—CK or CPK (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant)                      | CHD Risk Category                      | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|--|--|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Gosai 2008 <sup>26</sup><br>Crossover      | reference range<br>males: 0-46 U/L;<br>females: 0-36 U/L | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)    | Omega-3                    | 48 | 1             | No Treatment  | 48 | 0             |                                | N/A                 | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A  | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)    | Omega-3                    | 50 | 1             | No Treatment  | 50 | 0             |                                | N/A                 | Medium                                |
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A  | Mixed:<br>Low and/or mod to high risk  | Simvastatin (10-40)  | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                | N/A                 | Medium                                |

**Evidence Table 125. KQ3—Dichotomous—Constipation**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel         | NR                                  | At high risk for CHD                   | Warfarin (3.5)                  | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                | No events occurred. No data reported. | Medium                                |
| Roth 2009 <sup>60</sup><br>Parallel        | NR                                  | Unclear                                | Fenofibrates (130)              | Omega-3                    | 84 | 1             | Placebo       | 83 | 5             |                                |                                       | Medium                                |
| Gosai 2008 <sup>26</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)               | Omega-3                    | 44 | 16            | No Treatment  | 46 | 18            |                                | N/A                                   | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)               | Omega-3                    | 50 |               | No Treatment  | 50 | 0             |                                | N/A                                   | Medium                                |
| Jiang 2005 <sup>32</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)       | Ginkgo biloba              |    | 1             | No Treatment  |    | 0             |                                | N/A                                   | Medium                                |
| Jiang 2005 <sup>32</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)       | Ginger                     |    | 0             | No Treatment  |    | 0             |                                |                                       | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 – single dose)         | Omega-3                    |    | 1             | Placebo       |    | 0             |                                |                                       | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed: Low and/or Moderate             | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 1             | No Treatment  | 24 | 0             | NR                             | N/A                                   | Medium                                |

**Evidence Table 126. KQ3—Dichotomous—Creatinine (raised)**

| Author Year<br>Study Design             | Definition of outcome (if relevant)   | CHD Risk Category          | CVD drug (dose mg/d)     | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|---|---|----------------------------|--------------------------|----------------------------|-----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel | creatinine levels (also creatine phosphokinase, or homocysteine)                    | Unclear                    | Simvastatin (40)         | Omega-3                    | 122 |               | Placebo       |    |               | NR                             | no numeric data reported. no significant effect of omega 3 + statin during the course of the trial   | Medium                                |
| Napoli 1998 <sup>52</sup><br>Parallel   | Data imputed- there were no differences between baseline and post treatment values. | Unclear                    | Pravastatin (20-40)      | Vitamin E                  |     | 0             | No Treatment  |    | 0             |                                | No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
| Reyes 1984 <sup>59</sup><br>Parallel    | NR  | Mixed: Low and/or Moderate | Hydrochlorothiazide (50) | Magnesium                  |     | 0             | Placebo       | 8  | 0             |                                |  | Medium                                |

**Evidence Table 126. KQ3—Dichotomous—Creatinine (raised) (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant)                             | CHD Risk Category                  | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|---|------------------------------------|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Roth 2009 <sup>60</sup><br>Parallel        | blood CPK increase  | Unclear                            | Fenofibrate (130)   | Omega-3                    | 13 | 0             | Placebo       | 83 | 1             |                                |                     | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel    | Unclear if this is the correct def.: creatinemia ( /150 mmol/l) | At high risk for CHD               | Fenofibrate (200)   | Co-Q10                     | 84 |               | No Treatment  | 17 |               |                                |                     | Low-medium                            |
| Watson 1999 <sup>66</sup><br>Crossover     | N/A   | At high risk for CHD               | ACE inhibitors (no description), furosemide, digoxin, also hydralazine and/or nitrates (NR) | Co-Q10                     |    | 0             | Placebo       |    | 0             | NR                             | N/A                 | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A   | Mixed: Low and/or Moderate         | Ticlopidine (250 – single dose)   | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             | NR                             | N/A                 | Medium                                |
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A   | Mixed: Low and/or mod to high risk | Simvastatin (10-40)   | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                | N/A                 | Medium                                |
| Paolissa 1992 <sup>56</sup><br>Crossover   | N/A   | At high risk for CHD               | Nifedipine (88)   | Vitamin E                  |    | 0             | Placebo       |    | 0             |                                | N/A                 | Medium                                |

**Evidence Table 127. KQ3—Dichotomous—Parallel—Diarrhea**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|--|---------------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel      | NR                                  | At high risk for CHD                   | Warfarin (3.5)                  | Ginseng                    | 12  |               | No Treatment  | 13  | 0             |                                | No events occurred. No data reported. | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | NR                                  | Unclear                                | Simvastatin (40)                | Omega-3                    | 122 | 3             | Placebo       | 132 | 3             |                                |                                       | Medium                                |
| McDowell 1994 <sup>44</sup><br>Parallel | NR                                  | Unclear                                | Simvastatin (20)                | Vitamin E                  | 8   | 0             | Placebo       | 8   | 1             |                                |                                       | Medium                                |
| McDowell 1994 <sup>44</sup><br>Parallel | NR                                  | Unclear                                | Simvastatin (20)                | Vitamin E                  | 8   | 1             | Placebo       | 8   | 0             |                                |                                       | Medium                                |
| Paolissa 1992 <sup>57</sup><br>Parallel | NR                                  | Unclear                                | Hydrochlorthiazide (25)         | Magnesium                  | 9   | 0             | Placebo       | 9   | 0             |                                |                                       | Medium                                |
| Roth 2009 <sup>60</sup><br>Parallel     | NR                                  | Unclear                                | Fenofibrates (130)              | Omega-3                    | 84  | 4             | Placebo       | 83  | 5             |                                |                                       | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover     | N/A                                 | Mixed: Low and/or Moderate             | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24  | 3             | No Treatment  | 24  | 1             | NR                             | N/A                                   | Medium                                |
| Jiang 2005 <sup>32</sup><br>Crossover   | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)       | Ginkgo biloba              |     | 0             | No Treatment  |     | 0             |                                |                                       | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 – single dose)         | Omega-3                    |     | 0             | Placebo       |     | 1             |                                | N/A                                   | Medium                                |
| Maki 2008 <sup>41</sup><br>Crossover    | N/A                                 | Mixed: Low, Moderate and high risk     | Simvastatin (20)                | Omega-3                    | 40  | 3             |               | 40  | 1             |                                |                                       | Medium                                |
| Jiang 2005 <sup>32</sup><br>Crossover   | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)       | Ginger                     |     | 1             | No Treatment  |     | 0             |                                |                                       | Medium                                |

**Evidence Table 128. KQ3—Dichotomous—Dizziness**

| Author Year<br>Study Design              | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel       | NR                                  | At high risk for CHD                   | Warfarin (3.5)       | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                | No events occurred. No data reported. | Medium                                |
| Tankanow 2003 <sup>65</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.25)       | Hawthorn                   | 8  | 1             | No Treatment  | 8  | 0             |                                |                                       | Medium                                |



**Evidence Table 129. KQ3—Dichotomous—Fasting blood glucose**

| Author Year Study Design           | Definition of outcome (if relevant)  | CHD Risk Category          | CVD drug (dose mg/d)     | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|--|----------------------------|--------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Napoli 1998 <sup>52</sup> Parallel | Data imputed—there were no differences between baseline and post treatment values. | Unclear                    | Pravastatin (20-40)      | Vitamin E                  |    | 0             | No Treatment  |    | 0             |                                | No differences in routine laboratory tests or adverse events were registered during the study in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups. | Medium                                |
| Reyes 1984 <sup>59</sup> Parallel  | NR   | Mixed: Low and/or Moderate | Hydrochlorothiazide (50) | Magnesium                  | 13 | 0             | Placebo       | 8  | 0             |                                |  | Medium                                |

**Evidence Table 130. KQ3-Dichotomous—Fishy taste**

| Author<br>Year<br><br>Study<br>Design      | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category                | CVD<br>drug<br>(dose<br>mg/d)    | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group<br>2: Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk of<br>Bias (ROB)<br>Assessment |
|--|---|-------------------------------------|----------------------------------|----------------------------------|----|---------------------|------------------|----|---------------------|--------------------------------------|------------------------|---|
| Mueller<br>1991 <sup>51</sup><br>Crossover | N/A                                       | Mixed:<br>Low<br>and/or<br>Moderate | ASA<br>(325 –<br>single<br>dose) | Omega-3                          |    | 4                   | Placebo          |    | 0                   |                                      |                        | Medium                                      |

**Evidence Table 12. KQ3—Dichotomous—Flatulence**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)    | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|-------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Roth 2009 <sup>60</sup><br>Parallel        | NR                                  | Unclear                                | Fenofibrates (130)      | Omega-3                    | 84 | 1             | Placebo       | 83 | 3             |                                |   | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)       | Omega-3                    | 50 |               | No Treatment  | 50 |               | NR                             | No treatment related trends regarding ECG or other clinical or laboratory markers were found (no specific data) | Medium                                |
| Tankanow 2003 <sup>65</sup><br>Crossover   | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.25)          | Hawthorn                   | 8  | 1             | No Treatment  | 8  | 0             |                                |   | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 – single dose) | Omega-3                    |    | 0             | Placebo       |    | 1             |                                |   | Medium                                |

**Evidence Table 132. KQ3—Dichotomous—Flushing**

| Author Year Study Design             | Definition of outcome (if relevant) | CHD Risk Category | CVD drug (dose mg/d)    | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|-------------------|-------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Isley 2007 <sup>31</sup><br>Parallel | NR                                  | Unclear           | Niacin (500); ASA (325) | Omega-3                    | 8  |               | No Treatment  | 7  |               |                                | no data reported. Difference between groups in flushing is not significant. | Medium                                |

**Evidence Table 133. KQ3—Dichotomous—Gastrointestinal adverse events**

| Author Year<br>Study Design                | Definition of outcome (if relevant)                                       | CHD Risk Category                  | CVD drug (dose mg/d)  | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|---|------------------------------------|---|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel    | NR  | Unclear                            | Simvastatin (40)  | Omega-3                    | 122 | 5             | Placebo       | 132 | 3             |                                |  | Medium                                |
| D'Arcangues 2004 <sup>13</sup><br>Parallel | NR  | Mixed: Low and/or Moderate         | ASA (80)  | Vitamin E                  | 121 |               | No Treatment  | 122 |               |                                | Treatment course was for 10 days. But followup went on for up to 1 year. | Medium                                |
| Garg 1995 <sup>24</sup><br>Parallel        | NR  | At high risk for CHD               | ASA and/or pentoxifylline (NR)                                    | Ginkgo biloba              | 29  | 4             | Placebo       | 26  | 3             |                                |  | Medium-high                           |
| Roth 2009 <sup>60</sup><br>Parallel        | NR  | Unclear                            | Fenofibrate (130)   | Omega-3                    | 84  | 7             | Placebo       | 83  | 5             |                                |  | Medium                                |
| Dehmer 1988 <sup>17</sup><br>Parallel      | belching, dyspepsia flatulence in tx group vs. Dyspepsia in control group | At high risk for CHD               | Aspirin (325)+ Dipyridamole (225) + Calcium channel blockers (NR) | Omega-3                    | 43  | 7             | No Treatment  | 39  | 3             |                                |  | Medium                                |
| Eritsland 1996 <sup>21</sup><br>Parallel   | NR  | At high risk for CHD               | Warfarin (NR)   | Omega-3                    | 174 | 9             | No Treatment  | 145 | 0             |                                |  | Medium                                |
| Eritsland 1996 <sup>21</sup><br>Parallel   | NR  | At high risk for CHD               | Aspirin (300)   | Omega-3                    | 143 | 7             | No Treatment  | 148 | 12            |                                |  | Medium                                |
| Maki 2008 <sup>41</sup><br>Crossover       | N/A   | Mixed: Low, Moderate and high risk | Simvastatin (20)  | Omega-3                    | 40  | 1             | Placebo       | 40  | 1             |                                |  | Medium                                |

**Evidence Table 133. KQ3—Dichotomous—Gastrointestinal adverse events (continued)**

| Author Year<br>Study Design           | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)      | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-------------------------------------|--|---------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Wolf 2006 <sup>68</sup><br>Crossover  | N/A                                 | Mixed: Low and/or Moderate             | ASA (500)                 | Ginkgo biloba              | 50 | 6             | Placebo       | 50 | 9             |                                |                     | Low-medium                            |
| Mauro 2003 <sup>43</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.5 single dose) | Ginkgo biloba              |    | 1             | No Treatment  |    |               |                                |                     | Medium                                |

**Evidence Table 134. KQ3—Dichotomous—Generalized edema**

| Author<br>Year<br><br>Study<br>Design   | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category                           | CVD drug<br>(dose<br>mg/d) | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group<br>2:<br>Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias (ROB)<br>Assessment |
|---|---|--|----------------------------|----------------------------------|----|---------------------|---------------------|----|---------------------|--------------------------------------|------------------------|---|
| Maki<br>2008 <sup>41</sup><br>Crossover | N/A                                       | Mixed:<br>Low,<br>Moderate<br>and high<br>risk | Simvastatin<br>(20)        | Omega-3                          | 40 | 0                   | Placebo             | 40 | 2                   |                                      |                        | Medium                                      |

**Evidence Table 135. KQ3—Dichotomous—Glomerular filtration rate (GFR)**

| Author Year<br>Study Design          | Definition of outcome (if relevant)            | CHD Risk Category        | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|--|--------------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Young 2007 <sup>70</sup><br>Parallel | calculated glomerular filtration rate < 45/min | Mixed: Mod and high risk | Simvastatin (10-40)  | Co-Q10                     | 22 | 0             | Placebo       | 22 | 0             |                                | Exclusion criteria included: calculated glomerular filtration rate <45 ml/min' and results state: "renal function, ...[was] not altered with either regime." Thus, counts of 0 and 0 were added for each arm | Medium                                |



**Evidence Table 13. KQ3—Dichotomous—Headache**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel         | N/A                                 | At high risk for CHD                   | Warfarin (3.5)                  | Ginseng                    | 12  |               | No Treatment  | 13  | 0             |                                | No events occurred. No data reported.                                    | Medium                                |
| D'Arcanques 2004 <sup>13</sup><br>Parallel | N/A                                 | Mixed: Low and/or Moderate             | ASA (80)                        | Vitamin E                  | 121 |               | No Treatment  | 122 |               |                                | Treatment course was for 10 days. But followup went on for up to 1 year. | Medium                                |
| Gosai 2008 <sup>26</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)               | Omega-3                    | 44  | 5             | No Treatment  | 46  | 7             |                                |  | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)               | Omega-3                    | 50  |               | No Treatment  | 50  |               |                                |  | Medium                                |
| Maki 2008 <sup>41</sup><br>Crossover       | N/A                                 | Mixed: Low, Moderate and high risk     | Simvastatin (20)                | Omega-3                    | 40  | 1             | Placebo       | 40  | 1             |                                |  | Medium                                |
| Tankanow 2003 <sup>65</sup><br>Crossover   | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.25 )                 | Hawthorn                   | 8   | 1             | No Treatment  | 8   | 0             |                                |  | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 – single dose)         | Omega-3                    |     | 1             | Placebo       |     | 1             |                                |  | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed: Low and/or Moderate             | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24  | 2             | No Treatment  | 24  | 0             |                                |  | Medium                                |

**Evidence Table 14. KQ3—Dichotomous—Hematuria**

| Author Year<br>Study Design          | Definition of outcome (if relevant) | CHD Risk Category | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|-------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Macan 2006 <sup>40</sup><br>Parallel | NR                                  | Unclear           | Warfarin (NR)        | Garlic                     | 22 | 0             | Placebo       | 26 | 0             |                                |                     | Medium                                |

**Evidence Table 138. KQ3—Dichotomous—Hyperglycemia**

| Author Year<br>Study Design          | Definition of outcome (if relevant) | CHD Risk Category                  | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|------------------------------------|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Maki 2008 <sup>41</sup><br>Crossover | N/A                                 | Mixed: Low, Moderate and high risk | Simvastatin (20)                | Omega-3                    | 40 | 2             | Placebo       | 40 | 1             |                                |                     | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover  | N/A                                 | Mixed: Low and/or Moderate         | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             |                                |                     | Medium                                |

**Evidence Table 139. KQ3—Dichotomous—Hypoglycemia**

| Author Year<br>Study Design         | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|-------------------------------------|-------------------------------------|----------------------------|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Crossover | N/A                                 | Mixed: Low and/or Moderate | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             |                                |                     | Medium                                |

**Evidence Table 140. KQ3—Dichotomous—Hyperkalaemia**

| Author Year<br>Study Design            | Definition of outcome (if relevant) | CHD Risk Category          | CVD drug (dose mg/d)     | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|----------------------------|--------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Ferraro 2009 <sup>22</sup><br>Parallel | serum potassium > 5.5 mEq/l)        | Unclear                    | Ramipril (10)            | Omega-3                    | 15 | 0             | No Treatment  | 15 | 0             |                                |                     | Medium                                |
| Reyes 1984 <sup>59</sup><br>Parallel   | NR                                  | Mixed: Low and/or Moderate | Hydrochlorothiazide (50) | Magnesium                  | 13 | 0             | Placebo       | 8  | 0             |                                |                     | Medium                                |

**Evidence Table 141. KQ3—Dichotomous—Hypokalaemia**

| Author<br>Year<br><br>Study<br>Design   | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category                           | CVD drug<br>(dose<br>mg/d) | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group<br>2:<br>Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias (ROB)<br>Assessment |
|---|---|--|----------------------------|----------------------------------|----|---------------------|---------------------|----|---------------------|--------------------------------------|------------------------|---|
| Maki<br>2008 <sup>41</sup><br>Crossover | N/A                                       | Mixed:<br>Low,<br>Moderate<br>and high<br>risk | Simvastatin<br>(20)        | Omega-3                          | 40 | 1                   | Placebo             | 40 | 1                   |                                      |                        | Medium                                      |

**Evidence Table 142. KQ3—Dichotomous—Indigestion**

| Author Year<br>Study Design        | Definition of outcome (if relevant) | CHD Risk Category    | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|------------------------------------|-------------------------------------|----------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel | NR                                  | At high risk for CHD | Warfarin (3.5)       | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                | No events occurred. No data reported. | Medium                                |

**Evidence Table 143. KQ3—Dichotomous—Infection**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|-------------------|----------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---------------------|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel | NR                                  | Unclear           | Simvastatin (40)     | Omega-3                    | 122 | 4             | Placebo       | 132 | 1             |                                |                     | Medium                                |



**Evidence Table 144. KQ3—Dichotomous—INR**

| Author Year<br>Study Design          | Definition of outcome (if relevant) | CHD Risk Category | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|-------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Bender 1998 <sup>8</sup><br>Parallel | NR                                  | Unclear           | Warfarin (NR)        | Omega-3                    | 6  |               | No Treatment  | 5  |               |                                | numeric data is not separated by groups. Three patients with unstable INR withdrew but no group designation reported. | High                                  |

**Evidence Table 145. KQ3—Dichotomous—INR > 3.5**

| Author Year Study Design        | Definition of outcome (if relevant) | CHD Risk Category    | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments                   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------|-------------------------------------|----------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------------------------|---------------------------------------|
| Lee 2008 <sup>36</sup> Parallel | NR                                  | At high risk for CHD | Warfarin (3.5)       | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                | No events occurred. No data reported. | Medium                                |

**Evidence Table 146. KQ3—Dichotomous—Insomnia**

| Author Year<br>Study Design              | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Tankanow 2003 <sup>65</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.25)       | Hawthorn                   | 8  | 1             | No Treatment  | 8  | 0             |                                |                     | Medium                                |

**Evidence Table 147. KQ3—Dichotomous outcomes—Leukopenia**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                  | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|------------------------------------|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A                                 | Mixed: Low and/or mod to high risk | Simvastatin (10-40)             | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                |                     | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed: Low and/or Moderate         | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             |                                |                     | Medium                                |

**Evidence Table 148. KQ3—Dichotomous outcomes—Major bleeding**

| Author<br>Year<br><br>Study<br>Design                | Definition<br>of<br>outcome<br>(if<br>relevant) | CHD Risk<br>Category                            | CVD<br>drug<br>(dose<br>mg/d)        | Group 1:<br>Name<br>(supplement) | N1 | N1<br>with<br>event | Group 2:<br>Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias (ROB)<br>Assessment |
|--|---|---|--------------------------------------|----------------------------------|----|---------------------|------------------|----|---------------------|--------------------------------------|------------------------|---|
| Mohammed<br>Abdul<br>2008 <sup>49</sup><br>Crossover | N/A   | At low risk<br>for CHD<br>(0-1 risk<br>factors) | Warfarin<br>(26 –<br>single<br>dose) | Garlic                           | 12 | 0                   | No<br>Treatment  | 12 | 0                   |                                      |                        | Medium                                      |

**Evidence Table 149. KQ3—Dichotomous outcomes—Myalgia**

| Author Year<br>Study Design            | Definition of outcome (if relevant) | CHD Risk Category                  | CVD drug (dose mg/d)   | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name                        | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|------------------------------------|--|----------------------------|----|---------------|--------------------------------------|----|---------------|--------------------------------|--|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br>Parallel | NR                                  | Unclear                            | Atorvastatin (10)  | Co-Q10                     |    |               | Placebo                              |    |               |                                | "There were no complaints of myalgia or muscle weakness". Data not reported. | Medium                                |
| Caso 2007 <sup>11</sup><br>Parallel    | NR                                  | Unclear                            | Simvastatin (22);<br>Atorvastatin (7);<br>Pravastatin (2);<br>Lovastatin (1) | Co-Q10                     | 18 | 16            | Other dietary supplement – Vitamin E | 14 | 3             |                                |  | Low                                   |
| Maki 2008 <sup>41</sup><br>Crossover   | N/A                                 | Mixed: Low, Moderate and high risk | Simvastatin (20)   | Omega-3                    | 40 | 1             | Placebo                              | 40 | 1             |                                |  | Medium                                |

**Evidence Table 150. KQ3—Dichotomous—Nausea**

| Author Year<br>Study Design              | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Paolissa 1992 <sup>57</sup><br>Parallel  | NR                                  | Unclear                                | Hydrochlorothiazide (25)        | Magnesium                  | 9  | 0             | Placebo       | 9  | 0             |                                | "There were no complaints of myalgia or muscle weakness". Data not reported. | Medium                                |
| Roth 2009 <sup>60</sup><br>Parallel      | NR                                  | Unclear                                | Fenofibrate (130)               | Omega-3                    | 84 | 5             | Placebo       | 83 | 3             |                                |  | Medium                                |
| Tankanow 2003 <sup>65</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.25 )                 | Hawthorn                   | 8  | 2             | No Treatment  | 8  | 1             |                                |  | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover  | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 – single dose)         | Omega-3                    |    | 3             | Placebo       |    | 3             |                                |  | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover      | N/A                                 | Mixed: Low and/or Moderate             | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 2             | No Treatment  | 24 | 0             |                                |  | Medium                                |

**Evidence Table 151. KQ3—Dichotomous—Other adverse events**

| Author Year<br>Study Design            | Definition of outcome (if relevant)  | CHD Risk Category       | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|--|---------------------------------------|
| Mabuchi 2007 <sup>39</sup><br>Parallel | General Adverse events<br>Vital signs, urinalysis, serum chemical values or hematological values | Unclear                 | Atorvastatin (10)    | Co-Q10                     |    |               | Placebo       |    |               |                                | No clinically significant changes in vital signs, urinalysis, serum chemical values or hematological values." No data presented. | Medium                                |
| Gardner 2007 <sup>23</sup><br>Parallel | Upset stomach  | Mixed: Moderate to high | ASA (325)            | Ginkgo biloba              | 30 | 6             | Placebo       | 30 | 5             |                                |  | Low                                   |



**Evidence Table 151. KQ3—Dichotomous—Other adverse events (continued)**

| Author Year<br>Study Design             | Definition of outcome (if relevant) | CHD Risk Category | CVD drug (dose mg/d)     | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|-------------------------------------|-------------------|--------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---|---------------------------------------|
| Davidson 2007 <sup>14</sup><br>Parallel | Nasopharyngitis                     | Unclear           | Simvastatin (40)         | Omega-3                    | 122 | 4             | Placebo       | 132 | 3             |                                | Note: specific AEs were those reported by $\geq$ 1% of patients receiving simva + omega-3 that occurred with higher frequency than in those receiving simva + placebo. They include Nasopharyngitis, URT infection, diarrhea, dyspepsia, bronchitis, cystitis, alanine aminotransferase elevation and gastroenteritis | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | Bronchitis                          | Unclear           | Simvastatin (40)         | Omega-3                    | 122 | 2             | Placebo       | 132 | 2             |                                |   | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | Cystitis                            | Unclear           | Simvastatin (40)         | Omega-3                    | 122 | 2             | Placebo       | 132 | 1             |                                |   | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | Rhabdomyolysis                      | Unclear           | Simvastatin (40)         | Omega-3                    | 122 | 0             | Placebo       | 132 | 0             |                                | described as no AEs involved rhabdomyolysis   | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel | Pneumonia                           | Unclear           | Simvastatin (40)         | Omega-3                    | 122 | 1             | Placebo       | 132 | 0             |                                |   | Medium                                |
| McDowell 1994 <sup>44</sup><br>Parallel | Malaise                             | Unclear           | Simvastatin (20)         | Vitamin E                  | 8   | 1             | Placebo       | 8   | 1             |                                |   | Medium                                |
| McDowell 1994 <sup>44</sup><br>Parallel | Abdominal discomfort                | Unclear           | Simvastatin (20)         | Vitamin E                  | 8   | 0             | Placebo       | 8   | 2             |                                |   | Medium                                |
| Paolissa 1992 <sup>57</sup><br>Parallel | Adverse events (general)            | Unclear           | Hydrochlorothiazide (25) | Magnesium                  | 9   | 0             | Placebo       | 9   | 0             |                                |   | Medium                                |

**Evidence Table 151. KQ3—Dichotomous—Other adverse events (continued)**

| Author Year<br>Study Design              | Definition of outcome (if relevant)    | CHD Risk Category  | CVD drug (dose mg/d)   | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences   | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|--|--|------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--|---------------------|---------------------------------------|
| Roth 2009 <sup>60</sup><br>Parallel      | diabetes                               | Unclear  | Fenofibrate (130)      | Omega-3                    | 84  | 1             | Placebo       | 83  | 0             |  |                     | Medium                                |
| Liu 2003 <sup>37</sup><br>Parallel       | Adverse events (general) (Not defined) | Unclear  | Simvastatin (10)       | Omega-3                    | 19  | 0             | No Treatment  | 18  | 0             |  |                     | Medium                                |
| Glynn 2007 <sup>25</sup><br>Parallel     | Cancer                                 | Mixed: Low and/or moderate                                 | ASA (100)              | Vitamin E                  |     | 716           | Placebo       |     | 722           | Crude event risk ratio: 0.99<br>95%CI Lower: 0.89<br>95%CI Upper: 1.1<br>P: 0.86 |                     | Medium                                |
| Yuan 2004 <sup>71</sup><br>Parallel      | AE of clinical importance              | Mixed: Low and/or moderate                                 | Warfarin (5)           | Ginseng                    | 12  | 0             | No Treatment  | 8   | 0             |  |                     | Low                                   |
| Eritsland 1996 <sup>21</sup><br>Parallel | dysphagia                              | At high risk for CHD                                       | Warfarin (NR)          | Omega-3                    | 174 | 3             | No Treatment  | 145 | 0             |  |                     | Medium                                |
| Eritsland 1996 <sup>21</sup><br>Parallel | dysphagia                              | At high risk for CHD                                       | Aspirin (300)          | Omega-3                    | 143 | 3             | No Treatment  | 148 | 0             |  |                     | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel  | retinopathy                            | At high risk for CHD                                       | Fenofibrate (200)      | Co-Q10                     | 18  | 5             | No Treatment  | 17  | 6             |  |                     | Low-medium                            |
| Chan 2002 <sup>12</sup><br>Parallel      | N/A                                    | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)      | Omega-3                    | 11  | 0             | No Treatment  | 13  | 0             |  |                     | Medium                                |
| Avogaro 1974 <sup>3</sup><br>Crossover   | Nausea+ flushing                       | Unclear  | Propranolol (20 or 60) | Niacin                     | 10  | 0             | No Treatment  | 10  | 0             |  |                     | High                                  |
| Avogaro 1974 <sup>3</sup><br>Crossover   | Hypotension + asthma                   | Unclear  | Propranolol (20 or 60) | Niacin                     | 10  | 0             | No Treatment  | 10  | 1             |  |                     | High                                  |

**Evidence Table 152. KQ3—Dichotomous—Prothrombin time (above/below threshold)**

| Author Year<br>Study Design           | Definition of outcome (if relevant) | CHD Risk Category    | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|-------------------------------------|----------------------|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel    | N/A                                 | At high risk for CHD | Warfarin (3.5)       | Ginseng                    | 12 |               | No Treatment  | 13 | 0             |                                | No events occurred. No data reported.   | Medium                                |
| Napoli 1998 <sup>52</sup><br>Parallel | N/A                                 | Unclear              | Pravastatin (20-40)  | Vitamin E                  |    |               | No Treatment  |    |               |                                | No differences in routine laboratory tests or adverse events were registered during the study (data not shown); in particular there were no differences between the values recorded in each individual after treatment compared to baseline values, and no differences between the treatment groups.” | Medium                                |

**Evidence Table 153. KQ3—Dichotomous—Serious adverse events (composite outcome)**

| Author Year<br>Study Design              | Definition of outcome (if relevant) | CHD Risk Category                  | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|------------------------------------|----------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Bays 2010 <sup>6</sup><br>Parallel       | N/A                                 | Unclear                            | Atorvastatin (10-40) | Omega-3                    |     |               | Placebo       |     |               |                                | <5% in Omega-3 group and <5% in Placebo group  | Medium                                |
| Mabuchi 2007 <sup>39</sup><br>Parallel   | N/A                                 | Unclear                            | Atorvastatin (10)    | Co-Q10                     |     |               | Placebo       |     |               |                                | "There were no serious adverse events" Data not reported.  | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel  | N/A                                 | Unclear                            | Simvastatin (40)     | Omega-3                    | 122 | 4             | Placebo       | 132 | 1             |                                |  | Medium                                |
| Roth 2009 <sup>60</sup><br>Parallel      | N/A                                 | Unclear                            | Fenofibrate (130)    | Omega-3                    | 84  | 3             | Placebo       | 83  | 1             |                                |  | Medium                                |
| Maki 2008 <sup>41</sup><br>Crossover     | N/A                                 | Mixed: Low, moderate and high risk | Simvastatin (20)     | Omega-3                    |     | 1             | Placebo       |     | 0             |                                |  | Medium                                |
| McKenney 2006 <sup>45</sup><br>Crossover | N/A                                 | Mixed: Low and/or moderate         | Simvastatin (80)     | Omega-3                    | 24  | 1             | No Treatment  | 24  | 0             |                                |  | Medium                                |
| Wolf 2006 <sup>68</sup><br>Crossover     | N/A                                 | Mixed: Low and/or moderate         | ASA (500)            | Gingko Biloba              | 50  | 0             | Placebo       | 50  | 0             |                                | Other outcomes (both dichotomous and continuous) assessed in this study but not extracted: fibrinogen, D-dimers, quick value, coagulation factors (a mix), Protein C activity, Protein S activity, Platelet morphological assessment, Platelet orbitometric asse | Low-medium                            |

**Evidence Table 153. KQ3—Dichotomous—Serious adverse events (composite outcome)**

| Author Year<br>Study Design            | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)                              | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Jiang 2005 <sup>32</sup><br>Crossover  | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)                         | Gingko Biloba              |    | 0             | No Treatment  |    | 0             |                                |                     | Medium                                |
| Wirell 1994 <sup>67</sup><br>Crossover | N/A                                 | Unclear                                | metoprolol, atenolol, pindolol & propranolol (NR) | Magnesium                  | 19 |               | Placebo       | 20 | 0             |                                |                     | Medium                                |

**Evidence Table 154. KQ3—Dichotomous—Sinusitis**

| Author Year<br>Study Design          | Definition of outcome (if relevant) | CHD Risk Category                           | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|---|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Maki 2008 <sup>41</sup><br>Crossover | N/A                                 | Mixed:<br>Low,<br>Moderate<br>and high risk | Simvastatin (20)     | Omega-3                    | 40 | 0             | Placebo       | 40 | 2             |                                |                     | Medium                                |

**Evidence Table 155. KQ3—Dichotomous—Thrombocytopenia**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                     | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|---------------------------------------|---------------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A                                 | Mixed:<br>Low and/or mod to high risk | Simvastatin (10-40)             | Omega-3                    | 14 | 0             | Placebo       | 16 | 0             |                                |                     | Medium                                |
| Kim 2010 <sup>35</sup><br>Crossover        | N/A                                 | Mixed:<br>Low and/or Moderate         | Ticlopidine (250 – single dose) | Ginkgo biloba              | 24 | 0             | No Treatment  | 24 | 0             |                                |                     | Medium                                |

**Evidence Table 156. KQ3—Dichotomous—Total adverse events**

| Author Year                                | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)            | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|---|---------------------------------------|
| Lee 2008 <sup>36</sup><br>Parallel         | N/A                                 | At high risk for CHD                   | Warfarin (3.5)                  | Ginseng                    | 12  |               | No Treatment  | 13  | 0             |                                | No events occurred. No data reported.   | Medium                                |
| Gardner 2007 <sup>23</sup><br>Parallel     | N/A                                 | Mixed: Moderate to high                | ASA (325)                       | Ginkgo biloba              | 30  | 11            | Placebo       | 3   | 15            | P: 0.4                         | No difference between groups  | Low                                   |
| Davidson 2007 <sup>14</sup><br>Parallel    | N/A                                 | Unclear                                | Simvastatin (40)                | Omega-3                    | 122 | 51            | Placebo       | 132 | 63            |                                |   | Medium                                |
| Sconce 2007 <sup>61</sup><br>Parallel      | N/A                                 | Unclear                                | Warfarin ( 3.8-4.4 vs. 3.3-3.4) | Vitamin K                  | 35  | 0             | Placebo       | 33  | 2             |                                |   | Medium                                |
| D'Arcangues 2004 <sup>13</sup><br>Parallel | N/A                                 | Mixed: Low and/or Moderate             | ASA (80)                        | Vitamin E                  | 121 |               | No Treatment  | 122 |               | P: 0.0584                      | The difference in the occurrence of any side effect between the two groups was not significant. | Medium                                |
| Abdul 2010 <sup>1</sup><br>Crossover       | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25-single dose)       | Echinacea                  | 12  | 0             | No Treatment  | 12  | 0             |                                |   | Medium                                |
| Gosai 2008 <sup>26</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Rosuvastatin (40)               | Omega-3                    | 44  | 27            | No Treatment  | 46  | 30            |                                | N/A   | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors) | Atorvastatin (80)               | Omega-3                    | 50  | 12            | No Treatment  | 50  | 12            |                                | N/A   | Medium                                |
| McKenney 2006 <sup>45</sup><br>Crossover   | N/A                                 | Mixed: Low and/or Moderate             | Simvastatin (80)                | Omega-3                    | 24  | 9             | No Treatment  | 23  | 8             |                                |   | Medium                                |
| Mauro 2003 <sup>43</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.5 single dose)       | Ginkgo biloba              |     | 1             | No Treatment  |     | 0             |                                |   | Medium                                |



**Evidence Table 157. KQ3—Dichotomous—Upper respiratory infection**

| Author Year<br>Study Design          | Definition of outcome (if relevant) | CHD Risk Category                           | CVD drug (dose mg/d) | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments | Overall Risk of Bias (ROB) Assessment |
|--------------------------------------|-------------------------------------|---|----------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---------------------|---------------------------------------|
| Maki 2008 <sup>41</sup><br>Crossover | N/A                                 | Mixed:<br>Low,<br>Moderate<br>and high risk | Simvastatin (20)     | Omega-3                    | 40 | 0             | Placebo       | 40 | 2             |                                |                     | Medium                                |

**Evidence Table 158. KQ3—Dichotomous—Vomiting**

| Author<br>Year<br>Study<br>Design          | Definition<br>of outcome<br>(if relevant) | CHD Risk<br>Category | CVD drug<br>(dose mg/d)     | Group 1: Name<br>(supplement) | N1 | N1<br>with<br>event | Group 2:<br>Name | N2 | N2<br>with<br>event | Estimates of<br>Group<br>Differences | Additional<br>comments | Overall Risk<br>of Bias (ROB)<br>Assessment |
|--|---|----------------------|-----------------------------|-------------------------------|----|---------------------|------------------|----|---------------------|--------------------------------------|------------------------|---|
| Paolissa<br>1992 <sup>57</sup><br>Parallel | NR  | Unclear              | Hydrochlorothiazide<br>(25) | Magnesium                     | 9  | 0                   | Placebo          | 9  | 0                   |                                      |                        | Medium                                      |

**Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events**

| Author Year                                | Definition of outcome (if relevant)              | CHD Risk Category             | CVD drug (dose mg/d)              | Group 1: Name (supplement) | N1  | N1 with event | Group 2: Name | N2  | N2 with event | Estimates of Group Differences | Additional comments  | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------------------|-----------------------------------|----------------------------|-----|---------------|---------------|-----|---------------|--------------------------------|--|---------------------------------------|
| Bays 2010 <sup>6</sup><br>Parallel         | N/A  | Unclear                       | Atorvastatin (10-40)              | Omega-3                    | 123 | 8             | Placebo       | 122 | 6             |                                |  | Medium                                |
| Ferraro 2009 <sup>22</sup><br>Parallel     | N/A  | Unclear                       | Ramipril (10)                     | Omega-3                    | 15  | 0             | No Treatment  | 15  | 0             |                                |  | Medium                                |
| Mabuchi 2007 <sup>39</sup><br>Parallel     | N/A  | Unclear                       | Atorvastatin (10)                 | Co-Q10                     |     |               | Placebo       |     |               |                                | "There were no serious adverse events". Data not reported.               | Medium                                |
| Gardner 2007 <sup>23</sup><br>Parallel     | N/A  | Mixed: Moderate to high       | ASA (325)                         | Ginkgo biloba              |     | 3             | Placebo       |     | 2             |                                |  | Low                                   |
| Young 2007 <sup>70</sup><br>Parallel       | N/A  | Mixed: Moderate and high risk | Simvastatin (10 - 40)             | Co-Q10                     |     | 6             | Placebo       |     | 4             |                                |  | Medium                                |
| Davidson 2007 <sup>14</sup><br>Parallel    | N/A  | Unclear                       | Simvastatin (40)                  | Omega-3                    | 122 | 3             | Placebo       | 132 | 3             |                                | no description   | Medium                                |
| D'Arcangues 2004 <sup>13</sup><br>Parallel | discontinuation due to side effects of treatment | Mixed: Low and/or Moderate    | ASA (80)                          | Vitamin E                  | 121 | 30            | No Treatment  | 122 | 19            |                                | Treatment course was for 10 days. But followup went on for up to 1 year. | Medium                                |
| Nordøy 2000 <sup>54</sup><br>Parallel      | N/A  | Mixed: Low and/or Moderate    | Simvastatin (20)                  | Omega-3                    | 21  | 0             | Placebo       | 20  | 0             |                                |  | Medium                                |
| Garg 1995 <sup>24</sup><br>Parallel        | N/A  | At high risk for CHD          | ASA and/or pentoxiphylline (20)   | Ginkgo biloba              | 29  | 0             | Placebo       | 26  | 0             |                                |  | Medium-high                           |
| Paolissa 1992 <sup>57</sup><br>Parallel    | N/A  | Unclear                       | Hydrochlorthiazide (25)           | Magnesium                  | 9   | 0             | Placebo       | 9   | 0             |                                |  | Medium                                |
| Kaul 1992 <sup>34</sup><br>Parallel        | GI intolerance--stopped capsules of fish oil     | At high risk for CHD          | Calcium channel blocker, ASA (NR) | Omega-3                    | 58  | 2             | No Treatment  | 49  | 0             |                                |  | Low-medium                            |

**Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category  | CVD drug (dose mg/d)      | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments                                 | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---------------------------|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Nordøy 2003 <sup>55</sup><br>Parallel      | N/A                                 | Mixed: Moderate and high risk                              | Atorvastatin (10)         | Omega-3                    | 22 | 0             | Placebo       | 20 | 0             |                                |   | Low                                   |
| Roth 2009 <sup>60</sup><br>Parallel        | N/A                                 | Unclear  | Fenofibrate (130)         | Omega-3                    | 84 | 4             | Placebo       | 83 | 4             |                                |   | Medium                                |
| Isley 2007 <sup>31</sup><br>Parallel       | N/A                                 | Unclear  | Niacin (500); ASA (325)   | Omega-3                    | 8  |               | No Treatment  | 7  |               |                                |   | Medium                                |
| Bender 1998 <sup>8</sup><br>Parallel       | N/A                                 | Unclear  | Warfarin ( NR)            | Omega-3                    | 6  | 0             | No Treatment  | 5  | 0             |                                |   | High                                  |
| Chan 2002 <sup>12</sup><br>Parallel        | N/A                                 | At moderate/moderately high risk for CHD (2+ risk factors) | Atorvastatin (40)         | Omega-3                    | 11 | 0             | No Treatment  | 13 | 0             |                                |   | Medium                                |
| Playford 2003 <sup>58</sup><br>Parallel    | N/A                                 | At high risk for CHD                                       | Fenofibrate (200)         | Co-Q10                     | 18 |               | No Treatment  | 17 |               |                                |   | Low-medium                            |
| Abdul 2010 <sup>1</sup><br>Crossover       | N/A                                 | At low risk for CHD (0-1 risk factors)                     | Warfarin (25 single dose) | Echinacea                  | 12 | 0             | No Treatment  | 12 | 0             |                                |   | Medium                                |
| Gosai 2008 <sup>26</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors)                     | Rosuvastatin (40)         | Omega-3                    | 48 | 2             | No Treatment  | 48 | 4             |                                |   | Medium                                |
| Di Spirito 2008 <sup>19</sup><br>Crossover | N/A                                 | At low risk for CHD (0-1 risk factors)                     | Atorvastatin (80)         | Omega-3                    | 50 | 1             | No Treatment  | 50 | 0             |                                | This one is the same patient who had an elevated CK | Medium                                |
| Maki 2008 <sup>41</sup><br>Crossover       | N/A                                 | Mixed: Low, Moderate and high risk                         | Simvastatin (20)          | Omega-3                    |    | 2             | Placebo       |    | 1             |                                |   | Medium                                |
| McKenney 2006 <sup>45</sup><br>Crossover   | N/A                                 | Mixed: Low and/or Moderate                                 | Simvastatin (80)          | Omega-3                    | 24 | 1             | No Treatment  | 24 | 0             |                                |   | Medium                                |

**Evidence Table 159. KQ3—Dichotomous—Withdrawal due to adverse events (continued)**

| Author Year<br>Study Design                | Definition of outcome (if relevant) | CHD Risk Category                      | CVD drug (dose mg/d)                              | Group 1: Name (supplement) | N1 | N1 with event | Group 2: Name | N2 | N2 with event | Estimates of Group Differences | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|-------------------------------------|--|---|----------------------------|----|---------------|---------------|----|---------------|--------------------------------|---|---------------------------------------|
| Jiang 2005 <sup>32</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)                         | Gingko biloba              |    | 0             | No Treatment  |    | 0             |                                |   | Medium                                |
| Jiang 2004 <sup>33</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Warfarin (25 single dose)                         | Ginseng                    |    | 0             | No Treatment  |    | 0             |                                |   | Medium                                |
| Mauro 2003 <sup>43</sup><br>Crossover      | N/A                                 | At low risk for CHD (0-1 risk factors) | Digoxin (0.5 single dose)                         | Gingko biloba              |    | 0             | No Treatment  |    | 0             |                                |   | Medium                                |
| Balestrieri 1996 <sup>4</sup><br>Crossover | N/A                                 | Mixed: Low and/or mod to high risk     | Simvastatin (10 to 40)                            | Omega-3                    | 16 | 1             | Placebo       | 16 | 1             |                                | Two patients (one in each group) interrupted the study in the first month. One suffered from acute myocardial infarction, another one underwent a resection of abdominal aortic aneurysm. | Medium                                |
| Paolissa 1992 <sup>36</sup><br>Crossover   | N/A                                 | At high risk for CHD                   | Nifedipine (88)                                   | Vitamin E                  |    | 0             | Placebo       |    | 0             |                                |   | Medium                                |
| Mueller 1991 <sup>51</sup><br>Crossover    | N/A                                 | Mixed: Low and/or Moderate             | ASA (325 single dose)                             | Omega-3                    |    | 0             | Placebo       |    | 0             |                                |   | Medium                                |
| Wirell 1994 <sup>67</sup><br>Crossover     | N/A                                 | Unclear                                | metoprolol, atenolol, pindolol & propranolol (NR) | Magnesium                  | 19 |               | Placebo       | 20 | 0             |                                |   | Medium                                |
| Avogaro 1974 <sup>3</sup><br>Crossover     | N/A                                 | Unclear                                | Propranolol (20 or 60)                            | Niacin                     | 10 | 0             | No Treatment  | 10 | 1             |                                |   | High                                  |

**Evidence Table 160. KQ4—Continuous data—Absorption**

| Author Year<br>Study Design                     | Definition<br>of outcome | CHD Risk<br>Category | CVD<br>drug<br>(dose<br>mg/d) | Supplement/<br>Control | N | Post<br>treatment<br>Mean/<br>(Median)<br>SD/SE<br>Lower limit<br>(IQR, 95%<br>CI)<br>Upper Limit<br>(IQR, 95%<br>CI) | Mean change /<br>% change /<br>from baseline<br>/<br>SD /<br>P Value | Between group<br>differences in<br>Means / medians<br>SD /<br>P Value | Additional<br>comments | Overall Risk of<br>Bias (ROB)<br>Assessment |
|---|--------------------------|----------------------|-------------------------------|------------------------|---|---|--|---|------------------------|---|
| <i>Bioavailability (F)</i><br>– no outcome data |                          |                      |                               |                        |   |   |  |   |                        |   |

**Evidence Table 161. KQ4—Cmax**

| Author Year<br>Study Design               | Definition of outcome   | CHD Risk Category   | CVD drug (dose mg/d)           | Supplement/ Control               | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|---------------------|--------------------------------|-----------------------------------|----|---|---|---|---|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Cross-over      | ng/mL – measured after single dose of ticlopidine and single dose Ginkgo biloba   | Low and/or Moderate | Ticlopidine (250; single dose) | Ginkgo biloba (0.08; single dose) | 24 | Mean: 1071.6<br>SD: 484.1   | GMR: 963.7  | GMR <sub>diff</sub> : 1.03<br>Lower: 0.92<br>Upper: 1.16  | Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                     |                                | No treatment                      | 24 | Mean: 1027.0<br>SD: 437.2   | GMR: 932.6  |   |   |                                       |
| Hadjia 2010 <sup>28</sup><br>Cross-over   | µg/L  | Low (healthy men)   | Simvastatin (20)               | Garlic (600 mg twice daily)       | 10 | Mean: 5.25<br>SD: 6.32  | -   | -   | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 10 | Mean: 3.85<br>SD: 1.99  | -   | -   | -   | Medium                                |
| Hadjia 2010 <sup>28</sup><br>Cross-over   | µg/L  | Low (healthy men)   | Pravastatin (20)               | Garlic (600 mg twice daily)       | 10 | Mean: 14.2<br>SD: 6.7   | -   | -   | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 10 | Mean: 18.8<br>SD: 12.2  | -   | -   | -   | Medium                                |
| Tankanow 2003 <sup>65</sup><br>Cross-over | ng/mL: Measured after 10 days digoxin or 21 days digoxin + hawthorn   | Low (healthy)       | Digoxin (0.25)                 | Hawthorn (0.9)                    | 8  | Mean: 1.80<br>SD: 0.20  | -   | -   | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 8  | Mean: 2.10<br>SD: 0.60  | -   | -   | -   | Medium                                |
| Mauro 2003 <sup>43</sup><br>Cross-over    | ng/mL; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment | Low (healthy)       | Digoxin (0.5; single dose)     | <i>Ginkgo biloba</i> (0.24)       | 8  | Mean: 1.4<br>SD: 0.5  | -   | -   | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 8  | Mean: 1.6<br>SD: 0.3  | -   | -   | -   | Medium                                |

**Evidence Table 161. KQ4—Cmax (continued)**

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|--------------------|----|---|---|--|---|---------------------------------------|
| Jiang 2004 <sup>33</sup><br>Cross-over | R-Warfarin: µg/mL; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)        | 12 | Mean: 1.89<br>SD: 0.29<br>Lower: 1.70<br>Upper: 2.00  | -   | GMR <sub>diff</sub> : 0.98<br>Lower: 0.88<br>Upper: 1.09 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment       | 12 | Mean: 1.92<br>SD: 0.32<br>Lower: 1.70<br>Upper: 2.10  | -   |  |   |                                       |
|  | S-Warfarin: µg/mL; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)        | 12 | Mean: 1.93<br>SD: 0.31<br>Lower: 1.70<br>Upper: 2.10  | -   | GMR <sub>diff</sub> : 1.01<br>Lower: 0.90<br>Upper: 1.12 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI |                                       |
|  |   |                   |                            | No treatment       | 12 | Mean: 1.89<br>SD: 0.26<br>Lower: 1.70<br>Upper: 2.00  | -   |  |   |                                       |



Evidence Table 161. KQ4—Cmax (continued)

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value   | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|--------------------|----|---|---|---|---|---------------------------------------|
| Jiang 2005 <sup>32</sup><br>Cross-over | R-Warfarin: µg/mL; measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)       | 12 | Mean: 1.70<br>Lower: 1.50<br>Upper: 1.90  | -   | Ginger<br>GMR <sub>diff</sub> : 1.02<br>Lower: 0.95<br>Upper: 1.07<br><br>Ginkgo biloba<br>GMR <sub>diff</sub> : 1.03<br>Lower: 0.97<br>Upper: 1.10 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | Ginkgo biloba (12) | 12 | Mean: 1.80<br>Lower: 1.50<br>Upper: 2.00  | -   |   |   |                                       |
|  |   |                   |                            | No treatment       | 12 | Mean: 1.70<br>Lower: 1.40<br>Upper: 2.00  | -   |   |   |                                       |
|  | S-Warfarin: µg/mL; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)       | 12 | Mean: 1.70<br>Lower: 1.50<br>Upper: 2.00  | -   | Ginger<br>GMR <sub>diff</sub> : 1.01<br>Lower: 0.94<br>Upper: 1.07  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | Ginkgo biloba (12) | 12 | Mean: 0.12<br>Lower: 0.11<br>Upper: 0.13  | -   | Ginkgo biloba<br>GMR <sub>diff</sub> : 1.04<br>Lower: 0.97<br>Upper: 1.09   |   |                                       |

**Evidence Table 161. KQ4—Cmax (continued)**

| Author Year<br>Study Design                 | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control                         | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------------|--|----|---|---|--|---|---------------------------------------|
|   |   |                   |                            | No treatment                               | 12 | Mean:0.12<br>Lower: 0.11<br>Upper: 0.14   |   |  |   |                                       |
| Gosai 2008 <sup>26</sup><br>Cross-over      | ng/mL; 2 weeks treatment  | Low (healthy)     | Rovustatin (40)            | Omega-3 fatty acids (EPA, DHA or both) (4) | 42 | Mean: 25.51<br>SD: 11.75  | -   | GMR <sub>diff</sub> : 1.01<br>Lower: 0.94<br>Upper: 1.09 | % coefficient of variation:<br>Omega-3: 46.08<br>Control: 34.85 | Medium                                |
|   |   |                   |                            | No treatment                               | 41 | Mean: 24.3<br>SD: 8.47  | -   |  |   |                                       |
| Di Spirito 2008 <sup>19</sup><br>Cross-over | Atorvastatin; Day 14 steady state (ng/mL); 2 weeks treatment          | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 52.1<br>SD: 62  | -   | GMR <sub>diff</sub> : 1.03<br>Lower: 0.93<br>Upper: 1.14 | Upper and lower limits of between group difference = 90% CI     | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 50.9<br>SD: 51  | -   |  |   |                                       |
|   | 2-hydroxytorvastatin; Day 14 steady state; (ng/mL); 2 weeks treatment | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 45<br>SD: 59.3  | -   | GMR <sub>diff</sub> : 0.95<br>Lower: 0.85<br>Upper: 1.06 | Upper and lower limits of between group difference = 90% CI     | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 47.6<br>SD: 50  | -   |  |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup>           | R-Warfarin: µg/mL; measured after single dose warfarin                | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 1.9<br>Lower: 1.5<br>Upper: 2.2   | -   | GMR <sub>diff</sub> : 1.02<br>Lower: 0.80<br>Upper:1.40  | Upper and lower limits of individual group                      | Medium                                |

Evidence Table 161. KQ4—Cmax (continued)

| Author Year<br>Study Design               | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)       | Supplement/Control                            | N                                     | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|--|---------------------|----------------------------|---|---------------------------------------|---|---|--|---|---------------------------------------|
| Cross-over                                | following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.   |                     |                            | No treatment                                  | 12                                    | Mean: 1.8<br>Lower: 1.7<br>Upper: 2.0   | -   |  | data = 95% CI; Upper and lower limits of between group difference = 90% CI  |                                       |
|   | S-Warfarin: µg/mL; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose | Low (healthy)       | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                   | 12                                    | Mean: 1.9<br>Lower: 1.5<br>Upper: 2.2   | -   | GMR <sub>diff</sub> : 1.06<br>Lower: 0.70<br>Upper:1.47  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |  |                     | No treatment               | 12  | Mean: 1.8<br>Lower: 1.7<br>Upper: 1.9 | -   |   |  |   |                                       |
| McKenney 2006 <sup>45</sup><br>Cross-over | Simvastatin; C <sub>max</sub> over final dosing interval (ng/mL); 2 wk treatment.  | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 24                                    | Mean: 15.4<br>SD: 7.6   | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 23                                    | Mean: 13.5<br>SD: 6.1   | -   |  |   |                                       |
|   | Beta-hydroxy simvastatin; C <sub>max</sub> over final dosing interval (ng/mL); 2 wk treatment.   | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 24                                    | Mean: 6.1<br>SD: 3.6  | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 23                                    | Mean: 6.1<br>SD: 3.2  | -   |  |   |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over     | R-Warfarin: µg/mL (1 hour); measured after single dose warfarin following 2 wks pretreatment with  | Low (healthy)       | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12                                    | Mean:1.20<br>Lower: 1.10<br>Upper: 1.40   | -   | GMR <sub>diff</sub> : 0.98<br>Lower: 0.88<br>Upper: 1.10 | Upper and lower limits of individual group data = 95% CI; Upper and lower   | Medium                                |

Evidence Table 161. KQ4—Cmax (continued)

| Author Year<br>Study Design | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control                            | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|---|-------------------|----------------------------|---|----|---|---|--|---|---------------------------------------|
|                             | Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.   |                   |                            | No treatment                                  | 12 | Mean: 1.30<br>Lower: 1.10<br>Upper: 1.50  | -   |  | limits of between group difference = 90% CI   |                                       |
|                             | S-Warfarin: µg/mL (1 hour); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 1.30<br>Lower: 1.10<br>Upper: 1.43  | -   | GMR <sub>diff</sub> : 0.97<br>Lower: 0.86<br>Upper: 1.10 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|                             |   |                   |                            | No treatment                                  | 12 | Mean: 1.30<br>Lower: 1.10<br>Upper: 1.60  | -   |  |   |                                       |

**Evidence Table 162. KQ4—Tmax (hours)**

| Author Year<br>Study Design               | Definition of outcome   | CHD Risk Category   | CVD drug (dose mg/d)           | Supplement/ Control                 | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|---------------------|--------------------------------|-------------------------------------|----|---|---|---|---|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Cross-over      | Hours – measured after single dose of ticlopidine and single dose Ginkgo biloba   | Low and/or Moderate | Ticlopidine (250; single dose) | Ginkgo biloba (0.08; single dose)   | 24 | Median: 1.50 Range – L: 1.00 H: 3:00  | -   | GMR <sub>diff</sub> : 0.27<br>Lower: NR<br>Upper: NR      | Upper and lower limits of between group difference = 90% CI   | -                                     |
|   |   |                     |                                | No treatment                        | 24 | Median: 1.75 Range – L: 1.00 H: 3:00  | -   |   |   |                                       |
| Tankanow 2003 <sup>65</sup><br>Cross-over | hours: Measured after 10 days digoxin or 21 days digoxin + hawthorn   | Low (healthy)       | Digoxin (0.25)                 | Hawthorn (0.9)                      | 8  | Mean: 1.00 SD: 0.50   | -   | -   | -   | -                                     |
|   |   |                     |                                | No treatment                        | 8  | Mean: 1.30 SD: 0.50   | -   |   |   |                                       |
| Mauro 2003 <sup>43</sup><br>Cross-over    | hours; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment.  | Low (healthy)       | Digoxin (0.5; single dose)     | <i>Ginkgo biloba</i> (0.24)         | 8  | Mean: 1.30 SD: 0.50   | -   | -   | -   | -                                     |
|   |   |                     |                                | No treatment                        | 8  | Mean: 1.40 SD: 0.60   | -   |   |   |                                       |
| Hajda 2010 <sup>28</sup><br>Cross-over    | Hours   | Low (healthy)       | Pravastatin (20)               | Garlic extract (600 mg twice daily) | 10 | Mean: 1.1 SD: 0.4   | -   | -   | -   | Medium                                |
|   |   |                     |                                | No treatment (before)               | 10 | Mean: 1.0 SD:0.5  | -   |   |   |                                       |
| Jiang 2004 <sup>33</sup><br>Cross-over    | R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)       | Warfarin (25; single dose)     | Ginseng (3)                         | 12 | Mean: 1.30 SD: 0.52 Lower: 0.95 Upper: 1.65   | -   | GMR <sub>diff</sub> : 1.11<br>Lower: 0.78<br>Upper: 1.44  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|   |   |                     |                                | No treatment                        | 12 | Mean: 1.34 SD: 0.48 Lower: 1.02 Upper: 1.66   | -   |   |   |                                       |

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|--|----|---|---|--|---|---------------------------------------|
|  | S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.                          | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)                                | 12 | Mean: 1.30<br>SD: 0.55<br>Lower: 0.95<br>Upper: 1.65                                    | -   | GMR <sub>diff</sub> :1.20<br>Lower: 0.77<br>Upper: 1.62  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |   |                   |                            | No treatment                               | 12 | Mean: 1.29<br>SD: 0.51<br>Lower: 0.97<br>Upper: 1.62                                    | -   |  |   |                                       |
| Jiang 2005 <sup>32</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                               | 12 | Mean:1.60<br>Lower: 1.10<br>Upper: 2.10   | -   | <u>Ginger</u><br>GMR <sub>diff</sub> : 0.72<br>Lower: 0.67<br>Upper: 0.77<br><br><u>Ginkgo biloba</u><br>GMR <sub>diff</sub> : 0.79<br>Lower: 0.73<br>Upper:0.85 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |   |                   |                            | Ginkgo biloba (12)                         | 12 | Mean: 1.60<br>Lower: 0.60<br>Upper: 2.70  | -   |  |   |                                       |
|  |   |                   |                            | No treatment                               | 12 | Mean: 2.10<br>Lower: 1.40<br>Upper: 2.80  | -   |  |   |                                       |
|  | S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                               | 12 | Mean: 1.60<br>Lower: 1.10<br>Upper: 2.10  | -   | <u>Ginger</u><br>GMR <sub>diff</sub> :0.68<br>Lower: 0.63<br>Upper:0.73<br><br><u>Ginkgo biloba</u><br>GMR <sub>diff</sub> :0.79<br>Lower: 0.73<br>Upper:0.85    | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |   |                   |                            | <i>Ginkgo biloba</i> (12)                  | 12 | Mean: 1.40<br>Lower: 0.90<br>Upper: 1.90  | -   |  |   |                                       |
|  |   |                   |                            | No treatment                               | 12 | Mean: 2.10<br>Lower: 1.40<br>Upper: 2.80  | -   |  |   |                                       |
| Gosai 2008 <sup>26</sup><br>Cross-over | hours; 2 weeks treatment  | Low (healthy)     | Rovustatin (40)            | Omega-3 fatty acids (EPA, DHA or both) (4) | 42 | Mean: 4.50<br>Median: 4.50<br>Median Range –<br>L: 1.00<br>H: 6.00                      | -   | -  | -   | -                                     |

| Author Year<br>Study Design                 | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d) | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------|--|----|---|---|---|---------------------|---------------------------------------|
|   |   |                   |                      | No treatment                               | 41 | Mean: 4.47<br>Median: 4.50<br>Median Range –<br>L: 2.00<br>H: 6.00                      | -   |   |                     |                                       |
| Di Spirito 2008 <sup>19</sup><br>Cross-over | Atorvastatin; over the final dosing interval (hours); 2 weeks treatment | Low (healthy)     | Atorvastatin (80)    | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 1.43<br>SD: 1.09<br>Median: 1.00<br>Median range –<br>L: 0.36<br>H: 4.10          | -   | -   | -                   | -                                     |
|   |   |                   |                      | No treatment                               | 49 | Mean: 1.35<br>SD: 0.97<br>Median: 1.00<br>Median range –<br>L: 0.50<br>H: 4.00          | -   |   |                     |                                       |
|   | 2-hydroxytorvastatin; Day 14 steady state; (ng/mL); 2 weeks treatment   | Low (healthy)     | Atorvastatin (80)    | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 2.10<br>SD: 1.10<br>Median: 1.67<br>Median range –<br>L: 0.50<br>H: 6.00          | -   | -   | -                   | -                                     |

| Author Year<br>Study Design                     | Definition of outcome   | CHD Risk Category   | CVD drug (dose mg/d)       | Supplement/ Control                        | N  | Post treatment Mean/ (Median / SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments                                       | Overall Risk of Bias (ROB) Assessment |
|---|---|---------------------|----------------------------|--|----|--|---|---|---|---------------------------------------|
|   |   |                     |                            | No treatment                               | 49 | Mean: 1.88<br>SD: 0.95<br>Median: 1.67<br>Median range – L: 0.75<br>H: 4.00              | -   |   |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)       | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 1.8<br>Lower: 0.70<br>Upper: 2.90  | -   | -   | Upper and lower limits of individual group data = 95% CI; | -                                     |
|   |   |                     |                            | No treatment                               | 12 | Mean: 1.40<br>Lower: 1.10<br>Upper: 1.60   | -   |   |   |                                       |
|   | S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose  | Low (healthy)       | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 1.30<br>Lower: 1.10<br>Upper: 1.60   | -   | -   | Upper and lower limits of individual group data = 95% CI  | -                                     |
|   |   |                     |                            | No treatment                               | 12 | Mean: 1.40<br>Lower: 1.10<br>Upper: 1.60   | -   |   |   |                                       |
| McKenney 2006 <sup>45</sup><br>Cross-over       | Simvastatin; over final dosing interval (hours); 2 wk treatment.  | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4) | 24 | Mean: 2.40<br>SD: 2.60   | -   | -   | -   | -                                     |
|   |   |                     |                            | No treatment                               | 23 | Mean: 2.60<br>SD: 1.90   | -   |   |   |                                       |



| Author Year<br>Study Design           | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)       | Supplement/ Control                           | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments                                      | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|--|---------------------|----------------------------|---|----|---|---|---|--|---------------------------------------|
|                                       | Beta-hydroxy simvastatin; over final dosing interval (hours); 2 wk treatment.  | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 24 | Mean: 5.50<br>SD: 2.30  | -   | -   | -  | -                                     |
|                                       |  |                     |                            | No treatment                                  | 23 | Mean: 5.60<br>SD: 2.00  | -   |   |  |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)       | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 2.00<br>Lower: 1.50<br>Upper: 2.40  | -   | GMR <sub>diff</sub> : 0.98<br>Lower: 0.88<br>Upper: 1.10  | Upper and lower limits of individual group data = 95% CI | -                                     |
|                                       |  |                     |                            | No treatment                                  | 12 | Mean: 2.00<br>Lower: 1.30<br>Upper: 2.60  | -   |   |  |                                       |
|                                       | S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)       | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 1.70<br>Lower: 1.10<br>Upper: 2.20  | -   | -   | Upper and lower limits of individual group data = 95% CI | -                                     |
|                                       |  |                     |                            | No treatment                                  |    |   |   |   |  |                                       |

**Evidence Table 163. KQ4—Continuous data—Distribution**

| Author Year<br>Study Design            | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|----------------------------|---------------------|----|---|---|---|---|---------------------------------------|
| <i>Volume of distribution (Vd)</i>     |  |                   |                            |                     |    |   |   |   |   |                                       |
| Jiang 2004 <sup>33</sup><br>Cross-over | R-Warfarin: V/F (L/kg); measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 0.10<br>SD: 0.02<br>Lower: 0.10<br>Upper:0.12   | -   | GMR <sub>diff</sub> :1.03<br>Lower: 0.95<br>Upper: 1.10   | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |  |                   |                            | No treatment        | 12 | Mean:0.10<br>SD: 0.02<br>Lower: 0.09<br>Upper: 0.13   | -   |   |   |                                       |
|  | S-Warfarin: V/F (L/kg); measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 0.13<br>SD: 0.03<br>Lower: 0.11<br>Upper:0.15   | -   | GMR <sub>diff</sub> :1.04<br>Lower: 0.94<br>Upper:1.14    | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |  |                   |                            | No treatment        | 12 | Mean:0.12<br>SD: 0.03<br>Lower: 0.11<br>Upper: 0.14   | -   |   |   |                                       |

**Evidence Table 163. KQ4—Continuous data—Distribution (continued)**

| Author Year<br>Study Design            | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                    | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value   | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|----------------------------|--|----|---|---|---|---|---------------------------------------|
| Jiang 2005 <sup>32</sup><br>Cross-over | R-Warfarin: V/F (L/kg); measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                           | 12 | Mean:0.11<br>Lower: 0.10<br>Upper: 0.12   | -   | Ginger<br>GMR <sub>diff</sub> :0.97<br>Lower: 0.93<br>Upper:1.00<br><br>Ginkgo biloba<br>GMR <sub>diff</sub> :0.98<br>Lower: 0.95<br>Upper:1.01 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |  |                   |                            | Ginkgo biloba (12)                     | 12 | Mean:0.11<br>Lower: 0.10<br>Upper: 0.11   | -   |   |   |                                       |
|  |  |                   |                            | No treatment                           | 12 | Mean:0.12<br>Lower: 0.10<br>Upper: 0.13   | -   |   |   |                                       |
|  | S-Warfarin: V/F (L/kg); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                           | 12 | Mean:0.12<br>Lower: 0.11<br>Upper: 0.13   | -   | Ginger<br>GMR <sub>diff</sub> :1.03<br>Lower: 0.99<br>Upper:1.07<br><br>Ginkgo biloba<br>GMR <sub>diff</sub> :1.03<br>Lower: 0.99<br>Upper:1.08 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |  |                   |                            | Ginkgo biloba (12)                     | 12 | Mean:0.12<br>Lower: 0.11<br>Upper: 0.13   | -   |   |   |                                       |
|  |  |                   |                            | No treatment                           | 12 | Mean:0.12<br>Lower: 0.11<br>Upper: 0.14   | -   |   |   |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over  | R-Warfarin: V/F (L/kg); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.              | Low (healthy)     | Warfarin (25; single dose) | Echinacea (5.1; 23 mg total alkamides) | 12 | Mean:0.20<br>Lower: 0.13<br>Upper: 0.26   | -   | GMR <sub>diff</sub> :1.03<br>Lower: 0.93<br>Upper:1.14  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |
|  |  |                   |                            | No treatment                           | 12 | Mean:0.19<br>Lower: 0.13<br>Upper: 0.25   | -   |   |   |                                       |

**Evidence Table 163. KQ4—Continuous data—Distribution (continued)**

| Author Year<br>Study Design           | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control   | N | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change / % change from baseline / SD / P Value | Between group differences in Means / medians SD / P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---------------------------------------|---|-------------------|----------------------------|---|---|---|---|---|---|---------------------------------------|
| Abdul 2010 <sup>1</sup><br>Cross-over | S-Warfarin: V/F (L/kg); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides)<br>No treatment |   | Mean:0.23<br>Lower: 0.16<br>Upper: 0.30<br><br>Mean:0.21<br>Lower: 0.16<br>Upper: 0.27        | -<br><br>-  | GMR <sub>diff</sub> :1.09<br>Lower: 1.03<br>Upper:1.18    | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | -                                     |

**Evidence Table 164. KQ4—Continuous data—Clearance**

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                 | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|-------------------------------------|----|---|---|---|---|---------------------------------------|
| <b>Clearance (V/time)</b>              |   |                   |                            |                                     |    |   |   |   |   |                                       |
| Jiang 2004 <sup>33</sup><br>Cross-over | R-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)                         | 12 | Mean: 119<br>SD: 20<br>Lower: 106<br>Upper:131  | -   | GMR <sub>diff</sub> :1.10<br>Lower: 1.01<br>Upper: 1.20 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment                        | 12 | Mean:110<br>SD: 25<br>Lower: 94<br>Upper: 126   | -   |   |   |                                       |
|  | S-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)                         | 12 | Mean: 220<br>SD: 29<br>Lower: 201<br>Upper:238  | -   | GMR <sub>diff</sub> :1.12<br>Lower: 1.03<br>Upper:1.22  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment                        | 12 | Mean:198<br>SD: 38<br>Lower: 174<br>Upper: 223  | -   |   |   |                                       |
| Hajda 2010 <sup>28</sup>               | Clearance (CL/F) of statin (L/h)  | Low (healthy men) | Simvastatin (20)           | Garlic extract (600 mg twice daily) | 10 | Mean: 2146<br>SD: 1660  | -   | -   | -   | Medium                                |
|  |   |                   |                            | No treatment                        | 10 | Mean: 2349<br>SD: 1340  | -   | -   | -   |                                       |

**Evidence Table 164. KQ4—Continuous data—Clearance (continued)**

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                    | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value   | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|--|----|---|---|---|---|---------------------------------------|
| Hajda 2010 <sup>28</sup>               | Clearance (CL/F) of statin (L/h) (details not reported)   | Low (healthy men) | Pravastatin (20)           | Garlic extract (600 mg twice daily)    | 10 | Mean: 722<br>SD:440   | -   | -   | -   | Medium                                |
|  |   |                   |                            | No treatment                           | 10 | Mean: 834<br>SD: 928  | -   | -   |   |                                       |
| Jiang 2005 <sup>32</sup><br>Cross-over | R-Warfarin: CL/F (mL/min); measured after single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                           | 12 | Mean:131<br>Lower: 106<br>Upper: 156  | -   | Ginger<br>GMR <sub>diff</sub> :1.02<br>Lower: 0.95<br>Upper:1.10<br><br>Ginkgo biloba<br>GMR <sub>diff</sub> :1.00<br>Lower: 0.93<br>Upper:1.08 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | Ginkgo biloba (12)                     | 12 | Mean:126<br>Lower: 111<br>Upper: 141  | -   |   |   |                                       |
|  |   |                   |                            | No treatment                           | 12 | Mean:127<br>Lower: 106<br>Upper: 149  | -   |   |   |                                       |
|  | S-Warfarin: CL/F (mL/min); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                           | 12 | Mean:201<br>Lower: 171<br>Upper: 231  | -   | Ginger<br>GMR <sub>diff</sub> :1.05<br>Lower: 0.97<br>Upper:1.13<br><br>Ginkgo biloba<br>GMR <sub>diff</sub> :1.05<br>Lower: 0.98<br>Upper:1.12 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI |                                       |
|  |   |                   |                            | Ginkgo biloba (12)                     | 12 | Mean:200<br>Lower: 173<br>Upper: 227  | -   |   |   |                                       |
|  |   |                   |                            | No treatment                           | 12 | Mean:189<br>Lower: 167<br>Upper: 210  | -   |   |   |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over  | R-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with   | Low (healthy)     | Warfarin (25; single dose) | Echinacea (5.1; 23 mg total alkamides) | 12 | Mean:186.4<br>Lower: 140.5<br>Upper: 232.2  | -   | GMR <sub>diff</sub> :1.10<br>Lower: 0.97<br>Upper:1.14  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of                                   | Medium                                |

**Evidence Table 164. KQ4—Continuous data—Clearance (continued)**

| Author Year<br>Study Design                     | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                           | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------------|---|----|---|---|---|---|---------------------------------------|
|   | Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.   |                   |                            | No treatment                                  | 12 | Mean:178.3<br>Lower: 132.7<br>Upper: 223.4  | -   |   | between group difference = 90% CI   |                                       |
|   | S-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean:289.7<br>Lower: 218.2<br>Upper: 361.1  | -   | GMR <sub>diff</sub> :1.09<br>Lower: 1.01<br>Upper:1.18  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                   |                            | No treatment                                  | 12 | Mean:267.3<br>Lower:198.4<br>Upper: 336.3   | -   |   |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup><br>Cross-over | R-Warfarin: mL/h; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose.    | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                   | 12 | Mean: 121<br>Lower: 112<br>Upper: 131   | -   | GMR <sub>diff</sub> : 0.96<br>Lower: 0.84<br>Upper:1.11 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                   |                            | No treatment                                  | 12 | Mean: 123<br>Lower: 106<br>Upper: 140   | -   |   |   |                                       |
|   | S-Warfarin: mL/h; measured after single dose warfarin   | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                   | 12 | Mean: 202<br>Lower: 175<br>Upper: 229   | -   | GMR <sub>diff</sub> : 1.05<br>Lower: 0.94<br>Upper:1.17 | Upper and lower limits of individual group data = 95%   | Medium                                |

**Evidence Table 164. KQ4—Continuous data—Clearance (continued)**

| Author Year<br>Study Design               | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)        | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|--|---------------------|-----------------------------|--|----|---|---|---|---|---------------------------------------|
|   | following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose                              |                     |                             | No treatment                               | 12 | Mean: 213<br>Lower: 193<br>Upper: 232   | -   |   | CI; Upper and lower limits of between group difference = 90% CI |                                       |
| McKenney 2006 <sup>45</sup><br>Cross-over | CL/F (L/h) Total body clearance at steady state vs. time curve over the final dosing interval (0-24 h)   | Low and/or Moderate | Simvastatin (80)            | Omega-3 fatty acids (EPA, DHA or both) (4) | 21 | Mean: 838<br>SD: 477  | -   | -   | -   | Medium                                |
|   |  |                     |                             | No treatment                               | 18 | Mean: 872<br>SD: 402  | -   |   |   |                                       |
| Tankanow 2003 <sup>65</sup><br>Cross-over | mL/min; Measured after 10 days digoxin or 21 days digoxin + hawthorn   | Low (healthy)       | Digoxin (0.25; single dose) | Hawthorn (0.9)                             | 8  | Mean: 81<br>SD: 22  | -   | -   | -   | Medium                                |
|   |  |                     |                             | No treatment                               | 8  | Mean: 74<br>SD: 10  | -   |   |   |                                       |
| Mauro 2003 <sup>43</sup><br>Cross-over    | Oral clearance (L/h); Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment | Low (healthy)       | Digoxin (0.5; single dose)  | <i>Ginkgo biloba</i> (0.24)                | 8  | Mean: 26.6<br>SD: 18.1  | -   | -   | -   | Medium                                |
|   |  |                     |                             | No treatment                               | 8  | Mean: 31.7<br>SD: 24.9  | -   |   |   |                                       |
| Gosai 2008 <sup>26</sup><br>Cross-over    | Total body clearance at steady state (L/h); 2 weeks treatment  | Low (healthy)       | Rovustatin (40)             | Omega-3 fatty acids (EPA, DHA or both) (4) | 42 | Mean: 204<br>SD: 88.5   | -   | -   | % coefficient of variation:<br>Omega-3: 43.36<br>Control: 36.25 | Medium                                |
|   |  |                     |                             | No treatment                               | 41 | Mean: 208<br>SD: 75.3   | -   |   |   |                                       |



**Evidence Table 164. KQ4—Continuous data—Clearance (continued)**

| Author Year<br>Study Design                 | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d) | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------|--|----|---|---|---|---------------------|---------------------------------------|
| Di Spirito 2008 <sup>19</sup><br>Cross-over | Total body clearance at steady state vs. Time curve over the final dosing interval (0-24 h) | Low (healthy)     | Atorvastatin (80)    | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 413<br>SD: 179  | -   | -   | -                   | Medium                                |
|   |   |                   |                      | No treatment                               | 49 | Mean: 423<br>SD: 183  | -   |   |                     |                                       |

**Evidence Table 165. KQ4 Outcomes—Elimination rate**

| Author Year<br>Study Design | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control         | N | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/ % change from baseline/ SD/ P Value | Between group differences in Means/medians SD/ P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|-------------------|----------------------------|-----------------------------|---|---|--|--|---------------------|---------------------------------------|
| Mauro 2003 <sup>43</sup>    | Elimination rated of single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment | Low (healthy)     | Digoxin (0.5; single dose) | <i>Ginkgo biloba</i> (0.24) | 6 | Mean: 0.02<br>SD: 0.01  | -  | -  | -                   | Medium                                |
|                             |  |                   |                            | No treatment                | 6 | Mean: 0.03<br>SD: 0.02  | -  |  |                     |                                       |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2)**

| Author Year<br>Study Design               | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)           | Supplement/ Control               | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value | Additional comments | Overall Risk of Bias (ROB) Assessment |
|---|--|---------------------|--------------------------------|-----------------------------------|----|---|---|---|---------------------|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Cross-over      | hours – measured after single dose of ticlopidine and single dose Ginkgo biloba  | Low and/or Moderate | Ticlopidine (250; single dose) | Ginkgo biloba (0.08; single dose) | 24 | Mean: 13.5<br>SD: 5.6   | -   | GMR <sub>diff</sub> : 0.27                              |                     | Medium                                |
|   |  |                     |                                | No treatment                      | 24 | Mean: 11.2<br>SD: 4.8   | -   |   |                     |                                       |
| Tankanow 2003 <sup>65</sup><br>Cross-over | hours: Measured after 10 days digoxin or 21 days digoxin + hawthorn  | Low (healthy)       | Digoxin (0.25)                 | Hawthorn (0.9)                    | 8  | Mean: 48<br>SD: 6   | -   | -   | -                   | Medium                                |
|   |  |                     |                                | No treatment                      | 8  | Mean: 50<br>SD: 15  | -   |   |                     |                                       |
| Mauro 2003 <sup>43</sup><br>Cross-over    | hours; Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment. | Low (healthy)       | Digoxin (0.5; single dose)     | <i>Ginkgo biloba</i> (0.24)       | 6  | Mean: 44.0<br>SD: 19.6  | -   | -   | -                   | Medium                                |
|   |  |                     |                                | No treatment                      | 6  | Mean: 26.0<br>SD: 11.1  | -   |   |                     |                                       |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)**

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value                   | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|---------------------|----|---|---|---|---|---------------------------------------|
| Jiang 2004 <sup>33</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 47.9<br>SD: 7.8<br>Lower: 42.9<br>Upper: 52.9                                     | -   | GMR <sub>diff</sub> : 0.93<br>Lower: 0.88<br>Upper: 0.99                  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment        | 12 | Mean: 51.7<br>SD: 9.6<br>Lower: 45.6<br>Upper: 57.8                                     | -   |   |   |                                       |
|  | S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 29.2<br>SD: 5.2<br>Lower: 25.9<br>Upper: 32.4                                     | -   | GMR <sub>diff</sub> : 0.92<br>Lower: 0.85<br>Upper: 0.99                  | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI |                                       |
|  |   |                   |                            | No treatment        | 12 | Mean: 31.7<br>SD: 4.5<br>Lower: 28.8<br>Upper: 34.5                                     | -   |   |   |                                       |
| Jiang 2005 <sup>32</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 1 week pretreatment with Ginger,   | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)        | 12 | Mean:47.7<br>Lower: 42.6<br>Upper: 52.8   | -   | <u>Ginger</u><br>GMR <sub>diff</sub> : 0.94<br>Lower: 0.90<br>Upper: 1.01 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits                                      | Medium                                |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)**

| Author Year<br>Study Design | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control        | N                                   | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value                          | Additional comments   | Overall Risk of Bias (ROB) Assessment |  |
|-----------------------------|--|-------------------|----------------------------|---------------------------|-------------------------------------|---|---|--|---|---------------------------------------|--|
|                             | Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.  |                   |                            | Ginkgo biloba (12)        | 12                                  | Mean: 48.6<br>Lower: 44.7<br>Upper: 52.4  | -   | <u>Ginkgo biloba</u><br>GMR <sub>diff</sub> : 0.97<br>Lower: 0.92<br>Upper: 1.02 | of between group difference = 90% CI  |                                       |  |
|                             |  |                   |                            | No treatment              | 12                                  | Mean: 50.3<br>Lower: 45.8<br>Upper: 54.9  | -   |  |   |                                       |  |
|                             | S-Warfarin: hours; measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)              | 12                                  | Mean: 35.7<br>Lower: 30.0<br>Upper: 41.3  | -   | <u>Ginger</u><br>GMR <sub>diff</sub> : 0.99<br>Lower: 0.94<br>Upper: 1.04        | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |  |
|                             |  |                   |                            | <u>Ginkgo biloba</u> (12) | 12                                  | Mean: 35.1<br>Lower: 30.9<br>Upper: 39.3  | -   |  |   |                                       | <u>Ginkgo biloba</u><br>GMR <sub>diff</sub> : 0.98<br>Lower: 0.93<br>Upper: 1.04 |
|                             |  |                   |                            | No treatment              | 12                                  | Mean: 35.8<br>Lower: 31.1<br>Upper: 40.3  | -   |  |   |                                       |  |
|                             | Hajda 2010 <sup>28</sup>   | Statin half time. | Low (healthy)              | Simvastatin (20)          | Garlic extract (600 mg twice daily) | 10  | Mean: 5.0<br>SD: 1.9                            | -  | GMR (95% CI): 1.02 (0.81, 1.27)   | -                                     | Medium   |
| No treatment                |  |                   |                            |                           | 10                                  | Mean: 4.92<br>SD: 0.93  | -   | -  |   |                                       |  |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)**

| Author Year<br>Study Design                     | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------------|--|----|---|---|--|---|---------------------------------------|
| Hajda 2010 <sup>28</sup>                        | Statin half time.   | Low (healthy)     | Pravastatin (20)           | Garlic extract (600 mg twice daily)        | 10 | Mean: 3.57<br>SD: 1.11  | -   | GMR (95% CI): 0.92 (0.5, 1.13)                           | -   | Medium                                |
|   |   |                   |                            | No treatment                               | 10 | Mean: 3.75<br>SD: 0.66  | -   |  | -   |                                       |
| Di Spirito 2008 <sup>19</sup><br>Cross-over     | Atorvastatin; hours; 2 weeks treatment  | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 6.39<br>SD: 1.69  | -   | -  |   | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 6.66<br>SD: 3.81  | -   |  |   |                                       |
|   | 2-hydroxytorvastatin; hours; 2 weeks treatment  | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 7.17<br>SD: 3.44  | -   | -  |   | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 6.75<br>SD: 2.72  | -   |  |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup><br>Cross-over | R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 52.6<br>Lower: 47.4<br>Upper: 57.9  | -   | GMR <sub>diff</sub> : 0.98<br>Lower: 0.84<br>Upper: 1.14 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                   |                            | No treatment                               | 12 | Mean: 55.6<br>Lower: 46.2<br>Upper: 65.0  | -   |  |   |                                       |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)**

| Author Year<br>Study Design               | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)       | Supplement/ Control                           | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|--|---------------------|----------------------------|---|----|---|---|--|---|---------------------------------------|
|   | S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose | Low (healthy)       | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                   | 12 | Mean: 41.2<br>Lower: 35.1<br>Upper: 47.3  | -   | GMR <sub>diff</sub> : 0.99<br>Lower: 0.83<br>Upper: 1.18 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |  |                     |                            | No treatment                                  | 12 | Mean: 38.6<br>Lower: 35.7<br>Upper: 41.5  | -   |  |   |                                       |
| McKenney 2006 <sup>45</sup><br>Cross-over | Simvastatin; hours; 2 wk treatment.  | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 23 | Mean: 7.4<br>SD: 1.6  | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 23 | Mean: 9.9<br>SD: 5.5  | -   |  |   |                                       |
|   | Beta-hydroxy simvastatin; hours; 2 wk treatment.   | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 18 | Mean: 9.5<br>SD: 5.8  | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 18 | Mean: 9.4<br>SD: 5.9  | -   |  |   |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over     | R-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with   | Low (healthy)       | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 49.2<br>Lower: 44.3<br>Upper: 54.2  | -   | GMR <sub>diff</sub> : 0.98<br>Lower: 0.88<br>Upper: 1.10 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits                                      | Medium                                |

**Evidence Table 166. KQ4 Outcomes—Half life (T1/2) (continued)**

| Author Year<br>Study Design | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/Control                            | N  | Post treatment Mean/ (Median) SD/SE Lower limit (IQR, 95% CI) Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|-------------------|----------------------------|---|----|---|---|--|---|---------------------------------------|
|                             | Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose.  |                   |                            | No treatment                                  | 12 | Mean: 50.6<br>Lower: 44.9<br>Upper: 56.2  | -   |  | of between group difference = 90% CI  |                                       |
|                             | S-Warfarin: hours; measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 36.5<br>Lower: 34.1<br>Upper: 38.8  | -   | GMR <sub>diff</sub> : 0.95<br>Lower: 0.84<br>Upper: 1.08 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|                             |  |                   |                            | No treatment                                  | 12 | Mean: 38.6<br>Lower: 34.3<br>Upper: 43.0  |   |  |   |                                       |



**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC)**

| Author Year<br>Study Design               | Definition of outcome   | CHD Risk Category   | CVD drug (dose mg/d)           | Supplement/ Control               | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|---------------------|--------------------------------|-----------------------------------|----|---|---|--|---|---------------------------------------|
| Kim 2010 <sup>35</sup><br>Cross-over      | ng*h/mL (0 - ∞); measured after single dose of ticlopidine and single dose Ginkgo biloba  | Low and/or Moderate | Ticlopidine (250; single dose) | Ginkgo biloba (0.08; single dose) | 24 | Mean: 3466.00<br>SD: 1548.80  | GMR: 3145.00                                    | GMR <sub>diff</sub> : 1.10<br>Lower: 1.00<br>Upper: 1.20 | Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                     |                                | No treatment                      | 24 | Mean: 3240.00<br>SD: 1592.3   | GMR: 2568.00                                    |  |   |                                       |
| Tankanow 2003 <sup>65</sup><br>Cross-over | ng*h/mL (0 - ∞); Measured after 10 days digoxin or 21 days digoxin + hawthorn   | Low (healthy)       | Digoxin (0.25)                 | Hawthorn (0.9)                    | 8  | Mean: 73.00<br>SD: 20.00  | -   | -  | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 8  | Mean: 79.00<br>SD: 26.00  | -   |  |   |                                       |
| Mauro 2003 <sup>43</sup><br>Cross-over    | ng*h/mL (0 - ∞); Measured after single-dose administration of digoxin following 7 days pre-treatment with Ginkgo biloba or no pre-treatment | Low (healthy)       | Digoxin (0.5; single dose)     | <i>Ginkgo biloba</i> (0.24)       | 8  | Mean: 25.6<br>SD: 13.2  | -   | -  | -   | Medium                                |
|   |   |                     |                                | No treatment                      | 8  | Mean: 21.00<br>SD: 8.6  | -   |  |   |                                       |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design            | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|---|-------------------|----------------------------|---------------------|----|---|---|--|---|---------------------------------------|
| Jiang 2004 <sup>33</sup><br>Cross-over | R-Warfarin: $\mu\text{g}/\text{mL}\cdot\text{hr}$ (0 - $\infty$ ); measured after single dose warfarin following 1 week pretreatment with ginseng or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 108.1<br>SD: 18.3<br>Lower: 95.9<br>Upper: 120.2  | -   | GMR <sub>diff</sub> : 0.91<br>Lower: 0.84<br>Upper: 0.99 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment        | 12 | Mean: 120.9<br>SD: 32.9<br>Lower: 99.0<br>Upper: 142.7  | -   |  |   |                                       |
|  | S-Warfarin: $\mu\text{g}/\text{mL}\cdot\text{hr}$ (0 - $\infty$ ); measured after single-dose warfarin following 1 wk pretreatment with ginseng or no pretreatment. Subjects followed for 1 wk post warfarin dose.            | Low (healthy)     | Warfarin (25; single dose) | Ginseng (3)         | 12 | Mean: 57.8<br>SD: 7.4<br>Lower: 53.1<br>Upper: 62.5   | -   | GMR <sub>diff</sub> : 0.89<br>Lower: 0.82<br>Upper: 0.98 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |   |                   |                            | No treatment        | 12 | Mean: 65.4<br>SD: 13.8<br>Lower: 56.6<br>Upper: 74.1  | -   |  |   |                                       |
| Jiang 2005 <sup>32</sup>               | R-Warfarin: $\mu\text{g}\cdot\text{h}/\text{mL}$ (0 - $\infty$ ); measured after  | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)        | 12 | -   | -   | Ginger<br>GMR <sub>diff</sub> : 1.00                     | Upper and lower limits of between   | Medium                                |
|  |   |                   |                            | Ginkgo biloba (12)  | 12 | -   | -   |  |   |                                       |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design            | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                 | N                     | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value   | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|-------------------|----------------------------|-------------------------------------|-----------------------|---|---|---|---|---------------------------------------|
| Cross-over                             | single dose warfarin following 1 week pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for one more week post warfarin dose.  |                   |                            | No treatment                        | 12                    | -   | -   | Lower: 0.92<br>Upper:1.07<br><br><u>Ginkgo biloba</u><br>GMR <sub>diff</sub> : 0.98<br>Lower: 0.91<br>Upper:1.06  | group difference = 90% CI                                   |                                       |
|  | S-Warfarin: $\mu\text{g}^*\text{h}/\text{mL}$ (0 - $\infty$ ); measured after single-dose warfarin following 1 wk pretreatment with Ginger, Ginkgo biloba or no pretreatment. Subjects followed for 1 wk post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Ginger (3.6)                        | 12                    | -   | -   | <u>Ginger</u><br>GMR <sub>diff</sub> : 0.95<br>Lower: 0.89<br>Upper:1.03<br><br><u>Ginkgo biloba</u><br>GMR <sub>diff</sub> : 0.97<br>Lower: 0.89<br>Upper:1.03 | Upper and lower limits of between group difference = 90% CI | Medium                                |
| <u>Ginkgo biloba</u> (12)              |  |                   |                            | 12                                  | -                     | -   |   |   |   |                                       |
| No treatment                           |  |                   |                            | 12                                  | -                     | -   |   |   |   |                                       |
| Hajda 2010 <sup>28</sup><br>Cross over | $\text{ng}^*\text{h}/\text{mL}$ (0-24 hours)   | Low (healthy)     | Simvastatin (20)           | Garlic extract (600 mg twice daily) | 10                    | Mean: 22.1<br>SD: 25.7  | -   | GMR (95% CI): 1.37 (0.88, 2.12)   | -   | Medium                                |
| No treatment                           |  |                   |                            | 10                                  | Mean: 11.2<br>SD: 5.7 | -   |   |   |   |                                       |
| Hajda 2010 <sup>28</sup><br>Cross over | $\text{ng}^*\text{h}/\text{mL}$ (0-24 hours)   | Low (healthy)     | Pravastatin (20)           | Garlic extract (600 mg twice daily) | 10                    | Mean: 35.4<br>SD: 15.5  | -   | GMR (95% CI): 0.94 (0.65, 1.36)   | -   | Medium                                |
|  |  |                   |                            | No treatment                        | 10                    | Mean: 41.8<br>SD: 24.1  | -   |   |   |                                       |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design            | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d) | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value                  | Between group differences in Means/ medians SD/ P Value          | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|--|--|---------------------|----------------------|--|----|---|--|--|---|---------------------------------------|
| Gosai 2008 <sup>26</sup><br>Cross-over | ng*h/ml; 2 weeks treatment; Day 14 steady state  | Low (healthy)       | Rovustatin (40)      | Omega-3 fatty acids (EPA, DHA or both) (4) | 42 | Mean: 231.35<br>SD: 93.15   | GMR = 213.73   | GMR <sub>diff</sub> : 1.05<br>Lower: 0.99<br>Upper: 1.10         | % coefficient of variation: Omega-3: 40.26<br>Control: 33.18<br><br>Intra % coefficient of variation (Omega-3): 14.5<br><br>Upper and lower limits of between group difference = 90% CI | Medium                                |
|  |  |                     |                      | No treatment                               | 41 | Mean: 215.77<br>SD: 71.60   | GMR = 204.19   |  |   |                                       |
| Yuan 2004 <sup>71</sup>                | Change from wk1 to w4 (µg/mL/d); steady state: assessed after 3 days warfarin treatment before and after 3 weeks 3 weeks treatment with ginseng or placebo | Low and/or Moderate | Warfarin (5)         | Ginseng (2)                                | 12 | -   | Median <sub>change</sub> : -0.40<br>Range<br>L: -1.20<br>H: 0.20 | Median <sub>diff</sub> : -0.64<br>Range:<br>L: -1.25<br>H: -0.13 | -   | Medium                                |
|  |  |                     |                      | Placebo                                    | 8  | -   | Median <sub>change</sub> : 0.18<br>Range<br>L: -0.35<br>H: 1.40  |  |   |                                       |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design                     | Definition of outcome   | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                        | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|---|-------------------|----------------------------|--|----|---|---|--|---|---------------------------------------|
| Di Spirito 2008 <sup>19</sup><br>Cross-over     | Atorvastatin; Day 14 steady state (ng*h/mL) over final dosing interval; 2 weeks treatment   | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 212.50<br>SD: 46.70   | -   | GMR <sub>diff</sub> : 1.03<br>Lower: 0.97<br>Upper: 1.09 | Upper and lower limits of between group difference = 90% CI   | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 207.20<br>SD: 45.70   | -   |  |   |                                       |
|   | 2-hydroxytorvastatin; Day 14 steady state; (ng*h/mL); 2 weeks treatment   | Low (healthy)     | Atorvastatin (80)          | Omega-3 fatty acids (EPA, DHA or both) (4) | 49 | Mean: 275.00<br>SD: 37.90   | -   | GMR <sub>diff</sub> : 0.95<br>Lower: 0.85<br>Upper: 1.06 | Upper and lower limits of between group difference = 90% CI   | Medium                                |
|   |   |                   |                            | No treatment                               | 49 | Mean: 273.02<br>SD: 35.90   | -   |  |   |                                       |
| Mohammed Abdul 2008 <sup>49</sup><br>Cross-over | R-Warfarin: µg/mL*h (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 105.00<br>Lower: 96.30<br>Upper: 113.70   | -   | GMR <sub>diff</sub> : 0.99<br>Lower: 0.87<br>Upper: 1.13 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |   |                   |                            | No treatment                               | 12 | Mean: 108.70<br>Lower: 90.00<br>Upper: 127.30   | -   |  |   |                                       |
|   | S-Warfarin: µg/mL*h (0 - ∞); measured after single dose warfarin following 2 wks  | Low (healthy)     | Warfarin (25; single dose) | Garlic (4; 7.42 mg allicin)                | 12 | Mean: 65.50<br>Lower: 55.30<br>Upper: 75.60   | -   | GMR <sub>diff</sub> : 1.06<br>Lower: 0.95<br>Upper: 1.19 | Upper and lower limits of individual group data = 95% CI;   | Medium                                |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design               | Definition of outcome  | CHD Risk Category   | CVD drug (dose mg/d)       | Supplement/ Control                           | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|---|--|---------------------|----------------------------|---|----|---|---|--|---|---------------------------------------|
|   | pretreatment with garlic or no pretreatment. Subjects followed for one more week post warfarin dose  |                     |                            | No treatment                                  | 12 | Mean: 60.30<br>Lower: 54.50<br>Upper: 66.10   | -   |  | Upper and lower limits of between group difference = 90% CI   |                                       |
| McKenney 2006 <sup>45</sup><br>Cross-over | Simvastatin; AUCss over final dosing interval (ng*h/mL); 2 wk treatment.   | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 21 | Mean: 125.10<br>SD: 62.90   | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 18 | Mean: 116.60<br>SD: 64.00   | -   |  |   |                                       |
|   | Beta-hydroxy simvastatin: AUCss over final dosing interval (ng*h/mL); 2 wk treatment.  | Low and/or Moderate | Simvastatin (80)           | Omega-3 fatty acids (EPA, DHA or both) (4)    | 20 | Mean: 83.00<br>SD: 42.20  | -   | -  | -   | Medium                                |
|   |  |                     |                            | No treatment                                  | 17 | Mean: 83.90<br>SD: 44.40  | -   |  |   |                                       |
| Abdul 2010 <sup>1</sup><br>Cross-over     | R-Warfarin: mg*h/mL (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)       | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 74.9<br>Lower: 62.5<br>Upper: 87.2  | -   | GMR <sub>diff</sub> : 0.95<br>Lower: 0.88<br>Upper: 1.03 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|   |  |                     |                            | No treatment                                  | 12 | Mean: 79.4<br>Lower: 65.4<br>Upper: 93.4  | -   |  |   |                                       |

**Evidence Table 167. KQ4—Continuous data—Area under the curve (AUC) (continued)**

| Author Year<br>Study Design | Definition of outcome  | CHD Risk Category | CVD drug (dose mg/d)       | Supplement/ Control                           | N  | Post treatment Mean/ (Median) SD/SE<br>Lower limit (IQR, 95% CI)<br>Upper Limit (IQR, 95% CI) | Mean change/% change from baseline/ SD/ P Value | Between group differences in Means/ medians SD/ P Value  | Additional comments   | Overall Risk of Bias (ROB) Assessment |
|-----------------------------|--|-------------------|----------------------------|---|----|---|---|--|---|---------------------------------------|
|                             | S-Warfarin: mg*h/mL (0 - ∞); measured after single dose warfarin following 2 wks pretreatment with Echinacea or no pretreatment. Subjects followed for one more week post warfarin dose. | Low (healthy)     | Warfarin (25; single dose) | <i>Echinacea</i> (5.1; 23 mg total alkamides) | 12 | Mean: 49.0<br>Lower: 40.0<br>Upper: 57.9  | -   | GMR <sub>diff</sub> : 0.92<br>Lower: 0.85<br>Upper: 1.99 | Upper and lower limits of individual group data = 95% CI; Upper and lower limits of between group difference = 90% CI | Medium                                |
|                             |  |                   |                            | No treatment                                  | 12 | Mean: 53.9<br>Lower: 42.9<br>Upper: 64.8  |   |  |   |                                       |

**Evidence Table 168. Risk of bias assessment for all studies**

| <b>Author year<br/>Key<br/>question</b>   | <b>Selection bias</b><br><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at baseline<br/>or control for imbalance</b>  | <b>Purity/<br/>standardization of<br/>supplement<br/>described</b> | <b>Blinding</b><br><br>Outcome<br>Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br><br>Completeness<br>of outcome data | <b>Free of<br/>financial<br/>conflict of<br/>interest</b> | <b>Harms</b><br><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over<br/>trials</b><br><br>Appropriate<br>design/<br>absence of<br>carry-over<br>effect/<br>appropriate<br>analysis | <b>Overall risk<br/>of bias for<br/>gradable<br/>outcomes</b> |
|---|--|--|--|--|--|---|--|--|---|
| <b>Coenzyme<br/>Q10</b>                   |  |  |  |  |  |   |  |  |   |
| Mabuchi<br>2007 <sup>39</sup><br>KQ 2, 3  | Unclear/Unclear  | No major imbalance<br>Unclear: smoking, comorbidities,<br>blood pressure<br>Other: glucose levels sign. higher<br>in placebo group   | Yes  | All unclear<br>double-blind,<br>placebo controlled                   | Yes  | No  | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Young<br>2007 <sup>70</sup><br>KQ 1, 2, 3 | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline diet   | Unclear  | All unclear<br>double-blind,<br>placebo controlled                   | Unclear  | Yes   | Yes/Unclear/Yes  | N/A  | Medium  |
| Caso 2007 <sup>11</sup><br>KQ 2, 3        | Unclear/Yes  | No major imbalance<br>Unclear: Race, baseline diet,<br>smoking, concomitant<br>medications/supplements,<br>comorbidities, HDL-c, blood<br>pressure<br>Minor imbalance: > proportion of<br>women in Vit E group vs. CoQ10 | Yes  | Yes/Yes/Yes  | Yes  | Yes   | Yes/Yes/Yes  | N/A  | Low   |
| Playford<br>2003 <sup>58</sup><br>KQ 2, 3 | Unclear/Unclear  | No major imbalance<br>Unclear: Race  | Unclear  | All unclear<br>double-blind  | Yes  | Unclear   | No/Unclear/Unclear   | N/A  | Low-medium  |



**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key<br/>question</b>    | <b>Selection bias</b><br><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>  | <b>Purity/<br/>standardization of<br/>supplement<br/>described</b> | <b>Blinding</b><br><br>Outcome<br>Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br><br>Completeness<br>of outcome data | <b>Free of<br/>financial<br/>conflict of<br/>interest</b> | <b>Harms</b><br><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br><br>Appropriate<br>design/<br>absence of carry-<br>over effect/<br>appropriate<br>analysis | <b>Overall risk<br/>of bias for<br/>gradable<br/>outcomes</b> |
|--|--|--|--|--|--|---|--|--|---|
| Watson<br>1999 <sup>66</sup><br>KQ 1, 2, 3 | Unclear/Unclear  | Unclear  | No   | All unclear<br>double-blind,<br>placebo controlled                   | Unclear  | Unclear   | No/Unclear/Unclear   | Yes/Yes/Unclear  | Medium  |
| <b>Echinacea</b>                           |  |  |  |  |  |   |  |  |   |
| Abdul 2010 <sup>1</sup><br>KQ 2, 3, 4      | Unclear/Unclear  | No major<br>imbalance/Unclear  | Yes  | No/No/No<br>Open label trial   | Unclear  | No  | No/Unclear/Unclear   | Yes/Yes/Unclear  | Medium  |
| <b>Garlic</b>                              |  |  |  |  |  |   |  |  |   |
| Macan<br>2006 <sup>40</sup><br>KQ 2, 3     | Unclear/Unclear  | Major imbalance: for:<br>Gender - proportion of men<br>higher in placebo (77%) vs.<br>AGE (45%) group.<br>No other major imbalance<br>Unclear: Race, Baseline<br>diet, smoking | Yes  | All unclear<br>double-blind,<br>placebo controlled                   | Unclear  | No  | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Bordia 1998 <sup>9</sup><br>KQ 2, 3        | Unclear/Unclear  | All unclear  | Yes  | All unclear<br>placebo-controlled                                    | Unclear  | Yes   | Unclear/Unclear/Unclear  | N/A  | High  |
| Hajda,<br>2010 <sup>28</sup><br>KQ 4       | No/No  | Yes  | Yes  | No/No/No   | Unclear  | No  | No/No/Unclear  | Yes/Yes/Unclear  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>                | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>  | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of<br>harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|--|--|--|--|---|---|---|--|--|---|
| Budoff 2004 <sup>10</sup><br>KQ 1, 2, 3            | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline<br>diet, concomitant<br>medications/supplements,<br>blood pressure | Yes  | All unclear<br>double-blind, placebo<br>controlled            | Yes   | No  | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Mohammed<br>Abdul 2008 <sup>49</sup><br>KQ 2, 3, 4 | Unclear/Unclear  | Unclear  | Yes  | No/No/No<br>Open label trial                                  | No  | Yes   | Yes/Yes/Unclear  | Yes/Yes/Unclear  | Medium  |
| <b>Ginger</b>                                      |  |  |  |   |   |   |  |  |   |
| Jiang 2005 <sup>32</sup><br>KQ 3, 4                | Unclear/Unclear  | Unclear  | Yes  | No/No/No<br>Open label trial                                  | Yes   | Yes   | No/Unclear/Unclear   | Yes/Yes/Unclear  | Medium  |
| <b>Ginkgo biloba</b>                               |  |  |  |   |   |   |  |  |   |
| Gardner 2007 <sup>23</sup><br>KQ 2, 3              | Yes/Yes  | No major imbalance<br>Unclear: Baseline diet,<br>smoking, LDL-c/HDL-c  | Yes  | Yes/Yes/Yes   | Yes   | Yes   | Yes/Yes/Yes  | N/A  | Low   |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>    | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>  | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|--|---|--|---|--|---|---|---|--|---|
| Garg 1995 <sup>24</sup><br>KQ 1, 3     | Yes/Unclear   | No major imbalance for pre-specified variables<br>Unclear: Race, Baseline diet/nutrient status, comorbidity based on laboratory variables, LDL-c/HDL-c, Blood pressure<br>Other imbalance - speech problems between groups (GB 44.8% vs. Placebo 23.1%) and comorbidities such as DM | No  | Unclear/Unclear/Yes<br>double-blind, placebo controlled    | Yes   | Unclear                                       | No/No/Unclear   | N/A  | Medium-High                                       |
| Wolf 2006 <sup>68</sup><br>KQ 2, 3     | Yes/Unclear   | Unclear  | Yes   | All unclear,<br>double-blind, placebo controlled           | Yes   | Yes   | No/Unclear/Yes  | Yes/Yes/No   | Low-medium  |
| Kim 2010 <sup>35</sup><br>KQ 2, 3, 4   | Yes/Unclear   | Unclear  | Yes   | No/No/No<br>Open label trial                               | Yes   | No  | Unclear/Unclear/Unclear   | Yes/Yes/Unclear  | Medium  |
| Jiang 2005 <sup>32</sup><br>KQ 2, 3, 4 | Unclear/Unclear   | Unclear  | Yes   | No/No/No<br>Open label trial                               | Yes   | Yes   | No/Unclear/Unclear  | Yes/Yes/Unclear  | Medium  |
| Aruna 2007 <sup>2</sup><br>KQ 2        | Unclear/Unclear   | Unclear  | No  | No/No/No<br>Open label trial                               | Unclear   | Unclear                                       | No/Unclear/Unclear  | Yes/Unclear/Unclear  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>    | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>  | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|--|--|--|--|---|---|---|--|--|---|
| Mauro 2003 <sup>43</sup><br>KQ 3, 4    | Unclear/unclear  | Unclear  | Yes  | No/No/No<br>Open label trial                                  | Yes   | Yes   | No/Yes/Unclear   | Yes/Yes/Unclear  | Medium  |
| <b>Ginseng</b>                         |  |  |  |   |   |   |  |  |   |
| Lee 2008 <sup>36</sup><br>KQ 2, 3      | Unclear/Unclear  | No major imbalance<br>Unclear: Race, baseline<br>diet, smoking, some<br>concomitant medications,<br>LDL-c/HDL-c, Blood<br>pressure   | Yes  | No/No/No<br>Open label trial                                  | Yes   | Yes   | No/Unclear/Unclear   | N/A  | Medium  |
| Yuan 2004 <sup>71</sup><br>KQ 2, 3, 4  | Yes/Yes  | No major imbalance<br>Unclear: Comorbidities as<br>assessed by lab values<br>(restriction for clinical<br>assessment of<br>comorbidities), LDL-<br>c/HDL-c, blood pressure | Yes  | Yes/Yes/Yes   | Yes   | Yes   | No/Yes/Unclear   | N/A  | Low   |
| Jiang 2004 <sup>33</sup><br>KQ 2, 3, 4 | Unclear/unclear  | Yes  | Yes  | No/No/No<br>Open label trial                                  | Yes   | Unclear   | No/Unclear/Unclear   | Yes/Yes/Unclear  | Medium  |
| <b>Hawthorne</b>                       |  |  |  |   |   |   |  |  |   |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>         | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>   | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|---|--|---|--|---|---|---|--|--|---|
| Tanknow<br>2003 <sup>65</sup><br>KQ 2, 3, 4 | Unclear/Unclear  | Unclear   | Yes  | No/No/No<br>Open label trial                                  | Unclear   | Unclear   | No/Yes/Yes   | Yes/Yes/Yes  | Medium  |
| <b>Magnesium</b>                            |  |   |  |   |   |   |  |  |   |
| Paolisso<br>1992 <sup>67</sup><br>KQ 2, 3   | Unclear/Unclear  | All unclear   | Unclear  | Yes/Unclear/Unclear<br>double-blind, placebo<br>controlled    | Yes   | Unclear   | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Reyes 1984 <sup>69</sup><br>KQ 2, 3         | Unclear/Unclear  | Potential<br>confounding/imbalance:<br>Gender - more females in<br>treatment group but small<br>sample size<br>No major imbalance noted<br>for other prespecified<br>variables<br>Unclear: Smoking,<br>concomitant supplements<br>(medications controlled by<br>restriction), LDL-c/HDL-c | Yes  | All unclear<br>double-blind, placebo<br>controlled            | Yes   | Unclear   | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Wirell 1994 <sup>67</sup><br>KQ 1, 2, 3     | Unclear/Unclear  | Unclear   | Yes  | Unclear/Yes/Yes<br>double-blind, placebo<br>controlled        | Yes   | No  | No/Unclear/Unclear   | Yes/No/No  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>      | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>   | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|--|--|---|--|---|---|---|--|--|---|
| <b>Niacin</b>                            |  |   |  |   |   |   |  |  |   |
| Avogaro 1974 <sup>3</sup><br>KQ 2, 3     | Unclear/Unclear  | Unclear for pre-specified<br>variables<br>Other: Propranolol dosage<br>is different in the two<br>groups: Supplement +<br>CVD phase = 20 mg/day;<br>CVD only phase = 60<br>mg/day | No   | All unclear<br>matching placebo                               | No  | Unclear   | No/Unclear/Unclear   | Yes/No/Unclear   | High  |
| <b>Omega-3 fatty<br/>acids/fish oils</b> |  |   |  |   |   |   |  |  |   |
| Bays 2010 <sup>6</sup><br>K2, 3          | Unclear/Unclear  | No major imbalances<br>Unclear: Comorbidities,<br>Blood pressure.   | Yes  | All unclear<br>double-blind, placebo<br>controlled            | Yes   | No  | Yes/Unclear/Yes  | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>       | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>   | <b>Purity/<br/>standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---|---|---|--|--|---|---|---|--|---|
| Ferraro 2009 <sup>22</sup><br>KQ 2, 3     | Yes/Unclear   | No major imbalance for pre-specified variables<br>Unclear: Race, Baseline diet, smoking, some concomitant medications/supplements, comorbidities, LDL-c<br>Other - Class of erythrocyturia; Control group significantly more likely to be lower class than intervention group | Yes  | No/No/No<br>no blinding                                    | Yes   | Unclear                                       | Unclear/Unclear/Unclear   | N/A  | Medium  |
| Davidson 2007 <sup>14</sup><br>KQ 1, 2, 3 | Yes/Yes   | No major imbalance<br>Unclear: Baseline diet, smoking   | Yes  | All unclear<br>double-blind, placebo controlled            | Yes   | Unclear                                       | Unclear/Yes/Yes   | N/A  | Medium  |
| Meyer 2007 <sup>46</sup><br>KQ 2          | Yes/Unclear   | No major imbalance<br>Unclear: Race, Baseline diet, smoking, concomitant medications/supplements, lab values associated with comorbidities (but clinical presentation of comorbidities restricted/balanced), blood pressure   | Yes  | All unclear<br>placebo controlled                          | Unclear   | Yes   | N/A   | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>  | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>  | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|--------------------------------------|---|--|---|--|---|---|---|--|---|
| Neil 2010 <sup>53</sup><br>KQ2, 3    | Yes/Unclear   | Unclear  | Yes   | Yes/Yes/Double blind<br>Placebo controlled                 | Yes   | No  | No/No/No  | NA   | Low with respect to KQ2 outcomes                  |
| Svaneborg 2002 <sup>64</sup><br>KQ 2 | Unclear/Unclear   | Unclear for all  | Yes   | All unclear<br>double-blind, placebo controlled            | Unclear   | Unclear                                       | N/A   | N/A  | Medium  |
| Nordoy 2000 <sup>54</sup><br>KQ 2, 3 | Unclear/Unclear   | No major imbalance<br>Unclear: Race, smoking, comorbidities as assessed by lab variables (considered balanced by clinical variables), Blood pressure | Yes   | All unclear<br>double-blind, placebo controlled            | Yes   | Unclear                                       | Unclear/Unclear/Unclear   | N/A  | Medium  |
| Davidson 1997 <sup>15</sup><br>KQ 2  | Unclear/Unclear   | No major imbalance<br>Unclear: Race, smoking, Concomitant medications/supplements, comorbidities, Blood pressure                                     | Yes   | All unclear<br>double-blind, placebo controlled            | Yes   | Unclear                                       | N/A   | N/A  | High  |



**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>     | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>  | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---|---|--|---|--|---|---|---|--|---|
| Eritsland 1996 <sup>21</sup><br>KQ 1, 3 | Yes/Unclear   | No major imbalance<br>Unclear: Race, Baseline diet/nutrient status, comorbidities as assessed by laboratory variables (balanced as assessed by clinical variables)                               | Yes   | No/No/No   | Yes   | No  | Yes/Yes/Yes   | N/A  | Medium  |
| Yamamoto 1995 <sup>69</sup><br>KQ 1, 2  | Unclear/Unclear   | No major imbalance<br>Unclear: Baseline diet/nutrient exposure, smoking, Concomitant medications/supplements, comorbidities as assessed by laboratory values, Blood pressure                     | Yes   | No/No/No   | Unclear   | Unclear                                       | N/A   | N/A  | Medium  |
| Howe 1994 <sup>30</sup><br>KQ 2         | Unclear/Unclear   | No major imbalance<br>Unclear: Race, Baseline diet/nutrient status, smoking, Comorbidities as assessed by laboratory variables (balance/restriction based on clinical variables), Blood pressure | Yes   | All unclear<br>double-blind, placebo controlled            | Yes   | Unclear                                       | N/A   | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>   | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>   | <b>Purity/<br/>standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---------------------------------------|---|---|--|--|---|---|---|--|---|
| Kaul 1992 <sup>34</sup><br>KQ 1, 2, 3 | Yes/Unclear   | No major imbalance for prespecified variables<br>Unclear: Race, Baseline diet/nutrient status, Concomitant medications supplement (medications by restriction), Comorbidities, LDL-c/HDL-c, Blood pressure<br>Other: higher N of dilations in circumflex artery in controls vs. treatment group | Yes  | Yes/No/No  | Yes   | Unclear                                       | No/Yes/Yes  | N/A  | Low-Medium  |
| Nordøy 2003 <sup>55</sup><br>KQ 2, 3  | Unclear/Unclear   | No major imbalance<br>Unclear: Smoking, Comorbidities as assessed by laboratory measures (balanced/restriction based on clinical measures of comorbidity)   | Yes  | All unclear double-blind, placebo-controlled               | Yes   | Unclear                                       | No/Unclear/Unclear  | N/A  | Low   |
| Roth 2009 <sup>60</sup><br>KQ 1, 2, 3 | Unclear/Unclear   | No major imbalance<br>Unclear: Smoking, Blood pressure  | Yes  | All unclear double-blind, placebo-controlled               | Yes   | No  | Unclear/Unclear/Yes   | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>    | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>  | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|--|--|--|--|---|---|---|--|--|---|
| Isley 2007 <sup>31</sup><br>KQ 2, 3    | Unclear/Unclear  | No major imbalance<br>Unclear: Race, smoking,<br>Comorbidities as<br>assessed by laboratory<br>measures<br>(balanced/restriction<br>based on clinical<br>measures of comorbidity),<br>blood pressure   | Yes  | All unclear<br>placebo-controlled                             | Yes   | Yes   | No/Yes/Unclear   | N/A  | Medium  |
| Bender 1998 <sup>8</sup><br>KQ 1, 2, 3 | Unclear/Unclear  | Potential confounding:<br>Gender and age are<br>imbalanced<br>No major imbalance noted<br>for other prespecified<br>variables<br>Unclear: Baseline<br>diet/nutrient status,<br>smoking, comorbidities as<br>assessed clinically, LDL-<br>c/HDL-c, Blood pressure | Yes  | All unclear<br>double-blind, placebo<br>controlled            | Unclear   | No  | Unclear/Unclear/Unclear  | N/A  | High  |
| Chan 2002 <sup>12</sup><br>KQ 1, 2, 3  | Unclear/Unclear  | No major imbalance<br>Unclear: Race  | Yes  | All unclear<br>double-blind, placebo-<br>controlled           | Yes   | Unclear   | No/Unclear/Unclear   | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>         | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>  | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|---|--|--|--|---|---|---|--|--|---|
| Liu 2003 <sup>37</sup><br>KQ 1, 2, 3        | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline<br>diet/nutrient status,<br>smoking, Concomitant<br>medications supplement<br>(medications by<br>restriction), Comorbidities<br>as assessed by laboratory<br>measures (restriction<br>based on clinical<br>measures of comorbidity),<br>Blood pressure | Yes  | Yes/Unclear/No  | Unclear   | Unclear   | Unclear/Unclear/Unclear  | N/A  | Medium  |
| Dehmer 1988 <sup>17</sup><br>KQ 1, 2, 3     | Yes/Unclear  | No major imbalance<br>Unclear/not stated: Race,<br>Baseline diet/nutrient<br>status, Concomitant<br>medications/supplement,<br>Blood pressure  | Yes  | Yes/Unclear/No  | Yes   | Yes   | No/Unclear/Unclear   | N/A  | Medium  |
| Balestrieri<br>1996 <sup>4</sup><br>KQ 2, 3 | Unclear/Unclear  | Unclear  | Yes  | All unclear<br>double-blind, placebo-<br>controlled           | Yes   | Unclear   | Yes/Unclear/Unclear  | Yes/Yes/Yes  | Medium  |
| Lungershausen<br>1994 <sup>38</sup><br>KQ 2 | Unclear/Unclear  | Unclear  | Yes  | All unclear<br>double-blind, placebo-<br>controlled           | Unclear   | Unclear   | N/A  | Yes/No/Yes   | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>                 | <b>Selection bias</b><br>Appropriate sequence generation/<br>allocation concealment | <b>Comparable groups at baseline or control for imbalance</b> | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-over effect/<br>appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---|---|---|---|--|---|---|---|--|---|
| Hansen 1993 <sup>29</sup><br>KQ 2, 3                | Unclear/Unclear   | Unclear   | Yes   | All unclear<br>double-blind, placebo-controlled            | Unclear   | No  | No/Unclear/Unclear  | Yes/Yes/No   | Medium  |
| McKenney 2006 <sup>45</sup><br>KQ 2, 3, 4           | Unclear/Unclear   | Unclear   | No  | No/No/No<br>Open label trial                               | Yes   | No  | No/Unclear/Unclear  | Yes/Yes/Yes  | Medium  |
| Mueller 1991 <sup>51</sup><br>KQ 2, 3               | Yes/Unclear   | Unclear   | Yes   | Yes/Yes/Yes, double-blind,<br>placebo-controlled           | Unclear   | No  | No/Unclear/Unclear  | Yes/No/Unclear   | Medium  |
| Maki 2008 <sup>41</sup><br>KQ 1, 2, 3               | Unclear/Unclear   | No major imbalance  | No  | Yes/Yes/Yes  | Yes   | No  | No/Unclear/Unclear  | Yes/Unclear/Unclear  | Medium  |
| Gosai 2008 <sup>26</sup><br>KQ 3, 4                 | Unclear/Unclear   | Unclear   | Yes   | No/No/No<br>Open label trial                               | Unclear   | No  | No/Unclear/Unclear  | Yes/Yes/Unclear  | Medium  |
| Di Spirito 2008 <sup>19</sup><br>KQ 1, 3, 4         | Unclear/Unclear   | Unclear   | Yes   | No/No/No<br>Open label trial                               | Unclear   | No  | No/Unclear/Unclear  | Yes/Yes/No   | Medium  |
| <b>Red yeast rice extract</b> – no included studies |   |   |   |  |   |   |   |  |   |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>  | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>   | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|--|--|---|--|---|---|---|--|--|---|
| <b>Resveratrol</b> –<br>no included<br>studies                                     |  |   |  |   |   |   |  |  |   |
| <b>Vitamin A</b> - no<br>included<br>studies                                       |  |   |  |   |   |   |  |  |   |
| <b>Vitamin D<br/>(with or<br/>without<br/>calcium)</b> – no<br>included<br>studies |  |   |  |   |   |   |  |  |   |
| <b>Vitamin E</b>   |  |   |  |   |   |   |  |  |   |
| Glynn 2007 <sup>25</sup><br>KQ 1, 3  | Yes/Unclear  | No major imbalance<br>Unclear: Race, Baseline<br>diet/nutrient status,<br>Smoking, Concomitant<br>medications (but<br>restriction for<br>anticoagulants and some<br>supplements),<br>Comorbidities, LDL-<br>c/HDL-c, Blood pressure | Yes  | Yes/Yes/Yes   | Yes   | Yes   | Unclear/Yes/Yes  | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year<br/>Key question</b>       | <b>Selection bias</b><br>Appropriate<br>sequence<br>generation/<br>allocation<br>concealment | <b>Comparable groups at<br/>baseline or control for<br/>imbalance</b>   | <b>Purity/<br/>standardization<br/>of supplement<br/>described</b> | <b>Blinding</b><br>Outcome Assessors/Care<br>Provider/Patient | <b>Attrition bias</b><br>Completeness<br>of outcome<br>data | <b>Free of<br/>financial<br/>conflict<br/>of<br/>interest</b> | <b>Harms</b><br>Pre-specification/<br>active data collection/<br>appropriateness of harms<br>data collection | <b>Cross-over trials</b><br>Appropriate design/<br>absence of carry-<br>over effect/<br>appropriate analysis | <b>Overall<br/>risk of bias<br/>for<br/>gradable<br/>outcomes</b> |
|---|--|---|--|---|---|---|--|--|---|
| Sutken 2006 <sup>63</sup><br>KQ 2         | No/Unclear   | No major imbalance<br>Unclear: Race, Baseline<br>diet, comorbidity as<br>assessed by laboratory<br>measures (but<br>restriction/balance for<br>clinical measures of<br>comorbidity).  | Unclear  | No/No/No  | Yes   | Unclear   | N/A  | N/A  | High  |
| d'Arcangues<br>2004 <sup>13</sup><br>KQ 3 | Unclear/Yes  | No major imbalance<br>Unclear: Age, Race,<br>Baseline diet/nutrient<br>status, smoking,<br>Comorbidities as<br>assessed by laboratory<br>measures (restriction<br>based on clinical<br>variables), LDL-c/HDL-c,<br>blood pressure | Yes  | Yes/Yes/Yes   | Unclear   | Unclear   | No/Yes/Unclear   | N/A  | Medium  |
| Manuel 2004 <sup>42</sup><br>KQ 2, 3      | Yes/Unclear  | No major imbalance<br>Unclear: Race, smoking,<br>concomitant<br>medications/supplements<br>Other - neuropathy;<br>significantly greater in<br>placebo group at baseline   | Yes  | All unclear<br>matched placebo-control                        | Yes   | Unclear   | Unclear/Unclear/Unclear  | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| Author year Key question              | Selection bias<br>Appropriate sequence generation/ allocation concealment | Comparable groups at baseline or control for imbalance  | Purity/ standardization of supplement described | Blinding<br>Outcome Assessors/Care Provider/Patient | Attrition bias<br>Completeness of outcome data | Free of financial conflict of interest | Harms<br>Pre-specification/ active data collection/ appropriateness of harms data collection | Cross-over trials<br>Appropriate design/ absence of carry-over effect/ appropriate analysis | Overall risk of bias for gradable outcomes |
|---------------------------------------|---|---|---|---|--|--|--|---|--|
| Miyamoto 2004 <sup>46</sup><br>KQ 1   | Yes/Unclear   | No major imbalance<br>Unclear: Race, baseline diet/nutrient intake, confounding as assessed by laboratory measures (restriction w.r.t. clinical assessment of confounding), blood pressure  | Yes   | All unclear<br>double-blind, placebo-controlled     | Yes  | Yes                                    | N/A  | N/A   | N/A  |
| Micheletta 2004 <sup>47</sup><br>KQ 2 | Unclear/Unclear   | No major imbalance. Study states that no significant differences were present between the groups for the following variables, with no data reported: Age, gender, smoking, clinical assessment of comorbidity<br>Unclear: Race, baseline diet/nutrient intake, concomitant medications (supplements restricted), confounding as assessed by laboratory measures, LDL-c/HDL-c, blood pressure. | Yes   | No/No/No  | Yes  | Yes                                    | N/A  | N/A   | Medium                                     |



**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year Key question</b>         | <b>Selection bias</b><br>Appropriate sequence generation/ allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>  | <b>Purity/ standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/ active data collection/ appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/ absence of carry-over effect/ appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---|--|--|--|--|---|---|---|--|---|
| Duffy 2001 <sup>20</sup><br>KQ 2, 3     | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline diet, smoking, comorbidities as assessed by lab variables (considered balanced by clinical variables)                  | Yes  | Unclear/Unclear/Yes double-blind, placebo-controlled       | Yes   | Yes   | No/Unclear/Unclear  | N/A  | Medium  |
| Barbagallo 1999 <sup>5</sup><br>KQ 2, 3 | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline diet/nutrient statuses, smoking, LDL-c/HDL-c   | Unclear  | All unclear double-blind, placebo-controlled               | Unclear   | Unclear                                       | Unclear/Unclear/Unclear   | N/A  | Medium  |
| Motoyama 1998 <sup>50</sup><br>KQ 1     | Yes/Unclear  | No major imbalance<br>Unclear: Race, Baseline diet/nutrient statuses, comorbidities as assessed by laboratory variables (balanced as assessed by clinical variables) | Yes  | Yes/Unclear/Unclear placebo-controlled                     | Unclear   | Unclear                                       | N/A   | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year Key question</b>          | <b>Selection bias</b><br>Appropriate sequence generation/ allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>  | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/ active data collection/ appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/ absence of carry-over effect/ appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|--|--|--|---|--|---|---|---|--|---|
| Napoli 1998 <sup>62</sup><br>KQ 1, 2, 3  | Unclear/Unclear  | No major imbalance<br>Unclear: Gender, Race, Concomitant medications/supplements, comorbidities as assessed by clinical variables (balanced as assessed by laboratory variables), Blood pressure | Yes   | All unclear  | Unclear   | Yes   | Yes/Yes/Yes   | N/A  | Medium  |
| Steiner 1995 <sup>62</sup><br>KQ 1, 2, 3 | Unclear/Unclear  | No major imbalance<br>Unclear: Race, Baseline diet/nutrient status, concomitant medications/supplements, comorbidity based on laboratory variables.  | No  | All unclear double-blind, placebo-controlled               | Unclear   | No  | No/Unclear/Unclear  | N/A  | Low-Medium  |
| McDowell 1994 <sup>44</sup><br>KQ 2, 3   | Unclear/Unclear  | No major imbalance<br>Unclear: Age, Gender, Race, smoking, Comorbidities, Blood pressure   | Yes   | All unclear double-blind, placebo-controlled               | Yes   | No  | No/Unclear/Unclear  | N/A  | Medium  |

**Evidence Table 168. Risk of bias assessment for all studies (continued)**

| <b>Author year Key question</b>         | <b>Selection bias</b><br>Appropriate sequence generation/ allocation concealment | <b>Comparable groups at baseline or control for imbalance</b>   | <b>Purity/standardization of supplement described</b> | <b>Blinding</b><br>Outcome Assessors/Care Provider/Patient | <b>Attrition bias</b><br>Completeness of outcome data | <b>Free of financial conflict of interest</b> | <b>Harms</b><br>Pre-specification/ active data collection/ appropriateness of harms data collection | <b>Cross-over trials</b><br>Appropriate design/ absence of carry-over effect/ appropriate analysis | <b>Overall risk of bias for gradable outcomes</b> |
|---|--|---|---|--|---|---|---|--|---|
| Desideri 2003 <sup>18</sup><br>KQ 2     | Unclear/Unclear  | No major imbalance<br>Unclear: Race, comorbidities as assessed by laboratory measures (clinical measures balanced by restriction) | Yes   | All unclear<br>double-blind, no placebo                    | Yes   | Unclear                                       | N/A   | N/A  | Medium  |
| De 2002 <sup>16</sup><br>KQ 2, 3        | Unclear/Unclear  | Unclear   | Yes   | No/No/No<br>Open label study                               | Unclear   | No  | No/No/No  | Yes/No/Unclear   | High  |
| Paolisso 1995 <sup>56</sup><br>KQ 2, 3  | Unclear/Unclear  | Unclear   | Yes   | All unclear<br>double-blind, placebo-controlled            | Unclear   | Unclear                                       | No/Unclear/Unclear  | Yes/Yes/No   | Medium  |
| <b>Vitamin K</b>                        |  |   |   |  |   |   |   |  |   |
| Sconce 2007 <sup>61</sup><br>KQ 1, 2, 3 | Unclear/Unclear  | No major imbalance<br>Unclear: Baseline diet, smoking, LDL-c/HDL-c, blood pressure  | Yes   | Yes/Yes/Yes  | Yes   | Unclear                                       | Unclear/Unclear/Unclear   | N/A  | Medium  |

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## Appendix D. Excluded Studies

Appendix D lists all of the studies that were excluded from this review, categorized by reason for exclusion and alphabetized.

### Not Relevant Intervention(s)/Exposure(s) and Comparator(s)

Eligibility: Relevant dietary supplement VS. no dietary supplement (e.g. no treatment or placebo) OR Relevant dietary supplement VS. other relevant dietary supplement.

Clofibrate and niacin in coronary heart disease. *J Am Med Assoc* 1975 Jan 27;231(4):360-81. [PMID: 1088963].

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[New evidence of uselessness of intravenous glucose-insulin-potassium infusion in patients with ST-segment elevation myocardial infarction: results of meta-analysis of CREATE-ECLA and OASIS-6 trials]. [Review] [8 refs] [Russian]. *Kardiologiya* 2008;48(1):76 . [PMID: 18261001].

3 steps to stroke prevention and stroke recovery. Drink tea, take statins, and change negative lifestyle habits--even just one--to aid stroke risk reduction and recovery. *Duke Med Health News* 2009 May;15(5):4-5. [PMID: 19746513].

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## Not Relevant Population

Eligibility: Adults taking one or more specific cardiovascular drugs or class of drugs commonly used in the outpatient setting

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## **Not Relevant Study Design**

Eligibility criteria: Systematic review; or experimental/ observational comparative study (RCT, non-RCT, cohort, case-control, cross-sectional) with independent (concurrent or historical) control group including at least 5 participants

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Eligibility: Systematic review on dietary supplements meeting minimum criteria for inclusion

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Eligibility: English systematic review OR English/German primary study

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## Appendix E. Data Extraction Forms

Appendix E outlines in detail all of the questions that were used in screening the literature and ultimately determined whether a study was included or excluded. Furthermore, all data extracted from each study are also listed in this appendix.

### DSCI: Level 1, Broad Screen Form

Is this:

a systematic review or comparative primary study assessing the benefits or harms of dietary supplement use in a population of adults taking cardiovascular drugs

OR

a systematic review or primary study assessing the pharmacokinetics/dynamics of the shortlist of supplements relevant to Key Question 5?

- No
- Possibly/Yes

### DSCI: Level 2, Abstract Screen Form

- If the article meets at least one exclusion criterion (i.e., the record should be excluded) -SELECT ONLY THE FIRST RELEVANT EXCLUSION CRITERIA IN ORDER OF LIST.
- If the article does not meet any of the exclusion criteria (i.e., it is eligible for inclusion) OR if it is unclear based on the title and abstract if certain criteria are met (i.e., full text required) - SELECT 'YES/POSSIBLY'.
- If eligibility is unclear based on need for content expertise - SELECT 'CONTENT EXPERTISE NEEDED' and briefly explain where guidance is needed. (CVD, DS, other with detail)

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#### 1. Does this report discuss the use of relevant dietary supplements<sup>1</sup>?

- No - no dietary supplement(s) (SUBMIT FORM)
- Yes/Possibly - at least one relevant dietary supplement or Unclear based on title abstract (Respond to question 2)
- No - non-relevant dietary supplement(s) only (please state) (SUBMIT FORM)

---

#### 2. Does this report describe a study which is potentially relevant for KQ 1-4?

- No (study design)-not a SR, experimental/observational comparative study with independent control group (i.e., narrative review, commentary or uncontrolled empirical study) (exclude)
  - No (intervention/ctrl)-not comparing benefit/harms/PD/PK of relevant DS vs. relevant ctrl (see footnote 2) (exclude)
  - No (population) - not in adult taking CV drugs in outpatient setting (see footnote 3)(exclude)
  - Yes/Possibly (State: Study design; supplement(s); CV drug(s))
- 
- Unclear - need clinical content expertise (please specify: supplement, CV drug, other?)

- 
- No (language) - Non-English SR or Exp/Obsv not in English, Chinese or German (state if probable SR or primary study; language)
- 

**3. If you answered "NO" to question 2, does this study contain relevant information (e.g. clinical/SR studies providing indirect evidence: PK, PD) important for Introduction or Discussion sections? (non-consequential)**

- No
- Yes/Possibly

## **DSCI: Level 3, Full Text Screening Form for Key Questions 1 to 4**

PLEASE NOTE THE FOLLOWING:

If you have excluded a record for eligibility for KQ 1-4 (as stated with a response of 'No' to any of questions 1-5), please respond to the remaining unanswered questions 1-5 with 'NO RESPONSE - EXCLUDED IN OTHER QUESTION' and respond to question 6 accordingly. You must respond to all questions for each record.

**1. Relevant INTERVENTION/EXPOSURE(S) and COMPARATOR(S) (see footnotes 1 & 2)?**

- **Relevant dietary supplement VS. no dietary supplement** (e.g. no treatment or placebo) **OR**
- **Relevant dietary supplement VS. other relevant dietary supplement**

- Yes (Please specify [name] dietary supplement(s) - if many [e.g. review] state 'mixed')

- 
- No - no supplement or no appropriate comparator (EXCLUDE)

- Details present but content expertise requested (please describe)

- 
- NO RESPONSE - EXCLUDED IN OTHER QUESTION

- No - non-relevant supplement and/or comparator (please state) (EXCLUDE)
- 

**2. Full study, subgroup results or regression analysis in relevant POPULATION for KQ 1-4?**

- **Adults (majority  $\geq$  16 years old) taking one or more specific cardiovascular drugs or class of cardiovascular drugs commonly used in outpatient setting** (see footnote 3)

- Yes (Please state which CVD(s) or which class(es) of CVD)

- 
- No or unclear (specific CVD(s) or class(es) of CVDs not explicit) (EXCLUDE)

- Details available but content expertise requested (please describe)

- 
-

- NO RESPONSE – EXCLUDED IN OTHER QUESTION

### 3. Relevant STUDY DESIGN?

- **Systematic review meeting minimum eligibility requirements** (see footnote 4) **OR**
- **Experimental or observational comparative study** (RCT, non-RCT, cohort, case-control, cross-sectional) **with independent (concurrent or historical) control group** including at least 5 participants.
- Yes - Systematic review meeting minimum criteria for review eligibility (see footnote 3)
- Yes - Experimental or observational comparative study with independent control and at least 5 participants
- No - likely a RELEVANT, THOROUGH (w.r.t. search methods) systematic review but does NOT meet minimum criteria for review eligibility (EXCLUDE)
- No - experimental study without independent control (before and after study)
- None of the above (EXCLUDE)
- NO RESPONSE - EXCLUDED IN OTHER QUESTION

### 4. Relevant OUTCOME(S) for at least one of Key questions 1-4?

- KQ 1: Clinical efficacy/effectiveness cardiovascular outcomes
- KQ 2: Intermediate efficacy/effectiveness cardiovascular outcomes
- KQ 3: Clinical or intermediate harms outcomes
- KQ 4: Pharmacokinetic/pharmacodynamic outcomes

*Note: for list of relevant outcomes, please see review protocol*

- Yes
- No (EXCLUDE)
- NO RESPONSE - EXCLUDED IN OTHER QUESTION

### 5. Relevant LANGUAGE?

- **SR published in English**
- **Experimental or observational comparative study published in English or German**
- Yes - SR in English
- Yes - Exp/Obs study in English
- Yes - Exp/Obs study in German
- No - SR in other language (please state which)

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- No - Exp/Obs study in other language (please state which)

---

- NO RESPONSE - EXCLUDED IN OTHER QUESTION

### 6. Does this report include Mix of CVD drugs that are used by <80% of the population or the % of



patients using CVD drugs are not described? (Such studies will not be used in the evidence synthesis of the report--May 16)

Yes (please describe)

No

## DSCI: General Characteristics Form for Experimental Studies

Indicate NR if not reported and NA if not applicable. For percentages, just indicate the number without the percentage sign.

1. RefID: \_\_\_\_\_

2. Is subgroup data available?

*Please see supplemental guidance for data extraction.*

***If the answer is yes, please also fill out a separate form for each subgroup for which data have been presented.***

Yes

3. If yes, **ONLY ANSWER IF THIS IS A SUBGROUP FORM**: Check the subgroup to which this form applies.

- Age  $\geq$  65
- Age  $\geq$  80
- Ethnicity
- Gender
- Healthy Adults
- Participants with disorders of the liver (e.g., hepatitis, cirrhosis)
- Diabetes
- Participants with disorders of the kidney (e.g., reduced GFR, end stage renal disease)
- CVD drug for non-CVD indication
- Genetic polymorphisms

4. If yes, **ONLY ANSWER IF THIS IS A SUBGROUP FORM**: Indicate the CHD risk level of the subgroup.

*Please refer to supplemental guidance for data extraction.*

- At low risk for CHD (0-1 risk factor)
- At moderate/moderately high risk for CHD (2+ risk factors)
- At high risk for CHD
- Mixed (please specify)

Unclear

No

5. Does the study contain subgroups of subjects with either low, moderate, or high CHD risk?

*Please see supplemental guidance for data extraction.*

**If the answer is yes, please also fill out a separate form for each CHD risk level subgroup presented.**

Yes

6. If yes, **ONLY ANSWER IF THIS IS A CHD RISK LEVEL SUBGROUP FORM: Check the CHD risk subgroup to which this form applies.**

At low risk for CHD (0-1 risk factor)

At moderate/moderately high risk for CHD (2+ risk factors)

At high risk for CHD

No

7. Are any of the following presented as study-level covariates? (DO NOT ANSWER IF THIS IS A SUBGROUP FORM)

*Please see supplemental guidance for data extraction.*

Age  $\geq$  65 years

Age  $\geq$  80 years

Ethnicity

Gender

Healthy adults

Participants with disorders of the liver (e.g. hepatitis, cirrhosis)

Diabetes

Participants with disorders of the kidney (e.g. reduced GFR, end stage renal disease)

CVD drug for non-CVD indication

Genetic polymorphisms

None

8. Indicate the CHD risk level of the entire study population: (DO NOT ANSWER IF THIS IS A SUBGROUP FORM)

*Please see supplemental guidance for data extraction.*

At low risk for CHD (0-1 risk factors)

At moderate/moderately high risk for CHD (2+ risk factors)

At high risk for CHD

Mixed (please specify)

Unclear

9. Author (Smith, JA):

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10. Year of Publication

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11. Ref IDs of Companions

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12. Source of Funding (was the study supported by industry?)

*Please see supplemental guidance for data extraction.*

- Yes
- No
- Unclear

13. Region

- North America
- Central & South America
- Europe
- East Asia
- Rest of Asia
- Africa
- Australia/New Zealand
- Middle East
- Multiple regions (please describe)

---

Other (please describe)

---

Not reported

14. Setting

- General community
- Primary care
- Speciality clinic
- Mixed or other (please describe)

---

Not reported

15. List of inclusion criteria

---

16. List of Exclusion Criteria

---

17. Brief Summary of Population (include important risk factors): E.g. Elderly diabetic subjects with angina.

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18. Study Design

- Parallel randomized-controlled trial (RCT)
- Crossover RCT
- Pre-crossover RCT
- Controlled clinical trial (CCT)

19. Run-in Period (days): \_\_\_\_\_

20. Duration of Treatment (days) \_\_\_\_\_

21. Duration of Treatment in Period 2 (days) *FOR CROSSOVER TRIALS ONLY* \_\_\_\_\_

22. Wash-Out Period (days) *FOR CROSSOVER TRIALS ONLY* \_\_\_\_\_

23. Duration of Followup - measured from end of intervention (days) \_\_\_\_\_

24. Duration of Longest Followup (days) (i.e., the last followup point, which may include a long-term followup in the same study or a secondary publication)  
*Please refer to supplemental guidelines for data extraction* \_\_\_\_\_

25. With respect to intention-to-treat, select the statement that best describes the method used in the study.

- Intention-to-treat analysis (all randomized or initially enrolled)
- Only subjects who received treatment at start of the study
- Only subjects with followup data (who completed the study)
- Other (please describe)

---

Unclear

Not reported

26. Number screened (number of subjects screened initially using eligibility criteria)- NR if no data: \_\_\_\_\_

27. Number included (CCTs) or randomized \_\_\_\_\_

28. Number analyzed (number of subjects included in the analysis of results) \_\_\_\_\_

29. Was the number of dropouts or withdrawals reported?

- Yes (If yes, answer the next two questions below)

30. If yes, total number of dropouts or withdrawals:

Intervention Group 1 \_\_\_\_\_

Intervention Group 2 \_\_\_\_\_

Control Group \_\_\_\_\_

All Groups Combined \_\_\_\_\_

31. If yes, dropouts or withdrawals due to adverse events:

Intervention Group 1 \_\_\_\_\_

Intervention Group 2 \_\_\_\_\_

Control Group \_\_\_\_\_

All Groups Combined \_\_\_\_\_

No

## DETAILED POPULATION CHARACTERISTICS

### AGE

*Please see supplemental guidelines for data extraction and refer to formulas for calculating pooled means and SDs.*

- 32. Pooled mean age (years) \_\_\_\_\_
- 33. Pooled age SD (years) \_\_\_\_\_
- 34. Pooled age SE (years) \_\_\_\_\_
- 35. Median age (years) \_\_\_\_\_
- 36. Age: IQR-low (years) \_\_\_\_\_
- 37. Age: IQR-high (years) \_\_\_\_\_
- 38. Age: lower 95% CI (years) \_\_\_\_\_
- 39. Age: upper 95% CI (years) \_\_\_\_\_
- 40. Age range (min-max) (years) \_\_\_\_\_

### GENDER

- 41. Percentage of female subjects \_\_\_\_\_

### ETHNICITY

42. Select the ethnicities that were included in the study, and provide percentages.

- Caucasian \_\_\_\_\_
- African-American \_\_\_\_\_
- Hispanic \_\_\_\_\_
- Asian \_\_\_\_\_
- Native American \_\_\_\_\_
- African \_\_\_\_\_
- Other (please describe and provide percentage) \_\_\_\_\_
- Not reported \_\_\_\_\_

### MORBIDITIES

43. Indicate why subjects were taking CVD drug(s)

- Cardiovascular indication
- Non-cardiovascular indication(s) (please specify)
- Both (please describe)

\_\_\_\_\_  
 Other (please describe)

---

44. Did subjects have other comorbidities?

Yes (please list)

---

No

Not reported

**OTHER CO-INTERVENTIONS**

45. List of concomitant non-CVD medications taken by participants.

---

46. Was a dietary modification intervention administered?

Yes (please describe)

---

No

Not reported

47. Was an exercise intervention administered?

Yes (please describe)

---

No

Not reported

48. Was any other type of lifestyle intervention administered?

Yes (please describe)

---

No

Not reported

**DESCRIPTION OF CONTROL GROUP**

49. What did the control group receive?

Placebo. If the study provides further description of the placebo, please describe.

---

No treatment

Another type of dietary supplement (please specify)

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**DESCRIPTION OF INTERVENTION GROUP: DIETARY SUPPLEMENT(S)**

50. Supplement (select one)

Omega -3 (EPA, DHA or both)

Fish oils/marine oils

Magnesium

Garlic

- Ginko biloba
- Ginseng
- Vitamin E
- Vitamin K
- Vitamin A
- Vitamin D
- Vitamin D + Calcium
- Hawthorn
- Echinacea
- Coenzyme Q10
- Red yeast rice
- Niacin
- Resveratrol

51. Latin or other names used in this study for the supplement (e.g., *Crataegus oxyacantha* for Hawthorn)

---

52. Supplement Composition (e.g., % DHA + %EPA)

---

53. Is purity of the supplement reported?

- Yes (please describe - Please see supplemental guidance)
- 

- No

54. Is the supplement licensed in the region used?

- Yes
- No
- Not reported

55. Does the paper report where the supplement was manufactured?

- Yes (please describe)
- 

- No

56. Have storage conditions (e.g., temperature) for the supplement been reported?

- Yes (please describe - Please see supplemental guidance)
- 

- No

56. Is the origin of the supplement reported (e.g. plant leaves)?

- Yes (please describe)
- 

- No

58. Administered dosage of the supplement (indicate units, e.g. IU/day or mg/day)

---

59. What form was the supplement administered in?

- Capsule/Tablet
- Liquid
- Topical
- Mixed (please describe)

---

Other (please describe)

---

Not reported

60. What subtype of the supplement was administered? (e.g., carotenoid for Vitamin A; salt-form such as citrate for magnesium)

---

61. Are nutrient levels or biomarkers of the supplement reported (e.g., in blood or urine)?

*Please see supplemental guidance*

Yes (please describe)

---

No

62. Is there a second intervention group?

Yes (If yes, provide details of this supplement by answering the questions below.)

63. Supplement 2 (select one)

- Omega-3 (EPA, DHA or both)
- Fish oils/marine oils
- Magnesium
- Garlic
- Ginko biloba
- Ginseng
- Ginger
- Vitamin E
- Vitamin K
- Vitamin A
- Vitamin D
- Vitamin D + Calcium
- Hawthorn
- Echinacea
- Coenzyme Q10



- Red yeast rice
- Niacin
- Resveratrol

64. Latin or other names used in this study for supplement 2 (e.g., *Crataegus oxyacantha* for Hawthorn)

---

65. Supplement 2 Composition (e.g., % DHA + %EPA)

---

66. Is purity of supplement 2 reported?

- Yes (please describe - Please see supplemental guidance)

---

- No

67. Is supplement 2 licensed in the region used?

- Yes
- No
- Not reported

68. Does the paper report where supplement 2 was manufactured?

- Yes (please describe)

---

- No

69. Have storage conditions (e.g., temperature) for supplement 2 been reported?

- Yes (please describe - Please see supplemental guidance)

---

- No

70. Is the origin of supplement 2 reported (e.g. plant leaves)?

- Yes (please describe)

---

- No

71. Administered dosage of supplement 2 (indicate units, e.g. IU/day or mg/day)

---

72. What form was supplement 2 administered in?

- Capsule/Tablet
- Liquid
- Topical
- Mixed (please describe)

---

Other (please describe)

---

Not reported

73. What subtype of supplement 2 was administered? (e.g., carotenoid for Vitamin A; salt-form such as citrate for magnesium)

---

74. Are nutrient levels or biomarkers of supplement 2 reported (e.g., in blood or urine)?

*Please see supplemental guidance*

Yes (please describe)

---

No

No

**CVD DRUG(S) (Control and Intervention Groups)**

75. Brand name of CVD drug (used by >80% of study sample)

---

76. Chemical name of CVD drug (used by >80% of study sample):

---

77. Drug Category/Class:

- b-blockers
- Calcium channel blockers
- Alpha-blockers
- Antiarrhythmics
- Inotropics
- Anticoagulants

- Antiplatelets
- RAAS Antagonist: ACEI
- RAAS Antagonist: ARB
- RAAS Antagonist: Renin Inhibitor
- RAAS Antagonist: Aldosterone-Receptor Antagonist
- Antilipidemic: HMG Co-A Reductase Inhibitor
- Antilipidemic: Fibrate
- Antilipidemic: Bile acid sequestrant
- Antilipidemic: Other
- Diuretic: Thiazide/Thiazide-like
- Diuretic: Loop
- Diuretic: Other
- Vasodilator: Central/Direct
- Vasodilator: Nitrates/PDE-5 Inhibitors
- Vasodilator: Other

78. Mode of administration of CVD drug:

- Oral
  - Parenteral
  - Patch
  - Other (please indicate)
- 

79. Starting administered dosage of CVD drug (mg/day): \_\_\_\_\_

80. Final administered dosage of CVD drug (mg/day): \_\_\_\_\_

81. Mean administered dosage of CVD drug (mg/day): \_\_\_\_\_

82. Is the duration of treatment with this CVD drug the same as the supplement?

- Yes
- No
- Unclear

83. Was a second CVD drug administered to > 80% of the study sample?

- Yes (If yes, provide details of this drug by answering the questions below)

84. Brand name of CVD drug 2 (used by >80% of study sample)

---

85. Chemical name of CVD drug 2 (used by >80% of study sample):

---

86. Drug Category/Class (for CVD drug 2):

- b-blockers
- Calcium channel blockers
- Alpha-blockers
- Antiarrhythmics
- Inotropics
- Anticoagulants
- Antiplatelets
- RAAS Antagonist: ACEI
- RAAS Antagonist: ARB
- RAAS Antagonist: Renin Inhibitor
- RAAS Antagonist: Aldosterone-Receptor Antagonist
- Antilipidemic: HMG Co-A Reductase Inhibitor
- Antilipidemic: Fibrate
- Antilipidemic: Bile acid sequestrant
- Antilipidemic: Other
- Diuretic: Thiazide/Thiazide-like
- Diuretic: Loop
- Diuretic: Other
- Vasodilator: Central/Direct
- Vasodilator: Nitrates/PDE-5 Inhibitors
- Vasodilator: Other

87. Mode of administration of CVD drug 2:

- Oral
  - Parenteral
  - Patch
  - Other (please indicate)
- 

88. Starting administered dosage of CVD drug 2 (mg/day):

---

89. Final administered dosage of CVD drug 2 (mg/day): \_\_\_\_\_

90. Mean administered dosage of CVD drug 2 (mg/day): \_\_\_\_\_

91. Is the duration of treatment with this CVD drug 2 the same as the supplement?

- Yes
- No
- Unclear

No

92. Was a third CVD drug administered to > 80% of the study sample?

Yes (If yes, provide details of this drug by answering the questions below)

93. Brand name of CVD drug 3 (used by >80% of study sample)

\_\_\_\_\_

94. Chemical name of CVD drug 3 (used by >80% of study sample):

\_\_\_\_\_

95. Drug Category/Class (for CVD drug 3):

- b-blockers
- Calcium channel blockers
- Alpha-blockers
- Antiarrhythmics
- Inotropics
- Anticoagulants
- Antiplatelets
- RAAS Antagonist: ACEI
- RAAS Antagonist: ARB
- RAAS Antagonist: Renin Inhibitor
- RAAS Antagonist: Aldosterone-Receptor Antagonist
- Antilipidemic: HMG Co-A Reductase Inhibitor
- Antilipidemic: Fibrate
- Antilipidemic: Bile acid sequestrant
- Antilipidemic: Other
- Diuretic: Thiazide/Thiazide-like
- Diuretic: Loop
- Diuretic: Other
- Vasodilator: Central/Direct

- Vasodilator: Nitrates/PDE-5 Inhibitors
- Vasodilator: Other

96. Mode of administration of CVD drug 3:

- Oral
- Parenteral
- Patch
- Other (please indicate)

97. Starting administered dosage of CVD drug 3 (mg/day):

98. Final administered dosage of CVD drug 3 (mg/day): \_\_\_\_\_

99. Mean administered dosage of CVD drug 3 (mg/day): \_\_\_\_\_

100. Is the duration of treatment with this CVD drug 3 the same as the supplement?

- Yes
- No
- Unclear

No

101. **OTHER COMMENTS**

## DSCI: Statistical Interaction Form

RefID: \_\_\_\_\_

1. Does the study examine statistical interaction between cardiovascular drug and supplement?

Yes. If yes, describe method and conclusions.

---



---



---



---

No

2. Does the study include the following groups:

1. supplement only,
2. drug only,

- 3. supplement and drug combined and
- 4. a common control group

Yes. If yes, answer the following questions.

Indicate Outcome

Supplement Only Group (n/N):

Drug Only Group (n/N):

Supplement + Drug Group (n/N):

Control Group (n/N):

RR (Supplement vs. Control):

RR (Drug vs. Control)

RR (Supplement + Drug vs. Control)

OR (Supplement vs. Control)

OR (Drug vs. Control)

OR (Supplement + Drug vs. Control)

No

## DSCI: Continuous Outcomes Form

### PLEASE READ BEFORE STARTING:

- *N(included)* refers to either the number of participants included in a group of a controlled-clinical trial (CCT) or the number of participants randomized in a group in a randomized-controlled trial (RCT).

-Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

Select the outcome:

Complete a separate form for each relevant outcome reported in the study.

- Activated partial thromboplastin time (aPTT)
- Aggregation time
- Alanine transaminase (ALT)
- Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome.
- Anemia: Serum iron level
- Ankle-brachial index
- Area under the concentration curve (AUC)
- Arterial blood pressure

- Aspartate aminotransferase (AST)
- Bioavailability (F)
- Bleeding time
- Blood urea nitrogen (BUN)
- Body mass index (BMI)
- Carotid intima-media thickness (IMT), as measured by Doppler ultrasound
- Change in 10-year Framingham risk profile
- Clearance (Cl: volume of blood cleared of drug per unit time)
- Clotting time
- Concentration of drug transport proteins
- Coronary/cerebral arterial calcification score
- C-reactive protein (CRP)
- Creatinine
- Diastolic blood pressure (DBP)
- Ejection fraction
- Elimination rate constant (Kel) or Fraction of drug eliminated per unit time
- Fasting blood glucose
- Glomerular filtration rate (GFR)
- Glycosylated hemoglobin (HbA1c)
- Half-life (T<sub>1/2</sub>)
- High-density lipoprotein cholesterol (HDL-C)
- International normalized ratio (INR)
- Leukopenia: WBC count
- Lipoprotein A (Lp(a))
- Low-density lipoprotein cholesterol (LDL-C)
- Lymphopenia: Lymphocyte level
- Maximum concentration (C<sub>max</sub>)
- Neutropenia: Neutrophilic granulocyte count (ANC)
- Non-HDL-C
- Platelet aggregability. Specify outcome.
- Platelet count
- Prothrombin time (PT)
- Quality of Life
- Ratio of BUN/creatinine
- Systolic blood pressure (SBP)
- Time to reach maximum concentration (T<sub>max</sub>)
- Total cholesterol



- Triglycerides
  - Volume of distribution (Vd)
  - Other. Please specify.
- 

Definition of outcome if reported:

---

Other description of outcome:

---

Units \_\_\_\_\_

Length of longest randomized followup (from baseline)  
 (days-- each week = 7 days; each month = 30 days) \_\_\_\_\_

## **INDIVIDUAL GROUP DATA (Longest randomized post treatment followup)**

**Group 1** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_

- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug) \_\_\_\_\_
- CONTROL: Placebo \_\_\_\_\_
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

|             |       |      |       |            |       |
|-------------|-------|------|-------|------------|-------|
| N(included) | _____ | Mean | _____ | Median     | _____ |
| N(analyzed) | _____ | SD   | _____ | IQR – low  | _____ |
|             |       | SE   | _____ | IQR – high | _____ |

|                           |       |                  |       |                         |       |
|---------------------------|-------|------------------|-------|-------------------------|-------|
| Mean Change from baseline | _____ | % change in mean | _____ | Difference in median OR | _____ |
| SD                        | _____ | SD               | _____ | Difference in median %  | _____ |
| SE                        | _____ | SE               | _____ | IQR – lower             | _____ |
| 95% CI – lower            | _____ | 95% CI – lower   | _____ | IQR - upper             | _____ |
| 95% CI – upper            | _____ | 95% CI – upper   | _____ | 95% CI – lower          | _____ |
| p-value                   | _____ | p-value          | _____ | 95% CI – upper          | _____ |
|                           |       |                  |       | p-value                 | _____ |

**Group 2** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_
- Other supplement (intervention group). Please specify. \_\_\_\_\_

- CONTROL: No treatment (aside from CVD drug)
- CONTROL: Placebo
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

|             |       |      |       |            |       |
|-------------|-------|------|-------|------------|-------|
| N(included) | _____ | Mean | _____ | Median     | _____ |
| N(analyzed) | _____ | SD   | _____ | IQR – low  | _____ |
|             |       | SE   | _____ | IQR – high | _____ |

|                           |       |                  |       |                         |       |
|---------------------------|-------|------------------|-------|-------------------------|-------|
| Mean Change from baseline | _____ | % change in mean | _____ | Difference in median OR | _____ |
| SD                        | _____ | SD               | _____ | Difference in median %  | _____ |
| SE                        | _____ | SE               | _____ | IQR – lower             | _____ |
| 95% CI – lower            | _____ | 95% CI – lower   | _____ | IQR - upper             | _____ |
| 95% CI – upper            | _____ | 95% CI – upper   | _____ | 95% CI – lower          | _____ |
| p-value                   | _____ | p-value          | _____ | 95% CI – upper          | _____ |
|                           |       |                  |       | p-value                 | _____ |

**Group 3** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_

- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug) \_\_\_\_\_
- CONTROL: Placebo \_\_\_\_\_
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

|             |       |      |       |            |       |
|-------------|-------|------|-------|------------|-------|
| N(included) | _____ | Mean | _____ | Median     | _____ |
| N(analyzed) | _____ | SD   | _____ | IQR – low  | _____ |
|             |       | SE   | _____ | IQR – high | _____ |

|                           |       |                  |       |                         |       |
|---------------------------|-------|------------------|-------|-------------------------|-------|
| Mean Change from baseline | _____ | % change in mean | _____ | Difference in median OR | _____ |
| SD                        | _____ | SD               | _____ | Difference in median %  | _____ |
| SE                        | _____ | SE               | _____ | IQR – lower             | _____ |
| 95% CI – lower            | _____ | 95% CI – lower   | _____ | IQR - upper             | _____ |
| 95% CI – upper            | _____ | 95% CI – upper   | _____ | 95% CI – lower          | _____ |
| p-value                   | _____ | p-value          | _____ | 95% CI – upper          | _____ |
|                           |       |                  |       | p-value                 | _____ |

**Group 4** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_

- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug) \_\_\_\_\_
- CONTROL: Placebo \_\_\_\_\_
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

|             |       |      |       |            |       |
|-------------|-------|------|-------|------------|-------|
| N(included) | _____ | Mean | _____ | Median     | _____ |
| N(analyzed) | _____ | SD   | _____ | IQR – low  | _____ |
|             |       | SE   | _____ | IQR – high | _____ |

|                           |       |                  |       |                         |       |
|---------------------------|-------|------------------|-------|-------------------------|-------|
| Mean Change from baseline | _____ | % change in mean | _____ | Difference in median OR | _____ |
| SD                        | _____ | SD               | _____ | Difference in median %  | _____ |
| SE                        | _____ | SE               | _____ | IQR – lower             | _____ |
| 95% CI – lower            | _____ | 95% CI – lower   | _____ | IQR - upper             | _____ |
| 95% CI – upper            | _____ | 95% CI – upper   | _____ | 95% CI – lower          | _____ |
| p-value                   | _____ | p-value          | _____ | 95% CI – upper          | _____ |
|                           |       |                  |       | p-value                 | _____ |

## ESTIMATES OF GROUP DIFFERENCES

Has an adjusted analysis been presented for this outcome?

- Yes. If yes, list the variables that were adjusted for. \_\_\_\_\_
- No

### Crude Estimates

|   |            |   |  |
|---|------------|---|--|
| <b><u>Group 1 (select one)</u></b>        | <b>VS.</b> | <b><u>Group 2 (select one)</u></b>        | <b><u>Other details if needed (e.g., dose)</u></b> |
| <input type="checkbox"/> Coenzyme Q10     |            | <input type="checkbox"/> Coenzyme Q10     | _____  |
| <input type="checkbox"/> Echinacea        |            | <input type="checkbox"/> Echinacea        | _____  |
| <input type="checkbox"/> Fish/marine oils |            | <input type="checkbox"/> Fish/marine oils | _____  |
| <input type="checkbox"/> Garlic           |            | <input type="checkbox"/> Garlic           | _____  |
| <input type="checkbox"/> Ginger           |            | <input type="checkbox"/> Ginger           | _____  |
| <input type="checkbox"/> Gingko biloba    |            | <input type="checkbox"/> Gingko biloba    | _____  |
| <input type="checkbox"/> Ginseng          |            | <input type="checkbox"/> Ginseng          | _____  |
| <input type="checkbox"/> Hawthorn         |            | <input type="checkbox"/> Hawthorn         | _____  |
| <input type="checkbox"/> Magnesium        |            | <input type="checkbox"/> Magnesium        | _____  |
| <input type="checkbox"/> Niacin           |            | <input type="checkbox"/> Niacin           | _____  |

|                          |  |                          |  |       |
|--------------------------|--|--------------------------|--|-------|
| <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> | Red yeast rice                                     | <input type="checkbox"/> | Red yeast rice                                     | _____ |
| <input type="checkbox"/> | Resveratrol  | <input type="checkbox"/> | Resveratrol  | _____ |
| <input type="checkbox"/> | Vitamin A  | <input type="checkbox"/> | Vitamin A  | _____ |
| <input type="checkbox"/> | Vitamin D  | <input type="checkbox"/> | Vitamin D  | _____ |
| <input type="checkbox"/> | Vitamin D + Calcium                                | <input type="checkbox"/> | Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> | Vitamin E  | <input type="checkbox"/> | Vitamin E  | _____ |
| <input type="checkbox"/> | Vitamin K  | <input type="checkbox"/> | Vitamin K  | _____ |
| <input type="checkbox"/> | Other supplement (intervention group)              | <input type="checkbox"/> | Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> | CONTROL: Placebo                                   | <input type="checkbox"/> | CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | _____ |

|                           |       |                                   |       |   |       |
|---------------------------|-------|-----------------------------------|-------|---|-------|
| Crude Difference in Means | _____ | Crude Difference in % mean change | _____ | Crude difference in medians OR crude difference in median % | _____ |
| SD                        | _____ | SD                                | _____ | IQR – low   | _____ |
| SE                        | _____ | SE                                | _____ | IQR – high  | _____ |
| 95% CI - lower            | _____ | 95% CI – lower                    | _____ | 95% CI – lower  | _____ |
| 95% CI - upper            | _____ | 95% CI – upper                    | _____ | 95% CI – upper  | _____ |
| p-value                   | _____ | p-value                           | _____ | p-value   | _____ |

**Group 1 (select one) VS.**

- Coenzyme Q10
- Echinacea
- Fish/marine oils
- Garlic
- Ginger
- Gingko biloba
- Ginseng
- Hawthorn
- Magnesium
- Niacin

**Group 3 (select one)**

- Coenzyme Q10
- Echinacea
- Fish/marine oils
- Garlic
- Ginger
- Gingko biloba
- Ginseng
- Hawthorn
- Magnesium
- Niacin

**Other details if needed (e.g., dose)**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

|                          |  |                          |  |       |
|--------------------------|--|--------------------------|--|-------|
| <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> | Red yeast rice                                     | <input type="checkbox"/> | Red yeast rice                                     | _____ |
| <input type="checkbox"/> | Resveratrol  | <input type="checkbox"/> | Resveratrol  | _____ |
| <input type="checkbox"/> | Vitamin A  | <input type="checkbox"/> | Vitamin A  | _____ |
| <input type="checkbox"/> | Vitamin D  | <input type="checkbox"/> | Vitamin D  | _____ |
| <input type="checkbox"/> | Vitamin D + Calcium                                | <input type="checkbox"/> | Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> | Vitamin E  | <input type="checkbox"/> | Vitamin E  | _____ |
| <input type="checkbox"/> | Vitamin K  | <input type="checkbox"/> | Vitamin K  | _____ |
| <input type="checkbox"/> | Other supplement (intervention group)              | <input type="checkbox"/> | Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> | CONTROL: Placebo                                   | <input type="checkbox"/> | CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | _____ |

|                           |       |                                   |       |   |       |
|---------------------------|-------|-----------------------------------|-------|---|-------|
| Crude Difference in Means | _____ | Crude Difference in % mean change | _____ | Crude difference in medians OR crude difference in median % | _____ |
| SD                        | _____ | SD                                | _____ | IQR – low   | _____ |
| SE                        | _____ | SE                                | _____ | IQR – high  | _____ |
| 95% CI - lower            | _____ | 95% CI – lower                    | _____ | 95% CI – lower  | _____ |
| 95% CI - upper            | _____ | 95% CI – upper                    | _____ | 95% CI – upper  | _____ |
| p-value                   | _____ | p-value                           | _____ | p-value   | _____ |

**Group 2 (select one) VS.**

**Group 3 (select one)**

**Other details if needed (e.g., dose)**

|                          |                  |                          |                  |       |
|--------------------------|------------------|--------------------------|------------------|-------|
| <input type="checkbox"/> | Coenzyme Q10     | <input type="checkbox"/> | Coenzyme Q10     | _____ |
| <input type="checkbox"/> | Echinacea        | <input type="checkbox"/> | Echinacea        | _____ |
| <input type="checkbox"/> | Fish/marine oils | <input type="checkbox"/> | Fish/marine oils | _____ |
| <input type="checkbox"/> | Garlic           | <input type="checkbox"/> | Garlic           | _____ |
| <input type="checkbox"/> | Ginger           | <input type="checkbox"/> | Ginger           | _____ |
| <input type="checkbox"/> | Ginkgo biloba    | <input type="checkbox"/> | Ginkgo biloba    | _____ |
| <input type="checkbox"/> | Ginseng          | <input type="checkbox"/> | Ginseng          | _____ |
| <input type="checkbox"/> | Hawthorn         | <input type="checkbox"/> | Hawthorn         | _____ |
| <input type="checkbox"/> | Magnesium        | <input type="checkbox"/> | Magnesium        | _____ |
| <input type="checkbox"/> | Niacin           | <input type="checkbox"/> | Niacin           | _____ |

|                          |  |                          |  |       |
|--------------------------|--|--------------------------|--|-------|
| <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> | Red yeast rice                                     | <input type="checkbox"/> | Red yeast rice                                     | _____ |
| <input type="checkbox"/> | Resveratrol  | <input type="checkbox"/> | Resveratrol  | _____ |
| <input type="checkbox"/> | Vitamin A  | <input type="checkbox"/> | Vitamin A  | _____ |
| <input type="checkbox"/> | Vitamin D  | <input type="checkbox"/> | Vitamin D  | _____ |
| <input type="checkbox"/> | Vitamin D + Calcium                                | <input type="checkbox"/> | Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> | Vitamin E  | <input type="checkbox"/> | Vitamin E  | _____ |
| <input type="checkbox"/> | Vitamin K  | <input type="checkbox"/> | Vitamin K  | _____ |
| <input type="checkbox"/> | Other supplement (intervention group)              | <input type="checkbox"/> | Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> | CONTROL: Placebo                                   | <input type="checkbox"/> | CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | _____ |

|                           |       |                                   |       |   |       |
|---------------------------|-------|-----------------------------------|-------|---|-------|
| Crude Difference in Means | _____ | Crude Difference in % mean change | _____ | Crude difference in medians OR crude difference in median % | _____ |
| SD                        | _____ | SD                                | _____ | IQR – low   | _____ |
| SE                        | _____ | SE                                | _____ | IQR – high  | _____ |
| 95% CI - lower            | _____ | 95% CI – lower                    | _____ | 95% CI – lower  | _____ |
| 95% CI - upper            | _____ | 95% CI – upper                    | _____ | 95% CI – upper  | _____ |
| p-value                   | _____ | p-value                           | _____ | p-value   | _____ |

## Adjusted Estimates

|   |            |   |  |
|---|------------|---|--|
| <b><u>Group 1 (select one)</u></b>        | <b>VS.</b> | <b><u>Group 2 (select one)</u></b>        | <b><u>Other details if needed (e.g., dose)</u></b> |
| <input type="checkbox"/> Coenzyme Q10     |            | <input type="checkbox"/> Coenzyme Q10     | _____  |
| <input type="checkbox"/> Echinacea        |            | <input type="checkbox"/> Echinacea        | _____  |
| <input type="checkbox"/> Fish/marine oils |            | <input type="checkbox"/> Fish/marine oils | _____  |
| <input type="checkbox"/> Garlic           |            | <input type="checkbox"/> Garlic           | _____  |
| <input type="checkbox"/> Ginger           |            | <input type="checkbox"/> Ginger           | _____  |
| <input type="checkbox"/> Gingko biloba    |            | <input type="checkbox"/> Gingko biloba    | _____  |
| <input type="checkbox"/> Ginseng          |            | <input type="checkbox"/> Ginseng          | _____  |
| <input type="checkbox"/> Hawthorn         |            | <input type="checkbox"/> Hawthorn         | _____  |



- |   |   |       |
|---|---|-------|
| <input type="checkbox"/> Magnesium  | <input type="checkbox"/> Magnesium  | _____ |
| <input type="checkbox"/> Niacin   | <input type="checkbox"/> Niacin   | _____ |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> Red yeast rice                                     | <input type="checkbox"/> Red yeast rice                                     | _____ |
| <input type="checkbox"/> Resveratrol  | <input type="checkbox"/> Resveratrol  | _____ |
| <input type="checkbox"/> Vitamin A  | <input type="checkbox"/> Vitamin A  | _____ |
| <input type="checkbox"/> Vitamin D  | <input type="checkbox"/> Vitamin D  | _____ |
| <input type="checkbox"/> Vitamin D + Calcium                                | <input type="checkbox"/> Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> Vitamin E  | <input type="checkbox"/> Vitamin E  | _____ |
| <input type="checkbox"/> Vitamin K  | <input type="checkbox"/> Vitamin K  | _____ |
| <input type="checkbox"/> Other supplement (intervention group)              | <input type="checkbox"/> Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> CONTROL: Placebo                                   | <input type="checkbox"/> CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | _____ |

Adjusted Difference in Means \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted Difference in % mean change \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted difference in medians OR adjusted difference in median % \_\_\_\_\_

IQR - low \_\_\_\_\_

IQR - high \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

**Group 1 (select one) VS.**

- Coenzyme Q10
- Echinacea
- Fish/marine oils
- Garlic
- Ginger
- Gingko biloba
- Ginseng
- Hawthorn

**Group 3 (select one)**

- Coenzyme Q10
- Echinacea
- Fish/marine oils
- Garlic
- Ginger
- Gingko biloba
- Ginseng
- Hawthorn

**Other details if needed (e.g., dose)**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

- |   |   |       |
|---|---|-------|
| <input type="checkbox"/> Magnesium  | <input type="checkbox"/> Magnesium  | _____ |
| <input type="checkbox"/> Niacin   | <input type="checkbox"/> Niacin   | _____ |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> Red yeast rice                                     | <input type="checkbox"/> Red yeast rice                                     | _____ |
| <input type="checkbox"/> Resveratrol  | <input type="checkbox"/> Resveratrol  | _____ |
| <input type="checkbox"/> Vitamin A  | <input type="checkbox"/> Vitamin A  | _____ |
| <input type="checkbox"/> Vitamin D  | <input type="checkbox"/> Vitamin D  | _____ |
| <input type="checkbox"/> Vitamin D + Calcium                                | <input type="checkbox"/> Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> Vitamin E  | <input type="checkbox"/> Vitamin E  | _____ |
| <input type="checkbox"/> Vitamin K  | <input type="checkbox"/> Vitamin K  | _____ |
| <input type="checkbox"/> Other supplement (intervention group)              | <input type="checkbox"/> Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> CONTROL: Placebo                                   | <input type="checkbox"/> CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | _____ |

Adjusted Difference in Means \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted Difference in % mean change \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted difference in medians OR adjusted difference in median % \_\_\_\_\_

IQR - low \_\_\_\_\_

IQR - high \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

**Group 2 (select one) VS.**

**Group 3 (select one)**

**Other details if needed (e.g., dose)**

- |   |   |       |
|---|---|-------|
| <input type="checkbox"/> Coenzyme Q10     | <input type="checkbox"/> Coenzyme Q10     | _____ |
| <input type="checkbox"/> Echinacea        | <input type="checkbox"/> Echinacea        | _____ |
| <input type="checkbox"/> Fish/marine oils | <input type="checkbox"/> Fish/marine oils | _____ |
| <input type="checkbox"/> Garlic           | <input type="checkbox"/> Garlic           | _____ |
| <input type="checkbox"/> Ginger           | <input type="checkbox"/> Ginger           | _____ |
| <input type="checkbox"/> Gingko biloba    | <input type="checkbox"/> Gingko biloba    | _____ |
| <input type="checkbox"/> Ginseng          | <input type="checkbox"/> Ginseng          | _____ |

|                          |  |                          |  |       |
|--------------------------|--|--------------------------|--|-------|
| <input type="checkbox"/> | Hawthorn   | <input type="checkbox"/> | Hawthorn   | _____ |
| <input type="checkbox"/> | Magnesium  | <input type="checkbox"/> | Magnesium  | _____ |
| <input type="checkbox"/> | Niacin   | <input type="checkbox"/> | Niacin   | _____ |
| <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | <input type="checkbox"/> | Omega-3 (EPA / DHA / both)                         | _____ |
| <input type="checkbox"/> | Red yeast rice                                     | <input type="checkbox"/> | Red yeast rice                                     | _____ |
| <input type="checkbox"/> | Resveratrol  | <input type="checkbox"/> | Resveratrol  | _____ |
| <input type="checkbox"/> | Vitamin A  | <input type="checkbox"/> | Vitamin A  | _____ |
| <input type="checkbox"/> | Vitamin D  | <input type="checkbox"/> | Vitamin D  | _____ |
| <input type="checkbox"/> | Vitamin D + Calcium                                | <input type="checkbox"/> | Vitamin D + Calcium                                | _____ |
| <input type="checkbox"/> | Vitamin E  | <input type="checkbox"/> | Vitamin E  | _____ |
| <input type="checkbox"/> | Vitamin K  | <input type="checkbox"/> | Vitamin K  | _____ |
| <input type="checkbox"/> | Other supplement (intervention group)              | <input type="checkbox"/> | Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> | CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> | CONTROL: Placebo                                   | <input type="checkbox"/> | CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> | CONTROL: Other dietary supplement. Please specify. | _____ |

Adjusted Difference in Means \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI - lower \_\_\_\_\_

95% CI - upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted Difference in % mean change \_\_\_\_\_

SD \_\_\_\_\_

SE \_\_\_\_\_

95% CI – lower \_\_\_\_\_

95% CI – upper \_\_\_\_\_

p-value \_\_\_\_\_

Adjusted difference in medians OR adjusted difference in median % \_\_\_\_\_

IQR – low \_\_\_\_\_

IQR – high \_\_\_\_\_

95% CI – lower \_\_\_\_\_

95% CI – upper \_\_\_\_\_

p-value \_\_\_\_\_

**Comments**

# DSCI: Dichotomous Outcomes Form

## PLEASE READ BEFORE STARTING:

- *N(included)* refers to either the number of participants included in a group of a controlled-clinical trial (CCT) or the number of participants randomized in a group in a randomized-controlled trial (RCT).

- Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

---

RefID: \_\_\_\_\_

Select the outcome:

Complete a separate form for each relevant outcome reported in the study.

- Abdominal aortic aneurysm
- Activated partial thromboplastin time (aPTT) (above/below threshold). Indicate threshold. \_\_\_\_\_
- Acute coronary syndrome
- Adherence to prescribed cardiovascular drug regimen
- Adverse Event Other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event). Please specify. \_\_\_\_\_
- Alanine transaminase (ALT) (Raised)
- Allergic reactions (All types)
- Amputation
- Anaphylaxis/allergic shock
- Anemia
- Ankle-brachial index (above/below threshold). Indicate threshold. \_\_\_\_\_
- Arrhythmia (All types)
- Aspartate aminotransferase (AST) (Raised)
- Asthma
- Atrial fibrillation
- Bleeding time (above/below threshold). Indicate threshold. \_\_\_\_\_
- Blood urea nitrogen (BUN) (Raised)
- Carotid artery disease (not measured by IMT or Doppler). Please specify. \_\_\_\_\_
- Carotid dilation/stenting
- Carotid intima-media thickness (IMT), as measured by Doppler ultrasound (above/below threshold). Indicate threshold. \_\_\_\_\_
- Claudication (pain walking)

- Clotting time (above/below threshold). Indicate threshold. 

---
- Composite cardiovascular outcome (e.g. MI + Stroke + Vascular Death). Please specify. 

---
- Congestive heart/cardiac failure
- Constipation
- Coronary artery bypass graft (CABG)
- Coronary/cerebral arterial calcification score (above/below threshold). Indicate threshold. 

---
- C-reactive protein (above/below threshold). Indicate threshold. 

---
- Creatinine (Raised)
- Diarrhea
- Ejection fraction (above/below threshold). Indicate threshold. 

---
- Electrocardiographic (ECG) measurements or 24 hr ambulatory ECG/Holter monitoring. Please specify outcome. 

---
- Fasting blood glucose (above/below threshold). Indicate threshold. 

---
- Flatulence
- Gastrointestinal (GI) adverse events (All types)
- Gastrointestinal bleed (All types)
- Gastrointestinal bleed (Lower)
- Gastrointestinal bleed (Upper)
- Glycosylated hemoglobin (above/below threshold). Indicate threshold. 

---
- Heart block
- Heartburn
- Hematologic abnormality. Please specify outcome. 

---
- Hematuria
- Hemorrhagic stroke
- High-density lipoprotein cholesterol (HDL-C) (above/below threshold). Indicate threshold. 

---
- Hospitalization
- Hospitalization (Prolonged)
- Hypertension (HTN), new or worsening (e.g. need for change in therapy)
- Hypotension
- Internal bleed (All types)
- International normalized ratio (INR) (above/below threshold). Indicate threshold.
- Intracerebral bleed
- Intracranial bleed
- Intraventricular bleed

- Leukopenia
- Limb thrombosis/Leg ischemia
- Lipoprotein A (Lp(a)) (above/below threshold). Indicate threshold. 

---
- Liver damage/hepatitis
- Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). Indicate threshold. 

---
- Lymphopenia
- Mesenteric ischemia
- Metabolic syndrome
- Mortality (All-cause)
- Myocardial infarction (All types)
- Myocardial infarction (Fatal)
- Myocardial infarction (Non-fatal)
- Nausea
- Nausea and Vomiting (combined)
- Neurologic adverse events (All types)
- Neuropathy
- Neutropenia
- Non-HDL-C. specify threshold 

---
- Obesity
- Organ toxicity
- Percutaneous transluminal coronary angioplasty (PTCA/PCI/stenting)
- Peripheral revascularization (+/- stent)
- Platelet aggregability (above/below threshold). Indicate outcome and threshold. 

---
- Prolonged QT interval 

---
- Prothrombin time (above/below threshold). Indicate threshold. 

---
- Quality of Life
- Rash
- Ratio of BUN/creatinine (Raised)
- Renal replacement therapy (e.g. dialysis)
- Seizures
- Serious adverse events (composite outcome)
- Stroke (All types)
- Stroke (Fatal)
- Subretinal hemorrhage
- Sudden death

- Syncope
- Thrombocytopenia
- Thrombotic/Ischemic stroke
- Total cholesterol (above/below threshold). Indicate threshold. \_\_\_\_\_
- Transient ischemic attack (TIA) \_\_\_\_\_
- Triglycerides (above/below threshold). Indicate threshold. \_\_\_\_\_
- Unstable angina
- Valve replacement
- Valvular disease. Please specify outcome. \_\_\_\_\_
- Vascular death
- Ventricular fibrillation
- Ventricular tachycardia
- Vomiting
- Withdrawal due to adverse events
- Other. Please specify \_\_\_\_\_

Definition of outcome if reported:

\_\_\_\_\_

Other description of outcome:

\_\_\_\_\_

Length of longest randomized followup (from baseline) (days)  
 (1 week = 7 days and 1 month = 30 days)

\_\_\_\_\_

## **INDIVIDUAL GROUP DATA (Longest randomized post treatment followup)**

**Group 1** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_

- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_
- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug)
- CONTROL: Placebo
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

N(included)

\_\_\_\_\_

N(analyzed)

\_\_\_\_\_

n1(subjects free of event at baseline)

\_\_\_\_\_

n2(subjects with event)

\_\_\_\_\_

n3(events)

\_\_\_\_\_

n2/N(analyzed) (%)

*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*

\_\_\_\_\_

Event Risk (n2/n1)(%)

*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*

\_\_\_\_\_

**Group 2** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_



- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_
- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug)
- CONTROL: Placebo
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

N(included)

\_\_\_\_\_

N(analyzed)

\_\_\_\_\_

n1(subjects free of event at baseline)

\_\_\_\_\_

n2(subjects with event)

\_\_\_\_\_

n3(events)

\_\_\_\_\_

n2/N(analyzed) (%)

*Complete only if reported in the study (do not calculate).  
Only report the percentage number (without the % sign).*

\_\_\_\_\_

Event Risk (n2/n1)(%)

*Complete only if reported in the study (do not calculate).  
Only report the percentage number (without the % sign).*

\_\_\_\_\_

**Group 3** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Gingko biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_

- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_
- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug) \_\_\_\_\_
- CONTROL: Placebo \_\_\_\_\_
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

N(included) \_\_\_\_\_

N(analyzed) \_\_\_\_\_

n1(subjects free of event at baseline) \_\_\_\_\_

n2(subjects with event) \_\_\_\_\_

n3(events) \_\_\_\_\_

n2/N(analyzed) (%) \_\_\_\_\_

*Complete only if reported in the study (do not calculate).  
Only report the percentage number (without the % sign).*

Event Risk (n2/n1)(%) \_\_\_\_\_

*Complete only if reported in the study (do not calculate).  
Only report the percentage number (without the % sign).*

**Group 4** (select one)

- Coenzyme Q10. Other details if needed (e.g. dose). \_\_\_\_\_
- Echinacea. Other details if needed (e.g. dose). \_\_\_\_\_
- Fish/marine oils. Other details if needed (e.g. dose). \_\_\_\_\_
- Garlic. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginger. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginkgo biloba. Other details if needed (e.g. dose). \_\_\_\_\_
- Ginseng. Other details if needed (e.g. dose). \_\_\_\_\_
- Hawthorn. Other details if needed (e.g. dose). \_\_\_\_\_
- Magnesium. Other details if needed (e.g. dose). \_\_\_\_\_
- Niacin. Other details if needed (e.g. dose). \_\_\_\_\_
- Omega-3 (EPA, DHA, or both). Other details if needed (e.g. dose). \_\_\_\_\_
- Red yeast rice. Other details if needed (e.g. dose). \_\_\_\_\_
- Resveratrol. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin A. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin D + Calcium. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin E. Other details if needed (e.g. dose). \_\_\_\_\_
- Vitamin K. Other details if needed (e.g. dose). \_\_\_\_\_
- Other supplement (intervention group). Please specify. \_\_\_\_\_
- CONTROL: No treatment (aside from CVD drug) \_\_\_\_\_

- CONTROL: Placebo
- CONTROL: Other dietary supplement. Please specify. \_\_\_\_\_

N(included) \_\_\_\_\_

N(analyzed) \_\_\_\_\_

n1(subjects free of event at baseline) \_\_\_\_\_

n2(subjects with event) \_\_\_\_\_

n3(events) \_\_\_\_\_

n2/N(analyzed) (%) \_\_\_\_\_  
*Complete only if reported in the study (do not calculate).  
 Only report the percentage number (without the % sign).*

Event Risk (n2/n1)(%) \_\_\_\_\_  
*Complete only if reported in the study (do not calculate).  
 Only report the percentage number (without the % sign).*

**ESTIMATES OF GROUP DIFFERENCES**

| <u><b>Group 1 (select one)</b></u>                  | <b>VS.</b> | <u><b>Group 2 (select one)</b></u>                  | <u><i>Other details if needed (e.g., dose)</i></u> |
|---|------------|---|--|
| <input type="checkbox"/> Coenzyme Q10               |            | <input type="checkbox"/> Coenzyme Q10               | _____  |
| <input type="checkbox"/> Echinacea                  |            | <input type="checkbox"/> Echinacea                  | _____  |
| <input type="checkbox"/> Fish/marine oils           |            | <input type="checkbox"/> Fish/marine oils           | _____  |
| <input type="checkbox"/> Garlic                     |            | <input type="checkbox"/> Garlic                     | _____  |
| <input type="checkbox"/> Ginger                     |            | <input type="checkbox"/> Ginger                     | _____  |
| <input type="checkbox"/> Gingko biloba              |            | <input type="checkbox"/> Gingko biloba              | _____  |
| <input type="checkbox"/> Ginseng                    |            | <input type="checkbox"/> Ginseng                    | _____  |
| <input type="checkbox"/> Hawthorn                   |            | <input type="checkbox"/> Hawthorn                   | _____  |
| <input type="checkbox"/> Magnesium                  |            | <input type="checkbox"/> Magnesium                  | _____  |
| <input type="checkbox"/> Niacin                     |            | <input type="checkbox"/> Niacin                     | _____  |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both) |            | <input type="checkbox"/> Omega-3 (EPA / DHA / both) | _____  |
| <input type="checkbox"/> Red yeast rice             |            | <input type="checkbox"/> Red yeast rice             | _____  |
| <input type="checkbox"/> Resveratrol                |            | <input type="checkbox"/> Resveratrol                | _____  |
| <input type="checkbox"/> Vitamin A                  |            | <input type="checkbox"/> Vitamin A                  | _____  |
| <input type="checkbox"/> Vitamin D                  |            | <input type="checkbox"/> Vitamin D                  | _____  |
| <input type="checkbox"/> Vitamin D + Calcium        |            | <input type="checkbox"/> Vitamin D + Calcium        | _____  |
| <input type="checkbox"/> Vitamin E                  |            | <input type="checkbox"/> Vitamin E                  | _____  |
| <input type="checkbox"/> Vitamin K                  |            | <input type="checkbox"/> Vitamin K                  | _____  |
| <input type="checkbox"/> Other supplement           |            | <input type="checkbox"/> Other supplement           | _____  |





|   |   |       |
|---|---|-------|
| <input type="checkbox"/> Vitamin E  | <input type="checkbox"/> Vitamin E  | _____ |
| <input type="checkbox"/> Vitamin K  | <input type="checkbox"/> Vitamin K  | _____ |
| <input type="checkbox"/> Other supplement (intervention group)              | <input type="checkbox"/> Other supplement (intervention group)              | _____ |
| <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | <input type="checkbox"/> CONTROL: No treatment (aside from CVD drug)        | _____ |
| <input type="checkbox"/> CONTROL: Placebo                                   | <input type="checkbox"/> CONTROL: Placebo                                   | _____ |
| <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | <input type="checkbox"/> CONTROL: Other dietary supplement. Please specify. | _____ |

|                        |       |                           |       |
|------------------------|-------|---------------------------|-------|
| Crude Event Risk Ratio | _____ | Adjusted Event Risk Ratio | _____ |
| 95% CI - lower         | _____ | 95% CI – lower            | _____ |
| 95% CI - upper         | _____ | 95% CI – upper            | _____ |
| p-value                | _____ | p-value                   | _____ |
| Crude Event Odds Ratio | _____ | Adjusted Event Odds Ratio | _____ |
| 95% CI – lower         | _____ | 95% CI – lower            | _____ |
| 95% CI – upper         | _____ | 95% CI – upper            | _____ |
| p-value                | _____ | p-value                   | _____ |

**COMMENTS**

**DSCI: Continuous Outcomes Form for Cross-Over Studies**

**PLEASE READ BEFORE STARTING:**

- *N(included)* refers to either the number of participants included in a group of a controlled-clinical trial (CCT) or the number of participants randomized in a group in a randomized-controlled trial (RCT).

- Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

---

RefID: \_\_\_\_\_

1. Select the outcome:  
Complete a separate form for each relevant outcome reported in the study.

- Activated partial thromboplastin time (aPTT)
- Aggregation time
- Alanine transaminase (ALT)

- Anemia: Other parameter (e.g. ferritin, MCV, MCH). Specify outcome. \_\_\_\_\_
- Anemia: Serum iron level
- Ankle-brachial index
- Area under the concentration curve (AUC)
- Arterial blood pressure
- Aspartate aminotransferase (AST)
- Bioavailability (F)
- Bleeding time
- Blood urea nitrogen (BUN)
- Body mass index (BMI)
- Carotid intima-media thickness (IMT), as measured by Doppler ultrasound
- Change in 10-year Framingham risk profile
- Clearance (Cl: volume of blood cleared of drug per unit time)
- Clotting time
- Concentration of drug transport proteins
- Coronary/cerebral arterial calcification score
- C-reactive protein (CRP)
- Creatinine
- Diastolic blood pressure (DBP)
- Ejection fraction
- Elimination rate constant ( $K_{el}$ ) or Fraction of drug eliminated per unit time
- Fasting blood glucose
- Glomerular filtration rate (GFR)
- Glycosylated hemoglobin (HbA1c)
- Half-life ( $T_{1/2}$ )
- High-density lipoprotein cholesterol (HDL-C)
- International normalized ratio (INR)
- Leukopenia: WBC count
- Lipoprotein A (Lp(a))
- Low-density lipoprotein cholesterol (LDL-C)
- Lymphopenia: Lymphocyte level
- Maximum concentration ( $C_{max}$ )
- Neutropenia: Neutrophilic granulocyte count (ANC)
- Non-HDL-C
- Platelet aggregability. Specify outcome. \_\_\_\_\_
- Platelet count
- Prothrombin time (PT)

- Quality of Life
  - Ratio of BUN/creatinine
  - Systolic blood pressure (SBP)
  - Time to reach maximum concentration (Tmax)
  - Total cholesterol
  - Triglycerides
  - Volume of distribution (Vd)
  - Other. Please specify.
- 

2. Definition of outcome (optional – if reported):

---

3. Other description of outcome:

---

4. Units: \_\_\_\_\_

5. Pooled Data (Pre + Post cross over)

Pooled Supplement (select one)

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> Coenzyme Q10   | <input type="checkbox"/> Ginseng                     | <input type="checkbox"/> Resveratrol         |
| <input type="checkbox"/> Echinacea  | <input type="checkbox"/> Hawthorn                    | <input type="checkbox"/> Vitamin A           |
| <input type="checkbox"/> Fish/marine oils   | <input type="checkbox"/> Magnesium                   | <input type="checkbox"/> Vitamin D           |
| <input type="checkbox"/> Garlic   | <input type="checkbox"/> Niacin                      | <input type="checkbox"/> Vitamin D + Calcium |
| <input type="checkbox"/> Ginger   | <input type="checkbox"/> Omega-3 (EPA, DHA, or both) | <input type="checkbox"/> Vitamin E           |
| <input type="checkbox"/> Gingko biloba  | <input type="checkbox"/> Red yeast rice              | <input type="checkbox"/> Vitamin K           |
| <input type="checkbox"/> Other supplement (intervention group). Please specify. _____ |  |  |

|             |       |                |       |                  |       |
|-------------|-------|----------------|-------|------------------|-------|
| N(included) | _____ | Mean Change    | _____ | % change in mean | _____ |
| N(analyzed) | _____ | SD             | _____ | SD               | _____ |
| Mean        | _____ | SE             | _____ | SE               | _____ |
| SD          | _____ | 95% CI – lower | _____ | 95% CI – lower   | _____ |
| SE          | _____ | 95% CI – upper | _____ | 95% CI – upper   | _____ |
|             |       | p-value        | _____ | p-value          | _____ |



Pooled Control (select one)

- No treatment (aside from CVD drug)
- Placebo
- Other dietary supplement. Please specify. \_\_\_\_\_

|             |       |                |       |                  |       |
|-------------|-------|----------------|-------|------------------|-------|
| N(included) | _____ | Mean Change    | _____ | % change in mean | _____ |
| N(analyzed) | _____ | SD             | _____ | SD               | _____ |
| Mean        | _____ | SE             | _____ | SE               | _____ |
| SD          | _____ | 95% CI – lower | _____ | 95% CI – lower   | _____ |
| SE          | _____ | 95% CI – upper | _____ | 95% CI – upper   | _____ |
|             |       | p-value        | _____ | p-value          | _____ |

## ESTIMATES OF GROUP DIFFERENCES

6. Has an adjusted analysis been presented for this outcome?

- Yes. If yes, list the variables that were adjusted for. \_\_\_\_\_
- No

7. Mean between group differences: Crude estimates

**Supplement** (select one) **VS.**

**Control** (select one)

- |   |   |
|---|---|
| <input type="checkbox"/> Coenzyme Q10               | <input type="checkbox"/> No treatment (aside from CVD drug)                 |
| <input type="checkbox"/> Echinacea                  | <input type="checkbox"/> Placebo  |
| <input type="checkbox"/> Fish/marine oils           | <input type="checkbox"/> Other dietary supplement.<br>Please specify. _____ |
| <input type="checkbox"/> Garlic                     |   |
| <input type="checkbox"/> Ginger                     |   |
| <input type="checkbox"/> Gingko biloba              |   |
| <input type="checkbox"/> Ginseng                    |   |
| <input type="checkbox"/> Hawthorn                   |   |
| <input type="checkbox"/> Magnesium                  |   |
| <input type="checkbox"/> Niacin                     |   |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both) |   |
| <input type="checkbox"/> Red yeast rice             |   |
| <input type="checkbox"/> Resveratrol                |   |
| <input type="checkbox"/> Vitamin A                  |   |

- Vitamin D
- Vitamin D + Calcium
- Vitamin E
- Vitamin K
- Other. Please specify. \_\_\_\_\_

| Crude Difference<br>in Means <sup>+</sup> | _____ | Crude Difference in<br>% mean change <sup>+</sup> | _____ | Crude mean ratio <sup>++</sup> | _____ |
|---|-------|---|-------|--------------------------------|-------|
| SD  | _____ | SD  | _____ | SD                             | _____ |
| SE  | _____ | SE  | _____ | SE                             | _____ |
| 95% CI - lower                            | _____ | 95% CI – lower                                    | _____ | 95% CI – lower                 | _____ |
| 95% CI - upper                            | _____ | 95% CI – upper                                    | _____ | 95% CI – upper                 | _____ |
| p-value                                   | _____ | p-value   | _____ | p-value                        | _____ |

<sup>+</sup> Pre + post cross over

<sup>++</sup> Mean(treatment)/Mean(control) *Indicate as a ratio, not a fraction.*

8. Mean between group differences: Adjusted estimates

**Supplement (select one)** **VS.**

**Control (select one)**

- |   |   |
|---|---|
| <input type="checkbox"/> Coenzyme Q10               | <input type="checkbox"/> No treatment (aside from CVD drug)                 |
| <input type="checkbox"/> Echinacea                  | <input type="checkbox"/> Placebo  |
| <input type="checkbox"/> Fish/marine oils           | <input type="checkbox"/> Other dietary supplement.<br>Please specify. _____ |
| <input type="checkbox"/> Garlic                     |   |
| <input type="checkbox"/> Ginger                     |   |
| <input type="checkbox"/> Gingko biloba              |   |
| <input type="checkbox"/> Ginseng                    |   |
| <input type="checkbox"/> Hawthorn                   |   |
| <input type="checkbox"/> Magnesium                  |   |
| <input type="checkbox"/> Niacin                     |   |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both) |   |
| <input type="checkbox"/> Red yeast rice             |   |
| <input type="checkbox"/> Resveratrol                |   |
| <input type="checkbox"/> Vitamin A                  |   |
| <input type="checkbox"/> Vitamin D                  |   |
| <input type="checkbox"/> Vitamin D + Calcium        |   |

- Vitamin E
  - Vitamin K
  - Other. Please specify.
- 

| Adjusted Difference in Means <sup>+</sup> | _____ | Adjusted Difference in % mean change <sup>+</sup> | _____ | Adjusted mean ratio <sup>++</sup> | _____ |
|---|-------|---|-------|-----------------------------------|-------|
| SD  | _____ | SD  | _____ | SD                                | _____ |
| SE  | _____ | SE  | _____ | SE                                | _____ |
| 95% CI - lower                            | _____ | 95% CI – lower                                    | _____ | 95% CI – lower                    | _____ |
| 95% CI - upper                            | _____ | 95% CI – upper                                    | _____ | 95% CI – upper                    | _____ |
| p-value                                   | _____ | p-value   | _____ | p-value                           | _____ |

<sup>+</sup> Pre + post cross over  
<sup>++</sup> Mean(treatment)/Mean(control) *Indicate as a ratio, not a fraction.*

9. Do the measures of dispersion (SE/SD/95%CI) reported for this outcome include within patient differences?

- Yes
  - No
  - Unclear
- 

## COMMENTS

## DSCI: Dichotomous Outcomes Form for Cross-Over Studies

### PLEASE READ BEFORE STARTING:

- *N(included)* refers to either the number of participants included in a group of a controlled-clinical trial (CCT) or the number of participants randomized in a group in a randomized-controlled trial (RCT).

-Please do not indicate any units (including percentage signs) in the table cells. Numbers may be inputted to 2 decimal places, if that is the precision level reported in a study.

---

RefID: \_\_\_\_\_

1. Select the outcome:

*Complete a separate form for each relevant outcome reported in the study.*

- Abdominal aortic aneurysm
- Activated partial thromboplastin time (aPTT) (above/below \_\_\_\_\_)

- threshold). Indicate threshold. \_\_\_\_\_
- Acute coronary syndrome
  - Adherence to prescribed cardiovascular drug regimen
  - Adverse Event Other (other than neurologic, allergic, gastrointestinal, bleeding, withdrawal due to adverse event). Please specify. \_\_\_\_\_
  - Alanine transaminase (ALT) (Raised)
  - Allergic reactions (All types)
  - Amputation
  - Anaphylaxis/allergic shock
  - Anemia
  - Ankle-brachial index (above/below threshold). Indicate threshold.
  - Arrhythmia (All types)
  - Aspartate aminotransferase (AST) (Raised)
  - Asthma
  - Atrial fibrillation
  - Bleeding time (above/below threshold). Indicate threshold.
  - Blood urea nitrogen (BUN) (Raised)
  - Carotid artery disease (not measured by IMT or Doppler). Please specify.
  - Carotid dilation/stenting \_\_\_\_\_
  - Carotid intima-media thickness (IMT), as measured by Doppler ultrasound (above/below threshold). Indicate threshold. \_\_\_\_\_
  - Claudication (pain walking)
  - Clotting time (above/below threshold). Indicate threshold.
  - Composite cardiovascular outcome (e.g. MI + Stroke + Vascular Death). Please specify. \_\_\_\_\_
  - Congestive heart/cardiac failure
  - Constipation
  - Coronary artery bypass graft (CABG)
  - Coronary/cerebral arterial calcification score (above/below threshold). Indicate threshold. \_\_\_\_\_
  - C-reactive protein (above/below threshold). Indicate threshold. \_\_\_\_\_
  - Creatinine (Raised)
  - Diarrhea
  - Ejection fraction (above/below threshold). Indicate threshold. \_\_\_\_\_
  - Electrocardiographic (ECG) measurements or 24 hr ambulatory ECG/Holter monitoring. Please specify outcome. \_\_\_\_\_
  - Fasting blood glucose (above/below threshold). Indicate threshold. \_\_\_\_\_
  - Flatulence \_\_\_\_\_

- Gastrointestinal (GI) adverse events (All types)
- Gastrointestinal bleed (All types)
- Gastrointestinal bleed (Lower)
- Gastrointestinal bleed (Upper)
- Glycosylated hemoglobin (above/below threshold). Indicate threshold.
- Heart block
- Heartburn
- Hematologic abnormality. Please specify outcome. 

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- Hematuria
- Hemorrhagic stroke
- High-density lipoprotein cholesterol (HDL-C) (above/below threshold). Indicate threshold. 

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- Hospitalization
- Hospitalization (Prolonged)
- Hypertension (HTN), new or worsening (e.g. need for change in therapy)
- Hypotension
- Internal bleed (All types)
- International normalized ratio (INR) (above/below threshold). Indicate threshold.
- Intracerebral bleed
- Intracranial bleed
- Intraventricular bleed
- Leukopenia
- Limb thrombosis/Leg ischemia
- Lipoprotein A (Lp(a)) (above/below threshold). Indicate threshold. 

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- Liver damage/hepatitis
- Low-density lipoprotein cholesterol (LDL-C) (above/below threshold). Indicate threshold. 

---
- Lymphopenia
- Mesenteric ischemia
- Metabolic syndrome
- Mortality (All-cause)
- Myocardial infarction (All types)
- Myocardial infarction (Fatal)
- Myocardial infarction (Non-fatal)
- Nausea
- Nausea and Vomiting (combined)

- Neurologic adverse events (All types)
- Neuropathy
- Neutropenia
- Non-HDL-C. specify threshold 

---
- Obesity
- Organ toxicity
- Percutaneous transluminal coronary angioplasty (PTCA/PCI/stenting)
- Peripheral revascularization (+/- stent)
- Platelet aggregability (above/below threshold). Indicate outcome and threshold. 

---
- Prolonged QT interval
- Prothrombin time (above/below threshold). Indicate threshold. 

---
- Quality of Life 

---
- Rash
- Ratio of BUN/creatinine (Raised)
- Renal replacement therapy (e.g. dialysis)
- Seizures
- Serious adverse events (composite outcome)
- Stroke (All types)
- Stroke (Fatal)
- Subretinal hemorrhage
- Sudden death
- Syncope
- Thrombocytopenia
- Thrombotic/Ischemic stroke
- Total cholesterol (above/below threshold). Indicate threshold. 

---
- Transient ischemic attack (TIA) 

---
- Triglycerides (above/below threshold). Indicate threshold. 

---
- Unstable angina 

---
- Valve replacement
- Valvular disease. Please specify outcome. 

---
- Vascular death
- Ventricular fibrillation
- Ventricular tachycardia
- Vomiting
- Withdrawal due to adverse events
- Other. Please specify 

---

2. Definition of outcome if reported:

---

3. Other description of outcome:

---

4. Pooled Data (Pre + Post cross over)

Pooled Supplement (select one)

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> Coenzyme Q10   | <input type="checkbox"/> Ginseng                     | <input type="checkbox"/> Resveratrol         |
| <input type="checkbox"/> Echinacea  | <input type="checkbox"/> Hawthorn                    | <input type="checkbox"/> Vitamin A           |
| <input type="checkbox"/> Fish/marine oils   | <input type="checkbox"/> Magnesium                   | <input type="checkbox"/> Vitamin D           |
| <input type="checkbox"/> Garlic   | <input type="checkbox"/> Niacin                      | <input type="checkbox"/> Vitamin D + Calcium |
| <input type="checkbox"/> Ginger   | <input type="checkbox"/> Omega-3 (EPA, DHA, or both) | <input type="checkbox"/> Vitamin E           |
| <input type="checkbox"/> Gingko biloba  | <input type="checkbox"/> Red yeast rice              | <input type="checkbox"/> Vitamin K           |
| <input type="checkbox"/> Other supplement (intervention group). Please specify. _____ |  |  |

N(included)

---

N(analyzed)

---

n1(subjects free of event at baseline)

---

n2(subjects with event)

---

n3(events)

---

n2/N(analyzed) (%)

*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*

---

Event Risk (n2/n1)(%)

*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).*

---

Pooled Control (select one)

- No treatment (aside from CVD drug)
- Placebo
- Other dietary supplement. Please specify.

---

N(included) \_\_\_\_\_

N(analyzed) \_\_\_\_\_

n1(subjects free of event at baseline) \_\_\_\_\_

n2(subjects with event) \_\_\_\_\_

n3(events) \_\_\_\_\_

n2/N(analyzed) (%)  
*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).* \_\_\_\_\_

Event Risk (n2/n1)(%)  
*Complete only if reported in the study (do not calculate). Only report the percentage number (without the % sign).* \_\_\_\_\_

## ESTIMATES OF GROUP DIFFERENCES

5. Has an adjusted analysis been presented for this outcome?

- Yes. If yes, list the variables that were adjusted for. \_\_\_\_\_
- No

6. Pre + Post cross over: Mean between group comparisons

- | <u><b>Supplement</b></u> (select one) <b>VS.</b>    | <u><b>Control</b></u> (select one)  |
|---|---|
| <input type="checkbox"/> Coenzyme Q10               | <input type="checkbox"/> No treatment (aside from CVD drug)                 |
| <input type="checkbox"/> Echinacea                  | <input type="checkbox"/> Placebo  |
| <input type="checkbox"/> Fish/marine oils           | <input type="checkbox"/> Other dietary supplement.<br>Please specify. _____ |
| <input type="checkbox"/> Garlic                     |   |
| <input type="checkbox"/> Ginger                     |   |
| <input type="checkbox"/> Gingko biloba              |   |
| <input type="checkbox"/> Ginseng                    |   |
| <input type="checkbox"/> Hawthorn                   |   |
| <input type="checkbox"/> Magnesium                  |   |
| <input type="checkbox"/> Niacin                     |   |
| <input type="checkbox"/> Omega-3 (EPA / DHA / both) |   |
| <input type="checkbox"/> Red yeast rice             |   |
| <input type="checkbox"/> Resveratrol                |   |
| <input type="checkbox"/> Vitamin A                  |   |
| <input type="checkbox"/> Vitamin D                  |   |
| <input type="checkbox"/> Vitamin D + Calcium        |   |
| <input type="checkbox"/> Vitamin E                  |   |



- Vitamin K
- Other. Please specify.

|                        |       |                           |       |
|------------------------|-------|---------------------------|-------|
| Crude Event Risk Ratio | _____ | Adjusted Event Risk Ratio | _____ |
| 95% CI - lower         | _____ | 95% CI – lower            | _____ |
| 95% CI - upper         | _____ | 95% CI – upper            | _____ |
| p-value                | _____ | p-value                   | _____ |
| Crude Event Odds Ratio | _____ | Adjusted Event Odds Ratio | _____ |
| 95% CI – lower         | _____ | 95% CI – lower            | _____ |
| 95% CI – upper         | _____ | 95% CI – upper            | _____ |
| p-value                | _____ | p-value                   | _____ |

## COMMENTS

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