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Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms

A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Prepared by:
Kaiser Permanente Research Affiliates Evidence-based Practice Center
Kaiser Permanente Center for Health Research
Portland, OR

Investigators:
Evelyn P. Whitlock, MD, MPH
Selvi B. Williams, MD, MPH
Brittany U. Burda, MPH
Alisha Feightner, MPH
Tracy Beil, MS

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This systematic review was conducted in coordination with two other systematic reviews[1,2] and a decision model[3] to support the U.S. Preventive Services Task Force (USPSTF) in making updated clinical preventive service recommendations for aspirin in primary prevention. The original literature searches were completed in June 2014. In order to prepare a set of manuscripts derived from these reviews, we conducted updated literature searches through January 6, 2015 to identify newly published information since the original searches.

A single open-label randomized, controlled clinical trial in a cardiovascular disease (CVD) primary prevention population—the Japanese Primary Prevention Project (JPPP)[4]—was the only additional clinical research report located through the updated searches that met inclusion/exclusion criteria for any of the reviews. Outcomes from this study (nonfatal myocardial infarction [MI], nonfatal stroke [nonfatal cerebral infarction, intracranial hemorrhage, and undefined cardiovascular events], CVD mortality [fatal MI, cerebral infarction, intracranial hemorrhage, subarachnoid hemorrhage, and other fatal cardiovascular events], hemorrhagic stroke [fatal and nonfatal intracranial hemorrhage], and all-cause mortality) were incorporated into the final evidence reviewed by the USPSTF and resulted in updated inputs into the decision analysis.

This systematic review has NOT been updated to reflect the incorporation of results from JPPP. Updated results are reflected in the manuscript derived from this review, which is available for public comment at http://www.uspreventiveservicestaskforce.org. Results for this systematic review for outcomes unrelated to those reported in JPPP are current through January 6, 2015. No further updated literature searches have been undertaken.

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Structured Abstract

Background: Cancer is the second leading cause of death in United States. The net benefit for aspirin (ASA) in cardiovascular disease (CVD) primary prevention is controversial due to increased risks from bleeding alongside relatively modest cardiovascular benefits. Consideration of additional cancer prevention effects might clarify whether long-term, low-dose ASA may offer an overall health benefit for the two top causes of mortality in the United States.

Purpose: We conducted this review, alongside two companion reviews, to support the U.S. Preventive Services Task Force (USPSTF) in making evidence-based recommendations about the use of ASA for primary prevention in adults and to understand the risks of regular ASA use.

Data Sources: We used a systematic evidence review published in 2012 for cancer-specific and all-cause mortality outcomes and conducted a bridge search of PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials from 2011 to October 2013. For bleeding harms, we used four published systematic evidence reviews and conducted a search of PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials from January 1, 2010 to June 3, 2014 in PubMed and MEDLINE. We also reviewed all studies included and excluded for companion USPSTF reviews on ASA for colorectal cancer and CVD prevention and checked for additional relevant studies by reviewing reference lists of included studies and other published reviews or meta-analyses.

Study Selection: Two investigators independently reviewed 4,393 abstracts and 336 articles against previously established inclusion and exclusion criteria and critically appraised studies for risk of bias using USPSTF methods, supplemented by the Newcastle-Ottawa Scale for cohort studies and the Assessment of Multiple Systematic Reviews for systematic reviews. We included fair- or good-quality trials evaluating the effect of 75 mg or greater ASA at least every other day for 12 months or longer versus no ASA, in the absence of other antithrombotic medications, on cancer mortality, all-cause mortality, cancer incidence, and harms, primarily related to serious bleeding. We also included cohort studies meeting these criteria to evaluate potential harms of ASA.

Data Extraction and Analysis: For fair- and good-quality studies, one investigator abstracted study characteristics and outcomes into structured tables and a second verified accuracy. We assessed trials for heterogeneity using I^2 statistics and pooled trial-level results when appropriate using Mantel-Haenszel fixed effects to calculate relative risks (RRs) and Peto's odds ratios (OR). We focused on cancer effects and bleeding harms in CVD primary prevention trials, but also assessed results after including secondary CVD and colorectal adenoma prevention trials. Expected outcome rates with ASA intervention were calculated by multiplying simulated control group event rates for benefits as well as harms from the CVD primary prevention trials by the pooled RR estimate (and bounds of 95% confidence interval [CI]). The expected outcome rates were subtracted from the simulated control group rate to calculate the absolute risk reduction with 95% CI. We calculated expected outcomes using the minimum, maximum, and median control group rate for a given outcome to examine the range of results suggested by the primary studies.

Results: When restricting analyses to 10 CVD primary prevention trials with a median of 6.0 years of followup, we found a nonsignificantly reduced mortality due to cancer among 103,787 individuals randomized to ASA or no ASA over 3.7 to 10.1 years (RR, 0.96 [95% CI, 0.87 to 1.06]), corresponding to 0.14 fewer cancer deaths (95% CI, 0.21 more to 0.45 fewer) per 1,000 person-years. Effects on all cancer mortality remained nonstatistically significant in sensitivity analyses exploring the effect of excluding trials of greater than 100 mg per day, of average length of scheduled treatment less than 5 years, or of every other day dosing. Only when including trials of both primary and secondary CVD prevention with doses up to 1,200 mg per day and requiring daily dosing within a scheduled treatment duration of 4 years or more could we find a statistically significant cancer mortality benefit (RR, 0.83 [95% CI, 0.70 to 0.98]) as reported by others. All-cause mortality in 10 CVD primary prevention trials was statistically significantly reduced (RR, 0.94 [95% CI, 0.88 to 0.99]), corresponding to 0.57 fewer deaths (95% CI, 0.10 fewer to 1.15 fewer) per 1,000 person-years, but was sensitive to including longer-term followup results from one trial and some other changes in inclusion or exclusion criteria. When also including CVD secondary prevention trials, all-cause mortality was similarly reduced and remained statistically significant when requiring daily dosing, dosages of 100 mg or less, or at least 4 years of followup, but not when substituting longer-term followup results. Few reduced deaths were cardiovascular and reduced nonvascular noncancer deaths appeared to play a prominent role, but this deserves further exploration. Among 72,926 participants in six CVD primary prevention trials, cancer incidence was similar between ASA and no ASA groups (RR, 0.98 [95% CI, 0.93 to 1.04]), corresponding to 0.20 fewer incident cases (95% CI, 0.39 more to 0.69 fewer) per 1,000 person-years, and was only statistically significantly reduced when including both primary and secondary CVD prevention trials and restricting to daily dose interventions with at least 4 years of followup with doses ranging from 75 to 500 mg per day (RR, 0.86 [95% CI, 0.74 to 0.99]). Data from primary prevention populations are currently too sparse to robustly examine cancer incidence or mortality for any cancer type other than colorectal cancer, which is examined in a companion report. Among 10 CVD primary prevention trials, the risk of major GI bleeding was increased (OR, 1.59 [95% CI, 1.32 to 1.91]), corresponding to 0.29 more cases of bleeding (95% CI, 0.44 more to 0.16 more) per 1,000 person-years. Sensitivity analyses showed little variation, except nonsignificantly increased risk with daily dosing and nonsignificantly decreased risk with alternate-day dosing. Risk of hemorrhagic stroke or other intracranial bleeding tended to be increased in primary prevention trials (OR, 1.27 [95% CI, 0.98 to 1.66]), corresponding to 0.11 more cases (95% CI, 0.28 more to 0.01 fewer) per 1,000 person-years, with statistically significant effects only when both primary and secondary prevention trials were combined (OR, 1.43 [95% CI, 1.12 to 1.81]). When restricted to all trials of 100 mg or less, the risk tended to decrease (OR, 1.32 [95% CI, 1.00 to 1.75]). Relatively rare events limited analyses. Data from cohort studies indicated that baseline rates of serious bleeding are higher than suggested from trials, and data from trials as well as cohorts indicated considerable baseline bleeding rate variation according to age, sex, diabetes, hypertension, and perhaps other selected cardiovascular risk factors. Comedications such as nonsteroidal anti-inflammatory drugs appeared to modify baseline rates in cohort studies, as well as bleeding risks with low-dose ASA, although data adjusted for other risk factors suggested a more modest combined effect than earlier estimates. These and other bleeding risk factors could potentially have a large impact on the absolute number of excess cases of bleeding and therefore net benefit considerations.

Limitations: Data on cancer benefits were limited by few trials—particularly of low-dose ASA and in CVD primary prevention populations—with adequate length of followup, which also limited analyses for cancer site-specific effects. Few analyses adjusted for combined impact of risk factors on bleeding risks; intracranial bleeding/hemorrhagic strokes are relatively rare and thus incompletely studied, and other potential risks of long-term ASA use are also understudied. Most currently available trial data are from older studies not specifically designed for outcomes beyond CVD and major bleeding, and not considering contemporary medications such as statins. In-progress research will be very valuable in updating these findings.

Conclusions: Low-dose ASA use may eventually be shown to provide modest cancer mortality benefits in CVD primary prevention populations, but effects are not clearly established since current estimates are imprecise and relatively unstable. Modest reductions in all-cause mortality effect are more stable, but cannot be completely explained through cancer and/or CVD mortality reduction. Rates of serious bleeding, with and without ASA, are higher than previously suggested in clinical trial populations, and are very important when assessing the likely net benefit of low-dose ASA use as a chemopreventive agent in a more individualized or subpopulation-specific manner.

Abbreviations

AAA	Aspirin for Asymptomatic Atherosclerosis
ACBS	Asymptomatic Cervical Bruit Study
ACCEPT-D	Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes
AFASAK	Atrial Fibrillation, Aspirin and Anticoagulation
AFPPS	Aspirin/Folate Polyp Prevention Study
AHRQ	Agency for Healthcare Research and Quality
AMIS	Aspirin Myocardial Infarction Study
AMSTAR	Assessment of Multiple Systematic Reviews
APACC	Association por la Prevention par l'Aspirine due Cancer Colorectal
ARMD	age-related macular degeneration
ARR	absolute risk reduction
ASA	acetylsalicylic acid
ASCEND	A Study of Cardiovascular Events in Diabetes
ASPIRE	Aspirin to Prevent Recurrent Venous Thromboembolism
ASPREE	ASPirin in Reducing Events in Elderly
ATT	Antithrombotic Trialists
BMD	British Medical Doctors
BMI	body mass index
BMJ	British Medical Journal
CCT	controlled clinical trial
CDPA	Coronary Drug Project Aspirin
CHD	coronary heart disease
CI	confidence interval
COX	cyclooxygenase
CRC	colorectal cancer
CVD	cardiovascular disease
DNA	deoxyribonucleic acid
EAFT	European Atrial Fibrillation Trial
e.g.	for example
ESPS-2	European Stroke Prevention Study 2
ETDRS	Early Treatment Diabetic Retinopathy
FDA	Food and Drug Administration
GI	gastrointestinal
HOT	Hypertension Optimal Treatment
HPS	Health Professional Study
HR	hazard ratio
ICD	International classification of disease
JAST	Japanese Atrial Fibrillation Trial
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
k	number of studies
kg	kilogram
KQ	key question

mg	milligram(s)
MI	myocardial infarction
mm Hg	millimeters of mercury
n	number of participants
NHS	Nurse's Health Study
NNH	number needed to harm
NNT	number needed to treat
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PARIS	Persantine-Aspirin Reinfarction Study
PHS	Physician's Health Study
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PPI	proton pump inhibitor
PPP	Primary Prevention Project
RCT	randomized controlled trial
RR	relative risk
SALT	Swedish Aspirin Low-dose Trial
SAPAT	Swedish Angina Pectoris Aspirin Trial
SNDR	Swedish National Diabetes Register
SPAF	Stroke Prevention in Atrial Fibrillation
SSRI	selective serotonin reuptake inhibitor
TIA	transient ischemic attack
TPT	Thrombosis Prevention Trial
U.K.	United Kingdom
ukCAP	United Kingdom Colorectal Adenoma Prevention
UK-TIA	United Kingdom Transient Ischemic Attack
U.S.	United States
USPSTF	United States Preventive Services Task Force
WARFASA	Aspirin for the Prevention of Recurrent Venous Thromboembolism
WHS	Women's Health Study

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Chapter 1. Introduction

Rationale for Review

The U.S. Preventive Services Task Force (USPSTF) issued recommendations on aspirin (acetylsalicylic acid [ASA]) for primary prevention of cardiovascular disease (CVD) in 2009 and for prevention of colorectal cancer (CRC) in 2007. While planning the updates of these two topics, a nomination for ASA to prevent cancers was submitted as a new topic for the USPSTF. The USPSTF commissioned this new topic to be conducted simultaneously with the other reviews. The USPSTF wanted this review to determine whether additional outcomes related to cancer prevention might modify net benefit estimates among those taking ASA for primary prevention of CVD. This perspective for the systematic review was developed for several important reasons. First, the net benefit for ASA in CVD primary prevention is controversial,[1] as reflected in conflicting international guidelines.[2] This controversy stems from increased risks of bleeding alongside relatively modest cardiovascular benefits. Illuminating any additional cancer prevention effects of ASA might clarify whether (and for whom) long-term, low-dose ASA for primary prevention may offer an overall health benefit, a topic important for both clinicians and patients.[3] Second, most of the currently available research investigating the impact of low-dose ASA on cancer comes from trials of primary and secondary CVD prevention. Thus, the current evidence on primary prevention of cancer is most applicable to those taking it for primary or secondary CVD prevention. Finally, since the use of low-dose ASA in CVD secondary prevention is already recommended, while a better understanding of additional cancer benefits might be of interest, it would not change currently recommended treatments in those with pre-existing CVD.

Prevalence and Burden of Cancer

Cancer is defined as malignant neoplasia marked by the uncontrolled growth of cells, often with invasion of healthy tissues locally or throughout the body.[4] Cancers are classified by the type of tissue and the primary site in which the cancer originates (**Table 1**).

In 2014, there were an estimated 1.7 million new cases of cancer in the United States.[5] While the incidence of cancer is roughly 460 per 100,000 persons, rates are declining for most cancer sites.[5] The most common cancers expected to occur in men and women include lung, colorectal, prostate, and breast cancer (**Table 2**). The lifetime probability of being diagnosed with an invasive cancer is higher for men (45%) than for women (38%).[6] Women have a slightly higher probability of developing cancer before the age of 60 years.[6] The median age at diagnosis for all sites is 66 years.[5] In 2011, there were approximately 13.4 million men and women who were living with a history of cancer,[5] the most common sites being breast, colorectal, prostate, and skin cancer.[5]

Cancer is the second leading cause of death in United States[5] and accounts for one in four U.S. deaths.[6] In 2014, an estimated 585,720 Americans died from cancer.[5] The four most common cancer types (lung, colorectal, breast, and prostate cancer) account for nearly half of cancer

deaths (**Table 3**). As with incidence, however, death rates are declining for most cancer sites due to improvements in early detection and treatment.[5]

Both mortality and incidence rates differ by race and ethnicity (**Tables 2** and **3**). For cancer, African American men have higher incidence and mortality rates than white men. African American women, on the other hand, have a lower incidence rate than white women, but a higher death rate. Cancer incidence and mortality rates are lower in other racial and ethnic groups than whites and African Americans for all cancer sites combined and for the four most common types—lung, colorectal, prostate, and breast. Cancer types related to infectious agents, such as those of the stomach, are generally higher in minority populations. While survival rates among racial and ethnic groups have improved in recent decades, African Americans remain less likely to survive cancer than whites.[5]

The financial impact of cancer on the patient, family, and society is significant. National expenditures on cancer care have been steadily increasing in the United States, despite decreases in the incidence of some cancers. These increased costs have been attributed to population changes, including aging (i.e., cancer incidence is greatest in the elderly), the development and use of more expensive targeted treatments as standard of care, and increased survival rates. In 2010, the national cost of cancer care was estimated to be $124.6 billion. By 2020, this cost is projected to increase by 27 percent to an estimated $157.8 billion.[7] The largest cost increases are predicted for the continuing phase of care for prostate and breast cancer.[7]

Aspirin in Cancer Prevention

The goal of primary prevention is to prevent a cancer from developing or delaying the development of a malignancy. Primary prevention of cancers could complement the secondary prevention approach of screening to detect and treat early cancers to improve health outcomes. Primary prevention can include leading a healthy lifestyle, avoiding carcinogens, and using chemopreventive agents to reduce the risk of developing a malignancy.

Recently, several individual patient data (IPD) meta-analyses by Rothwell and colleagues (2010, 2011, 2012) have reported reductions in cancer mortality and incidence with ASA use. These analyses have generated much interest in its potential use for primary prevention of cancer.[8-10] ASA, like other nonsteroidal anti-inflammatory drugs (NSAIDs), acts by inhibiting cyclo-oxygenase enzymes (COX-1 and COX-2), which catalyze the production of a number of tissue-specific signaling lipids called prostanoids. Unlike other NSAIDs, ASA irreversibly inactivates the enzymes through selectively acetylating critical serine residues.[11] In platelets, COX-1 catalyzes the production of thromboxane A2, which is important for platelet aggregation and subsequent blood clotting. Platelets are particularly susceptible to low doses of ASA because they lack a nucleus and cannot regenerate COX enzymes. Doses of ASA in the 75 to 100 mg per day range inhibit nearly all of platelet COX-1 activity and the production of thromboxane A2. COX-1 is also highly expressed in gastric epithelial cells, where it produces prostaglandin E2 and is important for protecting the gastric mucosa.

COX-2 is expressed in a variety of tissues and is induced in others during inflammation, wound healing, and neoplasia. Multiple lines of evidence have suggested that COX-2 is the main

pathway through which ASA may reduce tumorigenesis. The transcription of the COX-2 gene has been found to be upregulated in human colorectal adenomas and CRC and to be associated with increased cell adhesion, phenotypic changes, resistance to apoptosis, and tumor angiogenesis.[12] Additionally, observational data indicate that ASA may selectively reduce the risk of CRC among individuals who overexpress COX-2 compared to those who do not.[13] Higher doses of ASA (>2,000 mg daily), delivered through repeated dosing (i.e., three or four times per day), however, are needed to sustain inhibition of COX-2 activity in nucleated cells.[11,12] Lower doses of daily ASA could potentially reduce tumor development through downstream effects on COX-1 platelet inhibition, and some lines of evidence support this mechanism. Activated platelets have induced COX-2 activity in monocytes. In addition, deletion of either COX1 or COX2 genes have reduced intestinal polyp formation in a mouse model.[11] Finally, enhanced thromboxane A2 production in a murine colon adenocarcinoma cell line promoted tumor angiogenesis and the development of tumor metastases.[12]

ASA for the prevention of cancer has the potential to change current practice. This is particularly true when one considers ASA's effects on CVD prevention in addition to cancer prevention. Indeed, much recent interest in the impact of ASA as a cancer chemopreventive agent has been to determine whether the net benefit (CVD plus cancer disease events prevented balanced against bleeding events caused) might broaden the population in whom regular low-dose ASA use could be beneficial.[14]

Harms of Aspirin Use

While ASA is widely regarded as a safe over-the-counter medication, its antiplatelet actions lead to an increased risk of bleeding. The level of bleeding risk depends on the dosage and duration of ASA, concurrent use of other medications, and patient susceptibility.[15-17] The most common serious harm is upper gastrointestinal (GI) bleeding, which has been linked to even low-dose ASA use.[18] Other serious bleeding events, including hemorrhagic stroke, have also been associated with ASA use.[16] While short-term ASA use (for pain or fever) is associated with minor GI events (including abdominal pain, dyspepsia, or nausea and vomiting[19]), it is rarely associated with serious GI events. Long-term, regular use of ASA has been linked to major bleeding events, although the duration of risk associated with long-term use has not been clearly established.

Recent observational studies have suggested a possible increase in age-related macular degeneration (ARMD) with regular ASA use in older adults,[20,21] and potential as well as established harms are important to consider for a chemopreventive agent.

Absolute contraindications of ASA use include individuals with active peptic ulcer, ASA allergy or intolerance, bleeding disorders or history of recent GI/intracranial bleeding, renal failure, severe liver disease, and thrombocytopenia. Relative contraindications include individuals younger than age 21 years (contraindicated in pediatric patients with viral illness) and those with concurrent use of anticoagulation therapy, concurrent use of NSAIDs, and poorly controlled hypertension, as it may increase the risk of intracranial bleeding.[22-24] The risks of ASA use increases with age and, as such, ASA use is cautioned in older adults.

Current Clinical Practice in the United States

Nearly 40 percent of the U.S. population older than age 50 years regularly uses ASA, primarily for the primary and secondary prevention of CVD.[25-28] ASA is not routinely prescribed as a primary prevention strategy for cancer and many organizations recommend against its use to prevent specific noncolorectal cancers (**Table 5**). Many health care organizations have focused on identifying CVD primary prevention patients at sufficiently high CVD risk to outweigh bleeding harms. As such, ASA use is recommended for use in specified populations and dosing regimens to prevent CVD.[29-33] More recent recommendations, however, do not recommend the use of ASA in CVD primary prevention as a population strategy. Instead, these recommendations focus more explicitly on the better articulation of individualized bleeding risks when considering ASA for primary prevention.[34-36]

Previous Related USPSTF Recommendations

The USPSTF has made no previous recommendations on the use of ASA to prevent cancers other than CRC. In 2007, the USPSTF recommended against the routine use of ASA and NSAIDs to prevent CRC in individuals at average risk for CRC (D recommendation).[37] The USPSTF concluded that the harms outweigh the benefits of treatment. This recommendation was based on good evidence that ASA increases GI bleeding and fair evidence that it increases the incidence of hemorrhagic strokes. Fair- to good-quality evidence showed ASA may be associated with a reduction in CRC.[38] In 2009, the USPSTF recommended the use of ASA for men ages 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions (MIs) outweighs the potential harms due to an increase in GI hemorrhage (A recommendation).[31] The USPSTF recommended the use of ASA for women ages 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in GI hemorrhage (A recommendation). The USPSTF concluded the evidence was insufficient to assess the balance of benefits and harms of ASA for CVD prevention in men and women age 80 years and older (I statement). The USPSTF recommended against the use of ASA for stroke prevention in women younger than age 55 years and for MI prevention in men younger than age 45 years (D recommendation).[39]

The Agency for Healthcare Research and Quality (AHRQ) commissioned three separate, but related, systematic evidence reviews on the use of ASA to prevent CVD, CRC, and cancer in adults.[40-42] The USPSTF will use these reviews, also considering a separate decision model,[43] to make evidence-based recommendations about the use of ASA to prevent CVD and/or cancer in adults.

Chapter 2. Methods

Scope and Purpose

This review was commissioned by AHRQ alongside two separate reviews to support the USPSTF in updating its previous recommendations on ASA for the primary prevention of CRC and CVD.[40,41] Specifically, this review undertook new Key Questions (KQs) assessing the effect of ASA on cancer incidence and mortality (as opposed to CRC incidence and mortality only, which is addressed in the companion review). In addition, this review served as an "umbrella" review, considering evidence from all three reviews to comprehensively address all-cause mortality and harms related to low-dose ASA use; this strategy was novel and was undertaken in recognition that ASA effects on these broader outcomes might be more appropriately or precisely estimated outside of a disease-specific perspective. Similarly, issues of bleeding risks with and without ASA use were assessed more comprehensively (i.e., considering data from included studies in both of the other reviews) and in more depth (considering observational studies) in this review than in the companion reviews.

KQs and Analytic Framework

We developed an analytic framework (**Figure 1**) and seven KQs to guide our review in consultation with AHRQ staff and the members of the USPSTF. This review addressed only three of the KQs (1, 2, and 6) since the other four specifically addressed the effect of ASA use on CRC outcomes and were examined in a separate review.[40]

1. Does regular aspirin use reduce total cancer mortality or all-cause mortality in adults taking (or eligible for) aspirin for primary prevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk[a], and comorbidities[b]?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
2. Does regular aspirin use reduce the incidence of cancers in adults taking (or eligible for) aspirin for primary prevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk[a],and comorbidities[b]?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
6. What are the serious harms of regular aspirin use for the primary prevention of cancer (i.e., at the dosage and duration required to achieve a preventive health effect) in adults appropriate for aspirin chemoprevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk[a], comorbidities[b], and concomitant medication use[c]?

[a] Baseline cancer risk includes family history and potentially other cancer risk factors if specified in the literature.
[b] We considered the following comorbid conditions, which are prevalent and/or may be differentially affected by ASA use in terms of benefits or harms: diabetes, liver disease, ulcer disease, and previous GI bleeding.

b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?

Data Sources and Searches

We conducted a literature search to identify existing systematic reviews and meta-analyses on ASA for the primary prevention of cancers. **Appendix A** includes our literature search strategies. To locate existing systematic reviews, we searched PubMed, the Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Institute of Medicine, BMJ Clinical Evidence, AHRQ Evidence-based Practice Center Program, National Health Service Health Technology Assessment Programme, and the National Institute for Health and Clinical Excellence for articles published from 2008 to May 3, 2013. We supplemented this search with references identified during the topic nomination and development process, as well as a separate literature search for systematic reviews of harms from ASA supplementation (**Appendix A**). From these searches, we identified high-quality systematic reviews and meta-analyses from which to bridge our primary literature searches.

For KQs 1 and 2 (benefits), we bridged our search from a 2012 meta-analysis conducted by Rothwell and colleagues that identified 51 randomized, controlled trials (RCTs) of the effects of daily ASA on cancer incidence, mortality, and nonvascular deaths from searches through May 2011.[10] We supplemented this body of literature with newly identified trials through our own comprehensive literature search of PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials from January 1, 2011 to June 3, 2014. For KQ 6 (harms), we identified four relevant systematic reviews on bleeding events that collectively identified 19 trials.[10,16,18,44] We supplemented this body of literature with newly identified trials through our own comprehensive search of PubMed, MEDLINE, and the Cochrane Central Registry of Controlled Trials from January 1, 2010 (bridging from the last search date [October 2010] of the most comprehensive review[16]) to June 3, 2014. For prospective cohort studies of harms, we bridged from the last search date of the 2006 USPSTF review on CRC,[38] searching from January 1, 2006 to June 3, 2014 in PubMed and MEDLINE only.

We also reviewed the included and excluded studies of the previous USPSTF reviews on ASA for CRC[38] and CVD prevention,[45] as well as those of the ongoing updated reviews,[40,41] to identify any relevant primary studies. We also reviewed the reference lists of included studies and other relevant reviews and meta-analyses to identify potentially relevant included studies that may not have been identified in our literature searches. We obtained additional references from expert reviewers and members of the public.

We managed all literature search results using the bibliographic management software program Reference Manager® version 12.0 (Thomason Reuters, New York, NY).

[c] Concurrent medications included nonASA NSAIDs and selective serotonin reuptake inhibitors.

Study Selection

Two investigators independently reviewed titles and abstracts using the screening platform Abstrackr.[46] The same investigators reviewed full-text articles of studies against prespecified criteria (**Appendix A Table 1**) to determine the final inclusion or exclusion status. A list of excluded studies is provided in **Appendix B**.

For all KQs, we included studies conducted in adults (age ≥40 years) that examined the use of ASA for any indication (e.g., primary prevention of cancer, primary or secondary prevention of CVD) if they reported relevant outcomes (i.e., all-cause mortality, cancer mortality and incidence, or harms). We excluded studies that included adult populations with a personal history of cancer or a high incidence of familial cancer syndromes (e.g., Lynch syndrome). We also excluded studies that only reported on CRC incidence and CRC-related mortality because these are included in a separate review.[40] We also did not include studies that only reported biomarkers, biologic or physiologic markers of cancer (e.g., breast density), precancerous markers, progression, metastasis, or recurrence. We included studies that reported on any serious GI bleeding and/or intracranial bleeding, including hemorrhagic stroke (fatal and nonfatal).

We included studies examining regular oral ASA use (minimum of 75 mg every other day) compared to no treatment or a placebo. We excluded studies that evaluated nonoral forms of ASA. We excluded interventions that included: nonASA antithrombotic medications (e.g., warfarin); ASA as a cotreatment with another chemopreventive (e.g., tamoxifen) or potentially chemopreventive agent; or lifestyle intervention. In addition, we excluded studies if authors did not report information on the dose of ASA used or if it was limited to irregular or occasional use. The duration of ASA treatment and study followup were restricted to 1 year or greater for all KQs.

For KQs 1 and 2 (benefits), we only included RCTs or controlled clinical trials reporting on relevant outcomes. For KQ 6 (harms), we included any trials or longitudinal cohort studies reporting on relevant harms. For all KQs, we excluded all other study designs (e.g., case-control, case report). We only included studies published in English and those conducted in countries with a "very high" Human Development Index in 2013.[47]

Quality Assessment and Data Abstraction

Two investigators independently assessed the quality of included studies using criteria defined by the USPSTF.[48] We supplemented this process with quality criteria for observational studies using the Newcastle-Ottawa Scale[49] and the Assessment of Multiple Systematic Reviews (AMSTAR) for systematic reviews.[50] We resolved disagreements in quality through discussion.

We excluded studies rated as poor quality according to these criteria (i.e., attrition >40%, differential attrition of >10%, other "fatal flaws," or the cumulative effects of multiple minor flaws and/or mission important information significant enough to limit our confidence in the validity of results) (**Appendix A Table 2**). Good-quality studies were those with adequate randomization techniques or selection of a representative cohort; allocation concealment; blinding of outcome assessors; comparable groups at baseline with specified eligibility criteria;

low attrition and adequate adherence to the intervention; and acceptable statistical methods. Good-quality systematic reviews included adequate inclusion and exclusion criteria, dual study selection, data extraction and quality assessment of included studies, comprehensive literature searches, descriptions of included studies, an assessment of publication bias, and appropriate meta-analytical methods. We downgraded our quality rating for studies and reviews to fair quality if they did not meet the majority of good-quality criteria.

One investigator abstracted data from all included studies into a customized Microsoft Access® database (Microsoft Corporation, Redmond, WA). A second investigator checked the data for accuracy. We abstracted study design characteristics, population demographics, intervention details, health outcomes (e.g., mortality), adverse events, and subgroup analyses (as necessary).

Data Synthesis and Analysis

Where possible, we examined stratified results by population: CVD primary prevention, CVD secondary prevention, and other (e.g., combined CVD prevention and CRC chemoprevention). CVD primary prevention included studies that enrolled patient populations without pre-existing CVD events, with or without CVD risk factors.[41] Because our inclusion criteria emphasized different outcomes, we included a few studies[51-53] in CVD primary prevention populations that could not be included in the companion review.[41] For each outcome, we report our findings for specific groups of studies as follows: 1) the subset of 10 CVD primary prevention trials also reporting CVD outcomes for the companion review; 2) the entire set of included trials for this review, regardless of population; 3) cohort studies of harms (KQ 6 only); and 4) the most recent complementary IPD and/or study-level meta-analyses.

Outcome data for analyses were based on primary trial reporting with a few exceptions. We used the number of participants with an outcome as reported by meta-analyses if none of the study's publications provided these data (e.g., Seshasai and colleagues reported on cancer deaths in the Physician's Health Study [PHS], which was not provided in any of the trial's publications). When study-level data provided in the meta-analyses differed from those available in the study publications, we chose data from the meta-analysis. The only exception was the data identified by Rothwell and colleagues[8] as cancer mortality in the Swedish Angina Pectoris Aspirin Trial (SAPAT), which the study classified as "participants stopping treatment prematurely due to malignant disease," and we treated as cancer incidence.[54]

For factorial trials with additional randomization to vitamins/antioxidants or placebo, we combined groups when there was no evidence of interaction since evidence from a recent systematic review supports no role for vitamins in the incidence of CVD.[55] In trials with additional randomization to a nonASA antithrombotic medication (alone or in combination with ASA), we did not include data from arms in which the nonASA antithrombotic medication was prescribed as specified a priori.

We calculated the average daily dose of ASA. For trials using alternate day dosing, we divided the alternate day dose in half to generate the daily dose. We used the following dosage definitions in our analysis: 1) high-dose ASA as any dose greater than 325 mg per day, 2) low-

dose ASA as any dose of 325 mg per day or less, and 3) very low-dose ASA as any dose of 100 mg per day or less.

We chose the Mantel-Haenszel fixed effects model as the primary statistical analysis method for outcomes to calculate relative risks (RRs) because most of the outcomes were rare (i.e., generally <10% of participants experienced any given event).[56] For events with a control group rate of less than 1 percent, we used Peto's odds ratio (OR) method.[56] For those outcomes with control groups rates between 1 and 5 percent (i.e., cancer mortality and all-cause mortality), we conducted sensitivity analyses using the Peto OR (data not shown).[56] We used a continuity correction factor of 0.5 if an arm reported no events. We assessed statistical heterogeneity using the I^2 statistic.

When events were reported as per unit of person-years and the number of person-years in each group was reported, we calculated the number of events in each group, as necessary.

For estimating net outcome effects, we calculated absolute effects across various types of outcomes (all-cause mortality; fatal CVD; nonfatal stroke; nonfatal MI/coronary event; major CVD event; cancer incidence; cancer mortality; major GI bleeding; and intracranial hemorrhage, including hemorrhagic stroke) for the 10 CVD primary prevention trials only. These trials differed in length of followup, so we first estimated total person-years of observation for each trial arm by multiplying the number of persons in each arm by the average length of followup. We simulated the control group rate for each outcome by dividing the total number of events in the control group by the total person-years of observation (**Appendix C**). We selected the minimum, maximum, and median control group rate for each outcome, excluding zeros and outliers, from the set of CVD primary prevention trials. To calculate the expected event rate with 95% confidence intervals (CIs) after ASA intervention, we multiplied each of the control group rates by the RR, and the upper and lower 95% CIs were calculated from pooling results from the CVD primary prevention trials or the CVD primary prevention trials in which ASA doses were 100 mg per day or less. We subtracted these values from the control group rate to calculate the absolute risk reduction (ARR) and 95% confidence limits. For outcomes in which the 95% CI for the ARR excluded zero, we calculated the number needed to treat to harm with 95% CI by dividing 1 by the ARR or its 95% confidence limits.

We limited our analysis of GI bleeding to major GI bleeding, defined as those requiring transfusion, requiring hospitalization, leading to death, or defined as major by the study investigators. If a trial reported transfusions and death from GI bleeding separately, we added these events together. If a trial only reported deaths from GI bleeding, we used the reported number for major GI bleeding (we recognize that these event rates will appear low compared to other studies also reporting nonfatal major GI bleeding). If a trial reported GI bleeding without any mention of severity, we did not include it in our analysis. In our analysis of intracranial bleeding, we included those defined as intracerebral, subdural, or subarachnoid hemorrhage or as hemorrhagic stroke (fatal and nonfatal).

We conducted sensitivity analyses removing the high-dose and/or the low-dose arms; very low-dose (≤100 mg per day) is the minimum dosage that showed a beneficial effect on CVD.[41] The only exception was the complete exclusion of the United Kingdom Transient Ischemic Attack (UK-TIA) trial from the high-dose sensitivity analysis for cancer mortality, as the data reported

by Rothwell and colleagues combined the low-dose (300 mg per day) and high-dose (1,200 mg per day) ASA arms. For harms, we excluded all high-dose studies and arms from the sensitivity analyses. We conducted additional sensitivity analyses including the removal of alternate-day dosing regimens and studies with followup of less than 4 and 5 years.

We explored prespecified subgroups of interest, including age, sex, race/ethnicity, baseline cancer risk (family history and other cancer risk factors), comorbid conditions (diabetes, liver disease, ulcer disease, and previous GI bleeding), and concomitant medications (nonASA NSAIDs and selective serotonin reuptake inhibitors [SSRIs]). We specifically abstracted relevant outcomes by subgroup, if reported (e.g., by sex). We were unable to pool results due to the limited number of contributing studies.

We also created funnel plots to explore publication bias for all outcomes (data not shown).

Expert Review and Public Comment

The research plan for this review was available for public comment from June 13, 2013 to July 10, 2013 and was largely focused on ASA use to prevent CRC. Based on public comment, the scope was expanded to examine all cancers. The final version of the research plan was posted in October 2013. The draft version of this report was reviewed by experts and federal partners. We compiled and addressed comments received as appropriate.

USPSTF Involvement

This research was funded by AHRQ under a contract to support the USPSTF. We consulted four USPSTF liaisons at key points in the review, including the development of the research plan (i.e., KQs, analytic framework, and inclusion/exclusion criteria), as well as finalizing the review. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the review, and assisted in the public comment on the draft research plan. The USPSTF and AHRQ had no role in the study selection, quality assessment, or drafting of the review.

Chapter 3. Results

Literature Search and Included Studies

From our review of 4,393 abstracts and 336 full-text articles (**Appendix A Figure 1**), we identified 34 studies (30 RCTs and four cohort studies) reported in 82 publications for inclusion. From our included studies, 19 RCTS evaluated cancer mortality (KQ 1),[51,57-74] 27 RCTs evaluated all-cause mortality (KQ 1),[53,54,57-81] 12 RCTs evaluated cancer incidence (KQ 2),[54,57,58,60-62,66-68,72,75,77] and 30 RCTs[51-54,57-82] and four cohort studies[83-86] evaluated adverse effects (KQ 6). A brief description of included trials and cohort studies can be found in **Tables 6** and **7**, respectively.

We also included the results from three publications that described IPD meta-analyses[8,10,87] and one that described study-level meta-analyses.[44] These meta-analyses provided additional unpublished data obtained from primary study investigators and included multiple meta-analyses on different subsets of trials to address sequential or differing hypotheses. We briefly describe the differences in inclusion and exclusion criteria for the main analyses from each publication relevant to our KQs in **Table 8**. We also identify which of the 10 main CVD primary prevention trials are included in each. Detailed study design, baseline demographics, and intervention characteristics of individual studies and meta-analyses are available in **Appendix D** and **Appendix E Tables 1–3**.

One or more outcomes relevant to our review were available from all 10 of the RCTs that were included in our companion systematic review[41] of ASA for the primary prevention of CVD: the Primary Prevention Project (PPP),[61] the Hypertension Optimal Treatment (HOT) study,[67] the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study,[70] PHS,[73] the Early Treatment Diabetic Retinopathy Study (ETDRS),[64] the British Medical Doctor (BMD) study,[72] the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) study,[57] the Thrombosis Prevention Trial (TPT),[69] the Aspirin for Asymptomatic Atherosclerosis (AAA) study,[66] and the Women's Health Study (WHS).[60] Three of these 10 trials were conducted among healthy male[72,73] or female health professionals[60] and the other seven among participants with increased levels of CVD risk due to conditions such as diabetes[57,64,70] or hypertension.[67] Only two of the trials of ASA for CVD primary prevention, WHS[60] and PHS,[73] also evaluated primary cancer prevention as a main study aim. We included three other CVD primary prevention trials that excluded patients who had apparent CVD at the time of enrollment that were not included by our companion review since CVD outcomes were not available.[51-53]

We included 13 trials that selected participants based on preexisting CVD (prior MI;[59,71,75] stroke or transient ischemic attack;[62,63,65,74] deep vein thrombosis or pulmonary emboli;[58,78] stable angina,[54] or atrial fibrillation[76,80,81]) and one that restricted enrollment to individuals with a cervical bruit and at least 50 percent carotid artery stenosis (though not symptomatic CVD).[79] Three additional included trials focused on colorectal adenoma recurrence and CRC prevention among participants with prior colon adenomas.[68,77,82]

Three of the cohort studies included for adverse outcomes included presumed mixtures of primary and secondary CVD prevention populations[83-85] and the fourth was restricted to persons

with diabetes and no prior CVD.[86]

KQ 1. Does Regular Aspirin Use Reduce Total Cancer Mortality or All-Cause Mortality in Adults Taking (or Eligible for) Aspirin for Primary Prevention?

Cancer Mortality

Cancer mortality outcomes were available from end-of-trial reporting, data linkage, or additional posttrial followup from 19 fair- or good-quality RCTs comparing ASA to no ASA control groups (**Appendix E Table 4**).[51,57-74] Cancer mortality outcomes were also available from two IPD meta-analyses conducted by Rothwell and colleagues (2011 and 2012)[8,10] and by type (11 sites separately, several types of groups) in one of these IPD meta-analyses.[8]

End-of-trial cancer mortality outcomes were available from 10 of the RCTs[57,60,61,64,66,67,69,70,72,73] that were included in our companion review on ASA for CVD primary prevention (n=103,787; 1,513 cancer deaths). Doses of ASA among these trials ranged from an average of 50 mg per day (prescribed as 100 mg every other day) to 650 mg per day and were intended to be delivered for an average of 3.6 to 10.1 years. WHS[60] and PHS[73] were the two largest trials, making up nearly 60 percent of all participants across the 10 CVD primary prevention trials and nearly 50 percent of cancer deaths. These were also the only two trials to evaluate low-dose ASA among healthy populations unselected for having cardiac risk factors, such as diabetes or hypertension. They differed from the other CVD primary prevention trials in ASA regimen, with ASA prescribed every other day instead of daily.

Across the 10 main CVD primary prevention trials, 760 of 52,724 participants randomized to ASA intervention and 753 of 51,063 participants randomized to control groups died from cancer (**Figure 2**). The risk of dying from cancer was 4 percent lower among patients allocated to ASA interventions compared to control groups, with no statistical heterogeneity (I^2=0.0%; p=0.891), but differences were not statistically significant (RR, 0.96 [95% CI, 0.87 to 1.06]). The absolute reduction in cancer mortality risk for someone with a median level of baseline risk (median among our included trials) would be 0.14 fewer cancer deaths per 1,000 person-years for patients allocated to ASA compared to no ASA. The 95% CI, however, includes an increase of 0.21 cancer deaths per 1,000 person-years in those taking ASA. Among the seven trials of very low-dose ASA (≤100 mg per day), results were similar (RR, 0.95 [95% CI, 0.85 to 1.06]) (**Table 9**). In other sensitivity analyses, the greatest reduction in risk of cancer death among patients allocated to ASA compared to no ASA occurred when restricting to trials of daily-dose ASA that also had an average intended followup of 4 years or greater. These results, however, remained not statistically significantly different. Relatively short duration of intended treatment and followup periods for many trials may have limited their ability to detect a cancer effect.

Nine additional fair- or good-quality CVD secondary prevention or colorectal adenoma prevention RCTs[51,58,59,62,63,65,68,71,74] provided cancer mortality outcomes. These trials were all relatively short term (1.8 to 4 years average followup), contributing just 12,697 additional study participants and 170 cancer deaths. Nonetheless, overall absolute cancer death rates in the

separate study populations were similar (1.46% over 3 to 10 years in a CVD primary prevention population and 1.34% over 1 to 4 years in a secondary prevention population), suggesting a higher short-term cancer death risk in nonprimary prevention populations. ASA doses ranged from 50 to 1,200 mg per day and four trials tested doses greater than 900 mg per day.[51,59,65,71] Across all 19 trials (n=116,484; 1,683 cancer deaths), cancer mortality among participants randomized to ASA compared to no ASA remained nonstatistically significant and imprecise (RR, 0.93 [95% CI, 0.85 to 1.03]) (**Figure 3**). In sensitivity analyses, a statistically significant risk reduction occurred only after restricting to trials of daily ASA that also had 4 years of followup or greater (k=7 RCTs; n=20,990; 559 cancer deaths) (**Table 9**). None of the trials in this subset evaluated low-dose ASA (≤325 mg) interventions in healthy adults without cardiac risk factors.

In an IPD meta-analysis by Rothwell and colleagues (2012) of 51 trials of any daily dose of ASA for longer than 90 days in any population (except secondary prevention of cancer or polyps), end-of-trial cancer deaths were reduced significantly (OR, 0.85 [95% CI, 0.76 to 0.96]), with similar results when analyses used nonvascular deaths as a surrogate when cancer-specific deaths were not reported.[10] Significant effects were confined to time periods of 5 years or longer after randomization (vs. 0 to 2.9 years or 3.0 to 4.9 years) when analyses were stratified by time of followup (32 trials contributing data), with support for an effect before 3 years only with higher-dose (≥300 mg) daily ASA. End-of-trial cancer deaths were not reported separately for the six low-dose CVD primary prevention trials, and analyses for cancer types mixed fatal and nonfatal cancers. As such, these data are reported as part of cancer incidence.

Rothwell and colleagues (2011) summarized cancer mortality effects in a separate time-to-event IPD meta-analysis of seven trials of any dosage of ASA with at least 4 years scheduled treatment duration (allowing cotreatments [e.g., warfarin] if both groups received them) in primary and secondary CVD prevention populations.[8] In 23,535 patients with 657 deaths (and a somewhat higher overall rate of cancer deaths of 2.8%), ASA reduced overall cancer mortality (hazard ratio [HR], 0.82 [95% CI, 0.70 to 1.06]), with effects beginning mainly after 5 years. Cancer-specific findings were limited by few cases and limited power due to reporting within followup periods only. Nonetheless, fewer lymphomas and CRC deaths were reported.

Findings differ from our primary analyses since Rothwell and colleagues (2011) represent time-to-event data, although a meta-analysis of event rates reported in the same publication (OR, 0.79 [95% CI, 0.68 to 0.92]) also differs from our findings. A more likely explanation relates to differences in included studies; just six of 10 studies in our CVD primary prevention trial analyses were represented in the Rothwell and colleagues analysis (TPT, JPAD, AAA, POPADAD, BMD, and ETDRS).[57,64,66,69,70,72] The additional trials in our analysis represent studies in CVD primary prevention populations with a median duration of scheduled treatment of less than 4 years (3.8 and 3.6 years for HOT and PPP, respectively)[61,67] or with every other day ASA treatment (WHS and PHS).[60,73] We excluded the other two additional studies in the analysis by Rothwell and colleagues[54,65] since they were CVD secondary prevention trials. For one trial, we included the outcome for cancer incidence (not mortality) since the outcome was the number of persons discontinuing treatment for a cancer diagnosis (SAPAT).[54] One final difference between the analyses was that Rothwell and colleagues' (2011) cancer mortality data also represented participants treated with warfarin (TPT).[69]

For our analysis of both primary and secondary prevention trials, all studies in Rothwell and colleagues (2011)[8] are included, but represent just seven of the 19 trials we pooled.[57,64-66,69,70,72] Our other 12 trials had treatment durations of less than 4 years or used alternate day ASA dosing.

We conducted a series of sensitivity analyses examining various aspirin regimens (**Table 9**). Restricting our analyses to the eight CVD primary prevention trials with at least 4 years treatment duration, like Rothwell and colleagues (2011), slightly changed our results. By further restricting our analysis to only studies with daily use and a minimum treatment duration, our cancer mortality results came closer to those of Rothwell and colleagues (13% nonstatistically significant benefit in our data compared to 21% statistically significant reduction in their data), despite excluding SAPAT, UK-TIA, and the warfarin arm of TPT. By adding a secondary prevention trial (UK-TIA), we essentially reproduced Rothwell and colleague's analysis (18% statistically significant reduction in cancer mortality; data not shown).

Thus, differences between meta-analyses of overall cancer mortality in our review and in Rothwell and colleagues' review (2011) primarily reflect choices for included studies, particularly our inclusion of WHS and PHS, which represent alternate day ASA use. Longer-term followup of WHS data (17.5 median years followup after 10.1 median years of scheduled alternate day 100 mg ASA) suggests delayed impact on any cancer outcome beyond 10 years, and confirmed an effect on invasive CRC incidence only, but not cancer incidence or mortality.[88] These data support expectation of some cancer effects from nondaily ASA use.

In an additional IPD meta-analysis, Rothwell and colleagues (2011)[8] reported 20-year cancer mortality for patients in three U.K.-based trials with at least 5 years of scheduled treatment.[65,69,72] Two trials were CVD primary prevention trials conducted exclusively in men.[69,72] The third trial was nearly three quarters male and restricted to patients with a prior transient ischemic attack or stroke.[65] Doses of ASA evaluated were 75, 300, 500, and 1,200 mg per day. At the time of randomization, 31 to 53 percent of participants were current smokers. Over 20 years, 1,378 cancer deaths occurred among 10,502 patients (13.1% overall cancer death rate). During the first 10 years of observation, patients allocated to ASA had 21 percent lower risk of cancer mortality compared to patients allocated to no ASA (HR, 0.79 [95% CI, 0.66 to 0.93]). Similar results were found for cancer mortality risk at 10 to 20 years (HR, 0.77 [95% CI, 0.67 to 0.89]) or for the entire period (HR, 0.78 [95% CI, 0.70 to 0.87]).

We focused on overall cancer mortality, since cancer-specific deaths from trial data applicable to low-dose CVD primary prevention populations were limited by power (i.e., few cases and data only within stratified time periods, not cumulative).[8] Nonetheless, in Rothwell and colleagues' (2011) IPD meta-analysis representing daily ASA use for 4 years or greater in mostly CVD primary prevention users, type-specific mortality was unaffected for any individual cancer within 5 years of followup, but reduced HRs were seen after 5 years or greater for solid GI cancer deaths (specifically, pancreatic cancer (HR, 0.25 [95% CI, 0.07 to 0.92]) and CRC (HR, 0.41 [95% CI, 0.17 to 1.00]), but not for solid nonGI or hematological cancers. By histological type, only incidence of adenocarcinomas was reduced in daily ASA users after at least 5 years of followup (HR, 0.53 [95% CI, 0.35 to 0.81]). No subtype analyses had interaction terms or statistical correction for multiple comparisons, and thus are most compatible with hypothesis generation.

All-Cause Mortality

All-cause mortality outcomes for participants randomized to ASA or no ASA were available from 27 fair- or good-quality RCTs (**Appendix E Table 5**).[53,54,57-81] Results were also available from two IPD meta-analyses.[10,87]

End-of-trial all-cause mortality outcomes were available from each of the 10 main CVD primary prevention RCTs (n=103,787; 4,403 deaths) (**Figure 4**).[57,60,61,64,66,67,69,70,72,73] Doses of ASA ranged from an average of 50 to 650 mg per day and were intended to be delivered for an average of 3.6 to 10.1 years. Overall, 2,199 of 52,724 patients allocated to ASA and 2,204 of 51,063 patients allocated to no ASA died from any cause.[57,60,61,64,66,67,69,70,72,73] The risk of mortality was 6 percent lower for the ASA group compared to the no ASA group and the difference was statistically significantly different (RR, 0.94 [95% CI, 0.88 to 0.99). Statistical heterogeneity across trials was minimal (I^2=0.0%; p=0.995). For a population with an annual mortality risk similar to the median control group risk (9.55 deaths per 1,000 person-years) among these included trials, ASA intervention would lead to 0.57 fewer deaths per 1,000 person-years. The number needed to treat for 1 year to benefit would be 1,754 (**Table 10**). Sensitivity analyses conducted in the CVD primary prevention review using Peto's OR found similar results (OR, 0.93 [95% CI, 0.88 to 0.99]).[41] When restricting by dose, dose frequency, or minimum length of followup or when substituting longer-term mortality effects at 17.5 years from WHS, however, all-cause mortality outcomes were no longer statistically significantly different (**Table 9**).

All-cause mortality results were available for 17 additional fair- or good-quality RCTs.[53,54,58,59,62,63,65,68,71,74-81] One of these, the Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation study, reported no significant difference in mortality between groups, but did not report the actual number of deaths per group.[80] The ongoing Aspirin in Reducing Events in Elder (ASPREE) study reported that no deaths occurred in either group during its initial year.[53] Neither of these two trials could be used in our meta-analysis. The remaining 15 trials included 22,826 randomized participants and 2,165 deaths. Average doses ranged from 50 to 1,200 mg ASA per day and average intended duration ranged from 1 to 4 years. Frequency of dosing was at least once per day for all additional trials.

When these additional trials were pooled with the 10 main CVD primary prevention trials (k=25 RCTs; n=126,613; 6,568 deaths), the relative reduction in risk of mortality for participants allocated to ASA compared to no ASA was similar to when analyses were restricted to the 10 CVD primary prevention trials, but slightly more precise (RR, 0.93 [95% CI, 0.89 to 0.98]) (**Figure 5**). Among the 13 trials of very low-dose ASA (≤100 mg/day), the results were similar (RR, 0.93 [95% CI, 0.87 to 0.99]). Results also remained similar in magnitude and statistically significantly different between ASA and no ASA groups in our other sensitivity analyses except when restricting to trials of every other day dosing or when substituting longer-term mortality effects at 17.5 years from WHS (**Table 9**).

In an IPD meta-analysis conducted by the Antithrombotic Trialists (ATT) Collaboration, all-cause mortality was not significantly affected in six trials of CVD primary prevention (RR, 0.95 [95% CI, 0.88 to 1.02]), but was reduced in secondary prevention trials (RR, 0.90 [95% CI, 0.82 to 0.99]) through an effect on vascular mortality, but not other mortality.[87]

All-cause mortality was not examined in any analysis of the set of 51 trials of any dose of daily ASA for primary or secondary CVD prevention assembled by Rothwell and colleagues (2012).[10] An analysis of 12 trials of mostly primary prevention using any dose of daily ASA (nine trials of ≤100 mg per day; three trials of 325, 500, or 1,000 mg daily) suggested 96 fewer deaths within those allocated to ASA over 1.3 to 8.2 years of ASA use. This result is primarily due to decreased nonvascular deaths (87 fewer deaths; OR, 0.88 [95% CI, 0.78 to 0.98]), as opposed to vascular deaths (9 fewer deaths; OR, 0.99 [95% CI, 0.87 to 1.12]). The majority of all deaths (n=2,426) were nonvascular (55%). Ascertainment methods were described and may have been different across studies (i.e., some but not all studies were updated based on data from a previous IPD meta-analysis by the ATT Collaboration[87] or using data provided by the study's authors). While this might have underestimated death rates, it would not clearly introduce any bias in determining cause of death (vascular vs. nonvascular). While relevant, these data may not be directly applicable to low-dose ASA use in a CVD primary prevention population.

KQ 2. Does Regular Aspirin Use Reduce the Incidence of Cancers in Adults Taking (or Eligible for) Aspirin for Primary Prevention?

Cancer Incidence

All cancer incidence outcomes were available from 12 fair- to good-quality RCTs[54,57,58,60-62,66-68,72, 75,77] (**Appendix E Table 6**). Only one trial (WHS) reported on incidence of specific cancers (14 sites separately or five grouped types), and this was among the 89 percent of survivors who opted for longer followup after a median of 10.1 years of very low-dose ASA (100 mg) every other day.[88] Cancer incidence, overall and by time to diagnosis, was reported by type (combining fatal and nonfatal cancers) in a separate IPD meta-analysis by Rothwell and colleagues (2012) of 32 trials of any dose of daily ASA.[10]

Six of the 10 CVD primary prevention trials had outcomes available for cancer incidence (n=72,926; 4,294 incident cancers) during the 3.8 to 10.1 years of average intended intervention.[57,60,61,66,67,72] All trials tested very low-dose ASA (≤100 mg) interventions except one that tested 500 mg ASA per day.[72] WHS evaluated every other day dosing,[60] whereas the other five trials evaluated daily dosing. Cancer occurred among 2,155 of 37,301 participants allocated to ASA groups and 2,139 of 35,625 participants allocated to no ASA control groups. Overall, the risk of cancer was 2 percent lower among those allocated to ASA compared to no ASA, with no statistically significant difference between groups (RR, 0.98 [95% CI, 0.93 to 1.04]) (**Figure 6**).

Heterogeneity across trials was minimal (I^2=1.5%; p=0.406). For a population with a baseline annual risk of cancer corresponding to the median control group rate in these trials (9.81 cancers per 1,000 person-years), about 0.2 fewer cancers per 1,000 person-years would be expected with ASA use, but 95% CI for the absolute change in risk ranged from a reduction of 0.69 cases per 1,000 person-years to an increase of 0.39 cases per 1,000 person-years for those allocated to ASA compared to no ASA (**Table 10**). None of the sensitivity analyses of the end-of-trial data from CVD primary prevention trials resulted in a statistically significant impact of ASA use on cancer (**Table 9**).

In the one CVD primary prevention trial with posttrial followup (WHS), overall cancer incidence (5,071 cases, excluding nonmelanoma skin cancers) was not reduced among ASA users in age-adjusted analyses (HR, 0.97 [95% CI, 0.92 to 1.03]) after a median of 17.5 years followup, whether data were cumulative or considered within-trial or posttrial periods separately.[88] Most cancers were breast cancers (2,070), followed by CRC (451) and lung cancers (431). Of these most common cancers, only CRC incidence was reduced (cumulative HR, 0.80 [95% CI, 0.67 to 0.97]), with a delay of effect beginning only in the posttrial period (i.e., >10 years). For the only other cancer with at least 400 cases—uterine cancer (455 cases)—ASA use was not associated with reduced incidence (HR, 1.00 [95% CI, 0.83 to 1.20]). Other cancer types were relatively uncommon and the lack of significant findings may be due to lack of statistical power. Even when grouped by type, only GI cancer incidence was reduced in the posttrial followup period, while incidence of urinary tract, respiratory tract, reproductive tract, and hematologic cancers was unaffected.

We identified six additional CVD secondary prevention or colorectal adenoma prevention trials for which data on cancer incidence were available (**Figure 7**) during average intended interventions that ranged from 2 to 4 years.[54,58,62,68,75,77] These trials contributed a total of 12,639 additional participants and 263 cancer cases. Five trials evaluated low-dose ASA interventions (≤325 mg/day),[54,58,62,68,77] of which four had a very low-dose ASA arm (≤100 mg/day),[54,58,62,77] and one trial (Aspirin Myocardial Infarction Study) evaluated 1,000 mg ASA total per day.[75] ASA was prescribed as either daily or more frequent dosing (split into two doses per day in two trials).[62,75] A meta-analysis of all 12 trials showed results similar to those among the CVD primary prevention trials alone and remained nonstatistically significant and imprecise (**Table 9**). In sensitivity analyses, the greatest reduction in risk of cancer incidence was seen when restricting to trials of daily or more frequent dosing and at least 4 years of intended duration of treatment (k=4; n=11,800; 671 cancer cases) (**Table 9**). In this subanalysis, the risk of cancer among patients allocated to ASA was 14 percent lower than among those allocated to no ASA and the difference was marginally statistically significant.

In time-to-event IPD meta-analysis by Rothwell and colleagues (2012) of 32 trials of any dose of daily ASA, overall cancer risk (combining fatal and nonfatal cancers) was reduced only after greater than 3 years of followup (OR, 0.79 [95% CI, 0.70 to 0.90]), and then only for grouped reproductive cancers (OR, 0.54 [95% CI, 0.36 to 0.82]). All site-specific cancers, however, were relatively rare (<1,000 cancer cases of all types with >3 years followup) and, as such, there was insufficient power for smaller effects.[10]

KQs 1a and 2a. Does the Effect of Aspirin Vary by a Priori Subgroups: Age, Sex, Race/Ethnicity, Baseline Cancer Risk, and Comorbidities?

Overall, few trials assessed for variability in the effect of ASA on cancer mortality, all-cause mortality, or cancer incidence by our a priori subgroups. Among trials that completed these assessments, risk of these outcomes was not statistically significantly different between ASA and no ASA groups within any of the subgroups examined. In addition, only one trial (WHS)[60] reported results of testing between subgroups for statistical interactions, as is recommended.[89,90]

Several individual included trials restricted enrollment to one subgroup based on sex, nationality, history of colon adenoma, or diabetes mellitus diagnosis; however, these trials also differed in terms of other important potentially confounding study- and patient-level characteristics, making indirect comparisons of results across trials difficult to interpret. Additional data relevant to variation in effect by age and sex subgroups (cancer incidence only) were available from an IPD meta-analysis that pooled outcomes from the six CVD primary prevention trials (n=35,535) that tested daily ASA interventions at doses less than 300 mg per day only.[10] Tables showing data relevant to a priori selected subgroups are presented in **Appendix F**.

Cancer Mortality and All-Cause Mortality

Cancer mortality outcomes for ASA and no ASA groups were reported separately by sex subgroups for one trial (**Appendix F Table 1**).[65] In this trial, the RR of cancer mortality was nonstatistically significantly lower for participants in ASA groups compared to no ASA groups, for both men and women. Results of statistical testing are not reported for either sex. For all-cause mortality, outcomes were reported separately by sex in four trials,[64,65,67,75] by age group in two trials,[65,75] and by presence or absence of diabetes diagnosis in one trial (**Appendix F Table 2**).[61] No statistically significant differences in risk of all-cause mortality between ASA and no ASA groups were reported within any of the subgroups examined in any of the trials. Trends for the RR of all-cause mortality for ASA compared to no ASA groups were different between men and women in two trials[65,67] (nonstatistically significant risk reduction with ASA for men and nonstatistically significant risk increase for women). Results were different between patients with and without diabetes in one trial[61] (nonstatistically significant risk reduction in all-cause mortality with ASA for patients without diabetes and nonstatistically significant risk increase for patients with diabetes); however, results by age or sex were too sparse and mixed for any overall conclusions. Testing for statistical interactions was not reported. Available evidence was insufficient to determine if effects of ASA compared to no ASA on all-cause mortality vary between men and women or patients with and without diabetes.

Cancer Incidence

For cancer incidence, stratified analyses for subgroups based on age and family history of cancer were available from WHS, the largest single included trial, which enrolled nearly 40,000 women (**Appendix F Table 3**).[60] Cancer incidence was not statistically significantly different between ASA and no ASA groups within any subgroup. Results of testing for statistical interactions were nonsignificant ($p>0.30$ for both age and family history of cancer). Results were also available for cancer incidence in age and sex subgroups from an IPD meta-analysis by Rothwell and colleagues (2012) of six trials of ASA doses of less than 300 mg for CVD primary prevention.[10] Cancer occurring at 3 years or later after randomization was reduced by about 20 to 30 percent among ASA compared to no ASA groups within each age and sex subgroup. These results overall indicate that the effect of ASA compared to no ASA on cancer incidence was not different for subgroups based on age, sex, or family history of cancer.

KQs 1b and 2b. Does the Effect of Aspirin Vary by Delivery of Intervention (e.g., Dose, Frequency, Duration, Formulation, and Recency of Use)?

Results relevant to variation of the effect of ASA on cancer mortality, all-cause mortality, and cancer incidence were available from our sensitivity analyses (relevant to dose, frequency, and duration) (**Table 9**) and also from two IPD meta-analyses by Rothwell and colleagues (relevant to duration).[8,10] The IPD meta-analyses were restricted to daily dose interventions and therefore could not evaluate potential variation in effect of ASA with dose frequency (i.e., daily vs. every other day). Data were limited to address type-specific cancer effects and insufficient to address variation in effect related to ASA formulation or recency of use.

Dose

In our sensitivity analyses, restricting to trials of low- (≤325 mg/day) or very low-dose (≤100 mg/day) ASA did not impact our estimates of the RR of cancer mortality, all-cause mortality, or cancer incidence except for slightly reducing the precision of the estimates (**Table 9**). For all-cause mortality, the statistically significant 6 to 7 percent reduction in risk among ASA compared to no ASA groups (when including trials of all doses) was no longer statistically significant among the CVD primary prevention trials when restricting to low- (≤325 mg/day) or very low-dose (≤100 mg/day) ASA only. This result remained similar in magnitude to the estimate that included all trials, suggesting reduced power rather than differences in effect by dosage. Exploratory analyses by Rothwell and colleagues (2011) suggested no difference in low- (75 mg) versus higher-dose (≥300 mg) ASA on reduced risk of adenocarcinoma deaths, but these results could be confounded and need confirmation.

Duration

Results of the two IPD meta-analyses by Rothwell and colleagues (2011 and 2012) indicate that the effects of daily ASA on cancer mortality and cancer incidence vary based on the duration of ASA treatment.[8,10] Data for time from randomization to cancer death during the trials were available for participants in 32 of 51 primary or secondary CVD prevention trials testing daily ASA compared to no ASA for 90 days or greater (n=65,973 patients; 85% of patients in all 51 trials). The risk of cancer death from 0 to 2.9 years and 3 to 4.9 years after randomization was not different between groups. The risk of cancer death occurring at 5 years or later after randomization, however, was 37 percent lower for patients allocated to ASA compared to no ASA (OR, 0.63 [95% CI, 0.49 to 0.82]).[10] A separate analysis by Rothwell and colleagues (2011) of seven primary or secondary CVD prevention trials with at least 4 years of mean or median scheduled treatment found the same pattern.[8] Results of testing for statistical interactions between ASA and duration of treatment were not reported for either of these two analyses. In posttrial followup of three trials, longer treatment duration was significantly related to decreased 20-year risk of nonhematological cancers (p=0.01 for interaction), with no benefit for less than 5 years intended use and greatest benefit for 7.5 years or greater. Exploratory analyses suggested minimal treatment duration (≥5 to 10 years) and latency to mortality reduction (5 to 20 years) may vary for specific cancers, but studies were too methodologically and clinically

heterogeneous for strong conclusions. Analyses on variation in the effect of ASA on all-cause mortality with duration of treatment were not reported.

Rothwell and colleagues (2012) examined time from randomization to cancer incidence during trial followup among participants in the six CVD primary prevention trials of daily ASA of less than 300 mg per day versus no ASA (n=35,535).[10] Risk of cancer incidence was similar between groups during the first 3 years after randomization, but was 19 percent lower among patients allocated to ASA versus no ASA at 3 to 4.9 years and 29 percent reduced at 5 years or greater (0 to 2.9 years: HR, 1.00 [95% CI, 0.88 to 1.15]; 3 to 4.9 years: HR, 0.81 [95% CI, 0.67 to 0.98]; ≥5 years: HR, 0.71 [95% CI, 0.57 to 0.89]). Testing for interaction between ASA and duration of followup beyond 3 years was significant (p=0.04). For one of the five trials,[70] data on cancer mortality were substituted for cancer incidence.

In our sensitivity analyses, outcomes between ASA and no ASA groups remained similar to main findings for cancer mortality, all-cause mortality, and cancer incidence when analyses were restricted to trials of 4 years or greater average duration (**Table 9**). We do not have data on the length of time after randomization to these outcomes, however, so cannot distinguish between events that occurred after shorter versus longer periods of intervention.

Frequency

In our sensitivity analyses restricting to trials of daily-dose ASA, the magnitude of RR reduction in cancer mortality and cancer incidence for ASA compared to no ASA groups tended to be greater than in our main analyses that included all trials (two with every other day dosing), but neither approaches yielded a statistically significant difference between treatment groups (**Table 9**). When restricting to trials of daily dose ASA in which the average intended duration was 4 years or greater and also including secondary CVD prevention or colon adenoma populations, the relative reduction in cancer mortality and cancer incidence became statistically significant for ASA groups compared to no ASA groups (cancer mortality: RR, 0.83 [95% CI, 0.70 to 0.98]; cancer incidence: RR, 0.86 [95% CI, 0.74 to 0.99]); these findings, however, were not statistically significant when limited to CVD primary prevention trials. For all-cause mortality, findings among trials of daily dose ASA were similar in magnitude to main results and remained statistically significant, regardless of duration considerations.

KQ 6. What Are the Serious Harms of Regular Aspirin Use for the Primary Prevention of Cancer (i.e., at the Dosage and Duration Required to Achieve a Preventive Health Effect) in Adults Appropriate for Aspirin Chemoprevention?

We identified 30 RCTs that reported on associated harms with ASA use in populations seeking benefits for primary and secondary CVD prevention or for CRC/adenoma prevention (**Table 6**; **Appendix E Tables 1–3**). Thirteen were in CVD primary prevention populations (including the 10 from the other ASA review on the topic),[41] 14 were in CVD secondary prevention populations, and three were in CRC/adenoma prevention populations. Dosages ranged from 50 to 1,200 mg per day on average, with a duration of use from 1 to 10.1 years. Given the overall

findings on CVD,[41] all-cause mortality, and cancer incidence and mortality, the most applicable evidence on harms represents lower-dose ASA use (<325 mg per day or every other day) up through about 10 years.

In addition, we identified four recent fair- or good-quality cohort studies reporting on bleeding risks in individuals with and without low-dose ASA use (**Table 7**; **Appendix E Tables 1–3**).[83-86] Three cohort studies included a presumed mixture of primary and secondary CVD prevention populations,[83-85] while the fourth was limited to patients with diabetes and no prior CVD;[86] this study was quite limited in the types of bleeding outcomes reported. Dosages ranged from 75 to 300 mg per day and duration of followup from 3.9 to 11.4 years. We limited cohort data to those examining lower-dose ASA use (≤325 mg) or those reporting data separately among lower-dose users, with no active cotreatments. Limited specificity about ASA exposure (e.g., providing average weekly intake in categories of tablet sizes) prevented us from using two cohort studies for estimating absolute rates of harms with low-dose ASA,[83,84] although these cohort studies were useful in examining effect modification.

We also included the most recent IPD meta-analysis by Rothwell and colleagues (2012)[10] and the ATT Collaboration[87] and recent study-level meta-analysis by Seshasai and colleagues focused on trials;[44] each of these reported harms in ways that complement our findings from primary studies.

Major GI Bleeding

Among the 10 CVD primary prevention trials, seven reported major GI bleeding events (defined as any GI bleeding requiring transfusion, requiring hospitalization, leading to death, or defined as major by the study investigators) with ASA use (**Figure 8**; **Appendix E Table 7**).[60,66,67,69,70,72,73] Dosages ranged from 50 to 162.5 mg per day in all but one trial (500 mg per day).[72] Duration of use and followup ranged from 4 to 10.1 years. Among ASA users, major GI bleeding risk was increased (Peto OR, 1.59 [95% CI, 1.32 to 1.91]), with low heterogeneity in the pooled result (I^2=22.2%). Absolute bleeding would be increased by 0.29 events per 1,000 person-years of exposure to ASA intervention for a population with a baseline risk similar to the median level among our included trials (**Table 10**). Sensitivity analyses (**Table 11**) excluding the two trials with dosages above 100 mg essentially did not change the pooled estimate. When we pooled all primary and secondary prevention trials with major GI bleeding outcomes (k=15) (**Figure 9**), absolute bleeding risks were somewhat higher, with no heterogeneity (Peto OR, 1.63 [95% CI, 1.37 to 1.95]; I^2=0%). In sensitivity analyses (**Table 11**) that excluded six studies[63,65,72,73,75,79] with dosages above 100 mg, bleeding estimates for all trials were reduced to those in the CVD primary prevention studies. Although pooled results for all 15 trials, when stratified by primary versus secondary CVD prevention, suggested somewhat higher bleeding risks in secondary prevention trials, there was no statistically significant interaction by prevention type, and the two groups of trials varied in dosage and time frame for ASA administration (data not shown).

An IPD meta-analysis conducted by the ATT Collaboration[87] of six primary prevention trials[60,61,67,69,72,73] reported major extracranial bleeding defined as mainly GI and usually requiring transfusion or resulting in death. Five of six trials were also represented in our major study-level GI bleeding meta-analysis reported above. We excluded the one trial included by the ATT Collaboration[87] because it did not report outcomes compatible with our definition;[61] we were able to include two additional trials due to a later publication date.[66,70] The rate of major

extracranial bleeding reported for the control group in each trial in the IPD meta-analysis of six primary prevention trials ranged from 0.04 to 0.18 percent per year (0.4 to 1.8 events per 1,000 person-years). There were a total of 554 major extracranial bleeding events in all six studies over 3.7 to 10.1 years of followup. Overall, ASA use increased major extracranial bleeding from 0.07 to 0.10 percent per year (rate ratio, 1.54 [95% CI, 1.30 to 1.82]). This difference translated to an average of 0.3 more major extracranial bleeding events per 1,000 persons taking ASA for 1 year. We approximated person-years of followup for the larger range of CVD primary prevention trials available for our review. Our method yielded similar estimates, tending to be lower if different from the IPD meta-analysis by the ATT Collaboration[87] (**Table 14**). As an example, in the two studies with at least 100 total major bleeding events (WHS and HOT) included in both approaches, our approximate estimates were quite similar to those from the IPD meta-analysis (i.e., we calculated 0.47 vs. 0.5 per 1,000 person-years for WHS and the IPD meta-analysis, respectively; we calculated 1.04 vs. 1.8 per 1,000 person-years for HOT and the IPD meta-analysis, respectively). With either method, baseline major extracranial bleeding rates between CVD primary prevention populations varied widely—by four- to five-fold.

Major extracranial bleeding events tended to be higher in secondary prevention studies, although relatively few CVD secondary prevention trials (five of 16) reported major bleeding events, with imprecise results (rate ratio, 2.69 [95% CI, 1.25 to 5.76]) and similar potential for confounding, as noted for our stratified meta-analyses.

A subsequent IPD meta-analysis by Rothwell and colleagues (2012)[10] of six primary prevention trials[57,61,66,67,69,70] of daily low-dose ASA (75 to 100 mg per day) shared just three trials with the previous IPD meta-analysis and four with our analysis due to its focus on very low-dose daily ASA use only. First events of major extracranial bleeding events, as previously defined, were found to differ significantly by time to followup (2.9 years or earlier vs. 3.0 years or later; p=0.006), with increased odds of bleeding confined to the earlier time period only (OR, 1.95 [95% CI, 1.47 to 2.59]). The average followup, however, was less than 5 years in three of the trials (3.6, 3.8, and 4.4 years for PPP, HOT, and JPAD, respectively), which made ascertainment unequal between the two time periods.

De Berardis and colleagues examined hospitalizations for major bleeding events (including hospitalizations for intracranial as well as extracranial bleeding) in a population of 372,850 community-dwelling individuals in Italy (186,425 new users of ASA [≤300 mg] ages 30 to 95 years, matched using propensity scoring to 186,425 never-users). Bleeding rates reflected 1.6 million person-years of observations and a median followup of 5.7 years (interquartile range, 2.4 to 6.0 years).[85] Among never-users of ASA, there were on average 3.60 major bleeding events per 1,000 person-years (95% CI, 3.48 to 3.72). However, unadjusted baseline major bleeding event rates among never-users of ASA varied from a low of 0.61 per 1,000 person-years in those younger than age 50 years to a high of 12.00 per 1,000 person-years in those with previous hospitalization for GI problems. To be considered a current user, studies required an ASA prescription within 2.5 months of bleeding events, and former users were excluded from analyses. The never-user group and current-user group differed at baseline on a number of sociodemographic characteristics, but major bleeding event rates differed only slightly over 6 years (1.8% vs. 1.9%, respectively). There were 6,907 first hospitalizations for major bleeding events, of which about two thirds (4,487) were GI bleeding, one third (2,464) were intracranial hemorrhages, and a few (44) included both sites. Incidence rates for hospitalizations for major

bleeding events were 5.58 (95% CI, 5.39 to 5.77) per 1,000 person-years in ASA users compared to 3.60 (95% CI, 3.48 to 3.72) in nonusers. Incidence rate ratios (IRRs) increased with ASA use (IRR, 1.55 [95% CI, 1.48 to 1.63]) overall, with no difference in effect size by bleeding site (i.e., GI vs. intracranial).

Ekstrom and colleagues examined "ventricular hemorrhage" (International Statistical Classification of Diseases and Related Health Problems [ICD], 10th revision codes K92.0-92.2 corresponding to hematemesis, melena, GI hemorrhage, unspecified) in 18,646 patients with diabetes in Sweden (4,608 with continuous low-dose ASA use and 14,038 without ASA treatment) for a mean followup of 3.9 years.[86] There were no statistically significant increases in risk of fatal and nonfatal ventricular hemorrhage among those taking ASA (adjusted HR, 1.27 [95% CI, 0.77 to 2.09]); ICD codes examined did not include all types of GI hemorrhage, such as those associated with ulcers.

Intracranial Bleeding, Including Hemorrhagic Stroke

Nine of the 10 CVD primary prevention trials reported rates of intracranial bleeding, including hemorrhagic strokes (**Figure 10**; **Appendix E Table 8**). Across all studies, absolute rates tended to be higher among those taking ASA (129 events per 50,868 individuals) compared to those not taking ASA (96 events per 49,208 individuals), although with relatively minimal differences (0.1 additional intracranial bleeding events per 1,000 persons taking ASA for about 1 year). The risk was increased 27 percent, not a statistically different result, with no heterogeneity (Peto OR, 1.27 [95% CI, 0.98 to 1.66]; I^2=0.0%). In sensitivity analyses restricting to trials with 100 mg of ASA or less (**Table 11**), bleeding risk with ASA tended to decrease (Peto OR, 1.19 [95% CI, 0.88 to 1.61]). When secondary CVD and other prevention trials were combined with CVD primary prevention trials of any dosage (**Figure 11**), however, the OR of intracranial bleeding was significantly increased (OR, 1.43 [95% CI, 1.12 to 1.81]), with no heterogeneity. Absolute differences would be 0.18 additional bleeding events per 1,000 persons taking ASA for 1 year. When combined studies were limited to 100 mg or less (**Table 11**), the risk tended to decrease (Peto OR, 1.32 [95% CI, 1.00 to 1.75]).

In the large Italian cohort study described above, IRRs for intracranial hemorrhage increased with ASA use (IRR, 1.54 [95% CI, 1.43 to 1.67]), which is very similar to the IRR for major bleeding events overall or for GI bleeding.[85] About one third of first episodes of hospitalization for major bleeding events were for intracranial hemorrhages. In the Swedish cohort study, HRs for fatal and/or nonfatal cerebral hemorrhage were increased, but not statistically significantly (fatal and nonfatal: adjusted HR, 1.26 [95% CI, 0.70 to 2.25]; fatal: adjusted HR, 1.60 [95% CI, 0.51 to 6.05]).[86] One IPD meta-analysis of six primary prevention trials from the ATT Collaboration found a relative increase in the yearly event rates for hemorrhagic strokes (RR, 1.32 [95% CI, 1.00 to 1.75]).[87]

Other Bleeding Outcomes

Seshasai and colleagues conducted a study-level meta-analysis of bleeding outcomes, including nine of the 10 CVD primary prevention trials.[44] They calculated the number of "nontrivial" bleeding events in each trial arm by adding the number of participants who had fatal bleeding

from any site; cerebrovascular or retinal bleeding; bleeding from a hollow viscus; bleeding requiring hospitalization and/or transfusion; or study-defined major bleeding, regardless of source. Among 102,621 participants with mean followup of 6.0 years, those allocated to ASA had an excess risk of nontrivial bleeding events (9.7 events per 1,000 person-years) compared to those allocated to placebo or no ASA (7.4 events per 1,000 person-years; random effects OR, 1.31 [95% CI, 1.14 to 1.50]). When excluding the higher dosage study (BMD),[72] the risk was similar (OR, 1.31 [95% CI, 1.14 to 1.51]). The results were also similar—but the magnitude tended to be higher (OR, 1.39 [95% CI, 1.11 to 1.73])—when restricting to trials of low-dose ASA (i.e., <100 mg per day).

Quantitatively measured heterogeneity for nontrivial bleeding events across the trials was considerable (I^2=65.7% [95% CI, 30.3 to 83.1]) and was explored by Seshasai and colleagues[44] for possible sources through stratified analyses of studies in groupings based on differing trial characteristics (**Table 12**). Results indicated that publication period (before 2000), number of bleeding events per study (<500), and daily ASA use were each significantly associated with a greater effect of ASA on nontrivial bleeding events (**Table 12**). The authors concluded, however, that these study-level characteristics could not sufficiently explain the heterogeneity observed. There were about five times the number of total bleeding as nontrivial bleeding events, and the risk of having *any* bleeding event among participants in the ASA group compared to the control groups was also increased, but heterogeneity for this estimate was extremely high (I^2=98.0% [95% CI, 97.3 to 98.5]). Since individual factors (i.e., age, male sex, diabetes, current smoking) have been shown to be significantly related to bleeding risks in IPD meta-analyses of a subset of these studies,[87] explaining the residual heterogeneity would likely require IPD meta-analysis. Without such data, average estimates for these other bleeding outcomes would not be clearly clinically applicable. In the single CVD primary prevention trial that provided time-based bleeding risks for within-trial and posttrial periods,[88] cumulative incidence of GI bleeding events (any type, not just major) increased linearly over the within-trial period to a cumulative GI bleeding risk of about 6.5 percent over a median of 10.1 years in placebo users. Among participants allocated to ASA, cumulative bleeding events increased linearly to about 7.5 percent over 10.1 years (HR, 1.15 [95% CI, 1.07 to 1.24]). The absolute difference was 1 percent at about 10 years, and no further differences accrued posttrial. GI bleeding rates were markedly reduced and to similarly low levels in posttrial followup participants (cumulative incidence of 0.9% over a median posttrial followup of 7.2 years).[88]

Ulcers

We identified four trials that examined the occurrence of GI ulcers among the CVD primary prevention trials (**Appendix E Table 9**). We rated one as good-quality[66] and three as fair-quality for harms outcomes.[72,73,88] Ulcers were reported among 0.5 to 4.7 percent of control group participants during the course of the trials (**Table 13**). While the reason for variation in the control group rates may have reflected differing time points of followup (4.7% represented cumulative cases over 10 years, most others were around 5 years), trials also differed in terms of whether participants with GI ulcers at baseline were clearly excluded (in two trials only),[72,73] the percent of female participants (0% to 100%), and the method of ascertaining adverse events (e.g., self-report vs. physician confirmation). In all of the studies, GI ulcers were more common among patients randomized to the ASA group compared to the control group, ranging from 20 to 75

percent higher risk. The increased RR was statistically significant in two of the four trials.[72,88] Similar patterns were seen among the secondary prevention and cohort studies.

ARMD

ARMD outcomes were reported for two good-quality RCTs (**Appendix E Table 10**), the female-only WHS[91] and male-only PHS.[92] Both were 2x2 factorial trials evaluating alternate day ASA (100 mg in WHS and 325 mg in PHS) with or without vitamin E among health professionals. Neither trial reported statistically significant increased risk of ARMD (with or without vision loss) or visually significant ARMD (defined as 20/30 or worse and attributable to ARMD) among those allocated to the ASA group compared to those allocated to the control group. In both trials, self-reported ARMD diagnoses were confirmed by review of medical records, although blinding of outcome assessment was reported only for WHS. Results were calculated using Cox proportional hazard regression models for both studies, adjusting for age and vitamin E random allocation (both studies) and beta-carotene random allocation (WHS only).

In PHS, 117 cases of ARMD (with or without vision loss) were confirmed among 21,216 male participants. Fifty-one cases occurred in the ASA group and 66 in the placebo group (adjusted RR, 0.77 [95% CI, 0.54 to 1.11]). Visually significant ARMD occurred among 25 men in the ASA group and 32 in the placebo group (adjusted RR, 0.78 [95% CI, 0.46 to 1.32]). In subgroup analyses by age, the RRs tended to be lower among older men, but the interaction effects were not statistically significant. Baseline hypertension (defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥95 mm Hg, or treatment for hypertension) had a statistically significant interaction with the relationship between ASA and ARMD, with or without vision loss (p=0.04 for interaction). Among men reporting baseline hypertension, ASA group assignment was associated with a reduced risk of ARMD (adjusted RR, 0.35 [95% CI, 0.15 to 0.83]). Among men without hypertension, there was no significant association between ASA group and ARMD (RR, 0.95 [95% CI, 0.63 to 1.44]). Analyses of ARMD in the PHS data were restricted to participants who reported no ARMD at baseline and who had at least 7 years of observation.

In WHS, 693 cases of ARMD (with or without vision loss) were confirmed among 39,421 female participants over an average of 10 years. Assignment to the ASA group was not associated with the development of ARMD (adjusted HR, 1.03 [95% CI, 0.88 to 1.21]). The risk of ARMD with vision loss was nonsignificantly reduced among the ASA group (111 vs. 134 cases in the ASA and control groups, respectively; adjusted HR, 0.82 [95% CI, 0.64 to 1.06]). Women allocated to the ASA group had a nonsignificant 10 percent reduced risk of developing advanced ARMD compared to the placebo group (26 vs. 29 cases in the ASA and placebo groups, respectively; adjusted HR, 0.90 [95% CI, 0.53 to 1.52]). The relationship between ASA group assignment and ARMD appeared to be modified by self-reported use of multivitamins. Among multivitamin current nonusers, the risk of ARMD was significantly reduced by 32 percent within the ASA group compared to the control group (HR, 0.68 [95% CI, 0.49 to 0.95]). Among multivitamin users, in contrast, there was a nonsignificant 14 percent increase among the ASA group compared to the control group (HR, 1.14 [95% CI, 0.76 to 1.70]; p=0.053 for interaction). In WHS, ARMD was diagnosed by blinded review of medical records. Analyses were conducted using Cox proportional hazard regression, adjusting results for age at baseline and randomized vitamin E and beta-carotene assignments.

KQ 6a. Does the Effect of Aspirin Vary by a Priori Subgroups (Age, Sex, Race/Ethnicity, Baseline Cancer Risk, Comorbid Conditions, or Concomitant Medication Use)?

Few trials evaluated variability in harmful effects of ASA by our a priori subgroups. We had some data to evaluate age, sex, and diabetes subgroups, but no information on subgroups based on cancer risk or liver disease and little on previous ulcer disease or GI bleeding. In fact, many trials restricted patient enrollment to those without bleeding risk factors, excluding those: with a history of ASA intolerance or contraindications (22 of 30 trials [eight of the CVD primary prevention trials]); with a history of prior GI or other bleeding (nine of 30 trials [three of the CVD primary prevention trials]) or history of ulcer (13 of 30 trials [six of the CVD primary prevention trials]); or who indicated current or possible future use of other NSAIDS (10 of 30 trials [one CVD primary prevention trial]) or antiplatelets/anticoagulants (22 of 30 trials [six of the CVD primary prevention trials]). Others focused exclusively on subpopulations, such as persons with diabetes.[57,64,70]

Among the two prospective cohort studies with sufficient ASA exposure documentation to allow reasonably precise exposure outcome estimates, one excluded history of hemorrhagic stroke or any medical condition or medication predisposing to such bleeding.[86] The other study[85] excluded former ASA users, but otherwise reported bleeding risks associated with many of these factors in a relatively unselected cohort of new low-dose ASA users matched to controls. Although ASA exposures were measured in ways that prevented precise risk estimates associated with ASA use in the other two large cohort studies,[83,84] these studies were used to examine effect modification within strata of ASA exposure. Overall, bleeding risks associated with ASA in this review largely reflect the fact that many individuals at increased risk had limited or no representation in the included studies; further, assessment of individualized bleeding risks associated with ASA use was limited by lack of detailed study reporting and relatively limited IPD meta-analysis addressing bleeding harms.

Even where reported, subgroup findings related to differential bleeding harms with ASA use must be carefully considered, since these may reflect underlying (baseline) differences in risk of bleeding in that subgroup or actual effect modification, wherein ASA differently affects RRs of bleeding in that subgroup of users compared to the larger group of ASA users versus nonusers. The "excess risk" of harm with ASA use (above baseline risks and attributable to ASA) is of most interest to decisionmakers interested in ASA chemoprevention.[93] These issues would be best separated by considering both the absolute and relative risks of bleeding (baseline risk) among nonusers of ASA overall and for a priori subgroups, as well as a priori subgroup-specific absolute and relative risks of bleeding among low-dose ASA users versus nonusers. Accordingly, we report data for these measures where available, clarifying differences between data estimating baseline risks (**Table 14**) and those estimating excess risks wherever possible (**Table 15**). Further, since harms estimates may vary by population type and characteristics of the ASA regimen (dose, frequency, duration), as well as by study design (study type, duration of followup), we also consider these factors in a companion question below.

Age

Major Bleeding (GI and Cerebral)

Absolute rates of hospitalization for major bleeding events (GI and cerebral) from adequately sized studies were available for age-specific subgroups in one very large population-based cohort study with greater than 1.6 million person-years of observation comparing new users of ≤300 mg ASA per day (presumably for either primary and secondary prevention) with propensity-score matched never-users.[85] Among never-users, unadjusted incidence rates of hospitalization for major bleeding events over 6 years increased significantly during each age decile after 50 years from a low of 0.61 events (95% CI, 0.41 to 0.91) per 1,000 person-years in those ages 30 to 50 years to a high of 6.93 events (95% CI, 6.51 to 7.38) per 1,000 person-years in those age 80 years or older (**Table 14**). During each decade, incidence rates among never-users approximately doubled, ranging from 1.40 events (95% CI, 1.24 to 1.58) per 1,000 person-years in those ages 50 to 59 years, to 2.58 events (95% CI, 2.40 to 2.77) per 1,000 person-years in those ages 60 to 69 years, to 4.61 events (95% CI, 4.39 to 4.85) per 1,000 person-years in those ages 70 to 79 years. Among current ASA users, absolute incidence rates of hospitalization for major bleeding events also increased with each decade of older age, from 2.48 events (95% CI, 2.19 to 2.82) per 1,000 person-years in those ages 50 to 59 years to 10.60 events (95% CI, 9.91 to 11.23) per 1,000 person-years in those age 80 years or older. For each age decade, incidence rates for hospitalization for major bleeding events among low-dose ASA users were comparable to those of nonASA users one decade older. Thus, the unadjusted baseline risk of hospitalization for major bleeding events increased with age, as did the excess risk with ASA use, particularly among those age 70 years and older, in whom excess major bleeding events exceeded 2.0 per 1,000 person-years of ASA use.

The effect of ASA on major bleeding risk (IRRs in ASA users vs. never-users) differed significantly by age (p=0.009 for interaction).[85] Low-dose ASA users younger than age 50 years had a significantly elevated IRR (3.17 [95% CI, 1.99 to 5.05]). IRRs of major bleeding with ASA use were also consistently increased about 1.5 times in those age 60 years and older (ages 60 to 69 years: IRR, 1.53 [95% CI, 1.38 to 1.69]; ages 70 to 79 years: 1.49 [95% CI, 1.38 to 1.60]; age ≥80 years: 1.52 [95% CI, 1.39 to 1.66]), but was lower in magnitude than in younger users. Thus, age modified the RR associated with ASA use due to very low baseline risks in younger adults. After adjusting for multiple factors, including ASA use, each additional year of age was associated with a 5 percent higher incidence rate for hospitalization for major bleeding events (IRR, 1.05) (**Table 15**).

Major GI/Extracranial Bleeding

In a separate IPD meta-analysis of six CVD primary prevention trials by the ATT Collaboration, absolute yearly incidence of bleeding increased with each decade of age after adjusting for multiple baseline risk factors, including allocation to ASA use (**Table 15**).[87] For each subsequent decade, rate ratios increased for major extracranial bleeding (2.15 [95% CI, 1.93 to 2.39]). One of these trials that included about 7 percent of all participants taking low-dose ASA included in this analysis, however, used a higher dose (500 mg) of ASA, which could modestly inflate these estimates.[72] As a whole, available data reflect increased baseline risk for bleeding with aging, controlling for ASA use, in a primary prevention population. The effect of ASA versus no ASA

on major extracranial bleeding, however, was similar among participants younger than 65 age years (rate ratio, 1.53 [95% CI, 1.16 to 2.03]) and among those age 65 years or older (rate ratio, 1.55 [95% CI, 1.08 to 2.21]; p=1.0 for interaction).

Prospective cohort studies also found no difference in HRs for major GI bleeding with ASA use by those younger than age 60 years compared to older men or women (p>0.50 for interaction).[83,84] These two studies, however, are not strong evidence against age-based effect modification, since ASA exposure in these studies was likely insufficient to sensitively detect differing effects.

Intracranial Bleeding, Including Hemorrhagic Stroke

One IPD meta-analysis by the ATT Collaboration of six CVD primary prevention studies suggested age (per decade) (**Table 15**) increased hemorrhagic stroke risk by 59 percent in analyses adjusting for other risks and ASA use (rate ratio, 1.59 [95% CI, 1.33 to 1.90]).[87]

Sex

Sex-specific absolute rates of GI bleeding were reported in two sex-specific trials in CVD primary prevention populations.[60,73] Bleeding events (serious or otherwise) were generally defined too differently in the two trials to be comparable, except for fatal GI hemorrhages, which were exceedingly rare and therefore imprecise.

In IPD meta-analysis conducted by the ATT Collaboration[87] of six CVD primary prevention trials, adjusted for multiple baseline risk factors, including allocation to ASA use, rates of major extracranial bleeding were about twice as high in men than women; no sex differences were seen in hemorrhagic stroke rates.[87] These data reflect increased baseline risk for bleeding with male sex, controlling for other risk factors (**Table 15**).

Based on cohort data from the previously described Italian population-based cohort study comparing new ASA users of 300 mg or less per day with propensity-score matched never-users,[85] unadjusted absolute rates for hospitalization for major bleeding events in male never-users were elevated (4.50 per 1,000 person-years [95% CI, 4.30 to 4.70]) whether compared to female never-users (2.86 per 1,000 person-years [95% CI, 2.72 to 3.01]) or all never-users (3.60 [95% CI, 3.48 to 3.72]) (**Table 14**). Among current ASA users, men experienced 6.42 hospitalizations for major bleeding events (95% CI, 6.14 to 6.72) per 1,000 person-years, with an excess of 1.63 hospitalizations compared to women. This excess event rate was similar to that between male and female nonusers, suggesting that male sex was associated with increased bleeding risk that was maintained, but not further modified, with low-dose ASA use.

Within sex-specific categories in the same cohort study, IRRs in ASA users versus nonusers were significantly different in men compared to women (p=0.001 for interaction) and slightly lower (1.43 vs. 1.67), although both estimates hovered around 1.5 times, and absolute differences with ASA use were virtually the same (1.92 vs. 1.93 hospitalizations for major bleeding events per 1,000 person-years). These relative effect differences likely reflect the baseline difference in bleeding risk between men and women, which was confirmed by the persistence of an increased

IRR for men compared to women (1.69 [95% CI, 1.61 to 1.79]) after adjusting for multiple other risk factors, including ASA use (**Table 15**).

A separate cohort study in persons with diabetes found no differences between men and women in any bleeding outcomes, although event rates were small, limiting firm conclusions.[86]

Race/Ethnicity

Race/ethnicity status for enrolled populations was reported in relatively few trials (k=9).[59,64,70,71,75,77,78,81] No bleeding risks were stratified by race/ethnicity. Thus, racial/ethnic minorities (i.e., those of Hispanic, African, Native and Pacific Islander, and Asian other than Japanese descent) are clearly underrepresented in trials reporting these population characteristics, and likely underrepresented in most others, given their geographical location. The baseline rate of intracranial hemorrhage among control group participants was the highest in the single Japanese CVD primary prevention trial (1.25 events per 1,000 person-years), among all of the CVD primary prevention trials, based on our method of estimating control group rates. This estimate, however, represents only seven events and therefore is not stable. Participants in the trial had a high prevalence of several risk factors for intracranial hemorrhage (mean age of 64.5 years, >50% with hypertension, and >50% current or former smokers). Because of this, the independent role of race/ethnicity cannot be determined with the available data.

Diabetes Mellitus

Four CVD primary prevention trials[51,57,64,70] and one cohort study[86] limited their study populations to those with diabetes mellitus. One primary prevention trial[61] and one cohort study[85] included a broader population and reported harms results in the subpopulation of those with diabetes mellitus.

Based on limited data (due to low study event rates and use of different bleeding outcomes), many trials limited to populations with diabetes could not be used to estimate absolute bleeding risks in patients with diabetes, with or without ASA use. Relative upper GI bleeding risks (number of events or per person), however, were increased about three-fold in ASA users with diabetes compared to nonusers with diabetes in one of the two trials reporting this outcome,[70] but not the other.[57] In one CVD primary prevention trial that reported subgroup effects among the population with diabetes, nonfatal GI bleeding events over 3.7 years tended to be exaggerated with ASA use (7 times greater in diabetic ASA users vs. nonusers compared to 4 times greater in the whole population of ASA users vs. nonusers), although event rates were too sparse to allow for robust statistical comparisons.[61]

One IPD meta-analysis by the ATT Collaboration of six CVD primary prevention studies found no apparent modification of ASA's effect on major extracranial bleeding by prior diabetes status, although less than 10 percent of the population had prior diabetes diagnoses, which limits the statistical power. In adjusted analyses, diabetes mellitus increased major extracranial bleeding by 55 percent (95% CI, 13% to 214%) after adjusting for ASA use, and also tended toward increased hemorrhagic stroke risk, but these estimates were more imprecise (74% [95% CI, -5% to 317%]) due to small numbers of events (**Table 15**).[87]

Absolute bleeding risks among persons with diabetes could be estimated in two cohort studies.[85,86] Among never-users of ASA from the large Italian cohort, unadjusted incidence rates for hospitalization for major bleeding events were 5.35 (95% CI, 4.97 to 5.76) per 1,000 person-years in patients with diabetes compared to 3.32 (95% CI, 3.20 to 3.45) in those without diabetes (IRR, 1.61 [95% CI, 1.49 to 1.75]).[85] In contrast, among current low-dose ASA users, incidence rates for hospitalization for major bleeding events were high, but were similar between those with and without diabetes (5.83 and 5.53 per 1,000 person-years, respectively). The IRRs indicated a very similar increase in bleeding risk (61% to 66%) from having diabetes (vs. not) in those not taking ASA, and from taking ASA (vs. not) in those without diabetes (IRR, 1.61 to 1.66). These data would indicate that baseline risk of bleeding among persons with diabetes is elevated, but there may be little excess risk associated with ASA use. Diabetes status itself could be associated with other bleeding risks. In an analysis adjusted for multiple other baseline risk factors and ASA use, diabetes status alone was still associated with increased rates of hospitalization for major bleeding events, but more modestly (36% increase [95% CI, 28% to 44%]). Among 18,646 Swedish patients with diabetes known to be free of CVD, absolute bleeding events for all fatal and nonfatal hemorrhages (cerebral or gastric) were 2.4 per 1,000 person-years.[86] Adjusted HRs showed a trend toward further increased risk in those taking low-dose ASA (1.41 [95% CI, 0.99 to 1.99]), which indicates an approximate rate of 1.7 events per 1,000 person-years for fatal/nonfatal hemorrhages in nonASA users. Events were too rare (157 total hemorrhages) to subdivide further with much precision. This cohort study is further limited in estimating benefits or harms, since each individual was censored after incidence of their first outcome, regardless of type.

In summary, adjusted analyses from IPD meta-analysis of primary prevention trials and a very large cohort study indicate an increased risk of major bleeding in persons with diabetes (36% to 55%); data were mixed as to whether low-dose ASA further increased bleeding risk, and further research would be informative.

Other Bleeding Risk Factors

Although not part of our a priori subgroups, we evaluated other major risk factors for CVD besides age, sex, and diabetes post hoc as potential risk factors for bleeding-associated harms, since an IPD meta-analysis by the ATT Collaboration of six CVD primary prevention trials found that risk factors for CVD outcomes (i.e., current smoking, hypertension) that would increase absolute benefits from ASA use were also associated with increased bleeding risks.[87] We also considered whether overall CVD risk or indication (primary vs. secondary CVD prevention) was associated with bleeding risks.

Smoking

No data on current smoking and bleeding risk was reported in any included CVD primary prevention trial. Two cohort studies with relatively imprecise ASA exposure data reported no effect modification on GI bleeding risk by smoking status in women or men.[83,84] Current smoking more than doubled hemorrhagic stroke rates (with a more modest 56% increased rate of major extracranial bleeding risk) in an IPD meta-analysis by the ATT Collaboration after adjusting for other risks and ASA use (**Table 15**).[87]

Hypertension

One CVD primary prevention trial[67] and one cohort study[85] considered whether hypertension status affected bleeding risks with ASA. Patients with hypertension were judged to be at medium (15% to 20%) or high (≥20%) 10-year risk of cardiovascular death, nonfatal stroke, or nonfatal MI. Major fatal and nonfatal bleeding events (204 events total) per 1,000 person-years were somewhat higher in the high CVD risk group taking placebo compared to the medium CVD risk group (3.0 vs. 1.4 events per 1,000 person-years, respectively), although treatment-subgroup interactions were not significant. With ASA use, both groups experienced an absolute risk increase of 1.3 to 1.5 events per 1,000 person-years.

In the analyses conducted by the ATT Collaboration of IPD adjusting for other risks and ASA use, increases in mean blood pressure (per 20 mm Hg) more than doubled hemorrhagic stroke rates (with a more modest 32% increased rate of major extracranial bleeding) (**Table 15**).[87]

In an Italian cohort study,[85] absolute unadjusted rates of hospitalization for major bleeding events among never-users of ASA with hypertension were 4.23 (95% CI, 4.06 to 4.40) per 1,000 person-years compared to 2.74 (95% CI, 2.59 to 2.90) in never-users without hypertension (IRR, 1.54). In contrast, among current low-dose ASA users, incidence rates for hospitalization for major bleeding events were high, but quite similar between those with and without hypertension (5.69 and 5.42 per 1,000 person-years, respectively). Unlike in patients with diabetes, bleeding risks increased with ASA use in both those with and without hypertension (34% and 98%, respectively). In an analysis adjusted for multiple other baseline risk factors, hypertension status was associated with a more modest (14%) greater IRR for major bleeding events.

CVD Risk Categories

Few CVD primary prevention trials reported baseline CVD risk categories[60,67,69] and only one reported bleeding risk by CVD risk status. This trial found increased event rates, but no treatment-subgroup interaction among patients with well-managed hypertension at medium or high CVD risk.[67]

Primary Versus Secondary Prevention

Among all 30 trials of ASA for any primary or secondary prevention use included in our review, 15 reported major GI bleeding events after 1 to 10 years of followup. In study-level meta-analyses stratified by population (CVD primary prevention, CVD secondary prevention, and CRC/adenoma prevention), RR estimates associated with ASA use appeared higher (after excluding ASA doses >300 mg), although the 95% CI overlapped and the p-value for interaction was not significant. Event rates were relatively low across all arms (0.27% to 0.64%), with much fewer participants and, therefore, fewer absolute events in the CVD secondary prevention trials. Our findings were consistent, but weaker, for intracranial hemorrhage due to even fewer events. Restricting to dosages of 100 mg or less, however, removed much of the distinction by population. A separate IPD meta-analysis by the ATT Collaboration was suggestive of increased risk of major extracranial bleeding in secondary prevention trials compared to primary prevention (rate ratio, 2.69 [95% CI, 1.25 to 5.70] and 1.54 [95% CI, 1.30 to 1.82], respectively), but were too sparsely reported (only five of 16 secondary prevention trials reporting a total of 30

events compared to 570 in primary prevention trials) to confirm whether these bleeding risks varied between these populations.[87] A large population-based cohort study[85] did not examine CVD risk, per se, but did find that a history of previous hospitalization for CVD problems (a weak surrogate for a secondary prevention population) significantly increased hospitalization for major bleeding events in ASA nonusers compared to either those without such a history or to all nonusers; multivariate analyses confirmed an independent increase in rates of major bleeding event hospitalization in those with prior CVD hospitalization (IRR, 1.29 [95% CI, 1.10 to 1.51]). Altogether, these data do not clearly confirm or exclude a higher bleeding risk with ASA use for those with selected cardiovascular risk factors or in CVD secondary prevention populations in general.

Previous Ulcer or GI Bleeding History

One good-quality cohort study reported the impact of previous hospitalization for GI problems among never-users and current low-dose ASA users.[85] Less than 1 percent of individuals had this history overall, with prior GI-related hospitalizations less common among current low-dose ASA users (0.67%) than among never-users (1.13%). Among never-users, unadjusted incidence rates for hospitalization for major bleeding events among those with a GI-hospitalization history were 12.00 events (95% CI, 10.03 to 14.44) per 1,000 person-years. Among low-dose ASA users with a GI-hospitalization history, unadjusted incidence rates were 14.00 events (95% CI, 10.70 to 18.24) per 1,000 person-years and not significantly higher than never-users (IRR, 1.16 [95% CI, 0.84 to 1.60]). After adjusting for other risk factors, including ASA use, previous hospitalization for GI problems had the largest impact on increased incidence rates for hospitalization for major bleeding events with an IRR of 2.87 (95% CI, 2.46 to 3.35), suggesting a relative contraindication for ASA use among these individuals (**Table 15**).

Concomitant Medication Use

We specified a priori examination of the concurrent use of SSRIs and nonASA NSAIDs since these are likely in CVD primary prevention populations. None of the CVD primary prevention trials reported bleeding results considering comedication usage; many trials excluded those who were using or might use medications associated with increased bleeding risks, although few specifically excluded nonASA NSAIDs or SSRIs. Among the 10 CVD primary prevention trials, six reported baseline medication usage;[57,60,61,66,70] these focused mainly on diabetes, hypertension, or lipid-lowering medications and none reported on SSRIs or nonASA NSAIDs. One additional CVD primary prevention study,[51] five CVD secondary prevention trials,[54,59,65,71,75] and no adenoma prevention trials reported baseline medication usage. Three CVD secondary prevention trials from the 1980s or early 1990s reported that 6 to 15 percent of participants had regular, weekly, or daily ASA use at baseline.[65,71,75]

Among the included cohort studies, one included many participants taking comedications, including NSAIDs (35%), SSRIs (5%), antihypertensives (57%), oral anticoagulants (7%), systemic corticosteroids (9%), statins (25%), and proton pump inhibitors (PPIs) (46%).[85] This good-quality cohort study reported the impact of NSAIDs, SSRIs, and other medications on bleeding risk in current users and never-users of low-dose ASA. Among never-users, those who used SSRIs had significantly increased unadjusted incidence rates for hospitalization for major

bleeding events (4.09 events [95% CI, 3.90 to 4.28] per 1,000 person-years) compared to those who did not use SSRIs (3.61 events [95% CI, 3.49 to 3.73] per 1,000 person-years), but not those using NSAIDs or ASA as an analgesic compared to those not using those medications. Unadjusted absolute incidence rates of hospitalization for major bleeding events in ASA users did not appear to be modified by baseline NSAID use, although SSRI and low-dose ASA users had no increased risk above SSRI users alone. In this data set, the use of ASA as an analgesic (along with low-dose ASA) suggested a very high, but imprecisely estimated, risk for major bleeding hospitalization events (11.40 events [95% CI, 5.45 to 24.00] per 1,000 person-years). In multivariable adjusted analyses including ASA use and other risk factors, NSAID use independently increased major bleeding risk (adjusted IRR, 1.10 [95% CI, 1.05 to 1.16]) (**Table 15**); several other comedications also did so, and more strongly (e.g., anticoagulants and antiplatelets). These data suggest that the major bleeding event risks are mildly increased when NSAID use is combined with low-dose ASA. SSRIs do not appear to have a strong additional effect, and other comedication use could be of greater concern. Adjusted analyses suggested a protective effect of statins (IRR, 0.67 [95% CI, 0.62 to 0.71]) and PPIs (IRR, 0.84 [95% CI 0.80 to 0.88]). These results would be important to replicate.

Two cohort studies that could not be used to estimate absolute bleeding risks due to incomplete information on exposure evaluated whether there was effect modification by concurrent medication use in those who reported taking two or more 325-mg ASA tablets per week over the prior 2 years.[83,84] Neither study found a significant interaction between NSAID use and increased risk of major GI bleeding with ASA use ($p \geq 0.50$),[83,84] although imprecise exposure data could also affect these analyses.

KQ 6b. Does the Effect of Aspirin Vary by Delivery of Intervention (e.g., Dose, Frequency, Duration, Formulation, and Recency of Use)?

Although the body of literature evaluating ASA benefits and harms varies considerably in terms of ASA regimens assessed, most of the evidence to assess differences is indirect and subject to confounding by other between-study differences. One of the included trials purposefully evaluated variations in dosage,[65] but none did so for frequency, duration, or formulation of low-dose ASA within their study designs. Cohort studies either restricted to a single low-dose,[86] did not evaluate dosage effects within the included range of low-dose ASA,[85] or could not provide precise dosage-related risk estimates due to exposure measurement issues.[83,84] These studies, however, may address qualitative trends or effect modification within strata of ASA use.[83,84]

An IPD meta-analysis by Rothwell and colleagues (2012) did not primarily look at issues of intervention delivery, often restricting studies to reduce variability in intervention characteristics.[10] One study-level meta-analysis of CVD primary prevention trials found that risks of nontrivial bleeding varied significantly by period of publication, with increased risks reported in earlier publications (before 2000), studies with fewer events (<500 total), and in regimens of daily versus alternate day ASA use, although frequency comparisons represent between-study rather than within-study differences.[44] Any apparent differences between studies

should be viewed cautiously due to potential confounding by other between-study differences (i.e., methodological as well as clinical heterogeneity).

Dose

Only one trial varied ASA dosage and found that there was more GI bleeding in 1,200 mg users (11 events per 1,000 person-years) than in 300 mg users (7 events per 1,000 person-years) or those taking placebo (3 events per 1,000 person-years).[65] In cohort data, major GI bleeding risks adjusted for age were increased (RR, 1.56 [95% CI, 1.41 to 1.73]) in women with regular ASA use (defined as two or more 325-mg tablets each week for the prior 2 years) compared to nonregular ASA users.[84] After adjusting for duration of use, women taking the highest cumulative ASA dosage (>14 tablets per week) had more than twice the risk of major GI bleeding than nonASA users (RR, 2.24 [95% CI, 1.66 to 3.03]). Similarly, higher daily dosages of ASA use in men (325 vs. 81 mg) tended to be associated with higher rates of GI bleeding (3.5 vs. 2.7 events per 1,000 person-years, respectively), although multivariable adjusted RRs compared to nonASA users were not statistically significantly different between the two dosages (1.67 [95% CI, 1.20 to 2.33] vs. 1.17 [95% CI, 0.89 to 1.53]), perhaps due to limited event rates (146 events in ASA users and 139 events in nonusers).[83] In both of these cohorts, trend analyses strongly supported the impact of increasing cumulative weekly dosage within both short- and long-term regular ASA users, for lower as well as upper GI bleeding. This was particularly true in women[83,84] and for subarachnoid hemorrhages in men age 55 years and older.[94] In contrast, a study-level meta-analysis of CVD primary prevention trials reported no difference in harmful effects between studies with 100 mg daily or more compared to lesser dosages; however, this study-level meta-regression did not control for other known study-level differences, including event rates, year of publication, and dosage frequency.[44] Thus, while the majority of evidence in our review supports dose-related bleeding risks with ASA use, there may be fewer differences within the range of low-dose ASA usage commonly employed in primary prevention.

Frequency

All CVD primary prevention trials evaluated daily ASA use, except two trials that evaluated 100 mg ASA every other day in women[60] and 325 mg ASA every other day in men.[73] However, apparent differences from other trials employing daily use could be confounded by other between-study differences, such as baseline rates of bleeding. When considered together in study-level meta-analysis, trials employing every other day ASA use had lower elevations in nontrivial bleeding risk (OR, 1.16 [95% CI, 1.05 to 1.29]) compared to trials in daily users (OR, 1.48 [95% CI, 1.17 to 1.86]; p=0.002 for interaction).[44] These analyses, however, do not control for other between-study differences (baseline event rates, period of publication). In cohort studies, most bleeding cases in recent years in the Health Professional Study (2000 to 2008) were in those with daily use (106 of 146 participants), as opposed to less than daily use.[83] In the Nurse's Health Study, there was a significant trend for GI bleeding with greater number of ASA tablets per week.[84]

Duration

Bleeding risks associated with low-dose ASA use are apparent early on and likely persist throughout usage. In WHS, cumulative incidence of GI bleeding appeared to increase in those allocated to 100 mg of ASA every other day compared to those taking placebo throughout the median 10.1 years of followup.[88] Other data has suggested bleeding risk may be most pronounced early on.

Stratified meta-analysis of major extracranial bleeding in an IPD meta-analysis by Rothwell and colleagues (2012) of six CVD primary prevention trials suggested greater risk at 0 to 2.9 years versus 3 years or later (OR, 1.95 [95% CI, 1.47 to 2.59] vs. 1.04 [95% CI, 0.73 to 1.49]; p=0.006), with a significant interaction between time as a continuous variable and major extracranial bleeding (p=0.003), without major heterogeneity in absolute annual risks.[10] Risks decreased over time in the placebo group from 41 to 35 events per 10,000 person-years, suggesting something other than a diminution of ASA effect; this effect most likely represents reduced time at risk due to unequal followup in the 3 year or later time period compared to the up to 3 year time period in three of six trials (i.e., total mean/median years of followup: 3.6 years in PPP, 3.8 years in HOT, and 4.4 years in JPAD). We were unable to evaluate time-to-event data in our study-level meta-analysis.

Limited cohort data address whether the magnitude effect is the same throughout the periods of active ASA usage, also considering the degree of persistence. Among daily users (>6 days per week or six to 14 full-dose [325 mg] tablets per week), relative GI bleeding risks were similarly increased among those taking ASA for less than or greater than 5 years.[83] Among regular users (two or more 325-mg ASA tablets per week), duration of ASA use for greater than 5 years did not alter the impact of increasing dosage on bleeding risk.[84] Thus, limited but consistent data suggests bleeding risks appear to be maintained, not increased, but also not diminished with long-term use.

Formulation

None of our included studies varied ASA formulations experimentally, although some allowed formulation changes as needed for individuals as part of the protocol. Formulations varied somewhat across studies (regular, controlled release, enteric coated, soluble), but many studies did not report the formulation and studies differed in many other aspects. No IPD meta-analysis examined the impact of formulation on risk of harms or benefits.

Recency of Use

The only study with information on recency of use was the WHS trial,[88] but data were highly limited due to poor quality of ascertaining most posttrial harms and by high cross-over during the posttrial period. Nonetheless, data from this study suggest relatively rapid attenuation of increased GI bleeding and ulcer risks after cessation of ASA.

Chapter 4. Discussion

Summary of Evidence

This review focused on the impact of ASA use on all cancers combined because data were too sparse to allow estimates of cancer incidence or mortality for individual cancers (with the exception of CRC, which is covered in a separate report). A summary of the evidence for specific cancers taken from previous systematic reviews and meta-analyses addressing trials, cohort studies, and case-control studies is provided in **Appendix G**. Ongoing research will be important in further delineating specific cancer effects.

Similarly, our interpretation of the evidence is primarily based in the context of determining any additional benefit on cancer incidence or mortality in those taking ASA for CVD primary prevention. We did not focus on additional cancer benefits in those taking ASA for CVD secondary prevention since that use is outside the usual scope of the USPSTF and is firmly recommended, even without considering potential additional beneficial outcomes.

We attempted to examine a coherent body of evidence to determine additional all cancer incidence and mortality effects in those taking ASA for CVD primary prevention, as well as considering the most applicable evidence for estimating all-cause mortality and ASA-related bleeding harms. The available bodies of evidence for each of the important outcomes in this review varied considerably in the populations, dosages, and durations of treatment they represent. There was further variation in definitions of important outcomes. Primarily due to the differing timeframe over which risks and benefits might be expected to occur (within the first year for bleeding risks to at least 5 and perhaps 10 to 20 years for many cancer effects), many previous analyses of cancer outcomes have relied on subsets of studies that offer longer-term followup. However, these also differ somewhat or substantially in terms of the populations and interventions they represent from the body of CVD primary prevention trials. Thus, due to the clinical application of interest for this review, our primary analyses were focused on the cancer impact as shown in the CVD primary prevention trials that form the basis for the current USPSTF systematic review,[41] with a further emphasis on very low-dose ASA (≤100 mg daily or every other day), in line with the USPSTF approach in 2009.[31] We conducted a series of sensitivity analyses within this set of studies as well as within the larger set of studies representing broader primary and secondary CVD prevention to compare and contrast our findings with those of other recent reports.

We first summarize our findings at the population level of the relative effects of ASA on cancer, all-cause mortality, and bleeding outcomes, which were the major harms demonstrated. We then consider the importance of baseline risk in moderating the absolute effect of ASA and explore appropriate baseline bleeding rate estimation and its modification by bleeding risk factors and ASA. Finally, we consider challenges and future directions in applying this evidence to individuals.

Aspirin Effects on Cancer Mortality

When focused on the 10 CVD primary prevention trials, our main analysis, we found nonsignificantly reduced mortality due to cancer (RR, 0.96 [95% CI, 0.87 to 1.06]). We found no difference when we stratified results by time period of followup (<5 vs. ≥5 years), although trials with longer-term followup tended to show a larger cancer mortality reduction (RR, 0.94) than those lasting less than 5 years (RR, 1.01). Sensitivity analyses (**Table 9**) excluding higher dosages above 100 mg had little effect on the point estimate for cancer mortality benefit (RR, 0.95), while excluding studies of every other day dosages increased the suggested benefit (RR, 0.93). When we combined all trials in our review (primary and secondary CVD prevention), the overall estimate changed little (RR, 0.93). These added studies, however, primarily had very short-term followup (<4 years) in which mortality effects from cancer prevention would be unlikely. By restricting to treatment durations of 4 years or greater and considering only trials utilizing daily ASA dosing only, we found a statistically significant cancer mortality benefit (RR, 0.83 [95% CI, 0.70 to 0.98]) among primary and secondary CVD prevention trials, close to that reported by Rothwell and colleagues.

Our findings differ from those reported in a study-level meta-analysis of eight trials; Rothwell and colleagues (2011) found a 21 percent statistically significant reduction (95% CI, 8% to 32%) in cancer mortality using a somewhat different set of included studies than our CVD primary prevention trials analysis.[8] These studies differed in that Rothwell and colleagues required daily ASA use for at least 4 years and included both secondary and primary CVD trial data. Working from our set of 10 CVD primary prevention trials, we could almost reproduce their results by eliminating large U.S. studies of alternate day ASA use (PHS, WHS),[60,73] restricting to trials with at least 4 years duration, and adding results from one secondary prevention trial (UK-TIA) (our analysis of this restricted set of studies produced an 18% statistically significant cancer mortality benefit compared to their estimate of 21%).[65] We believe our original analysis, which includes the alternate day studies, is preferable since alternate day low-dose ASA use is an important part of the evidence base estimating CVD primary prevention, and cancer impact by alternate day dosing is now known to be possible. WHS has recently demonstrated a reduction in CRC incidence with alternate day dosing and followup beyond 10 years.[88]

Data from seven of the eight trials summarized in a study-level meta-analysis by Rothwell and colleagues (2011) were further analyzed by the same group through an IPD meta-analysis.[8] Time-to-event data suggested an impact on cancer mortality primarily in deaths after 5 years. In analyses that included only a smaller set of three primary and secondary prevention trials with posttrial followup to 20 years, Rothwell and colleagues found a significant reduction (21% to 23%) in cancer mortality at 0 to 10 years as well as at 10 to 20 years in patients with at least 5 years of scheduled ASA treatment duration (n=10,502; 1,378 cancer deaths). However, these results may not be broadly applicable to a CVD primary prevention population taking low-dose ASA. These three trials (TPT, UK-TIA, BMD) primarily utilized higher dosages of ASA (300 to 1,200 mg daily) and almost exclusively represented men, 31 to 53 percent of whom were current smokers.[65,69,72] The applicability of these trials is important when considering ASA's effect on CRC mortality as well, since these trials represent three of the four studies demonstrating long-term CRC mortality benefits.[40] Whether these studies might separately represent an identifiable primary care population eligible and willing to take daily ASA for at least 5 years for cancer prevention is not clear, but this was not the main purpose of our review.

None of the main findings from our review suggested a statistically significant benefit for all-cancer mortality in primary and secondary CVD populations taking ASA, and others have concluded no protective role for ASA on cancer mortality in the CVD primary prevention population based on very similar analyses.[44] All of our pooled estimates were imprecise, with relatively wide CIs consistent with slight harm, no benefit, or substantial benefit, depending on the body of evidence summarized. Better precision could be gained through longer followup and time-to-event analyses among all available CVD primary prevention trials.

Aspirin Effects on All-Cause Mortality

All-cause mortality was significantly reduced (RR, 0.94 [95% CI, 0.88 to 0.99]) in the 10 CVD primary prevention trials and when all studies were retained in the analysis. These results, however, were somewhat sensitive to changes in which data were utilized (**Table 9**). For instance, when we substituted longer-term mortality effects at 17.5 years from WHS for 10-year data, point estimates for all-cause mortality moved closer to 1.0 and none of the sensitivity analyses were statistically significant. Also, we found no statistically significant effect in any of our sensitivity analyses when combining only trials most applicable to a CVD-cancer primary prevention application (i.e., very low-dose ASA [≤100 mg/day], likely sufficient for cancer as well as cardiovascular effects), although these results could reflect reduced power. In this analysis of studies most applicable to a CVD-cancer primary prevention application, currently available results are consistent with some benefit (6%), but we cannot rule out substantial benefit, no effect, or slight harm. When longer-term WHS data are substituted, all-cause mortality results are consistent with a lesser benefit, but we cannot rule out some benefit, no effect, or some harm.

When we combined primary and secondary prevention trials, all-cause mortality results showed a significant and consistent benefit (RR, 0.93 [95% CI, 0.89 to 0.98]), with no change when restricting to dosages of 100 mg or less (**Table 9**). Since these added studies mostly contributed very short-term followup (<4 years) and resulted in no significant impact on cancer mortality, the mechanism for mortality effects must be through CVD or other causes. This interpretation would be consistent with the IPD meta-analysis by the ATT Collaboration that showed an all-cause mortality benefit in secondary, but not primary, prevention trials.[87] This interpretation would also be consistent with a study-level meta-analysis by Rothwell and colleagues (2012) that found a reduction in nonvascular deaths (OR, 0.88 [95% CI, 0.78 to 0.98]), but not vascular deaths (OR, 0.99 [95% CI, 0.87 to 1.12]), when combining 12 trials of CVD primary prevention populations testing daily ASA of any dosage.[10]

Differences in observed or expected all-cause mortality effects between primary and secondary prevention populations likely reflect the relative impact of nonvascular deaths, since these have been reported to vary significantly in their relative contribution to all-cause mortality (representing only 10% to 20% of total deaths in high-dose ASA trials among those with existing CVD to up to 70% of deaths in those taking low-dose ASA for primary prevention). In the CVD primary prevention trials in our review, about two thirds of all deaths were attributed to nonvascular causes.[44] Nonvascular deaths, however, are not clearly due to cancers. Just 61 percent of nonvascular deaths in these CVD primary prevention trials were attributed to cancer,[44] which is quite consistent with the 58 percent of all nonvascular deaths attributed to cancer in 34 primary and secondary prevention trials.[10] Thus, approximately 20 to 25 percent of all deaths in

CVD primary prevention trials were due to nonvascular noncancer causes, and among all the mortality subtypes, nonvascular noncancer deaths tended to show the greatest mortality reduction from ASA use (OR, 0.90 [95% CI, 0.76 to 1.07]).[44]

We conclude that there would not be certain benefit on all-cause mortality in a CVD primary prevention population taking very low-dose ASA (≤100 mg daily) for both CVD and cancer prevention within 6 to 10 years of followup, although such a benefit was apparent in a secondary prevention population. Although a statistically significant beneficial effect on all-cause mortality was suggested in some of our meta-analyses of ASA use in CVD primary prevention trials, the 95% CI included a range of effects that may reflect imprecision or heterogeneity of effects among subpopulations. Lack of statistical heterogeneity in the pooled estimates does not completely eliminate this possibility, since these statistical tests are known to have low power. Given that a CVD primary prevention population may include persons with a range of risk factors or other diseases, it is unclear whether a uniform overall mortality effect across all subpopulations represented in a CVD primary prevention pool should be expected; nonvascular causes of death were prominent contributors to overall mortality in CVD primary prevention trials and aspirin appeared to most robustly reduce nonvascular noncancer deaths. Further research to clarify the types of deaths and their timing across various subpopulations within an overall population using ASA for CVD primary prevention would be extremely informative.

Aspirin Effects on Cancer Incidence

Fewer CVD primary prevention trials reported a cancer incidence outcome. Where reported, effects within 10 years were generally small (2% reduction) and not statistically significant, even when restricted to studies with daily dosing schedules and at least 4 years of scheduled treatment (**Table 9**). Among all of our study-level meta-analyses, only the analysis that included either primary or secondary CVD prevention populations assigned to daily ASA (75 to 500 mg) for at least 4 years showed a statistically significant reduction in cancer incidence after 4.2 to 8.2 years. Recent longer-term followup from a CVD primary prevention trial of every other day 100 mg ASA for 10 years in women (WHS) further supports a complex interaction of ASA dosage, frequency, and duration in cancer incidence effects overall, as well as for specific cancers.[88] In WHS, cumulative incidence of invasive CRC began to diverge between ASA allocated and unallocated arms at 10 years, with a substantial reduction in the hazards of invasive CRC over 17.5 median years of total followup (HR, 0.80 [95% CI, 0.67 to 0.97]). As in WHS, benefits for CRC and other cancers are likely delayed in some of the lower dosage ASA studies, for up to or even beyond 10 years. Thus, longer-term followup for many trials would be needed to confidently demonstrate (or exclude) cancer-specific and overall cancer effects. Given current limitations in available trial data, additional trial results may be necessary before definitive conclusions about the protective effects of ASA, the size and timing of the chemopreventive benefit, any dose-response relationships, and trends in subgroup analyses can be firmly established.

Aspirin Effects on Population Bleeding Risks by Site

We found relatively consistent RR increases for most types of serious bleeding events with low-dose ASA use in our review, which is consistent with other meta-analyses.[87] RR estimates were

similar for major extracranial bleeding and for hospitalizations for first major bleeding events (intracranial and extracranial), as seen in a large cohort study. We found no substantially different RRs for serious bleeding with ASA use when varying the sets of trials we included to represent broader populations. Our sensitivity analyses restricting to the lowest dosages found the same result, although these comparisons are not robust (**Table 11**). Our pooled estimates from trials suggested at least a 19 percent increase in hemorrhagic strokes with 100 mg low-dose ASA use per day (or less), although estimated effects were quite imprecise due to relatively rare events; CIs were consistent with a larger harm or modest benefit. Sensitivity analyses revealed variability, with larger point estimates of increased risk when including CVD secondary prevention trials. This analysis also revealed some sensitivity to ASA dosage, but all analyses were curtailed by very few events.

One IPD meta-analysis by the ATT Collaboration of six CVD primary prevention trials found a relative increase in the yearly event rates for hemorrhagic strokes (RR, 1.32 [95% CI, 1.00 to 1.75]).[87] One cohort study suggested intracranial bleeding were not as rare as seen in the clinical trials (one third of first hospitalizations for major bleeding events for intracranial bleeding and two thirds for extracranial bleeding). In this cohort study, the RRs for intracranial and extracranial serious bleeding events with low-dose ASA use were quite similar, suggesting an increased bleeding risk at either site of about 54 percent. Precise estimates for intracranial bleeding events are difficult to achieve given their relative rarity and reporting differences between studies (as to what type of bleeding among intracerebral, subdural, intracranial, or ischemic is counted). As reported elsewhere, in CVD primary and secondary prevention populations, ischemic strokes are more frequent than hemorrhagic strokes, although hemorrhagic strokes accounted for more of the fatal strokes.[87] This suggests that the hemorrhagic strokes caused by ASA could be more serious than the ischemic strokes prevented by ASA. As such, a better understanding of their impact remains important.

In summary, RR estimates for serious bleeding events were relatively consistent for GI bleeding, but these estimates were imprecise and more variable for hemorrhagic strokes/intracranial bleeding.

Although we focused on major bleeding events resulting in transfusion, hospitalization, or death, we found synthesized data from the same CVD primary prevention trials by others suggesting different RRs associated with ASA use for other bleeding outcomes. For nontrivial bleeding events, RRs were somewhat lower (OR, 1.31 [95% CI, 1.14 to 1.50]). In a single 10-year study of 100 mg of alternate day ASA use, the risk was greatly reduced (HR, 1.15 [95% CI, 1.07 to 1.24]).[88] However, these bleeding outcomes reflected (any) self-reported GI bleeding diagnosis by a doctor in primarily middle-aged healthy women taking very low-dose ASA (100 mg every other day).[88] Thus, the reasonably consistent RR associated with serious bleeding events is likely not appropriate for estimating all other types of bleeding.

Estimating Population and Subpopulation Effects of Aspirin on Bleeding, Cancer, and CVD Outcomes

In the absence of a large RCT examining all outcomes, the effect of ASA on different outcomes can be difficult to estimate without a model. This is particularly true in the absence of clear

information on how baseline risk for events might vary in the target population. The most obvious source for estimates for baseline event rates are control group rates from the CVD primary prevention trials. However, almost none of the trials reported time-to-event data, and trials varied from an average of 3.6 to 10.1 years of followup. Therefore, we simulated control group event rates for all important outcomes for each of the 10 CVD primary prevention trials (**Table 10**) and used RRs for each outcome from pooling the same trials to estimate absolute effects of ASA for those at low, median, or high baseline risk. These results provided a range of likely outcomes across individuals enrolled in the primary prevention trials. For some outcomes (e.g., bleeding), trial-based rates have been questioned for potentially underestimating risks in clinical practice since trials exclude many individuals at increased bleeding risk from participation. Cohort estimates of baseline bleeding rates may more accurately reflect expectations for use in community practice by addressing less selected populations. We found that estimates from community-dwelling individuals are relatively sparse, particularly for low-dose ASA use alone. Precise exposure data can be difficult to capture for a ubiquitous over-the-counter and prescription medication such as ASA. Further, data on ulcers were much more sparse, and some previous approaches have included ulcers and dyspepsia alongside bleeding in their estimates of upper GI complications (although bleeding alone was 80% of events).[95] To represent the harm associated with bleeding, we compared trial and cohort data to address the degree to which trial estimates of population bleeding rates for GI and intracranial bleeding would be likely to underestimate those that would be seen in community practice.

Variation in Estimated Population Rates of Baseline Bleeding Events Without Aspirin Use Between Trials and Cohort Studies

Baseline Population Bleeding Rates From CVD Primary Prevention Trials

Although very few trials originally reported time-to-event analyses, time-to-event outcomes were available from the ATT Collaboration meta-analyses using IPD from six of the CVD primary prevention trials.[87] Combining these trials, major extracranial bleeding rates (mainly GI) in those not taking ASA averaged 0.07 percent per year (0.7 events per 1,000 person-years), but control group rates in individual trials suggested a considerable range. In the only two trials with at least 100 events (for reasonably stable estimates), baseline serious extracranial bleeding rates ranged four-fold, from 0.4 per 1,000 in low-risk middle-aged female health professionals[60] to 1.8 per 1,000 in older adults with hypertension.[67] We found a similarly broad range (2- to 4-fold differences in baseline extracranial bleeding risk) between trials when applying our person-years approximation method to the larger set of 10 CVD primary prevention trials. Control group bleeding estimates also tended to be higher in trials not restricted to CVD primary prevention populations. In mixed CVD primary and secondary prevention trials, the pooled control group rate of major extracranial bleeding events tended to be higher than in primary prevention trials (0.3% per year or 3 events per 1,000 person-years). Similarly, a meta-analysis of 24 mostly CVD secondary prevention trials, 1.4 percent of the overall placebo control group experienced GI hemorrhage of any severity over an average of 28 months (approximately 6 events per 1,000 person-years).[96] Thus, there was a fair amount of variation exhibited in baseline bleeding rates, even among trials with selective participant enrollment.

Baseline Population Bleeding Rates From Cohort Studies

Among the included cohort studies, rates of hospitalization for first major bleeding event (GI or intracranial) were estimated at 3.6 events per 1,000 person-years among never-users of low-dose ASA (≤300 mg), but showed considerable variability among subgroups (**Table 14**). The highest rates were almost four-fold higher (12.0 events per 1,000 person-years) and seen in those with prior GI hospitalizations. Although these absolute rates were crude and may reflect other bleeding risk factors, they illustrate a broad array of baseline bleeding rates. These rates also combine major cerebral as well as extracerebral bleeding events, limiting direct comparisons with estimates from trials. Since about two thirds of first bleeding events were GI bleeding, however, we calculated that cohort data suggest roughly 2.4 major GI bleeding events per 1,000 person-years in contrast to 0.7 events per 1,000 person-years from CVD primary prevention trials. Although intracranial bleeding was so rare that variation across trials couldn't be examined, control group rate estimates were again four- to five-fold higher when our calculated rate from cohort data (1.2 major intracranial bleeding events per 1,000 person-years) was compared to estimates from CVD primary prevention trials (0.27 events per 1,000 person-years).[87]

In an earlier systematic review of 12 population-based studies, the incidence rates of serious upper GI complications (bleeding, perforation, death, hospitalization, or visit to a specialist) were estimated at 1 case per 1,000 person-years based on relatively short-term observational studies in nonusers of prescription NSAIDs.[95] Incidence rates were shown to vary considerably by age and, to a lesser extent, sex.[95] Many others have used this review's incidence rate of 1 case per 1,000 person-years for estimating baseline serious upper GI complications, and assumed one to two excess cases of upper GI complications per 1,000 person-years of low-dose ASA use based on applying a range of RRs for bleeding with ASA use from observational studies[97] to this estimate. In a later publication, however, these same authors pointed out that this baseline bleeding rate assumption primarily represents a relatively low-risk group (men age <60 years or women age <70 years, all with no prior history of GI pain, ulcer, or concurrent use of NSAIDs) and would underrepresent excess cases if applied to others.[98]

Simulated Ranges for Population Event Rates

Table 10 represents events prevented and caused for those at low, medium, or high baseline risk for each major outcome, as represented by the lowest, median, and highest simulated control group event rates for that outcome seen in the CVD primary prevention trials. The events that were prevented were modest for cancer incidence or mortality for all levels of baseline event rates represented in these trials (and based on nonstatistically significant results from meta-analyses). Relatively larger numbers of nonfatal MI events would be prevented in those with medium or high baseline event rates compared to those with lower baseline event rates, as would also be true for major CVD events (which incorporates total MI, total stroke, and CVD mortality). However, for those represented by the medium cardiovascular event rate as well as the highest trial-based bleeding event rate, estimated increases in major bleeding events would be similar or greater than major CVD events or nonfatal MIs prevented. If higher baseline bleeding event rates, as suggested by cohort studies, are substituted, major bleeding events caused (GI bleeding plus intracranial hemorrhage, including hemorrhagic stroke) could exceed or come

close to matching cardiovascular events prevented, even for those with medium or high baseline cardiovascular event rates.

From these exercises, it is clear that crude simulations are unable to capture individual variability in baseline risks across multiple outcomes. It is also clear that baseline risk estimates for cardiovascular events, as well as for bleeding with and without ASA use, are very important in determining subpopulation and/or individual net benefit from low-dose ASA use. It is also clear that data to estimate extracranial bleeding rates are more robust than for intracranial bleeding, and that not all considerations of net benefit have therefore included these effects. Finally, cohort data suggest higher baseline bleeding rates than the median rates suggested by trials and are likely more applicable. The highest baseline rate of bleeding from trials just equals the previously derived baseline rate (i.e., 1 event per 1,000 person-years), which applies to middle-aged adults without significant risks. Substituting a somewhat higher baseline rate derived from cohort data (1.4 to 2.0 GI bleeding events per 1,000 person-years) still results in relatively low numbers of excess cases, well within the 1 to 2 excess cases projected elsewhere to apply only to a relatively low-risk population.[98] As we will next explore, however, excess cases estimates, at least for GI bleeding, can be projected to be much more variable than this based on known risk factors.

Estimating Bleeding Risks With Aspirin Use Among Subgroups

It has been clear for some time that age and sex are major factors in determining differences in bleeding risks associated with ASA use. The previous USPSTF recommendation carefully considered variations in bleeding risks with ASA use by age and sex. Increased bleeding risk due to ASA use can have a greater absolute impact when baseline factors (such as age or previous medical history) that increase bleeding risk are present, or if such patient factors enhance the harms of low-dose ASA use. Almost 20 years ago, Hallas and colleagues pointed out the importance of cohort data for estimating "excess risks" associated with ASA and other NSAID use.[93] Excess risk distinguishes between increased bleeding due to baseline factors (such as age or previous medical history) and bleeding attributable to low-dose ASA use alone. The excess risk for bleeding represents the absolute difference in bleeding incidence between users and nonusers of low-dose ASA who are otherwise similar. Some individuals may have such high baseline bleeding risks that ASA use may not be advisable. In some cases, factors that increase baseline bleeding risk (particularly when due to other medication use) may interact with ASA use, potentially modifying the relative effect of ASA. To address these related but separate issues, we have tried to distinguish between subgroups with greater ASA bleeding risks that are due to differing baseline bleeding risks from subgroup findings that represent potential effect modification (i.e., different RR for a bleeding outcome). While available data do not always support these distinctions, they may be conceptually important in projecting net impact.

Baseline Bleeding Rate Variation by Age and Sex

Age conferred strong, independent risk for extracranial bleeding in the IPD meta-analysis (adjusted RR, 2.15 [95% CI, 1.93 to 2.39 per decade]) as well as for intracranial bleeding (adjusted RR, 1.59 [95% CI, 1.33 to 1.90 per decade]).[87] Rates of hospitalizations for major bleeding events in never-users of ASA varied with other factors, but particularly with increasing age. Very low rates were seen in those younger than age 50 years and increased with age.[85]

These cohort data suggested a similarly increased relative rate of hospitalization for major bleeding events for each subsequent decade after age 50 years. Trial and cohort data reviewed here and elsewhere[95] support about a doubling of the RR of upper GI bleeding or complications for men compared to women, with a somewhat attenuated effect or no sex difference in intracranial bleeding.

Changes in RR of ASA-Induced Bleeding by Age and Sex

While it is widely recognized that bleeding risks vary among individuals, based on factors such as age and sex, available data did not suggest effect modification for the increased risk of bleeding with low-dose ASA use by sex. Cohort data showed a trend for the RR of bleeding with ASA use to be higher in ages younger than 60 years, reflecting the relatively greater impact of ASA on bleeding in the context of very low baseline bleeding rates in those younger than age 60 years. Nonetheless, absolute bleeding events were quite low in those younger than age 60 years compared to older ages (**Table 14**).

Baseline Bleeding Rate Variation by Previous GI Bleeding or Ulcers

Previous GI bleeding history was often an exclusion criterion in trials, along with history (or current diagnosis of) peptic ulcers. In one large cohort study in our review, the highest rates of major bleeding events occurred in those with or without a history of GI hospitalization with ASA.[85] After adjusting for bleeding risk factors, including ASA use, previous GI hospitalization increased the relative incidence rate of hospitalizations for major bleeding more than any other factor (IRR, 2.87). A previous review of cohort data suggested that history of GI pain/dyspepsia, uncomplicated ulcer, or complicated ulcer increased baseline risk for upper GI complications by two-, six-, and 10-fold, respectively. Previous ulcers or GI bleeding may be considered as relative or absolute contraindications to ASA use for primary chemoprevention, particularly in the absence of other medications to modify associated GI risk.

Changes in RR of ASA-Induced Bleeding by Medical History of GI Bleeding or Ulcers

In one large cohort study in this review,[85] there was no significant difference in the RR of major bleeding events with ASA use between those with and without a history of previous hospitalization for GI issues (a weak proxy for ulcer/previous bleeding). A separate systematic review including ASA cotreatment comparisons also found limited data on GI bleeding or ulcer-related history, but found an approximately 50 percent higher risk of major GI bleeding in studies that did not exclude patients with a history of GI bleeding compared to those that did.[16] Studies in CVD secondary prevention populations have confirmed the greatly increased risk associated with ASA use in those with GI bleeding or ulcer history.[99,100]

Baseline Bleeding Rate Variation by Diabetes or Other CVD Risk Factors

In the 2009 IPD meta-analysis of six CVD primary prevention trials by the ATT Collaboration, authors noted that CVD risk factors were also associated with increased bleeding risk.[87] Control group rates of extracranial bleeding events (but not intracranial bleeding) were available for subgroups. Baseline bleeding rates tended to be at least three times higher in subgroups based upon prior diabetes, age older than 65 years, prior vascular disease, predicted 5-year cardiovascular risk greater than 10 percent, systolic blood pressure greater than 160 mm Hg, or

diastolic blood pressure greater than 90 mm Hg. Baseline rates appeared about doubled in subgroups defined by current smoking, male sex, or body mass index greater than 30 kg/m^2. Varying degrees of increased extracranial bleeding rates at baseline were suggested in all of subgroups examined, except cholesterol.[87] In adjusted analyses of IPD, increasing age (per decade), male sex, diabetes mellitus, current smoking, and mean blood pressure per 20 mm Hg were all independently associated with increased rate ratios for major extracranial bleeding (after also adjusting for ASA use). Increasing age, mean blood pressure, and current smoking were associated with increased rates of hemorrhagic stroke after adjusting for ASA use.

Changes in RR of ASA-Induced Bleeding by Diabetes or Other CVD Risk Factors

An increased risk of major bleeding in patients with diabetes at baseline was apparent in adjusted analyses from an IPD meta-analysis of primary prevention trials and a very large cohort trial. Data were mixed as to whether low-dose ASA further increased elevated bleeding risk above baseline. In one large cohort study, low-dose ASA significantly increased rates of hospitalization for bleeding in patients without diabetes, but did not increase them in those with diabetes above already elevated baseline levels. This resulted in a paradoxical reduction in RR associated with low-dose ASA use in patients with diabetes. In addition to increased risk of extracranial bleeding among patients with diabetes (rate ratio, 1.55 [95% CI, 1.13 to 2.14]), RR of hemorrhagic stroke also tended to be increased in an IPD meta-analysis by the ATT Collaboration[87] (rate ratio, 1.74 [95% CI, 0.95 to 3.17]) after controlling for other risk factors, including ASA use. Net benefit determination is complicated in this important subpopulation given the potential increase in baseline bleeding risks in patients with diabetes for all bleeding outcomes and uncertainty about ASA's relative bleeding effects.

Available data were too sparse to clearly confirm or exclude a higher bleeding risk with ASA use in trials with previous CVD events (secondary prevention) compared to trials examining primary prevention. Similarly, among primary prevention trials, while risk-based data were limited, they suggested no statistically significant difference in ASA bleeding effects by 5-year coronary heart disease (CHD) risk.[87] As will be discussed further, however, some uncertainty remains about whether those at increased CVD risk are also at increased bleeding risk (with or without ASA). Any relationship between increased CVD risk and increased bleeding risk could be critical in appropriately identifying individuals for primary prevention with low-dose ASA.

Baseline Bleeding Rate Variation by Concomitant Medication Use

Many recent studies outside this review have focused on the excess risks associated with ASA use in the context of other medications, particularly those commonly used with ASA in CVD secondary prevention populations, such as other antiplatelets or anticoagulants. This review focused on the impact of two commonly used medications—NSAIDs and SSRIs—that might be commonly used in a primary prevention population. Many of the studies we examined excluded users of NSAIDs and other medications associated with increased bleeding risks for reasons of safety. Those that included these patients rarely reported results stratified by medication use. In the large cohort study that compared low-dose ASA users to propensity-score matched never-users, a number of medications (NSAIDs, SSRIs, ASA as an analgesic, other antiplatelets, oral anticoagulants, systemic corticosteroids, PPIs, and statins) were examined. Baseline bleeding rates were increased in those taking SSRIs but not NSAIDs; however, combined use of SSRIs

with ASA was not associated with increased hospitalization rates for major bleeding events above ASA use alone. These unadjusted data suggested no effect or at least a moderation of bleeding risk with ASA use in those taking SSRIs; SSRI use was also not an independent predictor of major bleeding events in adjusted analyses.

Other data on SSRIs and ASA are mixed, but largely consistent with a relatively modest overall effect of SSRIs on major bleeding that can be largely accounted for when controlling for other risk factors. SSRIs were reported to substantially increase upper GI bleeding risk, particularly among adults age 80 years and older or those with previous upper GI bleeding; excess GI bleeding due to SSRI use was estimated at 3.1 events per 1,000 person-years of use, if the association was causal.[101] A separate nested case-control study in U.K. primary care also found that current users of SSRIs, as well as past users, experienced the same increased RR of upper GI bleeding (about 85%) that was no longer significant after adjustment for other risk factors.[102] Nonetheless, a national retrospective cohort study in Taiwan suggests ongoing caution when prescribing SSRIs, particularly in older adults and those with previous GI bleeding, since users of "high-affinity SSRIs" had a 38 percent higher risk of severe GI events (bleeding ulcers) compared to users of "low-affinity SSRIs." Analyses were adjusted for NSAIDs but not for ASA use.[103]

In cohort data in our review, combined ASA and NSAID users and ASA users alone both had similarly increased rates of hospitalization for major bleeding, with no effect modification. Use of NSAIDs retained a small (10%), but significant, impact on increased rates of bleeding hospitalizations in analyses adjusted for ASA use and other risk factors. Other studies have suggested more greatly increased GI bleeding risk with combined low-dose ASA and NSAID use. A recent nested case-control study from 2000 to 2007 found a doubling of the RR for upper GI bleeding in users of combined NSAIDs and low-dose ASA (75 to 300 mg) compared to age-sex-time period matched low-dose ASA users alone.[102] Similarly, after excluding individuals at risk of bleeding, an earlier population-based cohort study in Sweden confirmed that concurrent use of NSAIDs in low-dose ASA users more than doubled the incidence of first upper GI bleeding compared to users of 100 to 150 mg ASA and users of low-dose ASA alone.[104] Cohort data cannot control for other bleeding risk differences, and when consistent, confirm increased risks with cotreatments, but are less useful for precise estimates of additional risks. Taken as a whole, available data suggest that excess major bleeding events are likely with NSAIDs in combination with low-dose ASA, although magnitude of effects may vary between specific types and dosages.

Although relatively modest impacts were found for the primary medications we examined, the large cohort study did suggest interactive effects for other medications more typically used in CVD secondary prevention situations (i.e., antiplatelets, oral anticoagulants). Combined ASA and other antiplatelet users had significantly higher rates of hospitalization for major bleeding events than users of either agent alone, with a somewhat elevated IRR for ASA use (IRR, 1.85). Combined ASA and anticoagulant users had the highest absolute rates, but a reduced IRR for ASA use (IRR, 1.27), illustrating the complexity of these data. In adjusted analyses, both medications independently increased hospitalizations for major bleeding events.[85]

Results from the same large cohort study also suggested a possible protective role of statin use on crude baseline risk for hospitalization for major bleeding events with or without low-dose

ASA use. Statin users experienced reduced hospitalization for major bleeding events incidence rates (33%) after multivariable adjustment. These findings were consistent in unadjusted as well as adjusted analyses.[85] In contrast, a nested case-control study in a separate U.K. primary care population found that current statin use was associated with increased upper GI bleeding (70% to 95%) in both current and past users (over the last year) that was no longer present after adjusting for other risk factors.[102] These data illustrate the potential confounding that can cause spurious associations (protective or harmful) in observational studies. Although largely beyond the scope of our review, these findings are intriguing and suggest future important areas for research and review.

Summary

Due to lack of data, we cannot reach firm conclusions about subgroup effects and how subgroup factors such as disease or risk factor status might interact with ASA use and/or other subgroup factors, such as age and sex. Data are clearest for elevated baseline bleeding rates by age, with further relative increases in men, and no apparent effect modification for ASA use by age or sex. Data are also clear for those with a previous history of GI bleeding or complications. In other subgroups defined by CVD risk factors, very limited data suggest elevated extracranial bleeding rates among many CVD risk factor subgroups, with a smaller set of risk factors possibly increasing intracranial bleeding rates. Although many separate patient factors appeared to be associated with increased bleeding risks, few showed clear effect modification with ASA use. With the exception of select medications, RR with ASA use apparently decreased in some subgroups with elevated baseline bleeding risk, such as individuals with diabetes. However, all of these comparisons examined each subgroup separately and without adjustment for other risk factors; further, findings were not completely consistent between trial and cohort data and deserve replication. Assumptions of higher baseline bleeding rates without significant effect modifications with ASA use are conservative, in that this approach will not underestimate important absolute differences.

Given the importance of characterizing bleeding risk across a population that might be candidates for ASA as a primary preventive agent, and the variability and complexity of effects among subgroups, we sought evidence for clinical tools that might individualize bleeding risk more accurately. Clinical tools available to support robust bleeding risk assessment for ASA use in this context are greatly needed, but remain very limited.

Valid Risk Prediction Tools for Bleeding Risks With Aspirin Primary Prevention

We located no clearly validated risk prediction tools for bleeding risks associated with ASA for primary prevention of CVD or cancers. A single tool based on systematic review of risk estimations and event incidence for upper GI complications (primarily bleeding) and CHD risk with low-dose ASA use (through 2011) has been published and made available in the public domain.[105] This tool does not address bleeding issues in sites other than the upper GI tract. The tool presumes a baseline incidence rate for upper GI complications of 1 event per 1,000 person-years, which is modified within 10-year age groups in those age 50 years and older (RR of 1.8, 2.4, 4.5, and 9.2 among ages 50 to 59, 60 to 69, 70 to 79, and 80 years and older, respectively,);

other modifiers are male sex (RR, 2.1), past ulcer (RR, 5.9) or dyspepsia history (RR, 2.0), and use of certain medications (NSAIDs, warfarin, clopidogrel, and PPIs), some of which may be more common in secondary prevention. The baseline and relative risk estimates used in this tool can be compared to those from studies included in our systematic review (listed by source in **Tables 14** and **15**).

The tool uses a multiplicative model, assuming a constant two-fold increased risk associated with low-dose ASA use (≤325 mg) in all baseline risk groups, but that NSAID use is modified by the effect of certain other risk factors. When retrospectively applied to two groups of patients from a multicenter national registry (904 age- and sex-matched individuals on similar durations of long-term low-dose ASA with and without peptic ulcer GI bleeding), the calculator predicted a greater number of upper GI complication events per 10,000 persons years in low-dose ASA users who had developed peptic ulcer bleeding versus those who had not (286 vs. 228 events), but the 95% CI overlapped. The tool was not applied to individuals at risk, but in a case-control comparison, with more events predicted in the group who represented those with 100 percent rate of events versus the group with no events. Thus, much more information is needed as to how well this tool would work prospectively to assess bleeding risk among individuals considering low-dose ASA prophylaxis. In an earlier analysis, use of similar RR increases for age, male sex, ulcer history, and ASA use applied to the proportion of participants in each category within the control groups of three trials of NSAID use in osteoarthritis or rheumatoid arthritis predicted upper GI complications reasonably well (observed: 8.6, 14.5, and 9.1 events per 1,000 person-years, respectively; predicted: 7.0, 8.1, and 9.5 events per 1,000 person-years, respectively).[98] In this instance, the tool was based on predicting risks at a population level and not applied to individuals at risk. In the same paper, the authors estimated an average of 5 excess cases of upper GI complications per 1,000 person-years among current users (likely including secondary as well as primary prevention) based on the prevalence of male sex, GI complications or ulcer history, and NSAID use among users of ASA for cardioprotection in population-based databases from the United Kingdom and Spain. However, excess cases were projected to vary substantially among individuals with varying levels of increased upper GI complications risk based on age, sex, medical history, and NSAID use.[98] Thus, factoring in additional factors that could modify bleeding risk for individuals or subpopulations will be very important.

Of note, the published tool we found also encompasses CVD benefit—using the 10-year Framingham CHD sex-specific risk prediction equations considering age, diabetes, smoking, hypertension, total cholesterol, and low-density lipoprotein cholesterol—and further incorporates bleeding risk modification through usage of treatments (PPIs, *Heliobacter pylori* infection eradication). Modifications of predicted bleeding risks under various scenarios attempts to facilitate the management of ASA-associated bleeding risks as part of the overall balancing of individual benefits and risks in an individual clinical encounter. This presumes the willingness to use PPIs as part of a primary prevention strategy.

Targeting Appropriate ASA Use Without a Robust Clinical Tool

Estimating the likely impact of ASA use on bleeding events remains one of the most critical issues facing clinicians considering its use for primary prevention of CVD or cancers. Assessment of bleeding risk based on age and sex, and excluding those at increased risk due to medical history or NSAID use, was recognized by the USPSTF in 2009 as part of its

recommendation for individuals considering ASA as primary prevention. Recent comments have reflected the growing understanding of the complexity of balancing the risk-benefit profile for low-dose ASA for primary prevention, in populations or individuals.[106,107] Careful assessment of individual bleeding risk may be particularly challenging due to its possible association with many well-established cardiovascular risk factors, which have also been used to target those more likely to benefit from a cardiovascular perspective.[108] Previous attempts to consider net benefits may underestimate bleeding risks if based on trial rather than cohort data.[108] While benefits and risks of any treatment should be individualized to the extent possible, it is particularly important for ASA when used as a primary preventive agent, with potentially substantial side effects that may limit its recommended use or adherence once recommended.[16]

We attempted to clarify subgroup findings by distinguishing those that may primarily represent different baseline risks from those that represent potentially differential effects of low-dose ASA use. However, despite the call for this type of data more than 20 years ago, we found only a single cohort study and an IPD meta-analysis that reported data in this way. Ideally, these would have allowed us to consistently consider whether important patient factors increase baseline bleeding risk, moderate relative bleeding effects of ASA, or both. However, we lacked complete data across all potential risk factors. From our review, it is clear that subpopulations based on age and sex remain important for considering effects of ASA on bleeding, and that ASA's relative bleeding effects do not vary by these factors. However, other potentially important subgroups, including diabetes, hypertension, and smoking, have emerged for whom data are not so clear. Understanding whether and how overall CVD risk levels may vary in their bleeding risks, according to their combinations of various risk factors, and further considering the impact of other comedications (statins, NSAIDs, antiplatelets) seems important to inform potential widescale adoption of ASA for primary chemoprevention. **Tables 14** and **15** summarize data from our review across major risk factors and major bleeding outcomes.

How Does Increased CVD Risk in a Primary Prevention Population Relate to Bleeding Risk With Aspirin?

In adjusted analyses of IPD, increasing age (per decade), male sex, diabetes mellitus, current smoking, and mean blood pressure per 20 mm Hg were all independently associated with increased rate ratios for major extracranial bleeding and for probable ischemic stroke (after also adjusting for ASA use). The strongest single risk factor for extracranial bleeding was older age, in which risk doubled with each decade. These same risk factors were associated with major CVD outcomes, with some variability by outcome. Risk factors of smoking, hypertension, and older age were associated with both greater rates of MI and stroke (and other CVD outcomes) and with greater rates of hemorrhagic stroke and major extracranial bleeding.[87] Hypertension and current smoking were associated with doubling of hemorrhagic stroke bleeding rates, the highest RRs of any factors examined, with a somewhat smaller impact on extracranial bleeding.

When diabetes or CVD risk factors were examined using cohort data, increased baseline bleeding rates in ASA never-users were reported for those with diabetes and those taking antihypertension medications; data on smoking status or other CVD risk factors were not provided. Diabetes, and to a lesser extent, hypertension, remained significant independent predictors of increased rates of hospitalizations for major bleeding events after controlling for

other risk factors and for ASA use. For these two factors, the impact of ASA use on top of the increased baseline bleeding rate was uncertain, with similar absolute event rates and significantly reduced RRs of bleeding in those with either condition using ASA compared to no ASA.

If elevated bleeding risk is associated with elevated CVD risk factors, then it is plausible that elevated CVD risk levels at the same percentage threshold may not be equivalent, in terms of the expected net benefit, due to variable associated bleeding risks. For example, an increased CVD risk level largely based on older age, male sex, and current smoking may be particularly associated with elevated GI bleeding risks and possibly less net benefit with ASA prophylaxis than in those in whom elevated CVD risk levels are based on cholesterol, diabetes, and hypertension; even though the latter may increase hemorrhagic stroke risk, it is much rarer. More completely understanding the combined impact of some of these risk factors on the likelihood of harms as well as benefits is important.

How Does Other Medication Use in a Primary Prevention Population Relate to Bleeding Risk With Aspirin?

One approach to limiting bleeding risk associated with comedications would be to limit low-dose ASA use as a primary preventive agent to individuals not taking other medications that increase bleeding risks, as many trials have done. Estimated bleeding risks with low-dose ASA use were presumed to exclude those taking other NSAIDs in the 2009 USPSTF review. In practice, however, combined use of medications that increase bleeding risk may be an issue not just at initiation of ASA chemoprevention, but in its proposed long-term use to achieve preventive benefits, particularly for cancer. A large prospective nationwide study among Swedish low-dose ASA users who were confirmed to be at least 80 percent adherent to prescribed ASA (75 to 160 mg) for the year prior to observation had relatively low use of GI-risk-associated drugs at ASA treatment initiation (1% used oral steroids, 1% warfarin, 2% NSAIDs, 2% clopidogrel).[109] During 2.5 median years of observation, 28 percent received more than one prescription for an NSAID, while fewer were repeatedly prescribed clopidogrel (5%), warfarin (6%), or oral steroids (5%). Although there was no untreated control group, comparison with the lowest risk group (low-dose ASA users with continuous, high adherence PPI use) showed that addition of any GI-risk-associated drug (NSAIDs, clopidogrel, oral steroids, or warfarin) for longer than 3 months increased the risk of severe GI events (ulcers or bleeding) after adjustment for other bleeding risk factors (HR, 1.73 [95% CI, 1.60 to 1.86]). Another recent systematic review confirmed the benefit of PPI coadministration in low-dose ASA, but studies were focused on patients with a history of gastric bleeding or at risk due to using other medications, such as clopidogrel.[16] Although data on the potential effect of PPIs were available from the large cohort study we reviewed, we did not formally consider concurrent PPI use to mitigate bleeding risks associated with low-dose ASA for primary prevention. Such an approach would complicate a primary preventive regimen, and there is no evidence to confirm that coadministration of long-term PPIs with ASA would confer the same benefits without additional harms. Finally, in terms of considering comedication usage, the potential for moderation of bleeding as well as CVD risks with statin use creates an additional uncertainty.

Role of Aspirin Dosage, Duration, Frequency, and Recency of Use in Bleeding Risk

Data from our review addressing issues around ASA dosage, duration, frequency, or recency were limited. While the majority of evidence in our review supported dose-related increases in bleeding risks with ASA use, there may be fewer differences within the range of low-dose ASA usage commonly employed in primary prevention. Previous systematic reviews largely support these conclusions; however, the remaining uncertainties in the data would argue for using the lowest possible dosages and frequency of ASA possible to achieve prevention benefits.

A previous systematic review of eight trials (for secondary prevention) and three cohort studies examined within-study variation in dosages from 30 to 1,200 mg. In studies reporting within-study comparisons, results clearly indicated increased major or serious bleeding events with doses above 100 or 165 mg compared to lower within-study doses, without clear evidence of additional CVD benefit in higher dosages.[110] Similarly, based on meta-analysis of 31 trials of ASA, authors concluded risks of hemorrhage (minor, total, stroke, and especially GI) were lowest in those taking the smallest dose of ASA (equivalent to ≤81 mg per day) compared to those taking higher dosages (equivalent to 325 mg per day).[111] Earlier systematic reviews of epidemiologic studies confirmed dose-response relationships with upper GI complications across low- and high-dose ASA use; risk remained elevated with low-dose ASA use (≤325 mg per day compared to nonusers).[97] When users were limited to 75 to 325 mg per day, however, dose-response relationships with upper GI complications were less clear.[97,112] While another previous systematic review of 14 trials of 75 to 325 mg of ASA for primary or secondary CVD prevention found no significant effect by dosage above and below 162.5 mg on major GI bleeding, any major bleeding, or intracranial bleeding, the effect estimates were very imprecise due to small numbers, especially in higher-dose studies, and could have been confounded by other between-study differences.[113] Thus, although data are not completely consistent, we believe that dose-response relationships are likely with the range of low-dose ASA use for at least some bleeding outcomes or some individuals. Using the lowest possible doses to achieve prevention benefits is prudent. Similarly, while less frequent usage may be associated with reduced bleeding risks, there are no experimental comparisons and few robust cohort comparisons. If alternate day use is equally effective for desired benefits, it may also be a prudent approach.

Although others have suggested reduction in risk of GI bleeding with longer duration of low-dose ASA use, we conclude that limited, but consistent, data suggest bleeding risks appear to be maintained, but not diminished, with long-term use.[10] This conclusion is based on critical appraisal of included studies in the previous review, indirect data from long-term cohort studies, and recent longer-term direct data from WHS.

We found no data varying type of formulation within our review, but earlier studies have suggested no benefit, and perhaps harm, to substituting enteric or buffered ASA for plain ASA. One cohort and one case-control study have reported that enteric coating did not seem to modify the observed increased risk of hospitalization for upper GI bleeding with low-dose ASA use;[104,112] cohort data suggest GI symptoms are not different in low-dose ASA users taking buffered instead of plain low-dose ASA (80 to 100 mg).[114] These more recent data showing no impact of formulation somewhat contradict, but likely supplant the first landmark systematic

review of epidemiologic studies[97] that was not limited to lower ASA dosages and included some data reflecting nonASA NSAIDs.

Limited data within our review suggested a return to baseline bleeding rates sometime after discontinuation of low-dose ASA, which was also found in an earlier cohort study after the first year[104] and in a recent nested case-control study showing reduced upper GI bleeding risk within 2 to 26 weeks after low-dose ASA discontinuation in secondary prevention users.[99]

Persistence and Discontinuation of Aspirin

Available data suggest that, for cancer benefits with ASA use to accrue, use must be continued for at least 4 or 5 years. Data from trials showing cancer benefits had adherence rates of 64 to 90 percent at 4 to 5 years, as reported in a companion report;[40] even within the ongoing support structure of trials, rates of discontinuation or nonadherence to recommended treatment were common across trials as treatment duration approached 4 or 5 years.

While we found no data on community rates of discontinuation of ASA for primary CVD or cancer prevention, one study examined discontinuation for at least 90 days among new users of low-dose ASA (75 to 300 mg per day) for secondary prevention in the Health Improvement Network primary care database in the United Kingdom from 2000 to 2007.[115] During a mean followup of 9.8 months, 21.4 percent of patients discontinued ASA at a median time to discontinuation of 3.7 months. Less than 10 percent of new users continuously used PPIs during their low-dose ASA use. In those with data over the first year, 76 percent of PPI nonusers were continuing low-dose ASA at 12 months, while 80 percent of continuous PPI users were continuing. Only warfarin use increased the risk of discontinuation among a range of medications, although some other medications (i.e., statins) showed a protective effect, and none of the associations were controlled for other factors. In a separate cohort study[109] of Swedish adults age 40 years or older receiving low-dose ASA (75 to 162 mg) for any reason, among those developing a GI or ulcer event (1.2% over 2.5 median years of followup), subsequent adherence to low-dose ASA was altered in two thirds, with 22 percent of those with adverse events discontinuing and 42 percent reducing their adherence to recommended usage.

Limitations of the Review

Limited data were available to assess cancer-specific effects.[8,60] Among men and women, cancer mortality data were most promising for GI sites and for mortality from adenocarcinomas, regardless of site. Future data should provide more precision as to any site-specific effects, and add further specification to minimal duration of required ASA use, dosage effects, and timing of cancer effects. We did not examine the evidence supporting the effect of low-dose ASA on metastatic disease, since this application would be considered disease management within the USPSTF rubric. Nonetheless, others may view this evidence as providing support to the overall consideration of ASA use in cancer prevention, since the findings are consistent mortality effects in prevention studies.

ASA is one of the most extensively studied medications with a worldwide literature. Setting exclusion criteria was necessary to manage the review scope. We did not search EMBASE

formally, so we may have missed some international literature, although the primary trials are well known and we relied on IPD meta-analyses by others. We excluded case-control studies since prior research showed a much higher summary estimate of the relative effects of ASA on harms.[97] Similarly, we excluded uncontrolled studies of ASA-related harms, since population differences in bleeding risks have been suggested.[87] While we excluded nested case-control studies and other uncontrolled observational studies per protocol, to round out the available data, we covered some of these studies (with a focus on recent data or previous influential systematic reviews) in our discussion.

Through our inclusion/exclusion criteria and approach to the analyses, we attempted to focus our cancer, all-cause mortality, and harms results on those that would be expected in a CVD primary prevention population using appropriately low doses of ASA. We conducted series of sensitivity analyses to explore the impact of restrictions in ASA frequency or dosage. We conducted indirect comparisons between the CVD primary population and the larger set of included studies, as well as IPD meta-analysis by the ATT Collaboration and recent study-level meta-analyses by Seshasai and colleagues providing data that complemented our primary findings. While we tried to display tradeoffs, such as those between power and applicability and different conclusions based on different approaches to what would be considered relevant data, the breadth of previous work makes it likely that we have not captured all nuances. Likewise, the perspective of focusing only on the context of ASA in CVD primary prevention could be viewed by some as unnecessarily limiting, even in this context of informing a preventive services recommendation.

We did not consider moderation of GI bleeding risks through PPI use, as no studies have determined whether its combined use with low-dose ASA modifies the expected CVD benefits. Importantly, there may be potential long-term risks that would need to be clarified, including possible effects on bone mineral density, increased infections, nutritional deficiencies, and increased gastric/colon cancer risks, as well as potential drug-drug interactions; these would require clarification before its administration as a primary preventive agent to those without disease.[116] Finally, the primary data for ASA effects on a range of health outcomes has not changed substantially over the last several years, but the field is poised to provide additional data in the near future. For example, two large trials in patients with diabetes are in progress (**Appendix H**) to address the issue of ASA use for primary prevention in those with diabetes: A Study of Cardiovascular Events in Diabetes (ASCEND)[117] and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D).[118] The ongoing ASPREE trial has recruited 19,000 adults age 70 years or older and randomized to ASA 100 mg daily versus placebo with a primary outcome of all-cause mortality, dementia incidence, or physical disability.[53] Other in-process ASA prevention trials may further clarify overall and subpopulation-specific all-cause mortality effects.

Future Research Needs

- *Bleeding risk assessment tools*: Development of an externally validated bleeding risk tool informed by real-world events (i.e., population registries accounting for prescription and nonprescription use of ASA and other medications as well as a range of other patient factors) would be tremendously powerful at the point of care for shared decisionmaking. Most registry data of low-dose ASA use are limited in terms of their comprehensiveness

for patient characteristics, medical history, cotreatments, ASA exposure, or the full range of outcomes. Over-the-counter availability in the United States further complicates tracking for ASA and important comedications. However, more complete and comprehensive data on the risks and moderators of ASA's effects on bleeding are critical for evidence-based preventive uses, including for cancers. Particularly given the rarity of many critical bleeding events, very large numbers of exposed lives are needed in these analyses. Since CVD risk factors also appear associated with increased bleeding risks (which may also vary somewhat between intracranial and extracranial sites), accurate risk tools that consider CVD risk and GI bleeding using the same variables would be most useful.

- *Confirming the net impact of ASA in the context of CVD risk management with statins and/or lifestyle modification*: Much of the data on ASA effects predates the use of statins and other approaches to moderate CVD risk for primary and secondary prevention. As noted in one IPD meta-analysis by the ATT Collaboration,[87] other approaches to reducing CVD risk would reduce the absolute benefit from low-dose ASA use, while not clearly also modifying the bleeding risks. Thus, a robust understanding of the expected net impact in a population being managed under current recommendations for CVD risk factors through modeling or additional research is critical.
- *Updated, longer-term followup of all CVD primary prevention trials for individual and total cancer incidence and mortality outcomes, CVD, serious bleeding, and other outcomes, with IPD meta-analyses*: Our review illustrates the somewhat fragmented nature of the current data supporting a comprehensive understanding of the overall impact of low-dose ASA in populations, subpopulations, and individuals. There are about 100,000 lives represented in the current CVD primary prevention trials. Longer-term followup of these and updated IPD meta-analyses, including all trials and longer-term followup for major outcomes, would provide more continuity. Incorporating all relevant beneficial and harmful outcomes into the analysis of ongoing trials of ASA use, if not already planned, might be possible and would be very useful. Similarly, any resolution possible to reduce the diversity of bleeding outcome categorizations between studies would be very helpful.
- *Determining the net impact of strategies to modify bleeding risk (on CVD/cancer benefits)*: Much recent literature focuses on approaches to moderate increased bleeding risk with low-dose ASA use, such as PPIs or *H. pylori* eradication. Experts suggest the application of these strategies to those at higher risk for bleeding, but confirm limited data on overall impact. Further research on the overall impact of cotherapies in CVD primary prevention populations would be extremely informative. Incorporation of these perspectives into the analysis of ongoing trials of ASA use, if not already planned, would be very useful.
- *Determining whether there is a clinically separate population for cancer prevention through low-dose ASA*: The strongly suggested mortality effects on colorectal and other cancers in selected trials with very long-term followup beg the question of whether there may be a separate clinical population for low-dose ASA to prevent specific cancers. As more data emerge on specific cancers (i.e., breast, pancreas) and on specific cancer sites (i.e., proximal vs. distal colon) and in specific populations (i.e., those with adenomas), a clearer picture for a discrete and separate population for ASA-related cancer chemoprevention could emerge. Similarly, as data on genetic factors associated with

cancer benefits with ASA use emerge, as they are beginning to in CRC, more specific targeting to minimize risks and maximize benefits may be possible.

Conclusion

In CVD primary prevention populations taking low-dose ASA for chemoprevention, a beneficial effect on cancer mortality or incidence is not clearly established. Data remain too limited for specific cancer effects, except perhaps for CRC, which is covered in a separate review. Data on specific factors that modify cancer risk, such as family history, were generally unavailable, since these data were primarily derived from CVD-oriented trials. Similarly, although a statistically significant beneficial effect on all-cause mortality has been shown in CVD secondary prevention populations and in some meta-analysis of CVD primary prevention trials, the 95% CI includes a range of effects that may reflect imprecision or a range of effects among subpopulations. Baseline bleeding risks and the effects of low-dose ASA alone or in combination with other common medications are not well studied in community-dwelling ambulatory populations who would be candidates for primary CVD or cancer prevention. Nonetheless, estimation of bleeding risks is increasingly recognized as critically important for valid assessment of expected net effects of ASA in primary prevention for cancer, CVD, and perhaps other conditions. No validated risk assessment tool is available for assessing bleeding risk for primary ASA chemoprevention, although more data have become available on the impact of risk factors, such as age, sex, CVD risk factors, and comedications, and their effects on increased bleeding risks alone or with ASA use. While the potential for identifying a subpopulation for safe, long-term low-dose ASA use to prevent multiple diseases remains tantalizing, it should be further informed by the large body of ongoing research.

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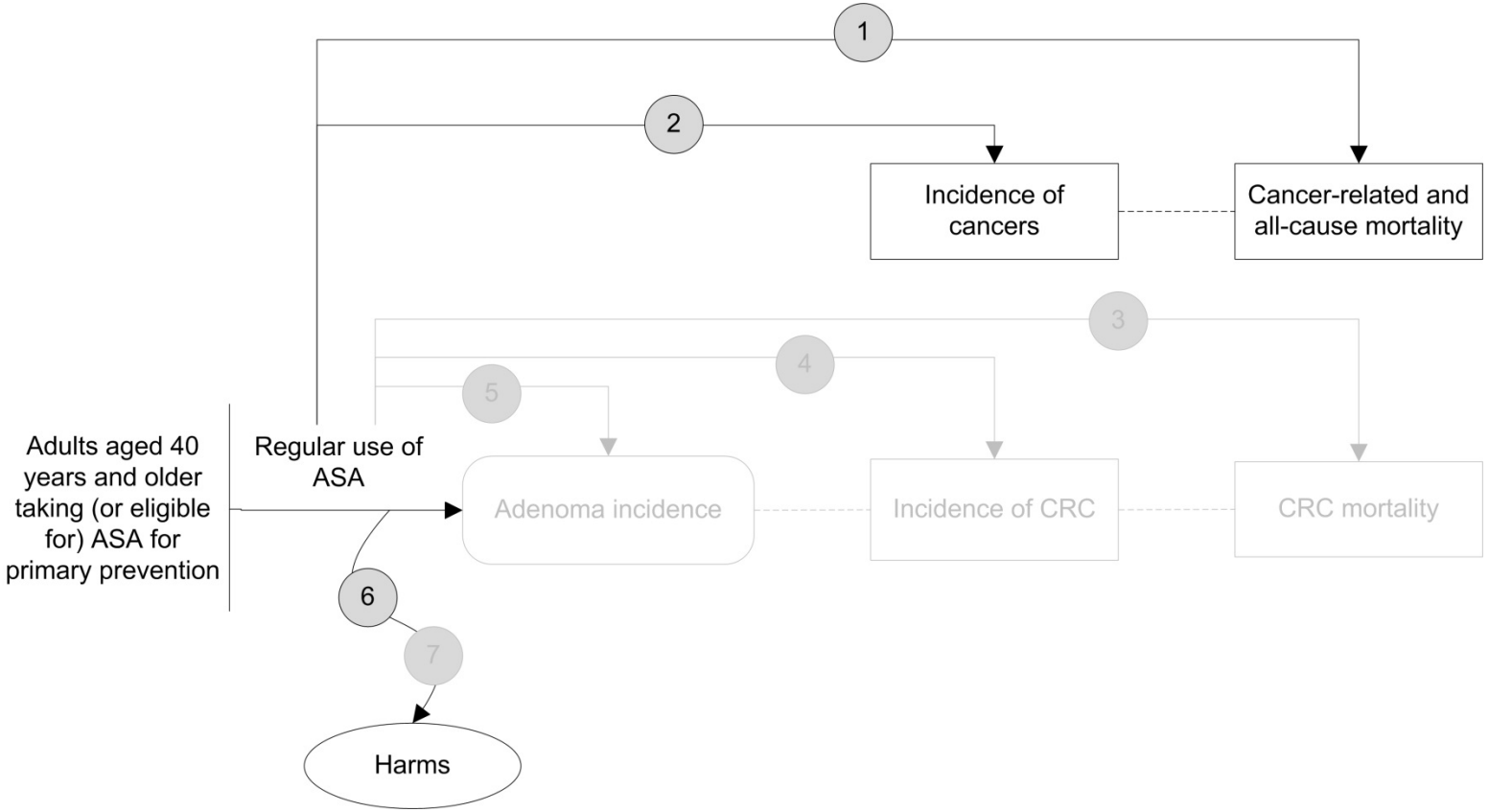
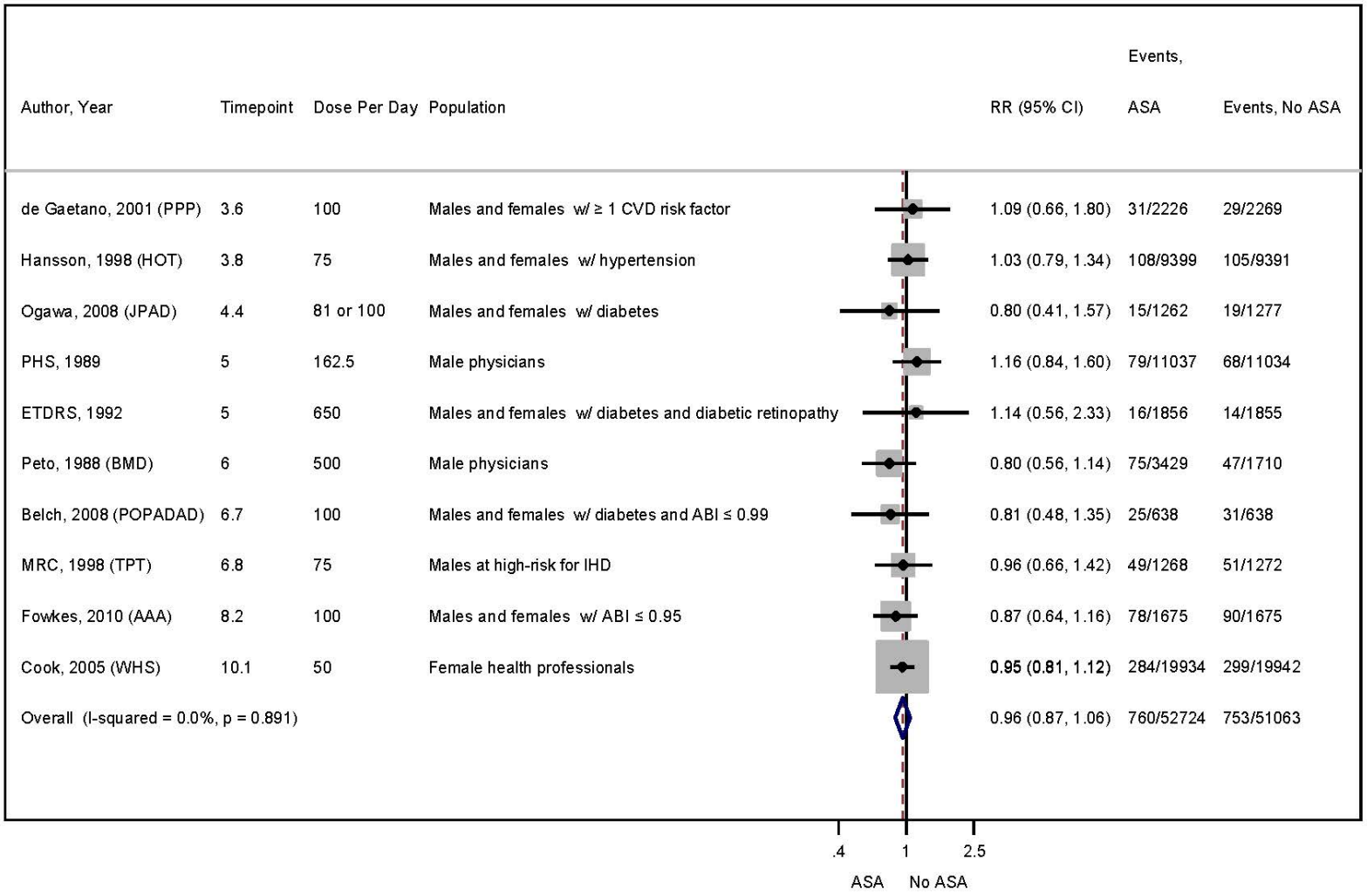
Figure 1. Analytic Framework



Abbreviations: ASA = acetylsalicylic acid, CRC = colorectal cancer

Note: The numbers on the analytic framework correspond to the Key Questions listed in the Methods section

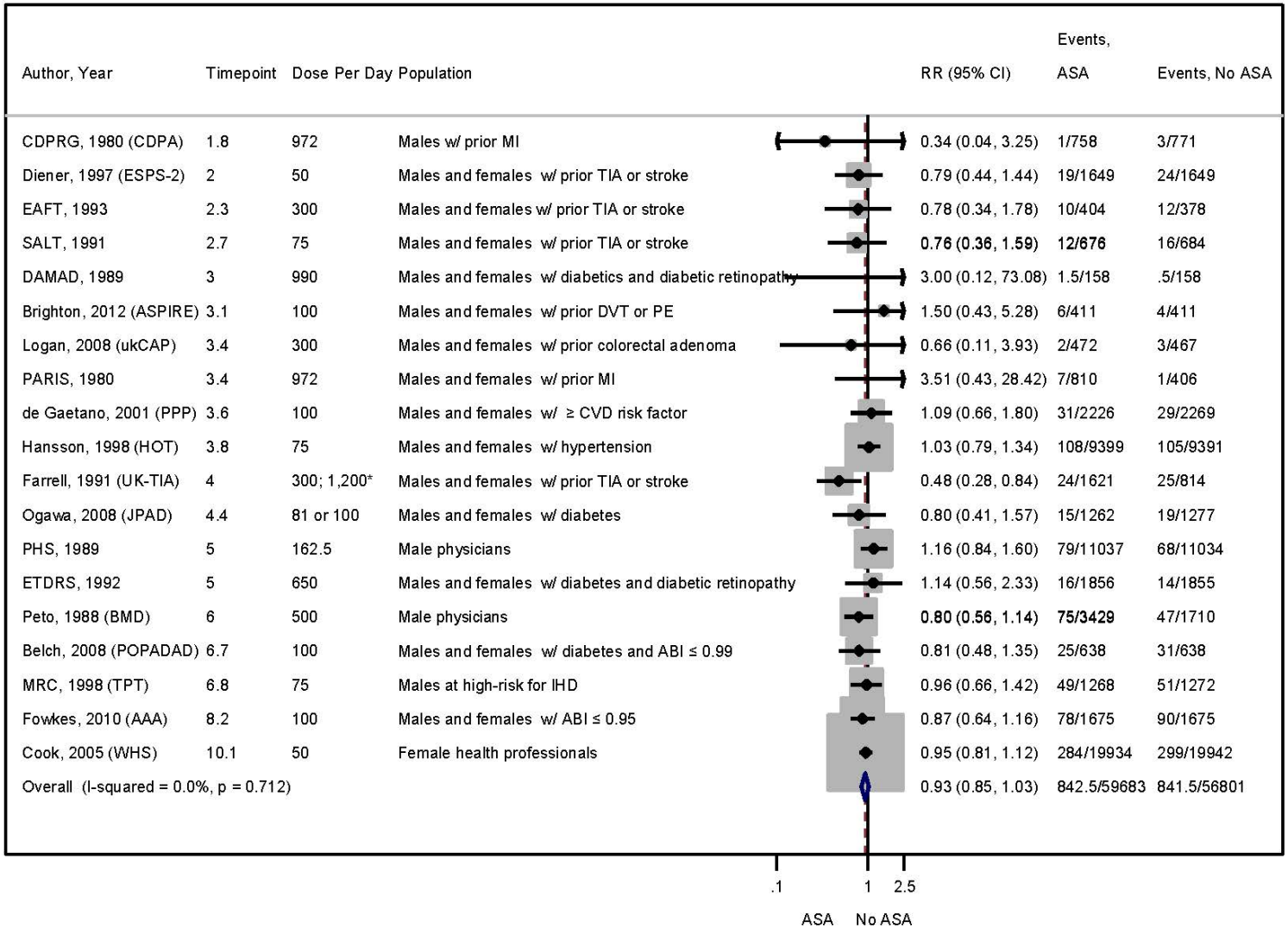
Figure 2. Forest Plot of Cancer Mortality, CVD Primary Prevention Trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; IHD = ischemic heart disease; RR = relative risk; w/ = with

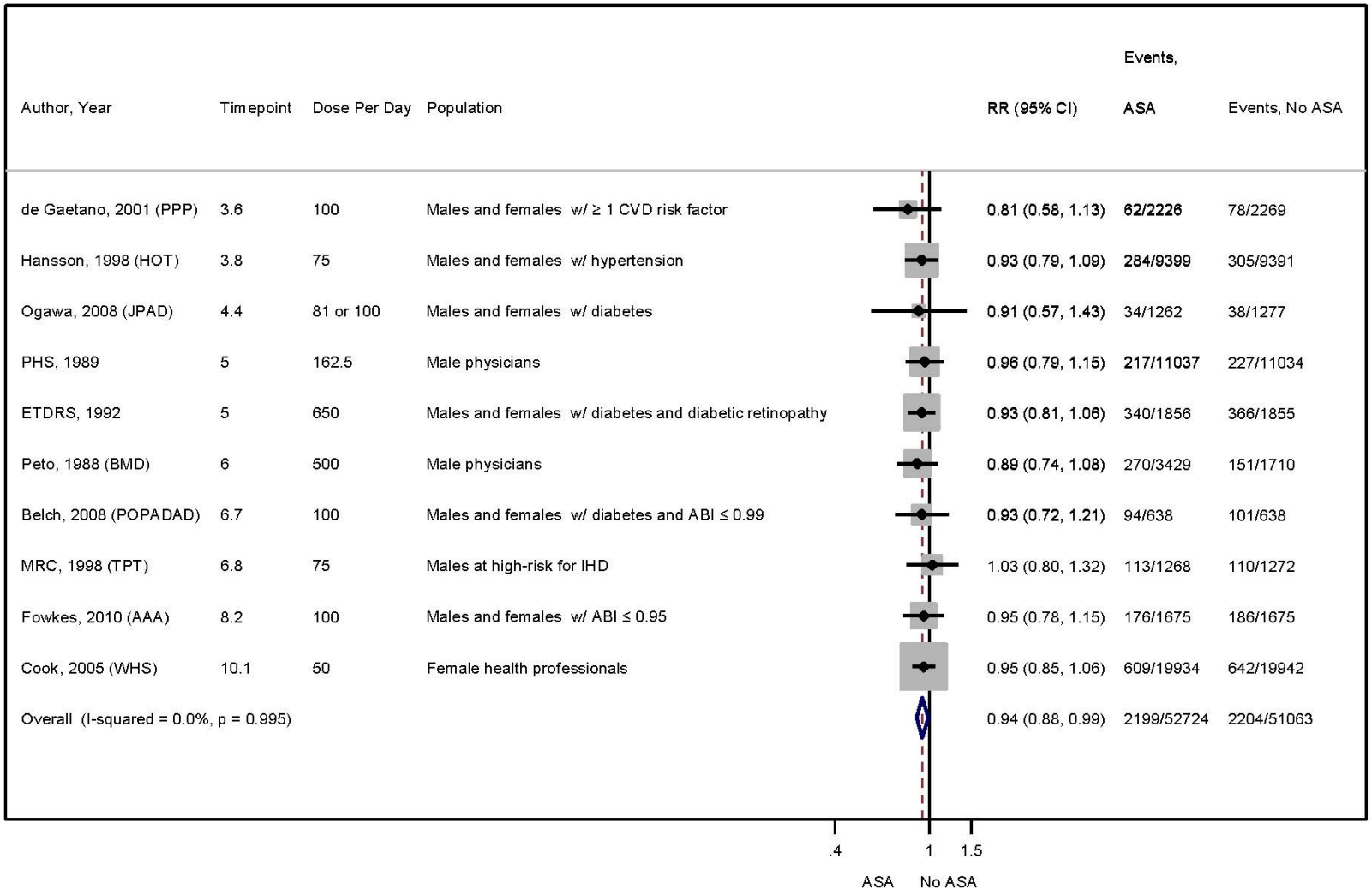
Figure 3. Forest Plot of Cancer Mortality, All Included Trials



*Trials included two separate ASA arms which were combined for analysis
Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis; IHD = ischemic heart disease; MI = myocardial infarction; RR = relative risk; PE = pulmonary emboli; TIA = transient ischemic attack; w/ = with

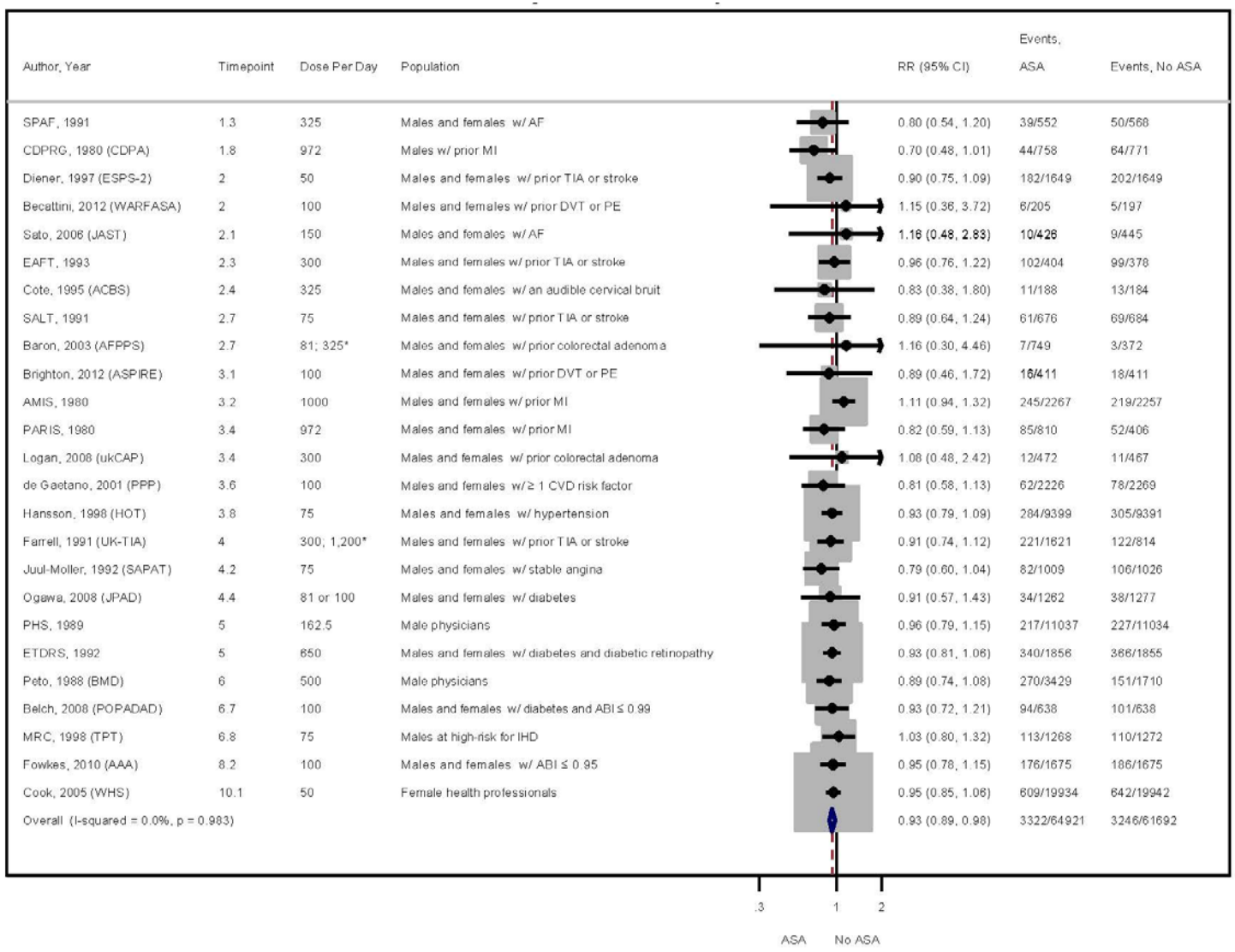
Figure 4. Forest Plot of All-Cause Mortality, CVD Primary Prevention Trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; IHD = ischemic heart disease; RR = relative risk; w/ = with

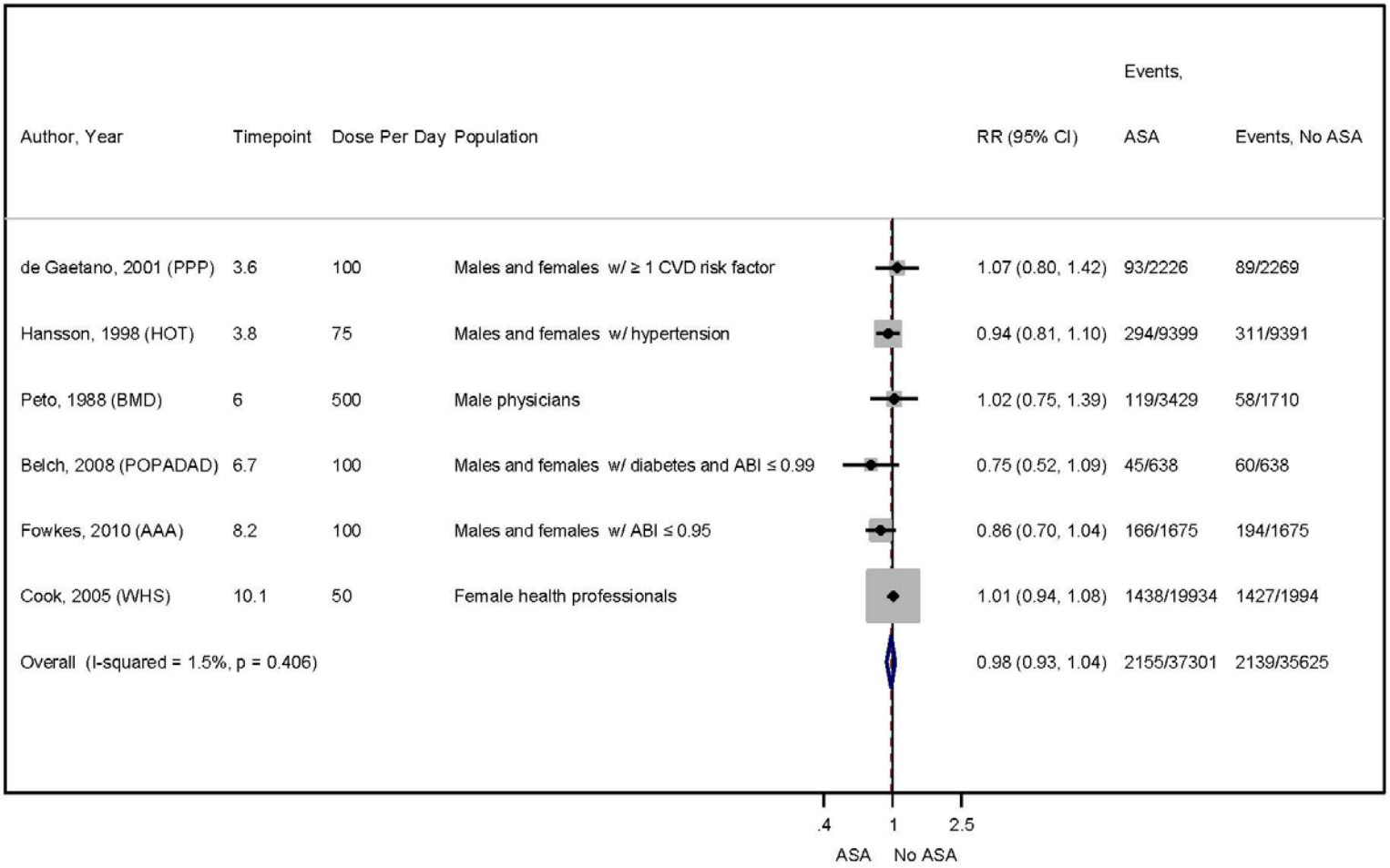
Figure 5. Forest Plot of All-Cause Mortality, All Included Trials



*Trials included two separate ASA arms which were combined for analysis
Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; AF = atrial fibrillation; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis; IHD = ischemic heart disease; MI = myocardial infarction; RR = relative risk; PE = pulmonary emboli; TIA = transient ischemic attack; w/ = with

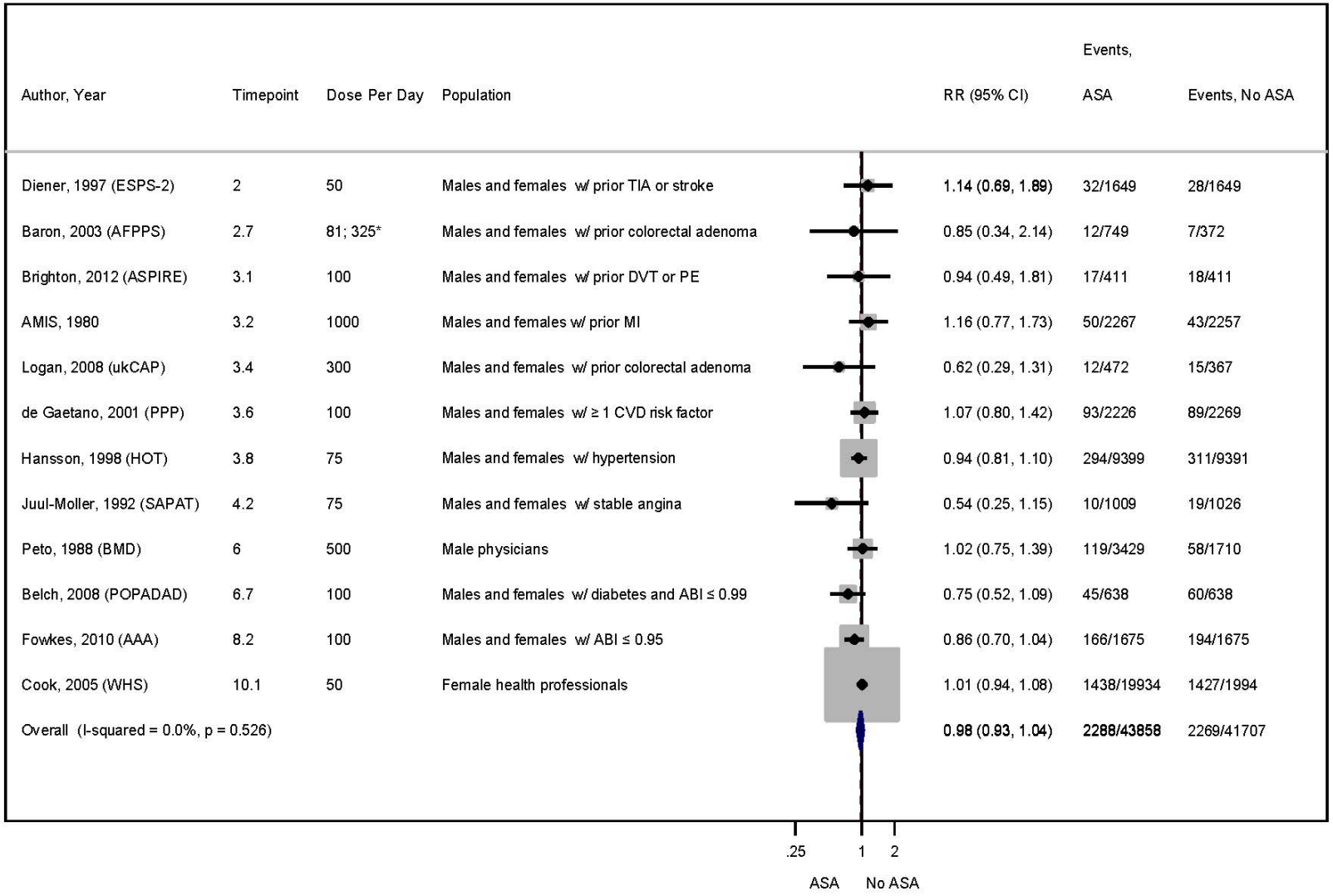
Figure 6. Forest Plot of Cancer Incidence, CVD Primary Prevention Trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; RR = relative risk; w/ = with

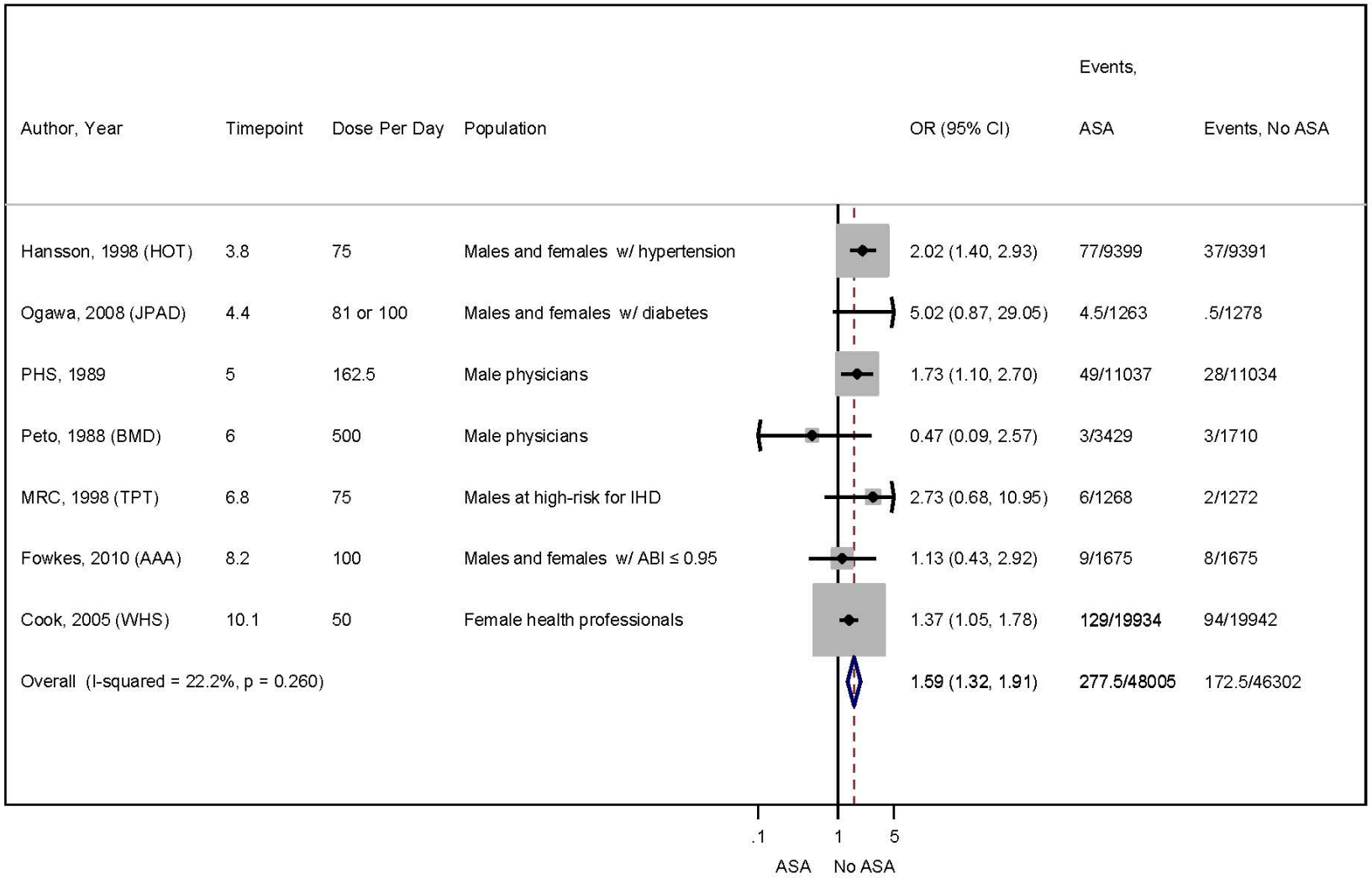
Figure 7. Forest Plot of Cancer Incidence, All Included Trials



*Trials included two separate ASA arms which were combined for analysis
Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis; MI = myocardial infarction; RR = relative risk; PE = pulmonary emboli; TIA = transient ischemic attack; w/ = with

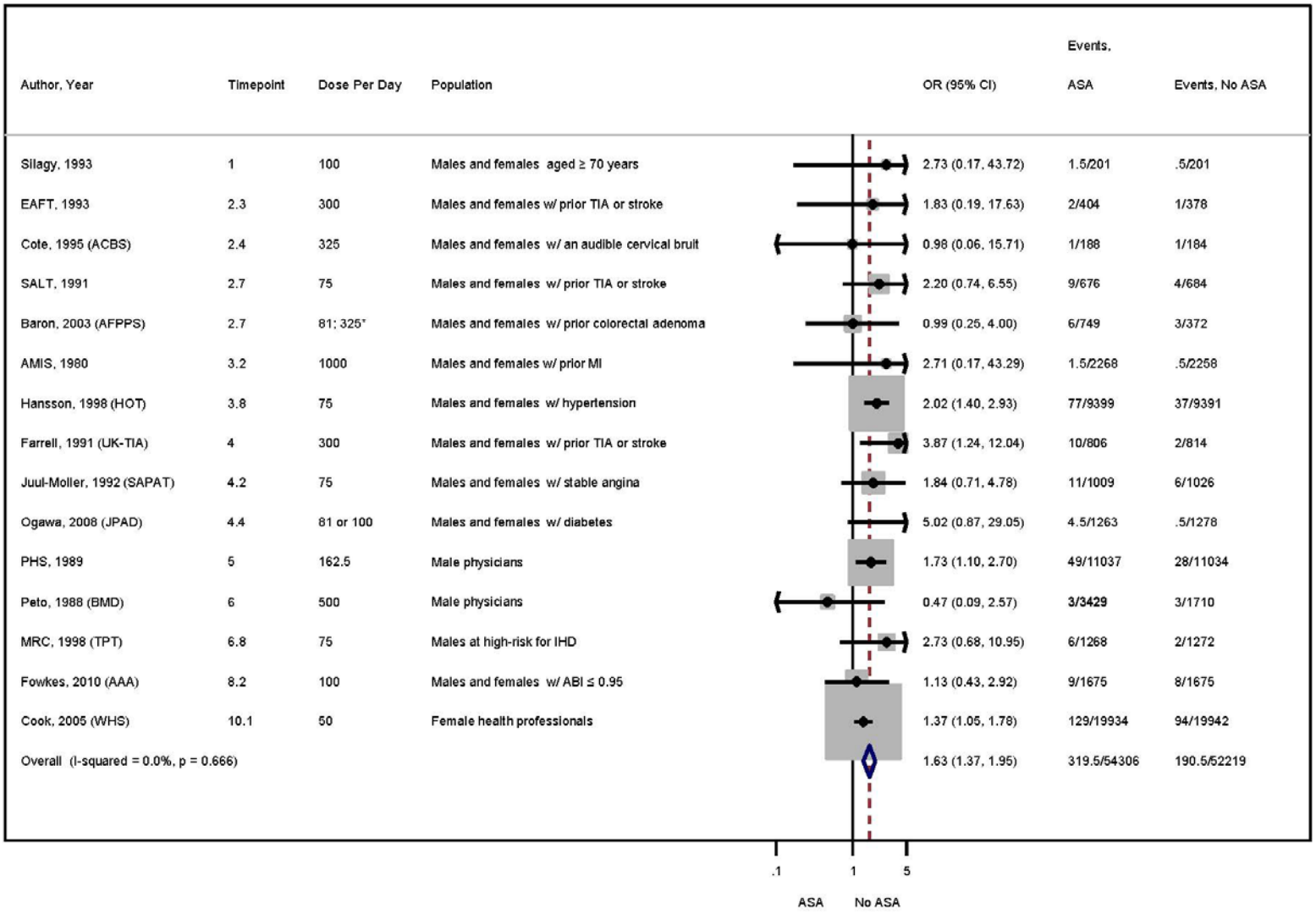
Figure 8. Forest Plot of Major GI Bleeding, CVD Primary Prevention Trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; IHD = ischemic heart disease; OR = odds ratio; w/ = with

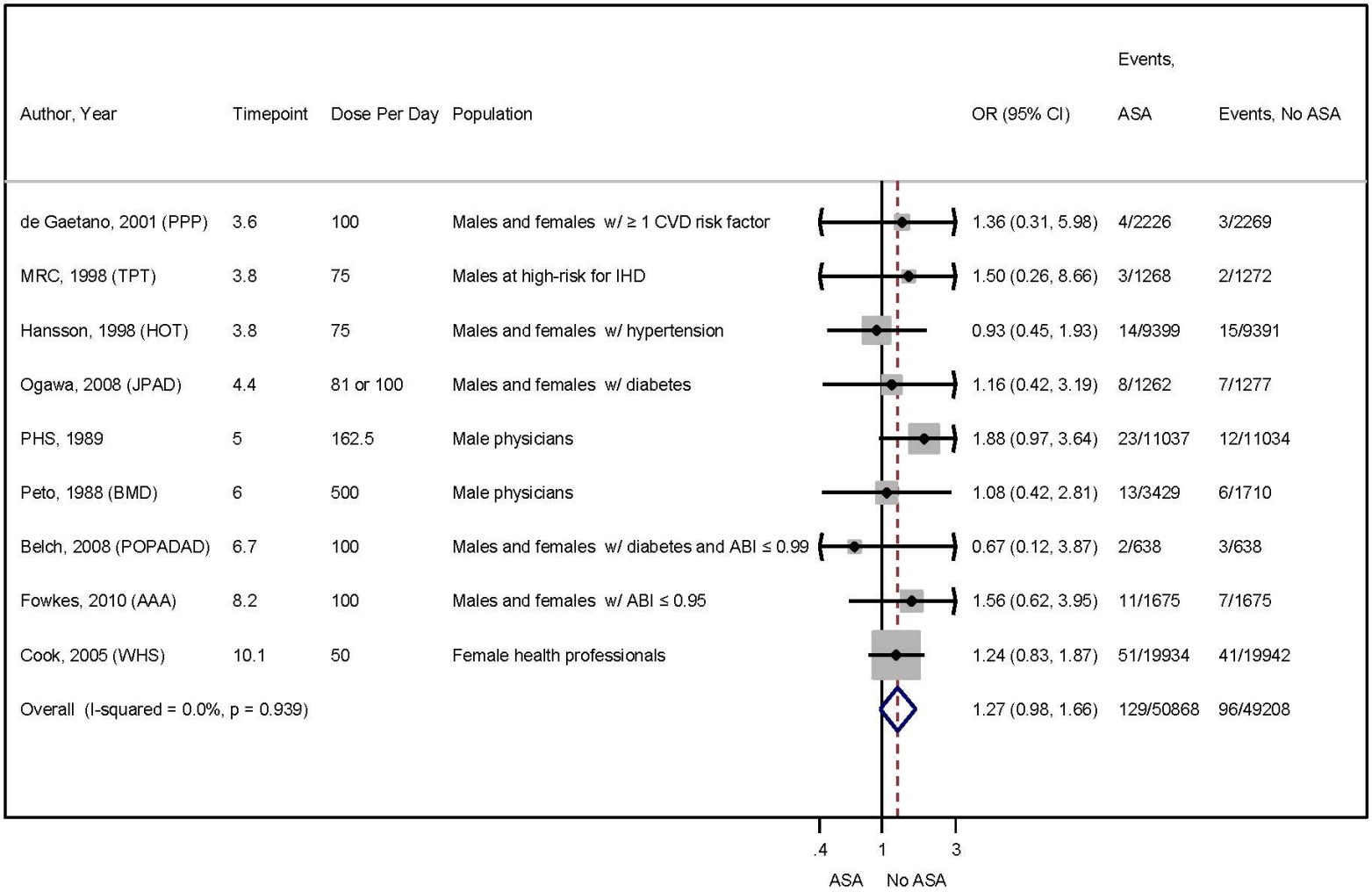
Figure 9. Forest Plot of Major GI Bleeding, All Included Trials



*Trial included two separate ASA arms which were combined for analysis
Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; MI = myocardial infarction; OR = odds ratio; TIA = transient ischemic attack; w/ = with

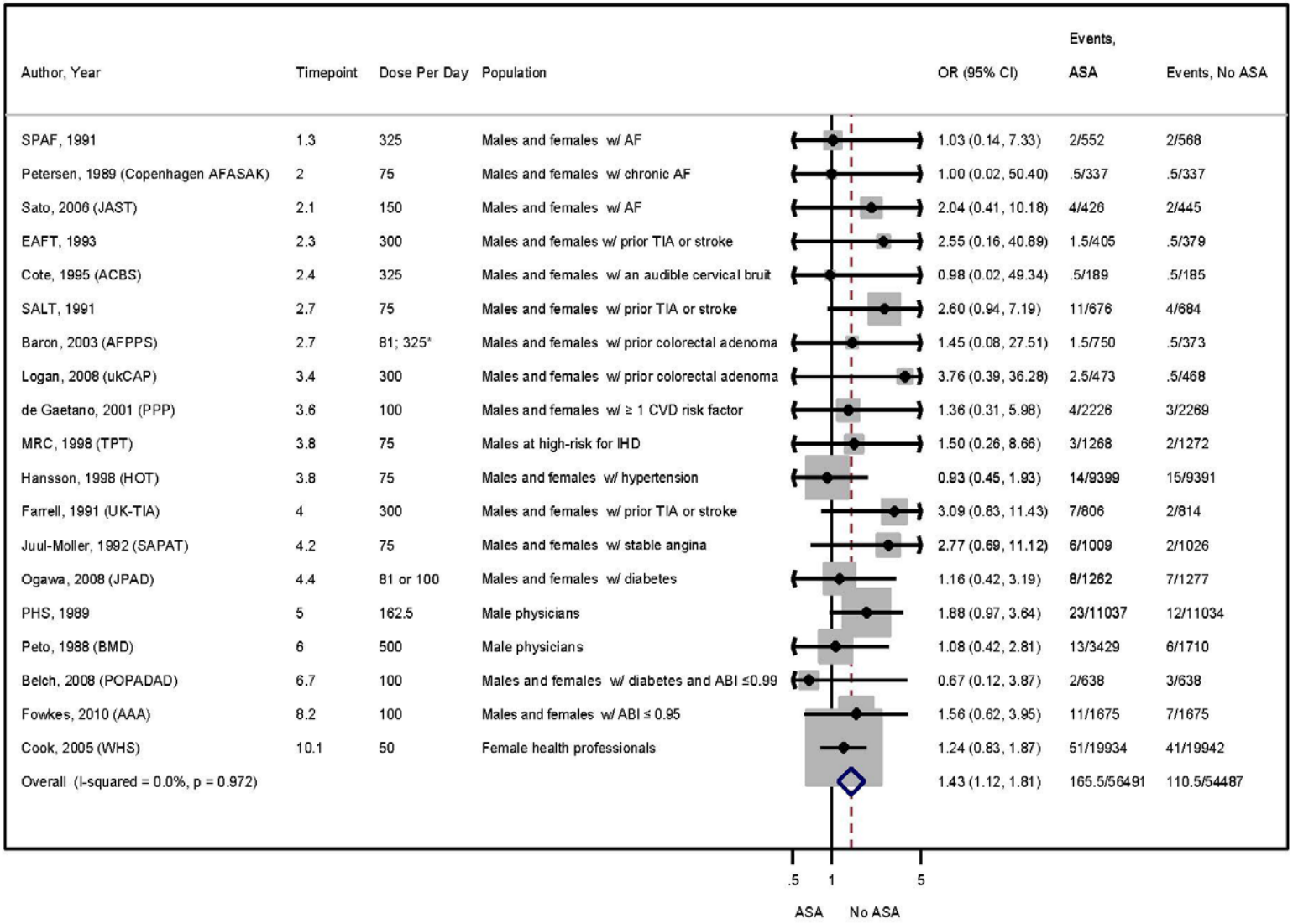
Figure 10. Forest Plot of Intracranial Bleeding, Including Hemorrhagic Stroke, CVD Primary Prevention Trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; IHD = ischemic heart disease; OR = odds ratio; w/ = with

Figure 11. Forest Plot of Intracranial Bleeding, Including Hemorrhagic Stroke, All Included Trials



*Trial included two separate ASA arms which were combined for analysis
Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: ABI = ankle-brachial index; AF = atrial fibrillation; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; IHD = ischemic heart disease; MI = myocardial infarction; OR = odds ratio; TIA = transient ischemic attack; w/ = with

Table 1. Classification of Cancers

Stage	Definition
Carcinoma	A malignant neoplasm of epithelial origin or cancer of the internal of external lining of the body. Included adenocarcinomas (carcinoma of an organ or gland) and squamous cell carcinoma (originating in the squamous epithelium).
Sarcoma	A cancer originating in the supporting and connective tissue (e.g., bones)
Myeloma	A cancer originating in the plasma cells of bone marrow
Leukemia	Cancer of the bone marrow (white blood cells)
Lymphoma	Cancer of the glands or nodes of the lymphatic system
Blastoma	A cancer originating in embryonic tissues or organs

Table 2. SEER Average Age-Adjusted Annual Incidence Rates per 100,000 Individuals of Selected Cancer Sites in the United States, 2007–2011

Site	Race/ethnicity	Male	Female
Any	White	532.1	424.4
	Black	600.9	398.8
	Asian/PI	331.0	293.0
	AI/AN	348.1	301.9
	Hispanic	409.1	325.6
Prostate	White	139.9	
	Black	223.9	
	Asian/PI	79.3	
	AI/AN	71.5	
	Hispanic	122.6	
Breast	White		128.0
	Black		122.8
	Asian/PI		93.6
	AI/AN		79.3
	Hispanic		93.2
Pancreas	White	14.0	10.7
	Black	17.2	14.2
	Asian/PI	10.7	8.9
	AI/AN	12.6	9.1
	Hispanic	12.3	10.3
Stomach	White	9.2	4.5
	Black	15.3	8.5
	Asian/PI	14.9	9.0
	AI/AN	12.9	7.3
	Hispanic	14.9	8.4
Esophagus	White	8.0	1.7
	Black	7.9	2.6
	Asian/PI	3.7	1.0
	AI/AN	4.8	1.9
	Hispanic	5.3	1.1
Lung and bronchus	White	72.4	53.8
	Black	93.0	51.2
	Asian/PI	49.4	28.1
	AI/AN	49.5	34.7
	Hispanic	40.4	26.1

Abbreviations: AI = American Indian; AN = Alaskan Native; PI = Pacific Islander.

Table 3. SEER Mortality Rates* From Selected Cancer Sites in the United States, 2007–2011

Site	Race/ethnicity	Male	Female
Any	White	213.1	149.8
	Black	276.6	171.2
	Asian/PI	132.4	92.1
	AI/AN	191.0	139.0
	Hispanic	152.1	101.2
Prostate	White	21.2	
	Black	50.9	
	Asian/PI	10.1	
	AI/AN	20.7	
	Hispanic	19.2	
Breast	White		22.1
	Black		30.8
	Asian/PI		11.5
	AI/AN		15.5
	Hispanic		14.8
Pancreas	White	12.5	9.4
	Black	15.3	12.5
	Asian/PI	8.3	7.1
	AI/AN	10.1	8.6
	Hispanic	9.6	7.7
Stomach	White	4.2	2.2
	Black	9.8	4.7
	Asian/PI	8.7	5.1
	AI/AN	8.1	3.8
	Hispanic	7.6	4.4
Esophagus	White	7.8	1.6
	Black	7.7	2.1
	Asian/PI	3.1	0.8
	AI/AN	6.1	1.6
	Hispanic	4.3	0.8
Lung and bronchus	White	63.2	40.4
	Black	78.5	37.2
	Asian/PI	35.5	18.4
	AI/AN	49.6	33.1
	Hispanic	31.3	14.1

*Average age-adjusted annual rates per 100,000 individuals.

Abbreviations: AI = American Indian; AN = Alaskan Native; PI = Pacific Islander

Table 4. Progression of Cancer Stages

Stage	Definition
0	Carcinoma in situ (limited to surface cells)
I	Localized cancer to one part of the body
II	Early locally advanced cancer to one part of the body
III	Late locally advanced cancer to one part of the body
IV	Metastasized cancer, spread to other organs or throughout the body

Table 5. Recommendations of ASA Use to Prevent Cancer (Excluding Colorectal Cancer) From Other Organizations

Organization, Year	Recommendation
American College of Chest Physicians, 2007[119]	Recommends against the use of ASA in the primary, secondary or tertiary prevention of **lung cancer** in individuals who are at risk for lung cancer and in patients with a history of lung cancer.
American Gastroenterological Association, 2011[120]	Recommends against the use of ASA solely to prevent **esophageal adenocarcinoma**.
British Society of Gastroenterology, 2011[121]	Unable to assert a recommendation that ASA could be chemopreventive for **gastric cancer** until ongoing studies completed.
European Society of Cardiology, 2012[30]	Recommends against the use of ASA in individuals without cardiovascular or cerebrovascular disease due to risk of major bleeding; **cancer risk was not considered** in this recommendation.
International Conference on Cancer Prevention, 2012[122]	Insufficient evidence on the risk-benefit profile to definitively recommend ASA use in the **prevention of cancer**.

Abbreviations: ASA = acetylsalicylic acid

Table 6. Brief Description of Included Trials

Prevention	Author, Year Quality	Design	Country	Mean Follow-up (years)	Population	N rand	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose, Concomitant Treatment, and Frequency	KQ1	KQ2	KQ6
CVD Primary Prevention	Belch, 2008 (POPADAD)[57] Fair	RCT, 2x2 factorial	Scotland	6.7†	Males and females w/ diabetes and ABI ≤ 0.99	1,276	60.3 (≥ 40)	55.9	100	31.1	100 mg alone or with antioxidants qd	✓	✓	✓
	Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	RCT, 2x2x2 factorial	United States	10.1	Female health professionals	39,876	54.6 (≥ 45)	100	2.6	13.1	100 mg alone or with vitamin E or beta-carotene qod	✓	✓	✓
	de Gaetano, 2001 (PPP)[61] Fair	RCT, 2x2 factorial	Italy	3.6	Males and females w/ ≥ 1 CVD risk factor	4,495	64.4 (≥ 50)	57.5	16.5	14.8	100 mg alone or with 300 mg vitamin E qd	✓	✓	✓
	ETDRS, 1992[64] Good	RCT, 2x2 factorial	United States	5	Males and females w/ diabetes and diabetic retinopathy	3,711	NR (18-70)	43.5	100	NR	650 mg qd	✓		✓
	Fowkes, 2010 (AAA)[66] Good	RCT	United Kingdom	8.2	Males and females w/ ABI ≤ 0.95	3,350	62.0 (50-75)	71.5	2.6	32.4	100 mg qd	✓	✓	✓
	Hansson, 1998 (HOT)[67] Fair	RCT, 2x2 factorial	International (Europe, North and South America, Asia)	3.8	Males and females w/ hypertension	19,193	61.5 (50-80)	47	8	15.9	75 mg qd	✓	✓	✓
	MRC, 1998 (TPT)[69] Good	RCT, 2x2 factorial	United Kingdom	6.8†	Males at high-risk for IHD	2,540	57.5 (45-69)	0	NR	41.3	75 mg qd	✓		✓
	Ogawa, 2008 (JPAD)[70] Fair	RCT	Japan	4.37†	Males and females w/ diabetes	2,539	64.5 (30-85)	45.4	100	21.2	81 or 100 mg qd	✓		✓

Table 6. Brief Description of Included Trials

Prevention	Author, Year Quality	Design	Country	Mean Follow-up (years)	Population	N rand	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose, Concomitant Treatment, and Frequency	KQ1	KQ2	KQ6
	Peto, 1988 (BMD)[72] Fair	RCT	United Kingdom	6	Male physicians	5,139	61.6 (NR)	0	2	12.9	500 mg, or 300 mg if requested qd	✓	✓	✓
	PHS, 1989[73] Good (KQ1); Fair (KQ6)	RCT, 2x2 factorial	United States	5.0	Male physicians	22,071	53.2 (40-84)	0	2.4	11	325 mg alone or with 50 mg beta-carotene qod	✓		✓
CVD Primary Prevention*	DAMAD, 1989[51] Fair	RCT	France, United Kingdom	3	Males and females w/ diabetics and diabetic retinopathy	314	46.7 (17-67)	35.4	100	NR	330 mg (990 mg total per day) tid	✓		✓
	Nelson, 2008 (ASPREE)[53] Fair	RCT	Australia	1	Males and females aged ≥ 70 years	209	76.2 (≥ 70)	59.3	0	4.3	100 mg qd	✓		✓
	Silagy, 1993[52] Fair	RCT	Australia	1	Males and females aged ≥ 70 years	400	73 (70-90)	51	NR	5.8	100 mg qd			✓
CVD Secondary Prevention	AMIS, 1980 Fair	RCT	United States	3.2	Males and females w/ prior MI	4,745	54.8 (30-69)	11.1	10.6	27.3	0.5 g (1.0 g total per day) bid	✓	✓	✓
	Becattini, 2012 (WARFASA)[78] Fair	RCT	Italy	2.0†	Males and females w/ prior DVT or PE	403	62.0 (≥ 18)	36.07	NR	NR	100 mg qd	✓		✓
	Brighton, 2012 (ASPIRE)[58] Good	RCT	Multinational (5 countries including Australia, New Zealand)	3.1†	Males and females w/ prior DVT or PE	822	54.5 (≥ 18)	45.6	NR	NR	100 mg qd	✓	✓	✓
	CDPRG, 1980 (CDPA)[59] Good	RCT	United States	1.83	Males w/ prior MI	1,529	NR (NR)	0	NR	NR	324 mg (972 mg total per day) tid	✓		✓

Table 6. Brief Description of Included Trials

Prevention	Author, Year Quality	Design	Country	Mean Follow-up (years)	Population	N rand	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose, Concomitant Treatment, and Frequency	KQ1	KQ2	KQ6
	Cote, 1995 (ACBS)[79] Fair	RCT	Canada	2.4	Males and females w/ an audible cervical bruit	372	66.7 (NR)	53	23.7	36.8	325 mg qd	✓		✓
	Diener, 1997 (ESPS-2)[62] Good	RCT, 2x2 factorial	Europe (13 countries)	2	Males and females w/ prior TIA or stroke	3,298	66.7 (≥ 18)	42.2	14.5	23.5	25 mg (50 mg total per day) bid	✓	✓	✓
	EAFT, 1993[63] Fair	RCT	Europe (13 countries), Israel	2.3	Males and females w/ prior TIA or stroke	782	73 (> 25)	44	13	19.1	300 mg qd	✓		✓
	Farrell, 1991 (UK-TIA)[65] Fair	RCT	United Kingdom	4	Males and females w/ prior TIA or stroke	2,449	59.8 (≥ 40)	26.9	4.4	53.1	150 mg (2 tablets; 300 mg total per day) bid or 300 mg (2 tablets; 1200 mg total per day) bid	✓		✓
	Juul-Moller, 1992 (SAPAT)[54] Fair	RCT	Sweden	4.2	Males and females w/ stable angina	2,035	67 (30-80)	48	NR	16	75 mg qd	✓	✓	✓
	PARIS, 1980[71] Good	RCT	United States, United Kingdom	3.4	Males and females w/ prior MI	1,216	56.3 (30-74)	13.2	NR	26.8	324 mg (972 mg total per day) tid	✓		✓
	Petersen, 1989 (Copenhagen AFASAK)[80] Fair	RCT	Denmark	2	Males and females w/ chronic AF	672	74.9 (38-91)	45.8	8.8	35.9	75 mg qd	✓		✓
	SALT, 1991[74] Good	RCT	Sweden	2.67	Males and females w/ prior TIA or stroke	1,360	67 (50-79)	34.2	12.9	25.4	75 mg qd	✓		✓
	Sato, 2006 (JAST)[81] Fair	RCT	Japan	2.1	Males and females w/ AF	871	65.1 (NR)	29.6	14	30.4	150-200 mg qd (or qod if 330 mg preferred)	✓		✓

Table 6. Brief Description of Included Trials

Prevention	Author, Year Quality	Design	Country	Mean Follow-up (years)	Population	N rand	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose, Concomitant Treatment, and Frequency	KQ1	KQ2	KQ6
	SPAF, 1991[76] Good	RCT	United States	1.3	Males and females w/ AF	1,120	67 (NR)	29.5	17.5	16	325 mg qd	✓		✓
Colorectal adenoma prevention	Baron, 2003 (AFPPS)[77] Good (KQ1); Fair (KQ2, KQ6)	RCT, 3x2 factorial	United States	2.7	Males and females w/ prior colorectal adenoma	1,121	57.5 (21-80)	36.5	NR	14.9	81 or 325 mg qd	✓	✓	✓
	Benamouzig, 2003 (APACC)[82] Fair	RCT	France	1	Males and females w/ prior colorectal adenoma	272	57.8 (18-75)	30.1	NR	23.16	160 or 300 mg qd			✓
	Logan, 2008 (ukCAP)[68] Fair	RCT, 2x2 factorial	United Kingdom, Denmark	3.4	Males and females w/ prior colorectal adenoma	945	57.8 (27.6-74.6)	43.1	NR	NR	300 mg alone or with 0.5 mg folic acid qd	✓	✓	✓

*These are three additional CVD primary prevention trials that were excluded from the companion systematic review as they reported no relevant outcomes[41]
†Median

Abbreviations: ABI = ankle brachial index; AF = atrial fibrillation; ASA= acetylsalicylic acid; bid= twice daily; CVD= cardiovascular disease; DVT= deep vein thrombosis; IHD = ischemic heart disease; KQ= key question; MI= myocardial infarction; mg= milligram(s); NR= not reported; PE= pulmonary embolism; qd= every day; qod= every other day; rand= randomized; RCT= randomized controlled trial; TIA = transient ischemic attack; tid= three times a day; w/= with

Table 7. Brief Description of Included Cohort Studies (KQ 6)

Author, Year Quality	Design	Country	Mean Followup (Years)	Population	N	Mean Age and Range (years)	% Female	% Diabetes	% Current Smokers	ASA Dose and Frequency
de Berardis, 2012[85] Good	Cohort, Retrospective	Italy	5.7*	Males and females aged ≥ 30 years, new aspirin users vs. never users	372,850	69.4 (30-95)	53.1	15	NR	≤ 300 mg with most recent prescription filled ≥ 75 days prior to bleeding event
Ekstrom, 2013 (SNDR)[86] Fair	Cohort, Prospective	Sweden	3.9	Males and females w/ diabetes	18,646	62.3 (30-80)	44.7	100	15.4	75 mg qd
Huang, 2010 (HPS)[83] Fair	Cohort, Prospective	United States	11.4	Male health professionals	32,989	60.9 (NR)	0	5.4	5.2	Any dose ≥ 2 times/week
Huang, 2011 (NHS)[84] Fair	Cohort, Prospective	United States	12.5	Female nurses	87,680	56.6 (30-55)	100	5	17.6	325 mg ≥ 2 tablets/week

*Median

Abbreviations: ASA= acetylsalicylic acid; mg= milligrams; NR= not reported; qd= daily; w/= with

Table 8. Comparison of Inclusion Criteria of Included Meta-Analyses*

Criteria	Rothwell 2011 Analysis 1	Rothwell 2011 Analysis 2	Rothwell 2012 Analysis 1	Rothwell 2012 Analysis 2	ATT Collaboration, 2009[87]	Seshasai, 2012[44]
Included populations	1° and 2° CVD prevention	1° and 2° CVD prevention	1° and 2° CVD prevention	1° CVD prevention	1° CVD prevention (non-diabetics) and 2° CVD prevention	1° CVD prevention
ASA dose	Any dose	Any dose	Any dose	< 300 mg/day	Any	Any
Frequency	Daily	Daily	Daily	Daily	Any	Any
Intervention duration	≥ 4 years	≥ 4 years	≥ 90 days	≥ 90 days	≥ 2 years	≥1 year
Total number of studies; participants; cancer outcomes	k=7, n=23,535; 657 cancer deaths	k=3; n=12,659†; 1,634 cancer deaths	k=34‡; n=69,224; 1,226 cancer deaths	k=6; n= 35,535; 1,632 incident cancers	k=22; n=112,000; no cancer outcomes	k=9, n=102,621; cancer deaths 1,512
1° CVD prevention studies	AAA, BMD, ETDRS, JPAD, POPADAD, TPT§	BMD, TPT§	AAA, BMD, ETDRS, HOT, JPAD, POPADAD, PPP, TPT	AAA, HOT, JPAD‖, POPADAD, PPP, TPT	BMD, HOT, PHS, PPP, TPT, WHS	AAA, BMD, HOT, JPAD, PHS, POPADAD, PPP¶, TPT, WHS
2° CVD prevention studies	UK-TIA**	UK-TIA	UK-TIA, EAFT, SALT, ESPS-2, SAPAT, 21 "small trials"	None	16 trials	None

*All outcomes occurred during trials except in 2nd analysis by Rothwell and colleagues (2011)[8] who report 20 year mortality for BMD, TPT, and UK-TIA
†Also conducted sub-analyses on 10,502 patients who had 5 or more years of treatment.
‡Also analyzed nonvascular death among 77,549 participants in 51 trials
§Includes arms of TPT in which anticoagulant was co-administered with ASA.
‖Substituted cancer mortality for nonfatal cancer
¶Not included for cancer mortality
**Included data from SAPAT for trial-level meta-analyses

Abbreviations: ASA = acetylsalicylic acid; CVD = cardiovascular disease; mg = milligram(s)

Table 9. Sensitivity Analyses by Dosage and Frequency of Cancer Incidence, Cancer Mortality, and All-Cause Mortality

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled RR (95% CI)	Pooled RR When Long-Term WHS Data Used*	Names of Trials
Cancer mortality	CVD Primary Prevention Trials	All trials	10	760/52,724	753/51,063	0.96 (0.87, 1.06)	0.97 (0.90, 1.05)	PPP, HOT, JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	8	669/47,439	692/47,498	0.97 (0.87, 1.08)	0.98 (0.90, 1.06)	PPP, HOT, JPAD, PHS, POPADAD, TPT, AAA, WHS
		Dose ≤ 100 mg per day	7	590/36,402	624/36,464	0.95 (0.85, 1.06)	0.97 (0.89, 1.05)	PPP, HOT, JPAD, POPADAD, TPT, AAA, WHS
		Daily dose	8	397/21,753	386/20,087	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)	PPP, HOT, JPAD, ETDRS, BMD, POPADAD, TPT, AAA
		Every other day dose	2	363/30,971	367/30,976	0.99 (0.86, 1.14)	0.99 (0.90, 1.09)	PHS, WHS
		Followup ≥ 5 years	7	606/39,837	600/38,126	0.94 (0.84, 1.06)	0.96 (0.89, 1.05)	WHS, TPT, POPADAD, AAA, PHS, BMD, ETDRS
		Followup ≥ 4 years	8	621/41,099	619/39,403	0.94 (0.84, 1.05)	0.96 (0.88, 1.04)	WHS, TPT, JPAD, POPADAD, AAA, PHS, BMD, ETDRS
		Followup ≥ 4 years and daily dose	6	258/10,128	252/8,427	0.87 (0.73, 1.03)	0.87 (0.73, 1.03)	TPT, JPAD, POPADAD, AAA, BMD, ETDRS
	All Included Trials	All trials	19	842/59,683	841/56,801	0.93 (0.85, 1.03)	0.95 (0.88, 1.03)	CDPA, ESPS-2, EAFT, SALT, DAMAD, ASPIRE, PARIS, ukCAP, PPP, HOT, UK-TIA, JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	13	718/51,051	751/51,087	0.96 (0.86, 1.06)	0.97 (0.90, 1.05)	ESPS-2, EAFT, SALT, ASPIRE, ukCAP, PPP, HOT, JPAD, PHS, POPADAD, TPT, AAA, WHS
		Dose ≤ 100 mg per day	10	627/39,138	668/39,208	0.94 (0.84, 1.05)	0.96 (0.88, 1.04)	ESPS-2, SALT, ASPIRE, PPP, HOT, JPAD, POPADAD, TPT, AAA, WHS
		Daily dose	17	479/28,712	474/25,825	0.89 (0.79, 1.01)	0.89 (0.79, 1.01)	CDPA, ESPS-2, EAFT, SALT, DAMAD, ASPIRE, PARIS, ukCAP, PPP, HOT, UK-TIA, JPAD, ETDRS, BMD, POPADAD, TPT, AAA
		Every other day dose	2	363/30,971	367/30,976	0.99 (0.86, 1.14)	0.99 (0.90, 1.09)	PHS, WHS
		Dose ≤ 325 mg per day and daily dose	11	355/20,080	384/20,111	0.93 (0.80, 1.07)	0.93 (0.80, 1.07)	ESPS-2, EAFT, SALT, ASPIRE, ukCAP, PPP, HOT, JPAD, POPADAD, TPT, AAA
		Followup ≥ 4 years	9	645/42,720	644/40,217	0.92 (0.82, 1.02)	0.95 (0.87, 1.03)	WHS, TPT, JPAD, POPADAD, AAA, PHS, UK-TIA, BMD, ETDRS

Table 9. Sensitivity Analyses by Dosage and Frequency of Cancer Incidence, Cancer Mortality, and All-Cause Mortality

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled RR (95% CI)	Pooled RR When Long-Term WHS Data Used*	Names of Trials
		Followup ≥ 4 years and daily dose	7	282/11,749	277/9,241	0.83 (0.70, 0.98)	0.83 (0.70, 0.98)	TPT, JPAD, POPADAD, AAA, UK-TIA, BMD, ETDRS
All-cause mortality	CVD Primary Prevention Trials	All trials	10	2,199/52,724	2,204/51,063	0.94 (0.88, 0.99)	0.97 (0.93, 1.02)	PPP, HOT, JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	8	1,589/47,439	1,687/47,498	0.94 (0.88, 1.01)	0.98 (0.93, 1.03)	PPP, HOT, JPAD, PHS, POPADAD, TPT, AAA, WHS
		Dose ≤ 100 mg per day	7	1,372/36,402	1,460/36,464	0.94 (0.88, 1.01)	0.99 (0.93, 1.04)	PPP, HOT, JPAD, POPADAD, TPT, AAA, WHS
		Daily dose	8	1,373/21,753	1,335/20,087	0.93 (0.86, 1.00)	0.93 (0.86, 1.00)	PPP, HOT, JPAD, ETDRS, BMD, POPADAD, TPT, AAA
		Every other day dose	2	826/30,971	869/30,976	0.95 (0.87, 1.04)	1.00 (0.94, 1.07)	PHS, WHS
		Followup ≥ 5 years	7	1,819/39,837	1,783/38,126	0.94 (0.89, 1.00)	0.98 (0.93, 1.03)	PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Followup ≥ 4 years	8	1,853/41,099	1,821/39,403	0.94 (0.89, 1.00)	0.98 (0.93, 1.03)	JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Followup ≥ 4 years and daily dose	6	1,027/10,128	952/8,427	0.93 (0.86, 1.02)	0.93 (0.86, 1.02)	JPAD, ETDRS, BMD, POPADAD, TPT, AAA
	All Included Trials	All trials	25	3,322/64,921	3,246/61,692	0.93 (0.89, 0.98)	0.96 (0.92, 1.00)	SPAF, CDPA, WARFASA, ESPS-2, JAST, EAFT, ACBS, SALT, AFPPS, ASPIRE, AMIS, ukCAP, PARIS, PPP, HOT, UK-TIA, SAPAT, JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	20	2,226/54,986	2,394/54,693	0.93 (0.88, 0.98)	0.96 (0.92, 1.01)	SPAF, WARFASA, ESPS-2, JAST, EAFT, ACBS, SALT, AFPPS, ASPIRE, ukCAP, PPP, HOT, UK-TIA (300 mg arm only), SAPAT, JPAD, PHS, POPADAD, TPT, AAA, WHS
		Dose ≤ 100 mg per day	13	1,722/40,729	1,863/40,803	0.93 (0.87, 0.99)	0.97 (0.92, 1.02)	ESPS-2, WARFASA, SALT, AFPPS (81 mg arm only), ASPIRE, PPP, HOT, SAPAT, JPAD, POPADAD, TPT, AAA, WHS

Table 9. Sensitivity Analyses by Dosage and Frequency of Cancer Incidence, Cancer Mortality, and All-Cause Mortality

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled RR (95% CI)	Pooled RR When Long-Term WHS Data Used*	Names of Trials
		Daily dose	23	2,496/33,950	2,377/30,716	0.93 (0.88, 0.98)	0.93 (0.88, 0.98)	SPAF, CDPA, WARFASA, ESPS-2, JAST, EAFT, ACBS, SALT, AFPPS, ASPIRE, AMIS, ukCAP, PARIS, PPP, HOT, UK-TIA, SAPAT, JPAD, ETDRS, BMD, POPADAD, TPT, AAA
		Every other day dose	2	826/30,971	869/30,976	0.95 (0.87, 1.04)	1.00 (0.94, 1.07)	PHS, WHS
		Dose ≤ 325 mg per day and daily dose	18	1,400/24,015	1,525/23,717	0.92 (0.85, 0.98)	0.92 (0.85, 0.98)	SPAF, WARFASA, ESPS-2, JAST, EAFT, ACBS, SALT, AFPPS, ASPIRE, ukCAP, PPP, HOT, UK-TIA, SAPAT, JPAD, POPADAD, TPT, AAA
		Followup ≥ 4 years	10	2,156/43,729	2,049/41,243	0.93 (0.88, 0.99)	0.97 (0.93, 1.02)	UK-TIA, SAPAT, JPAD, PHS, ETDRS, BMD, POPADAD, TPT, AAA, WHS
		Followup ≥ 4 years and daily dose	8	1,330/12,758	1,180/10,267	0.92 (0.85, 0.99)	0.92 (0.85, 0.99)	UK-TIA, SAPAT, JPAD, ETDRS, BMD, POPADAD, TPT, AAA
Cancer incidence	CVD Primary Prevention Trials	All trials	6	2,155/37,301	2,139/35,625	0.98 (0.93, 1.04)	0.97 (0.92, 1.01)	WHS, HOT, AAA, PPP, POPADAD, BMD
		Dose ≤ 325 mg per day	5	2,036/33,872	2,081/33,915	0.98 (0.92, 1.04)	0.97 (0.92, 1.01)	PPP, HOT, POPADAD, AAA, WHS
		Dose ≤ 100 mg per day	5	2,036/33,872	2,081/33,915	0.98 (0.92, 1.04)	0.97 (0.92, 1.01)	PPP, HOT, POPADAD, AAA, WHS
		Daily dose	5	717/17,367	712/15,683	0.93 (0.84, 1.03)	0.93 (0.84, 1.03)	PPP, HOT, BMD, POPADAD, AAA
		Every other day dose	1	1438/19934	1427/19,942	1.01 (0.94, 1.08)	0.98 (0.93, 1.03)	WHS
		Followup ≥ 5 years	4	1,768/25,676	1,739/23,965	0.98 (0.92, 1.05)	0.97 (0.92, 1.02)	WHS, POPADAD, AAA, BMD
		Followup ≥ 4 years	4	1,768/25,676	1,739/23,965	0.98 (0.92, 1.05)	0.97 (0.92, 1.02)	WHS, POPADAD, AAA, BMD
		Followup ≥ 4 years and daily dose	3	330/5,742	312/4,023	0.88 (0.75, 1.02)	0.88 (0.75, 1.02)	POPADAD, AAA, BMD
	All Included Trials	All trials	12	2,288/43,858	2,269/41,707	0.98 (0.93, 1.04)	0.97 (0.93, 1.01)	AFPPS, ESPS-2, SAPAT, AMIS, HOT, BMD, PPP, ukCAP, ASPIRE, WHS, POPADAD, AAA
		Dose ≤ 325 mg per day	10	2,119/38,162	2,168/37,740	0.97 (0.92, 1.03)	0.96 (0.92, 1.01)	ESPS-2, AFPPS, ASPIRE, ukCAP, PPP, HOT, SAPAT, POPADAD, AAA, WHS

Table 9. Sensitivity Analyses by Dosage and Frequency of Cancer Incidence, Cancer Mortality, and All-Cause Mortality

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled RR (95% CI)	Pooled RR When Long-Term WHS Data Used*	Names of Trials
		Dose ≤ 100 mg per day	9	2,107/37,690	2,153/37,373	0.98 (0.92, 1.04)	0.97 (0.92, 1.01)	ESPS-2, AFPPS, ASPIRE, PPP, HOT, SAPAT, POPADAD, AAA, WHS
		Daily dose	11	850/23,924	842/21,765	0.94 (0.85, 1.02)	0.94 (0.85, 1.02)	ESPS-2, AFPPS, ASPIRE, AMIS, ukCAP, PPP, HOT, SAPAT, BMD, POPADAD, AAA
		Every other day dose	1	1,438/19,934	1,427/19,942	1.01 (0.94, 1.08)	0.98 (0.93, 1.03)	WHS
		Dose ≤ 325 mg per day and daily dose	9	681/18,228	741/17,798	0.91 (0.82, 1.01)	0.91 (0.82, 1.01)	ESPS-2, AFPPS, ASPIRE, ukCAP, PPP, HOT, SAPAT, POPADAD, AAA
		Followup ≥ 4 years	5	1,778/26,685	1,758/24,991	0.98 (0.92, 1.04)	0.96 (0.92, 1.01)	WHS, SAPAT, AAA, POPADAD, BMD
		Followup ≥ 4 years and daily dose	4	340/6,751	331/5,049	0.86 (0.74, 0.99)	0.86 (0.74, 0.99)	SAPAT, POPADAD, AAA, BMD

*Raw data to left columns do not reflect this analysis

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; mg = milligram(s); RR = relative risk

Table 10. Absolute Risk Reduction and Number Needed to Treat or Harm With ASA, CVD Primary Prevention Trials

Included ASA Doses	Outcome	Risk Level‡	Baseline Risk of Outcome, Events per 10,000 p-y	Baseline Risk of Outcome, Events per 1,000 p-y	Events prevented per 10,000 p-y (95% CI)	Events prevented per 1,000 p-y (95% CI)	NNT-B per Year (95% CI)†	NNT-H per Year (95% CI)†
All ASA doses	All-cause mortality*	Low	31.9	3.19	1.9 (0.3 to 3.8)	0.19 (0.03 to 0.38)	5,263 (2,632 to 33,333)	--
		Med	95.5	9.55	5.7 (1.0 to 11.5)	0.57 (0.10 to 1.15)	1,754 (870 to 10,000)	--
		High	135.4	13.54	8.1 (1.4 to 16.3)	0.81 (0.14 to 1.63)	1,235 (613 to 7,143)	--
	Fatal CVD (fatal MI/ coronary, fatal stroke, and CVD mortality)*	Low	6.3	0.63	0.4 (-0.2 to 0.9)	0.04 (-0.02 to 0.09)	--	--
		Med	38.0	3.80	2.3 (-1.1 to 5.7)	0.23 (-0.11 to 0.57)	--	--
		High	46.2	4.62	2.8 (-1.4 to 6.9)	0.28 (-0.14 to 0.69)	--	--
	Nonfatal stroke*	Low	12.1	1.21	0.7 (-0.7 to 1.9)	0.07 (-0.07 to 0.19)	--	--
		Med	27.7	2.77	1.7 (-1.7 to 4.4)	0.17 (-0.17 to 0.44)	--	--
		High	48.4	4.84	2.9 (-2.9 to 7.7)	0.29 (-0.29 to 0.77)	--	--
	Nonfatal MI/coronary*	Low	9.0	0.90	1.8 (1.1 to 2.5)	0.18 (0.11 to 0.25)	5,556 (4,000 to 9,091)	--
		Med	29.3	2.93	5.9 (3.5 to 8.2)	0.59 (0.35 to 0.82)	1,695 (1,220 to 2,857)	--
		High	84.4	8.44	16.9 (10.1 to 23.6)	1.69 (1.01 to 2.36)	592 (424 to 990)	--
	Major CVD events*	Low	25.9	2.59	2.9 (1.3 to 4.1)	0.29 (0.13 to 0.41)	3,448 (2,439 to 7,692)	--
		Med	90.8	9.08	10.0 (4.5 to 14.5)	1.00 (0.45 to 1.45)	1,000 (690 to 2,222)	--
		High	159.5	15.95	17.5 (8.0 to 25.5)	1.75 (0.80 to 2.55)	571 (392 to 1,250)	--
	Cancer incidence	Low	56.5	5.65	1.1 (-2.3 to 4.0)	0.11 (-0.23 to 0.40)	--	--
		Med	98.1	9.81	2.0 (-3.9 to 6.9)	0.20 (-0.39 to 0.69)	--	--
		High	141.2	14.12	2.8 (-5.6 to 9.9)	0.28 (-0.56 to 0.99)	--	--
	Cancer mortality	Low	12.3	1.23	0.5 (-0.7 to 1.6)	0.05 (-0.07 to 0.16)	--	--
		Median	34.8	3.48	1.4 (-2.1 to 4.5)	0.14 (-0.21 to 0.45)	--	--
		High	72.5	7.25	2.9 (-4.4 to 9.4)	0.29 (-0.44 to 0.94)	--	--
	Major GI bleeding	Low	2.3	0.23	-1.4 (-2.1 to -0.7)	-0.14 (-0.21 to -0.07)	--	7,143 (4,762 to 14,286)
		Median	4.9	0.49	-2.9 (-4.4 to -1.6)	-0.29 (-0.44 to -0.16)	--	3,448 (2,273 to 6,250)
		High	10.4	1.04	-6.1 (-9.4 to -3.3)	-0.61 (-0.94 to -0.33)	--	1,639 (1,064 to 3,030)
		High‡	14.0‡	1.40‡	-8.3 (-12.7 to -4.5)	-0.83 (-1.27 to -0.45)	--	1,205 (787 to 2,222)
		High‡	20.0‡	2.00‡	-11.8 (-18.2 to -6.4)	-1.18 (-1.82 to -0.64)	--	847 (549 to 1,563)

Table 10. Absolute Risk Reduction and Number Needed to Treat or Harm With ASA, CVD Primary Prevention Trials

Included ASA Doses	Outcome	Risk Level‡	Baseline Risk of Outcome, Events per 10,000 p-y	Baseline Risk of Outcome, Events per 1,000 p-y	Events prevented per 10,000 p-y (95% CI)	Events prevented per 1,000 p-y (95% CI)	NNT-B per Year (95% CI)†	NNT-H per Year (95% CI)†
	ICH including hemorrhagic stroke	Low	2.0	0.20	-0.6 (-1.3 to 0.0)	-0.06 (-0.13 to 0.00)	--	--
		Med	4.2	0.42	-1.1 (-2.8 to 0.1)	-0.11 (-0.28 to 0.01)	--	--
		High	12.5	1.25	-3.4 (-8.3 to 0.3)	-0.34 (-0.83 to 0.03)	--	--
		High‡	17.0‡	1.70‡	-4.6 (-11.2 to 0.3)	-0.46 (-1.12 to 0.03)	--	--
ASA dose ≤ 100 mg per day	All-cause mortality*	Low	31.9	3.19	1.9 (-0.3 to 3.8)	0.19 (-0.03 to 0.38)	--	--
		Med	95.5	9.55	5.7 (-1.0 to 11.5)	0.57 (-0.10 to 1.15)	--	--
		High	135.4	13.54	8.1 (-1.4 to 16.3)	0.81 (-0.14 to 1.63)	--	--
	Fatal CVD (fatal MI/coronary, fatal stroke, and CVD mortality)**	Low	6.3	0.63	0.3 (-0.7 to 1.0)	0.03 (-0.07 to 0.10)	--	--
		Med	38.0	3.80	1.5 (-4.2 to 6.1)	0.15 (-0.42 to 0.61)	--	--
		High	46.2	4.62	1.8 (-5.1 to 7.4)	0.18 (-0.51 to 0.74)	--	--
	Nonfatal stroke*	Low	12.1	1.21	2.2 (0.6 to 3.5)	0.22 (0.06 to 0.35)	4,545 (2,857 to 16,667)	--
		Med	27.7	2.77	5.0 (1.4 to 8.0)	0.50 (0.14 to 0.80)	2,000 (1,250 to 7,143)	--
		High	48.4	4.84	8.7 (2.4 to 14.0)	0.87 (0.24 to 1.40)	1,149 (714 to 4,167)	--
	Nonfatal MI/coronary*	Low	9.0	0.90	1.3 (0.3 to 2.2)	0.13 (0.03 to 0.22)	7,692 (4,545 to 33,333)	--
		Med	29.3	2.93	4.4 (0.9 to 7.3)	0.44 (0.09 to 0.73)	2,273 (1,370 to 11,111)	--
		High	84.4	8.44	12.7 (2.5 to 21.1)	1.27 (0.25 to 2.11)	787 (474 to 4,000)	--
	Major CVD events*	Low	25.9	2.59	3.1 (1.3 to 4.7)	0.31 (0.13 to 0.47)	3,226 (2,128 to 7,692)	--
		Med	90.8	9.08	10.9 (4.5 to 16.3)	1.09 (0.45 to 1.63)	917 (613 to 2,222)	--
		High	159.5	15.95	19.1 (8.0 to 28.7)	1.91 (0.80 to 2.87)	524 (348 to 1,250)	--
	Cancer incidence	Low	56.5	5.65	1.1 (-2.3 to 4.5)	0.11 (-0.23 to 0.45)	--	--
		Med	98.1	9.81	2.0 (-3.9 to 7.8)	0.20 (-0.39 to 0.78)	--	--
		High	141.2	14.12	2.8 (-5.6 to 11.3)	0.28 (-0.56 to 1.13)	--	--
	Cancer mortality	Low	12.3	1.23	0.6 (-0.7 to 1.8)	0.06 (-0.07 to 0.18)	--	--
		Med	34.8	3.48	1.7 (-2.1 to 5.2)	0.17 (-0.21 to 0.52)	--	--
		High	72.5	7.25	3.6 (-4.4 to 10.9)	0.36 (-0.44 to 1.09)	--	--
	Major GI bleeding	Low	2.3	0.23	-1.3 (-2.2 to -0.7)	-0.13 (-0.22 to -0.07)	--	7,692 (4,545 to 14,286)

Table 10. Absolute Risk Reduction and Number Needed to Treat or Harm With ASA, CVD Primary Prevention Trials

Included ASA Doses	Outcome	Risk Level‡	Baseline Risk of Outcome, Events per 10,000 p-y	Baseline Risk of Outcome, Events per 1,000 p-y	Events prevented per 10,000 p-y (95% CI)	Events prevented per 1,000 p-y (95% CI)	NNT-B per Year (95% CI)†	NNT-H per Year (95% CI)†
		Med	4.9	0.49	-2.8 (-4.6 to -1.4)	-0.28 (-0.46 to -0.14)	--	3,571 (2,174 to 7,143)
		High	10.4	1.04	-6.0 (-9.9 to -3.0)	-0.60 (-0.99 to -0.30)	--	1,667 (1,010 to 3,333)
	ICH including hemorrhagic stroke	Low	2.0	0.20	-0.4 (-1.2 to 0.2)	-0.04 (-0.12 to 0.02)	--	--
		Med	4.2	0.42	-0.8 (-2.6 to 0.5)	-0.08 (-0.26 to 0.05)	--	--
		High	12.5	1.25	-2.4 (-7.6 to 1.5)	-0.24 (-0.76 to 0.15)	--	--

*Data from companion systematic review on CVD primary prevention[41]
†Only outcomes with statistically significant results had NNT calculated
‡Minimum, maximum, and median control group rate for each outcome, excluding zeros and outliers, from the set of CVD primary prevention trials

Abbreviations: ARR = absolute risk reduction; ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; GI = gastrointestinal; ICH = intracranial hemorrhage; mg – milligram(S); MI = myocardial infarction; NNT-B = number need to treat to benefit; NNT-H = number need to treat to harm; p-y = person-years

Table 11. Sensitivity Analyses by Dosage and Frequency of Major GI and Intracranial Bleeding, Including Hemorrhagic Stroke

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled OR (95% CI)	Names of Trials
Major GI bleeding	CVD Primary Prevention Trials	All trials	7	277/48,005	172/46,302	1.59 (1.32, 1.91)	HOT, JPAD, PHS, BMD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	6	274/44,576	169/44,592	1.61 (1.34, 1.94)	HOT, JPAD, PHS, TPT, AAA, WHS
		Dose ≤ 100 mg per day	5	225/33,539	141/33,558	1.58 (1.29, 1.95)	HOT, JPAD, TPT, AAA, WHS
		Daily dose	5	99/17,034	50/15,326	1.91 (1.37, 2.67)	HOT, JPAD, BMD, TPT, AAA
		Every other day dose	2	178/30,971	122/30,976	1.46 (1.16, 1.84)	PHS, WHS
	All Included Trials	All trials	15	319/54,306	190/52,219	1.63 (1.37, 1.95)	Silagy, EAFT, ACBS, SALT, AFPPS, AMIS, HOT, UK-TIA, SAPAT, JPAD, PHS, BMD, TPT, AAA, WHS
		Dose ≤ 325 mg per day	13	315/48,609	187/48,251	1.65 (1.39, 1.97)	Silagy, EAFT, ACBS, SALT, AFPPS, HOT, UK-TIA, SAPAT, JPAD, PHS, TPT, AAA, WHS
		Dose ≤ 100 mg per day	9	249/35,802	155/35,841	1.60 (1.31, 1.94)	Silagy, SALT, AFPPS, HOT, SAPAT, JPAD, TPT, AAA, WHS
		Daily dose	13	141/23,335	68/21,243	1.97 (1.48, 2.62)	Silagy, EAFT, ACBS, SALT, AFPPS, AMIS, HOT, UK-TIA, SAPAT, JPAD, BMD, TPT, AAA
		Every other day dose	2	178/30,971	122/30,976	1.46 (1.16, 1.84)	PHS, WHS
Intracranial bleeding including hemorrhagic stroke	CVD Primary Prevention Trials	All trials	9	129/50,868	96/49,208	1.27 (0.98, 1.66)	PPP, TPT, HOT, JPAD, PHS, BMD, POPADAD, AAA, WHS
		Dose ≤ 325 mg per day	8	116/47,439	90/47,498	1.29 (0.98, 1.70)	PPP, TPT, HOT, JPAD, PHS, POPADAD, AAA, WHS
		Dose ≤ 100 mg per day	7	93/36,402	78/36,464	1.19 (0.88, 1.61)	PPP, TPT, HOT, JPAD, POPADAD, AAA, WHS
		Daily dose	7	55/19,897	43/18,232	1.13 (0.76, 1.69)	PPP, TPT, HOT, JPAD, BMD, POPADAD, AAA
		Every other day dose	2	74/30,971	53/30,976	1.39 (0.98, 1.97)	PHS, WHS
	All Included Trials	All trials	19	165/56,491	110/54,487	1.43 (1.12, 1.81)	SPAF, Copenhagen AFASAK, JAST, EAFT, ACBS, SALT, AFPPS, ukCAP, PPP, HOT, TPT, UK-TIA, SAPAT, JPAD, PHS, BMD, POPADAD, AAA, WHS
		Dose ≤ 325 mg per day	18	152/53,062	104/52,777	1.45 (1.14, 1.86)	SPAF, Copenhagen AFASAK, JAST, EAFT, ACBS, SALT, AFPPS, ukCAP, PPP, HOT, TPT, UK-TIA, SAPAT, JPAD, PHS, POPADAD, AAA, WHS

Table 11. Sensitivity Analyses by Dosage and Frequency of Major GI and Intracranial Bleeding, Including Hemorrhagic Stroke

Outcome	Trials	Sensitivity Analysis	k	ASA (number of cases / number of participants)	No ASA (number of cases / number of participants)	Pooled OR (95% CI)	Names of Trials
		Dose ≤ 100 mg per day	11	112/38,802	85/38,884	1.32 (1.00, 1.75)	Copenhagen AFASAK, SALT, AFPPS, PPP, HOT, TPT, SAPAT, JPAD, POPADAD, AAA, WHS
		Daily dose	17	91/25,520	57/23,511	1.46 (1.05, 2.01)	SPAF, Copenhagen AFASAK, JAST, EAFT, ACBS, SALT, AFPPS, ukCAP, PPP, HOT, TPT, UK-TIA, SAPAT, JPAD, BMD, POPADAD, AAA
		Every other day dose	2	74/30,971	53/30,976	1.39 (0.98, 1.97)	PHS, WHS

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; CVD = cardiovascular disease; mg = milligram(s); RR = relative risk

Table 12. Nontrivial Bleeding According to Various Study-Level Characteristics[44]

Characteristics	Subgroup	OR (95% CI)	P-value for interaction
Period of publication	After the year 2000	1.33 (0.97 to 1.83)	0.004
	Before the year 2000	1.37 (1.16 to 1.61)	
Number of participants per study	≥ 5,000 participants	1.26 (1.07 to 1.47)	0.06
	< 5,000 participants	1.43 (1.05 to 1.93)	
Number of events per study	≥ 500 events	1.16 (1.05 to 1.29)	0.002
	< 500 events	1.48 (1.17 to 1.86)	
Average daily dose of ASA	≥ 100 mg	1.26 (0.99 to 1.61)	0.12
	< 100 mg	1.40 (1.08 to 1.82)	
Schedule of ASA treatment	Daily	1.48 (1.17 to 1.86)	0.002
	Alternate day	1.16 (1.05 to 1.29)	
Concomitant treatment	Yes	1.33 (1.05 to 1.69)	0.08
	No	1.26 (1.14 to 1.39)	

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; mg = milligrams; OR = odds ratio

Table 13. Results of Included CVD Primary Prevention Trials, Ulcers

Type of Ulcer	Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Peptic ulcer	Cook, 2013 (companion publication to Cook, 2005)[88] Good (KQ1,2); Fair (KQ6)	Ulcer, peptic (number of cases)	10	19934 19942	ASA No ASA	1115 (5.6%) 931 (4.7%)	ASA vs. No ASA: HR 1.20 (95% CI, 1.10 to 1.31), p≤0.001†
	Peto, 1988 (BMD)[72] Fair	Ulcer, peptic (number of participants)	6	3429 1710	ASA No ASA	88 (2.6%) 28 (1.6%)	ASA vs. No ASA: RR 1.57 (95% CI, 1.03 to 2.39)*, p≤0.05
	PHS, 1989[73] Good (KQ1); Fair (KQ6)	Ulcer, peptic (number of participants)	5	11037	ASA	156 (1.4%)	ASA vs. Placebo: RR 1.21 (95% CI, 0.96 to 1.52)*, p=0.11‡
GI ulcer	Fowkes, 2010 (AAA)[66] Good	Ulcer, GI (number of participants)	8.2	1675 1675	ASA Placebo	14 (0.8%) 8 (0.5%)	ASA vs. Placebo: RR 1.75 (95% CI, 0.74 to 4.16)*
	PHS, 1989[73] Good (KQ1); Fair (KQ6)	Ulcer, upper GI (number of participants)	5	11037 11034	ASA Placebo	169 (1.5%) 138 (1.3%)	ASA vs. Placebo: RR 1.22 (95% CI, 0.98 to 1.53), p=0.08‡

*Calculated
†Adjusted by age, vitamin E and beta-carotene treatment assignment
‡Adjusted by age and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; KQ = key question; RR = relative risk

Table 14. Absolute Bleeding Rates Among NonASA Control Groups, Overall and by Subpopulation, From Trials and Cohort Studies

Baseline Characteristic	**Major GI/Extracranial Bleeding‡** from ATT Collaboration, 2009[87]; events per 1,000 person-years	**Intracranial Bleeding/ Hemorrhagic Stroke** from ATT Collaboration, 2009[87]; events per 1,000 person-years	**Hospitalizations for Major Bleeding Event§** from cohort studies (de Berardis[85]); events per 1,000 person-years (95% CI)
All control group participants	0.7	0.3	3.60 (3.48 to 3.72) Major extracranial bleeding (approx..): 2.40 Major intracranial bleeding (approx.): 1.20
Age subgroups	< 65 years: 0.5 65+ years: 1.7	--	< 50 years: 0.61 (0.41 to 0.91) 50-59 years: 1.40 (1.24 to 1.58) 60-69 years: 2.58 (2.40 to 2.77) 70-79 years: 4.61 (4.39 to 4.85) 80+ years: 6.93 (6.51 to 7.38)
Sex subgroups	Male: 1.0 Female: 0.5	--	Male: 4.50 (4.3 to 4.70) Female: 2.86 (2.72 to 3.01)

‡Resulting in hospitalization, transfusion or death
§Combined GI bleeding and intracranial hemorrhage/hemorrhagic stroke

Abbreviations: ATT = Antithrombotic Trialists; CI = confidence interval; GI = gastrointestinal

Table 15. Relative Rate Ratios for Bleeding Among Subpopulations From Trials and Cohort Studies

Baseline Characteristic	**Major GI/Extracranial Bleeding‡** from ATT Collaboration, 2009[87] *Adjusted Rate Ratio (95% CI)*	**Intracranial Bleeding/Hemorrhagic Stroke** from ATT Collaboration, 2009[87] *Adjusted Rate Ratio (95% CI)*	**Hospitalizations for Major Bleeding Event§** from cohort study (de Berardis[85]) *Adjusted Incidence Rate Ratio (95% CI)*
Age	2.15 (1.93 to 2.39) per decade	1.59 (1.33 to 1.90) per decade	1.05 (1.05 to 1.05) per year
Male sex (vs. female)	1.99 (1.45 to 2.73)	1.11 (0.52 to 2.34)	1.69 (1.61 to 1.79)
Diabetes (yes vs. no)	1.55 (1.13 to 2.14)	1.74 (0.95 to 3.17)	1.36 (1.28 to 1.44)
Current Smoker (yes vs. no)	1.56 (1.25 to 1.94)	2.18 (1.57 to 3.02)	
Mean BP (per 20 mm Hg)	1.32 (1.09 to 1.58)	2.18 (1.62 to 2.87)	
Cholesterol (per 1 mmol/L)	0.99 (0.90 to 1.08	0.90 (0.77 to 1.07)	
BMI (per 5 kilograms):	1.24 (1.13 to1.35)	0.85 (0.71 to 1.02)	
Previous GI hospitalization (yes vs no)	---	---	2.87 (2.46 to 3.35)
Medication use (yes vs no):			
NSAIDS			1.10 (1.05 to 1.16)
ASA†			1.55 (1.48 to 1.63)* 1.61 (1.54 to 1.69)‖
Any antihypertensive			1.14 (1.08 to 1.19)
Statins			0.67 (0.62 to 0.71)
PPI			0.84 (0.80 to 0.88)

*Crude incidence rate ratio (95% CI)
†Used as an analgesic
‡Resulting in hospitalization, transfusion or death
§Combined GI bleeding and intracranial hemorrhage/hemorrhagic stroke
‖Adjusted incidence rate ratio

Abbreviations: ASA = acetylsalicylic acid; BMI = body mass index; CI = confidence interval; GI = gastrointestinal; mmol/L = millmoles per liter; mm Hg = millimeters of mercury; NSAID = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitor; vs = versus

Literature Search Strategies – Systematic Reviews (benefits)

Cochrane Database of Systematic Reviews

#1 Gastrointestinal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#2 Gastrointestinal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#3 Gastrointestinal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#4 Gastrointestinal next tumour*:ti,ab,kw from 2008 to 2013
#5 gastric next neoplasm*:ti,ab,kw from 2008 to 2013
#6 gastric next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#7 gastric next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#8 gastric next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#9 gastric next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#10 gastric next adenocarcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#11 Esophageal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#12 Esophageal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#13 Esophageal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#14 Esophageal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#15 Esophageal next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#16 oesophageal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#17 oesophageal next neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#18 oesophageal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#19 oesophageal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#20 oesophageal next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#21 Intestinal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#22 Intestinal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#23 Intestinal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#24 Intestinal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#25 Duodenal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#26 Duodenal nex cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#27 Duodenal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#28 Duodenal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#29 Ileal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#30 Ileal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#31 Ileal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#32 Ileal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#33 Jejunal next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#34 Jejunal next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#35 Jejunal next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#36 Jejunal next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#37 Stomach next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#38 Stomach next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#39 Stomach next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#40 Stomach next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#41 breast next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#42 breast next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews

#43 breast next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#44 breast next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#45 breast next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#46 lung next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#47 lung next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#48 lung next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#49 lung next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#50 lung next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#51 lung next adenocarcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#52 Bronchial next Neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#53 Bronchial next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#54 Bronchial next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#55 Bronchial next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#56 prostat* next neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#57 prostat* next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#58 prostat* next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#59 prostat* next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#60 prostat* next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#61 Pancreatic next neoplasm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#62 Pancreatic next cancer*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#63 Pancreatic next tumor*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#64 Pancreatic next tumour*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#65 Pancreatic next carcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#66 Pancreatic next adenocarcinoma*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#67 or #1-#66 from 2008 to 2013, in Cochrane Reviews
#68 Aspirin:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#69 "acetylsalicylic acid":ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#70 Salicylate*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews
#71 #68 or #69 or #70 from 2008 to 2013, in Cochrane Reviews
#72 #67 and #71 from 2008 to 2013, in Cochrane Reviews

DARE

1 (neoplasm*) OR (cancer*) OR (tumor*) OR (tumour*) OR (carcinoma*)
2 (adenocarcinoma*)
3 #1 OR #2
4 (Gastrointestinal) OR (gastric) OR (Esophageal) OR (oesophageal) OR (Intestinal) FROM 2008 TO 2013
5 (Duodenal) OR (Ileal) OR (Jejunal) OR (Stomach) OR (breast) FROM 2008 TO 2013
6 (lung) OR (Bronchial) OR (prostat*) OR (Pancreatic) FROM 2008 TO 2013
7 #4 OR #5 OR #6
8 #3 AND #7
9 (prevent*) IN DARE FROM 2008 TO 2013
10 #8 AND #9

HTA

1 (neoplasm*) OR (cancer*) OR (tumor*) OR (tumour*) OR (carcinoma*)
2 (adenocarcinoma*)
3 #1 OR #2
4 (Gastrointestinal) OR (gastric) OR (Esophageal) OR (oesophageal) OR (Intestinal) FROM 2008 TO 2013
5 (Duodenal) OR (Ileal) OR (Jejunal) OR (Stomach) OR (breast) FROM 2008 TO 2013
6 (lung) OR (Bronchial) OR (prostat*) OR (Pancreatic) FROM 2008 TO 2013
7 #4 OR #5 OR #6
8 #3 AND #7
9 (prevent*) IN HTA FROM 2008 TO 2013
10 #8 AND #9

PubMed

#20 #9 OR #16 OR #17 OR #18 Filters: Publication date from 2008/01/01; English
#19 #9 OR #16 OR #17 OR #18
#18 aspirin[ti] AND cancer[ti] AND (gastrointestinal[ti] OR breast[ti] OR lung[ti] OR prostat*[ti] OR pancreatic[ti] OR gastric[ti]) AND systematic[sb]
#17 #6 AND aspirin[tiab] AND #8 AND systematic[sb]
#16 #12 AND #13 AND #14 AND systematic[sb] AND (publisher[sb] OR in process[sb] OR pubmednotmedline[sb])
#15 #12 AND #13 AND #14 AND systematic[sb]
#14 prevent*[tiab]
#13 Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]
#12 #10 OR #11
#11 (breast[tiab] OR lung[tiab] OR Bronchial[tiab] OR prostat*[tiab] OR Pancreatic[tiab]) AND (Neoplasm*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])
#10 (Gastrointestinal[tiab] OR gastric[tiab] OR Esophageal[tiab] OR oesophageal[tiab] OR Intestinal[tiab] OR Duodenal[tiab] OR Ileal[tiab] OR Jejunal[tiab] OR Stomach[tiab]) AND (Neoplasm*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])
#9 #6 AND #7 AND #8 AND systematic[sb]
#8 "prevention and control" [Subheading] OR prevent*[tiab]
#7 "Aspirin"[Mesh] OR "Salicylates"[Mesh:NoExp]
#6 #1 OR #2 OR #3 OR #4 OR #5
#5 "Prostatic Neoplasms"[Mesh] OR "Pancreatic Neoplasms"[Mesh:NoExp]
#4 "Lung Neoplasms"[Mesh:NoExp] OR "Bronchial Neoplasms"[Mesh:NoExp] OR "Carcinoma, Bronchogenic"[Mesh:NoExp] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR "Small Cell Lung Carcinoma"[Mesh]
#3 "Breast Neoplasms"[Mesh:NoExp] OR "Breast Neoplasms, Male"[Mesh] OR "Carcinoma, Ductal, Breast"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh]
#2 "Duodenal Neoplasms"[Mesh] OR "Ileal Neoplasms"[Mesh] OR "Jejunal Neoplasms"[Mesh] OR "Stomach Neoplasms"[Mesh]

#1 "Gastrointestinal Neoplasms"[Mesh:NoExp] OR "Esophageal Neoplasms"[Mesh:NoExp] OR "Gastrointestinal Stromal Tumors"[Mesh] OR "Intestinal Neoplasms"[Mesh:NoExp]

Literature Search Strategies – Systematic Reviews (harms)

PubMed

#1 "Aspirin/adverse effects"[Mesh] AND systematic[sb] Filters: Publication date from 2008/01/01; English
#2 "Platelet Aggregation Inhibitors/adverse effects"[Majr] AND (aspirin[tiab] OR "acetylsalicylic acid"[tiab]) AND systematic[sb] Filters: Publication date from 2008/01/01; English
#3 "Aspirin"[Majr] AND (safety[tiab] OR harm*[tiab] OR adverse[tiab] OR gastrointestinal[tiab] OR bleed*[tiab] or hemorrhag*[tiab] OR haemorrhag*[tiab]) AND systematic[sb] Filters: Publication date from 2008/01/01; English
#4 ((aspirin[tiab] OR "acetylsalicylic acid"[tiab]) AND (safety[tiab] OR harm*[tiab] OR adverse[tiab] OR gastrointestinal[tiab] OR bleed*[tiab] or hemorrhag*[tiab] OR haemorrhag*[tiab]) AND (in process[sb] OR publisher[sb] OR pubmednotmedline[sb]) AND systematic[sb]) NOT "Clin Evid (Online)"[jour] Filters: Publication date from 2008/01/01; English
#5 #1 OR #2 OR #3 OR #4 = 187

Cochrane Database of Systematic Reviews

#1 aspirin:ti from 2008 to 2013, in Cochrane Reviews (Reviews only)
#2 "acetylsalicylic acid":ti from 2008 to 2013, in Cochrane Reviews (Reviews only)
#3 Platelet next Aggregation next Inhibit*:ti from 2008 to 2013, in Cochrane Reviews (Reviews only)
#4 #1 or #2 or #3 from 2008 to 2013, in Cochrane Reviews (Reviews only)
#5 safety:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#6 adverse:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#7 harm*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#8 gastrointestinal:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#9 bleed*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#10 hemorrhag*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#11 haemorrhag*:ti,ab,kw from 2008 to 2013, in Cochrane Reviews (Reviews only)
#12 #5 or #6 or #7 or #8 or #9 or #10 or #11 from 2008 to 2013, in Cochrane Reviews (Reviews only)
#13 #4 and #12 from 2008 to 2013, in Cochrane Reviews (Reviews only) = 12

DARE

1 (aspirin):TI OR (acetylsalicylic acid):TI IN DARE FROM 2008 TO 2013
2 (safety) OR (adverse) OR (harm*) OR (gastrointestinal) IN DARE FROM 2008 TO 2013
3 (bleed*) OR (hemorrhag*) OR (haemorrhag*) IN DARE FROM 2008 TO 2013

4 #2 OR #3
5 #1 AND #4 = 46 total (only 4 non-duplicates from PubMed or CDSR)

Literature Search Strategies – Primary Literature (benefits)

MEDLINE

1 Gastrointestinal Neoplasms/ ()
2 Esophageal Neoplasms/ ()
3 Gastrointestinal Stromal Tumors/ ()
4 Intestinal Neoplasms/ ()
5 Duodenal Neoplasms/ ()
6 Ileal Neoplasms/ ()
7 Jejunal Neoplasms/ ()
8 Stomach Neoplasms/ ()
9 Breast Neoplasms/ ()
10 Breast Neoplasms, Male/ ()
11 Carcinoma, Ductal, Breast/ ()
12 Inflammatory Breast Neoplasms/ ()
13 Lung Neoplasms/ ()
14 Bronchial Neoplasms/ ()
15 Carcinoma, Bronchogenic/ ()
16 Carcinoma, Non-Small-Cell Lung/ ()
17 Small Cell Lung Carcinoma/ ()
18 Prostatic Neoplasms/ ()
19 Pancreatic Neoplasms/ ()
20 gastrointestinal.ti,ab. ()
21 gastric.ti,ab. ()
22 esophageal.ti,ab. ()
23 esophagus.ti,ab. ()
24 oesophageal.ti,ab. ()
25 intestinal.ti,ab. ()
26 duodenal.ti,ab. ()
27 ileal.ti,ab. ()
28 jejunal.ti,ab. ()
29 stomach.ti,ab. ()
30 breast.ti,ab. ()
31 lung.ti,ab. ()
32 bronchia$.ti,ab. ()
33 prostat$.ti,ab. ()
34 (pancreas or pancreatic).ti,ab. ()
35 20 or 21 or 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 ()
36 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).ti,ab. ()
37 35 and 36 ()
38 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$).ti. ()

39 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 37 or 38 ()
40 Aspirin/ ()
41 Salicylates/ ()
42 (Aspirin or acetylsalicylic acid or Salicylate$).ti,ab. ()
43 40 or 41 or 42 ()
44 39 and 43 ()
45 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ ()
46 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
47 Random$.ti,ab. ()
48 control groups/ or double-blind method/ or single-blind method/ ()
49 clinical trial$.ti,ab. ()
50 controlled trial$.ti,ab. ()
51 meta analy$.ti,ab. ()
52 45 or 46 or 47 or 48 or 49 or 50 or 51 ()
53 44 and 52 ()
54 limit 53 to (english language and yr="2011 -Current") ()
55 remove duplicates from 54 ()

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 Gastrointestinal next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#2 Gastrointestinal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#3 Gastrointestinal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#4 Gastrointestinal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#5 Gastrointestinal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#6 Gastrointestinal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#7 gastric next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#8 gastric next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#9 gastric next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#10 gastric next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#11 gastric next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#12 gastric next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#13 Esophageal next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#14 Esophageal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#15 Esophageal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#16 Esophageal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#17 Esophageal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#18 Esophageal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#19 esophagus next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#20 esophagus next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#21 esophagus next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#22 esophagus next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#23 esophagus next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials

#24 esophagus next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#25 oesophageal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#26 oesophageal next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#27 oesophageal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#28 oesophageal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#29 oesophageal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#30 oesophageal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#31 Intestinal next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#32 Intestinal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#33 Intestinal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#34 Intestinal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#35 Intestinal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#36 Intestinal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#37 Duodenal next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#38 Duodenal nex cancer*:ti,ab,kw from 2011 to 2014, in Trials
#39 Duodenal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#40 Duodenal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#41 Duodenal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#42 Duodenal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#43 Ileal next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#44 Ileal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#45 Ileal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#46 Ileal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#47 Ileal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#48 Ileal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#49 Jejunal next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#50 Jejunal next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#51 Jejunal next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#52 Jejunal next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#53 Jejunal next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#54 Jejunal next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#55 Stomach next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#56 Stomach next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#57 Stomach next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#58 Stomach next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#59 Stomach next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#60 Stomach next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#61 breast next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#62 breast next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#63 breast next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#64 breast next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#65 breast next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#66 breast next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#67 lung next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#68 lung next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#69 lung next tumor*:ti,ab,kw from 2011 to 2014, in Trials

#70 lung next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#71 lung next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#72 lung next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#73 Bronchial next Neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#74 Bronchial next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#75 Bronchial next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#76 Bronchial next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#77 Bronchial next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#78 Bronchial next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#79 prostat* next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#80 prostat* next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#81 prostat* next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#82 prostat* next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#83 prostat* next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#84 prostat* next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#85 Pancrea* next neoplasm*:ti,ab,kw from 2011 to 2014, in Trials
#86 Pancrea* next cancer*:ti,ab,kw from 2011 to 2014, in Trials
#87 Pancrea* next tumor*:ti,ab,kw from 2011 to 2014, in Trials
#88 Pancrea* next tumour*:ti,ab,kw from 2011 to 2014, in Trials
#89 Pancrea* next carcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#90 Pancrea* next adenocarcinoma*:ti,ab,kw from 2011 to 2014, in Trials
#91 (neoplasm*:ti or cancer*:ti or tumor*:ti or tumour*:ti or carcinoma*:ti or adenocarcinoma*:ti) from 2011 to 2014, in Trials
#92 or #1-#91 from 2011 to 2014, in Trials
#93 Aspirin:ti,ab,kw from 2011 to 2014, in Trials
#94 "acetylsalicylic acid":ti,ab,kw from 2011 to 2014, in Trials
#95 Salicylate*:ti,ab,kw from 2011 to 2014, in Trials
#96 #93 or #94 or #95 from 2011 to 2014, in Trials
#97 #92 and #96 from 2011 to 2014, in Trials

PubMed

#6 Search #4 AND #5 AND publisher[sb] Filters: Publication date from 2011/01/01 to 2013/06/03; English
#5 Search Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]
#4 Search #1 OR #2 OR #3
#3 Search (neoplasm*[ti] OR cancer*[ti] OR tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti])
#2 Search (breast[tiab] OR lung[tiab] OR bronchial[tiab] OR prostat*[tiab] OR pancreatic[tiab] OR pancreas[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])
#1 Search (gastrointestinal[tiab] OR gastric[tiab] OR esophageal[tiab] OR esophagus[tiab] OR oesophageal[tiab] OR intestinal[tiab] OR duodenal[tiab] OR ileal[tiab] OR jejunal[tiab] OR stomach[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab])

Literature Search Strategies – Primary Literature (harms)

MEDLINE

Database: Ovid MEDLINE(R) without Revisions <1996 to June 3, 2014>, Ovid MEDLINE(R) Daily Update < June 3, 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 3, 2014>

Search Strategy:

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1 Aspirin/ ()
2 aspirin.ti,ab. ()
3 acetylsalicylic acid.ti,ab. ()
4 salicylate$.ti,ab. ()
5 1 or 2 or 3 or 4 ()
6 Mortality/ ()
7 Morbidity/ ()
8 Death/ ()
9 Hemorrhage/ ()
10 Gastrointestinal Hemorrhage/ ()
11 Stroke/ ()
12 Intracranial Hemorrhages/ ()
13 Cerebral Hemorrhage/ ()
14 safety.ti,ab. ()
15 harm$.ti,ab. ()
16 mortality.ti,ab. ()
17 toxicity.ti,ab. ()
18 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. ()
19 gastrointestinal.ti,ab. ()
20 bleed$.ti,ab. ()
21 hemorrhag$.ti,ab. (
22 haemorrhag$.ti,ab. ()
23 stroke$.ti,ab. ()
24 adverse effects.fs. ()
25 toxicity.fs. ()
26 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 ()
27 5 and 26 ()
28 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ ()
29 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
30 Random$.ti,ab. ()
31 control groups/ or double-blind method/ or single-blind method/ ()
32 clinical trial$.ti,ab. ()
33 controlled trial$.ti,ab. ()
34 meta analy$.ti,ab. ()

35 28 or 29 or 30 or 31 or 32 or 33 or 34 ()
36 27 and 35 ()
37 Animals/ not (Humans/ and Animals/) ()
38 36 not 37 ()
39 limit 38 to (english language and yr="2010 -Current") ()
40 remove duplicates from 39 ()

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1 Aspirin/ ()
2 aspirin.ti,ab. ()
3 acetylsalicylic acid.ti,ab. ()
4 salicylate$.ti,ab. ()
5 1 or 2 or 3 or 4 ()
6 Mortality/ ()
7 Morbidity/ ()
8 Death/ ()
9 Hemorrhage/ ()
10 Gastrointestinal Hemorrhage/ ()
11 Stroke/ ()
12 Intracranial Hemorrhages/ ()
13 Cerebral Hemorrhage/ ()
14 safety.ti,ab. ()
15 harm$.ti,ab. ()
16 mortality.ti,ab. ()
17 toxicity.ti,ab. ()
18 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. ()
19 gastrointestinal.ti,ab. ()
20 bleed$.ti,ab. ()
21 hemorrhag$.ti,ab. ()
22 haemorrhag$.ti,ab. ()
23 stroke$.ti,ab. ()
24 adverse effects.fs. ()
25 toxicity.fs. ()
26 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 ()
27 5 and 26 ()
28 limit 27 to (english language and yr="2006 -Current") ()
29 Cohort studies/ ()
30 Longitudinal studies/ ()
31 Prospective studies/ ()
32 Follow-up studies/ ()
33 cohort.ti,ab. ()
34 longitudinal.ti,ab. ()
35 prospective$.ti,ab. ()
36 (follow-up or followup).ti,ab. ()

37 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 ()
38 28 and 37 ()
39 remove duplicates from 38 ()

PubMed

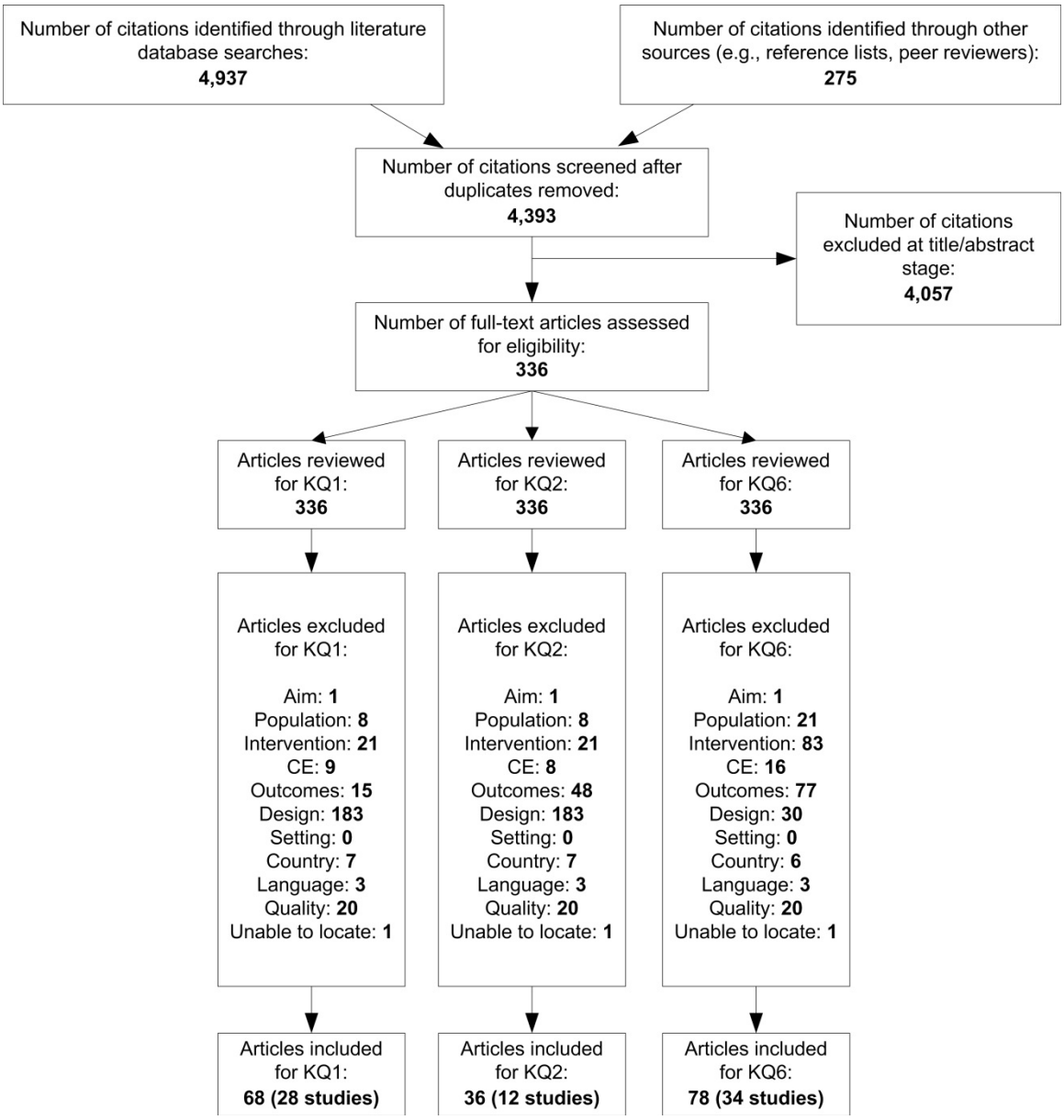
#4 Search #1 AND #2 AND #3 AND English[Language] AND publisher[sb] Filters: Publication date from 2010/01/01 to 2014/06/03
#3 Search random*[tiab] OR trial*[tiab] OR meta analy*[tiab]
#2 Search (safety[tiab] OR harm*[tiab] OR adverse[tiab] OR toxicity[tiab] OR mortality[tiab] OR morbidity[tiab] OR gastrointestinal[tiab] OR bleed*[tiab] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR stroke*[tiab])
#1 Search Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]
#7 Search #4 AND publisher[sb] Filters: Publication date from 2006/01/01 to 2014/06/03; English
#6 Search #4 AND publisher[sb] Filters: English
#4 Search #1 AND #2 AND #3
#3 Search cohort*[tiab] OR prospective*[tiab] OR longitudinal[tiab] OR followup[tiab] OR follow up[tiab]
#2 Search (safety[tiab] OR harm*[tiab] OR adverse[tiab] OR toxicity[tiab] OR mortality[tiab] OR morbidity[tiab] OR gastrointestinal[tiab] OR bleed*[tiab] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR stroke*[tiab])
#1 Search Aspirin[tiab] OR "acetylsalicylic acid"[tiab] OR Salicylate*[tiab]

Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 aspirin:ti,ab,kw from 2010 to 2014, in Trials
#2 "acetylsalicylic acid":ti,ab,kw from 2010 to 2014, in Trials
#3 salicylate*:ti,ab,kw from 2010 to 2014, in Trials
#4 platelet next aggregation next inhibit*:ti,ab,kw from 2010 to 2014, in Trials
#5 #1 or #2 or #3 or #4 from 2010 to 2014, in Trials
#6 safety:ti,ab,kw from 2010 to 2014, in Trials
#7 adverse:ti,ab,kw from 2010 to 2014, in Trials
#8 harm*:ti,ab,kw from 2010 to 2014, in Trials
#9 toxicity:ti,ab,kw from 2010 to 2014, in Trials
#10 mortality:ti,ab,kw from 2010 to 2014, in Trials
#11 morbidity:ti,ab,kw from 2010 to 2014, in Trials
#12 death*:ti,ab,kw from 2010 to 2014, in Trials
#13 gastrointestinal:ti,ab,kw from 2010 to 2014, in Trials
#14 bleed*:ti,ab,kw from 2010 to 2014, in Trials
#15 hemorrhag*:ti,ab,kw from 2010 to 2014, in Trials
#16 haemorrhag*:ti,ab,kw from 2010 to 2014, in Trials
#17 stroke*:ti,ab,kw from 2010 to 2014, in Trials
#18 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 from 2010 to 2014, in Trials
#19 #5 and #18 from 2010 to 2014, in Trials

#20 #1 or #2 or #3 from 2010 to 2014, in Trials
#21 #20 and #18

Appendix A Figure 1. Literature Flow Diagram



Abbreviations: CE = comparative effectiveness; KQ = Key Question

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Inclusion criteria	Exclusion criteria
Aim/Condition	**All KQs:** Any indication; cancer incidence and deaths reported as an outcome: • Primary prevention of cancer • Primary prevention of CVD (secondary prevention of CVD for sensitivity analyses)	**All KQs**: Secondary or tertiary prevention of cancer; treatment of cancer; cancer remission; cancer recurrence; cancer metastases
Population	**All KQs**: Adults aged 40 years and older	**All KQs:** • Non-human populations • Children and adolescents (aged < 18 years) • Studies where the majority of participants are aged < 40 years • Pregnant women • Institutionalized individuals (e.g., psychiatric inpatients) • Individuals in long-term care • Post-surgical patients • Contraindicated or not eligible for ASA chemoprevention • Symptomatic patients (e.g., those undergoing a diagnostic colonoscopy) Cancer-specific: • Personal history of cancers for which we are evaluating chemoprevention outcomes • High-incidence familial cancer syndromes (e.g., Lynch syndrome) for cancers for which we are evaluating chemoprevention outcomes
Intervention	**All KQs:** Aspirin • Oral • Minimum 75 mg every day or every other day • No maximum limit • Exposure of at least 12 months • Formulations include: tablet, enteric coated tablets, chewable tablets, effervescent tablets Both intervention and control (or exposed and unexposed) groups may be taking other medications or supplements	**All KQs:** • Irregular or occasional ASA use • Other non-ASA NSAID • Delivered via non-oral routes • Dosage information not reported • Non-tablet oral formulations (e.g., gum) • Co-administration with other chemopreventive (e.g., tamoxifen) or potentially chemopreventive agents (e.g., vitamin E) or lifestyle interventions (e.g., diet, exercise) • Co-administration with other non-ASA anti-thrombotic medications (e.g., warfarin, other anti-platelet agents)
Comparator	**All KQs**: • Placebo • No intervention	**All KQs**: Comparative effectiveness (i.e., any active agent or intervention – e.g., pharmacological, lifestyle intervention)
Outcomes	**KQs 1, 2 (health and cancer outcomes)**: • Incidence of cancer • Cancer-related mortality • All-cause mortality **KQ 6**: • GI bleeding • Hemorrhagic stroke • Other serious harms (e.g., age-related macular degeneration)	**All KQs:** Cancer-specific: • Biomarkers • Biologic or physiologic markers of cancer (e.g., serum PSA, breast density) • Pre-cancerous markers • Progression or metastasis • Recurrence **KQ 6:** Post-operative or minor bleeding

Appendix A Table 1. Inclusion and Exclusion Criteria

Category	Inclusion criteria	Exclusion criteria
Study design	**KQs 1, 2**: • RCTs • CCTs • Systematic reviews and meta-analyses of RCTs for evidence on benefits **KQ 6**: • RCTs • CCTs • Systematic reviews and meta-analyses analyses for evidence of harms • Large prospective cohort studies • Patient registries	**KQs 1, 2**: • Factorial designed studies where the aspirin versus placebo arm is not reported separately • Observational studies • Narrative reviews • Commentaries • Editorials • Narrative reviews **KQ 6**: • Case reports, • Case-control studies • Small or retrospective cohort studies • Case series • Commentaries • Editorials • Narrative reviews
Setting	**All KQs:** Outpatient	**All KQs:** Exclusively inpatient
Timing of outcome assessment	**All KQs:** 12 months or longer	**All KQs:** Less than 12 months
Country	**All KQs:** Any country with a 2013 Human Development Index of "Very High"	**All KQs:** Any country with less than a Human Development Index of "Very High"
Language	**All KQs:** English	**All KQs:** Other languages besides English
Study Quality	**All KQs:** Good and fair quality, according to USPSTF criteria	**All KQs:** Poor quality as defined by design-specific USPSTF criteria

Abbreviations: ASA = acetylsalicylic acid; CCT = clinical controlled trial; CVD = cardiovascular disease; KQ = Key Question; mg = milligram(s); NSAID = non-steroidal anti-inflammatory drug; PSA = prostate serum antigen; RCT = randomized controlled trial; USPSTF = U.S. Preventive Services Task Force

Appendix A Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the USPSTF methods[48]	• Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable followup? • Was there evidence of selective reporting of outcomes? • What was the funding source?
Observational studies, adapted from the Newcastle-Ottawa Scales[49]	• Was the exposed cohort representative? • Was the selection of the nonexposed cohort systematic? • Was eligibility criteria specified? • Were baseline characteristics well described? • Were groups similar at baseline? • Was the ascertainment of exposure reported? • Was the outcome of interest not present at baseline? • Were measurements equal, valid and reliable? • Were outcome assessors blinded? • Was there adequate followup time for an event to occur? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there adjustment for confounders? • What was the funding source?
Assessment of Multiple Systematic Reviews (AMSTAR)[50]	• Was an a priori design provided? • Was there duplicate study selection and data extraction? • Was a comprehensive literature search performed? • Was the status of publication used as an inclusion criteria? • Was a list of studies provided? • Was the scientific quality of the included studies assessed and documented? • Was the scientific quality of the included studies used appropriately in formulating conclusions? • Were the methods used to combine the findings of studies appropriate? • Was the likelihood of publication bias assessed? • Was the conflict of interest included?

Abbreviations: USPSTF = U.S. Preventive Services Task Force

Appendix B. Excluded Studies

Code	Reason for Exclusion
E1	Wrong aim or condition
E2	Wrong population
E2a	> 20% adults aged < 40 years at BL or mean age < 40 years
E3	Wrong intervention
E3a	Exposure to ASA < 12 months
E3b	Incorrect ASA dosage
E3c	Co-administration with chemopreventive agent
E3d	Co-administration with an anti-thrombotic agent (> 5%)
E4	Comparative effectiveness
E5	No relevant outcomes
E5a	Primary of secondary prevention of CRC cancer with no relevant outcomes
E5b	Primary prevention of CVD with no relevant outcomes
E6	Wrong study design
E7	Wrong setting
E8	Non High-HDI country
E9	Non-English
E10	Poor quality
E11	Unable to locate

1. Aspirin in coronary heart disease. The Coronary Drug Project Research Group. J Chronic Dis 1976 Oct;29(10):625-42. PMID: 789390. **KQ2E5.**
2. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. The Canadian Cooperative Study Group. N Engl J Med 1978 Jul 13;299(2):53-9. PMID: 351394. **KQ1E10, KQ2E10, KQ6E10.**
3. Persantine and aspirin in coronary heart disease. The Persantine-Aspirin Reinfarction Study Research Group. Circulation 1980 Sep;62(3):449-61. PMID: 7398002. **KQ2E5b.**
4. Persantine-aspirin reinfarction study. Design, methods and baseline results. By the persantine-aspirin reinfarction study research group. Circulation 1980 Sep;62(3 Pt 2):II1-42. PMID: 7408140. **KQ2E5b.**
5. Aspirin in coronary heart disease. The Coronary Drug Project Research Group. Circulation 1980 Dec;62(6 Pt 2):V59-V62. PMID: 7002353. **KQ2E5.**
6. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1988;318(4):262-4. PMID: 3275899. **KQ2E5.**
7. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989 Jul 20;321(3):129-35. PMID: 2664509. **KQ2E5b.**
8. Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy. A multicenter randomized controlled clinical trial. The DAMAD Study Group. Diabetes 1989 Apr;38(4):491-8. PMID: 2647556. **KQ2E5.**
9. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC Group. Lancet 1990 Oct 6;336(8719):827-30. PMID: 1976875. **KQ1E3a, KQ2E3a, KQ6E3a.**
10. Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. N Engl J Med 1990 Mar 22;322(12):863-8. PMID: 2407959. **KQ2E5.**
11. Design of a multicenter randomized trial for the Stroke Prevention in Atrial Fibrillation Study. The Stroke Prevention in Atrial Fibrillation Investigators. Stroke 1990 Apr;21(4):538-45. PMID: 2183405. **KQ2E5.**
12. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991 Aug;84(2):527-39. PMID: 1860198**,** **KQ2E5.**
13. Effects of aspirin treatment on diabetic retinopathy. Ophthalmology 1991;98(Suppl):757-65. PMID: 2062511. **KQ2E5.**
14. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology 1991 May;98(5 Suppl):741-56. PMID: 2062510. **KQ2E5.**

15. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. N Engl J Med 1991 Oct 31;325(18):1261-6. PMID: 1922220. **KQ1E4, KQ2E4, KQ6E4.**
16. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early treatment Diabetic Retinopathy Study report 12. ETDRS Investigators. JAMA 1992;268(10):1292-300. PMID: 1507375. **KQ2E5.**
17. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet 1993 Nov 20;342(8882):1255-62. PMID: 7901582. **KQ2E5.**
18. Low-dose aspirin in polycythaemia vera: a pilot study. Gruppo Italiano Studio Policitemia (GISP). Br J Haematol 1997 May;97(2):453-6. PMID: 9163613. **KQ1E2, KQ2E2, KQ6E2.**
19. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Lancet 1998 Jan 24;351(9098):233-41. PMID: 9457092. **KQ2E5b.**
20. The WASH study (Warfarin/Aspirin Study in Heart failure) rationale, design and end-points. Eur J Heart Fail 1999 Mar;1(1):95-9. PMID: 10937986. **KQ1E10, KQ2E10, KQ6E10.**
21. Summaries for patients. Occurrence of venous thromboembolism in women taking low-dose aspirin. Ann Intern Med 2007 Oct 16;147(8):I34. PMID: 17938386. **KQ1E6, KQ2E6, KQ6E6.**
22. Daily aspirin usage associated with lower cancer mortality. J Natl Cancer Inst 2012 Aug 10 PMID: 22888141. **KQ1E6, KQ2E6, KQ6E6.**
23. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): A randomized, controlled trial. Contemp Clin Trials 2013 Oct 7;36(2):555-64. PMID: 24113028. **KQ1E5, KQ2E5, KQ6E5.**
24. Abraham NS, Hartman C, Castillo D, et al. Effectiveness of national provider prescription of PPI gastroprotection among elderly NSAID users. American Journal of Gastroenterology 2008 Feb;103(2):323-32. PMID: 18289200. **KQ1E6, KQ2E6, KQ6E3.**
25. Abraham NS, Hartman C, Richardson P, et al. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. Circulation 2013 Oct 22;128(17):1869-77. PMID: 24025594. **KQ1E6, KQ2E6, KQ6E3b.**
26. Abu DH, Eloubeidi M, Tamim H, et al. Opposing effects of aspirin and anticoagulants on morbidity and mortality in patients with upper gastrointestinal bleeding. Journal of Digestive Diseases 2014 Jun;15(6):283-92. PMID: 24593260. **KQ1E8, KQ2E8, KQ6E8.**
27. Al-Shammari AMH, Naylor I, Naylor R. Aspirin brings about its beneficial effects by modification of diastolic blood pressure of smokers. J Appl Pharmacy 2012;3(4):651-4. PMID: None. **KQ1E3a, KQ2E3a, KQ6E3a.**
28. Allison M, Garland C, Chlebowski R, et al. The association between aspirin use and the incidence of colorectal cancer in women. Am J Epidemiol 2006 Sep 15;164(6):567-75. PMID: 16847042. **KQ1E6, KQ2E6, KQ6E5.**
29. Altman R, Boullon F, Rouvier J, et al. Aspirin and prophylaxis of thromboembolic complications in patients with substitute heart valves. J Thorac Cardiovasc Surg 1976 Jul;72(1):127-9. PMID: 1084448. **KQ1E4, KQ2E4, KQ6E4.**
30. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med 2012 Mar 6;156(5):350-9. PMID: 22393130. **KQ1E6, KQ2E6, KQ6E3b.**
31. Ariesen MJ, Algra A, Kappelle LJ. Antiplatelet drugs in the secondary prevention after stroke: differential efficacy in large versus small vessel disease? A subgroup analysis from ESPS-2. Stroke 2006 Jan;37(1):134-8. PMID: 16306466. **KQ1E6, KQ2E6, KQ6E5.**
32. Aronow HD, Califf RM, Harrington RA, et al. Relation between aspirin dose, all-cause mortality, and bleeding in patients with recent cerebrovascular or coronary ischemic events (from the BRAVO Trial). Am J Cardiol 2008 Nov 15;102(10):1285-90. PMID: 18993142. **KQ1E3, KQ2E3, KQ6E4.**

33. Arvanitakis Z, Grodstein F, Bienias JL, et al. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. Neurology 2008 Jun 3;70(23):2219-25. PMID: 18519870. **KQ1E6, KQ2E6, KQ6E5.**
34. Azoulay L, Dell'Aniello S, Simon T, et al. The concurrent use of antithrombotic therapies and the risk of bleeding in patients with atrial fibrillation. Thromb Haemost 2013 Mar 5;109(3):431-9. PMID: 23306435. **KQ1E6, KQ2E6, KQ6E6.**
35. Baigent C, Landray M, Leaper C, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis 2012;45(3):473-84. PMID: 15754269. **KQ1E2, KQ2E2, KQ6E2.**
36. Bardia A, Ebbert JO, Vierkant RA, et al. Association of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs with cancer incidence and mortality. J Natl Cancer Inst 2007 Jun 6;99(11):881-9. PMID: 17551148. **KQ1E6, KQ2E6, KQ6E3.**
37. Bardia A, Olson JE, Vachon CM, et al. Effect of aspirin and other NSAIDs on postmenopausal breast cancer incidence by hormone receptor status: results from a prospective cohort study. Breast Cancer Res Treat 2011 Feb;126(1):149-55. PMID: 20669045. **KQ1E6, KQ2E6, KQ6E5.**
38. Barry EL, Poole EM, Baron JA, et al. CYP2C9 variants increase risk of colorectal adenoma recurrence and modify associations with smoking but not aspirin treatment. Cancer Causes Control 2013 Jan;24(1):47-54. PMID: 23081681. **KQ1E6, KQ2E6, KQ6E5.**
39. Barthelemy O, Limbourg T, Collet JP, et al. Impact of non-steroidal anti-inflammatory drugs (NSAIDs) on cardiovascular outcomes in patients with stable atherothrombosis or multiple risk factors. Int J Cardiol 2013 Mar 10;163(3):266-71. PMID: 21719126. **KQ1E6, KQ2E6, KQ6E3a.**
40. Bauer T, Gitt A, Zahn R, et al. Impact of chronic antithrombotic therapy on hospital course of patients with acute myocardial infarction. Clin Cardiol 2009 Dec;32(12):718-23. PMID: 20027657. **KQ1E6, KQ2E6, KQ6E5.**
41. Becattini C, Agnelli G, Schenone A. Aspirin reduced recurrence of venous thromboembolism (VTE) after a first-ever, unprovoked VTE. Annals of Internal Medicine 2012;157(8):JC4-JC3. PMID: 23070505. **KQ1E6, KQ2E6, KQ6E6.**
42. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012 May 24;366(21):1959-67. PMID: 22621626. **KQ2E5.**
43. Benamouzig R, Yoon H, Little J, et al. APACC, a French prospective study on aspirin efficacy in reducing colorectal adenoma recurrence: design and baseline findings. Eur J Cancer Prev 2001 Aug;10(4):327-35. PMID: 11535875. **KQ1E5a, KQ2E5a.**
44. Benamouzig R, Deyra J, Martin A, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology 2003 Aug;125(2):328-36. PMID: 12891533. **KQ1E5a, KQ2E5a.**
45. Benito-Garcia E, Michaud K, Wolfe F. The effect of low-dose aspirin on the decreased risk of development of dyspepsia and gastrointestinal ulcers associated to cyclooxygenase-2 selective inhibitors. J Rheumatol 2007 Aug;34(8):1765-9. PMID: 17611980. **KQ1E6, KQ2E6, KQ6E3.**
46. Bentham P, Gray R, Sellwood E, et al. Aspirin in Alzheimer's disease (AD2000): a randomised open-label trial. Lancet Neurol 2008 Jan;7(1):41-9. PMID: 18068522. **KQ1E10, KQ2E10, KQ6E10.**
47. Berger JS, Brown DL, Burke GL, et al. Aspirin use, dose, and clinical outcomes in postmenopausal women with stable cardiovascular disease: the Women's Health Initiative Observational Study. Circ Cardiovasc Qual Outcomes 2009 Mar;2(2):78-87. PMID: 20031819. **KQ1E6, KQ2E6, KQ6E3b.**
48. Berisha B, Gashi M, Krasniqi X, et al. Limitations of CHADS2 scoring system in predicting stroke risk--need to change the age criteria. Med Arh 2011;65(1):27-9. PMID: 21534448. **KQ1E6, KQ2E6, KQ6E4.**

49. Bermingham M, Shanahan MK, O'Connell E, et al. Aspirin use in heart failure: is low-dose therapy associated with mortality and morbidity benefits in a large community population? Circulation 2014 Mar 1;7(2):243-50. PMID: 24493706. **KQ1E6, KQ2E6, KQ6E3d.**
50. Bertuccio P, Bravi F, Bosetti C, et al. Aspirin and gastric cancer risk. Eur J Cancer Prev 2010 Nov;19(6):426-7. PMID: 20881520. **KQ1E6, KQ2E6, KQ6E6.**
51. Biffi A, Halpin A, Towfighi A, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology 2010 Aug 24;75(8):693-8. PMID: 20733144. **KQ1E6, KQ2E6, KQ6E6.**
52. Bonville DJ, Ata A, Jahraus CB, et al. Impact of preinjury warfarin and antiplatelet agents on outcomes of trauma patients. Surgery 2011 Oct;150(4):861-8. PMID: 22000201. **KQ1E6, KQ2E6, KQ6E2.**
53. Bornebroek M, de Lau LM, Haag MD, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Neuroepidemiology 2007;28(4):193-6. PMID: 17851257. **KQ1E6, KQ2E6, KQ6E5.**
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Appendix C. Number of Events in the Control Group (per 1,000 Person-Years)

Study name	Average duration, years	N, CG	Total person-years, CG	Intracranial Hemorrhage including Hemorrhagic Stroke	Nontrivial Bleeding	GI Bleeding / Extracranial Bleeding	Cancer Incidence	Cancer Mortality	All-cause Mortality
HOT	3.8	9391	35,685.8	15 (0.42)	78 (2.19)	37 (1.04)	311 (8.72)	105 (2.94)	305 (8.55)
PPP	3.6	2269	8,168.4	3 (0.37)	9 (1.10)	NR	89 (10.90)	29 (3.55)	78 (9.55)
POPADAD	6.7	638	4,274.6	3 (0.70)	34 (7.95)	NR	60 (14.04)	31 (7.25)	101 (23.63)
AAA	8.2	1675	13,735.0	7 (0.51)	24 (1.75)	8 (0.58)	194 (14.12)	90 (6.55)	186 (13.54)
WHS	10.1	19942	201,414.2	41 (0.20)	3671 (18.23)	94 (0.47)	1427 (7.09)	299 (1.49)	642 (3.19)
JPAD	4.37	1277	5,580.5	7 (1.25)	7 (1.25)	0 (0)	NR	19 (3.41)	38 (6.81)
BMD	6	1710	10,260.0	6 (0.58)	2 (0.19)	3 (0.29)	58 (5.65)	47 (4.58)	151 (14.72)
PHS	5	11034	55,170.0	12 (0.22)	708 (12.28)	28 (0.51)	NR	68 (1.23)	227 (4.12)
TPT	6.8	1272	8,649.6	2 (0.23)	179 (20.70)	2 (0.23)	NR	51 (5.90)	110 (12.72)
ETDRS	5	1855	9,275.0	NR	NR	NR	NR	14 (1.51)	366 (39.46)

Note: The minimum, median and maximum control group rates for each outcome were calculated excluding zeros and outliers

Abbreviations: CG = control group; GI = gastrointestinal; NR = not reported

Description of Included Trials

Most of the 30 included RCTs[51-54,57-60,62-82,85] evaluated low-dose ASA interventions (≤ 325 mg/day) in the range of 50 to 325 mg per day. Seven trials evaluated high doses of ASA (> 325 mg/day) that ranged from 500 to 1,200 mg per day[51,59,64,65,71,72,75,77] and four trials evaluated more than one level of ASA dose.[65,70,77,82] ASA was prescribed once per day in most of the interventions. The two largest trials—the Women's Health Study (WHS)[60] and the Physicians Health Study (PHS)[73]—prescribed ASA every other day. A few studies also delivered ASA two[62,65,75] or three[51,59,71] times per day, but most of these were the high (>325 mg/day) dose interventions. While ASA was most commonly delivered in tablet form (with enteric or other coating in 10 trials), two trials evaluated soluble effervescent forms (or offered it as an option to the tablet form).[72,82] Twelve trials did not describe the formulation of ASA.[51,54,59,62,63,67,75-78,80,81]

Eight of the 30 included trials were conducted in the United States.[59,60,64,71,73,75-77] These trials included 76 to 97 percent white participants, when described.[60,64,71,75-77] The remaining trials were conducted in Europe,[51,54,57,61-63,66,68,69,72,74,78,80,82] Canada,[79] Australia,[52,53] or Japan.[70,81] Two trials were conducted in multiple countries.[58,67] Non-U.S. trials generally did not provide specific information about race or ethnicity of participants. Four of the included trials[59,69,72,73] were conducted exclusively among male participants and one trial was conducted among women.[60] The remaining trials included 11 to 72 percent females and included participants with a mean or median age at enrollment ranged from 47 to 76 years. Two trials (both conducted in Australia) restricted enrollment to patients aged 70 years or older.[52,53]

Many of the trials used a factorial design to evaluate at least one non-ASA intervention in addition to ASA such as vitamin E,[60,61] folic acid,[68,77] beta-carotene,[60,73] non-ASA antithrombotic agents,[62,69] or others.[57,64,67] For the two trials that evaluated a non-ASA antithrombotic agent as the second intervention (TPT and the European Stroke Prevention study [ESPS-2]),[62,69] we also excluded data from the ASA and no-ASA arms in which the antithrombotic agent were also prescribed.

Most of the included trials used computer-generated randomization or a random number table to assign treatments. Seven reported using block randomization.[63,64,74,76,79,81,82] Three trials did not clearly describe their randomization method (including two rated good quality[59,71]) and three did not report their method of randomization (all fair-quality trials).[52,54,75] A majority of the trials reported adequate allocation concealment through central allocation and a few[57,66,68,69] reported additional measures such as sequentially-numbered drug containers of identical appearance. It was unclear if 10 of the trials had adequate allocation concealment, however, including three rated as good quality.[59,76,77]

In the majority of trials, participants in ASA and control groups appeared to be similar at baseline for age, gender, and smoking status. Some trials also reported that BMI was similar between groups (WHS, AFPPS, the Warfarin and Apsirn study [WARFASA], the ASPirin in Reducing Events in the Elderly [ASPREE] study, and PHS).[53,57,60,69,73,77,78] Only a few trials, however, reported that groups were similar at baseline for levels of physical activity (WHS, PHS),[60,73] family history of cancer (WHS, APACC, ukCAP),[60,68,82] race (WHS, ETDRS, WARFASA, and AFPPS),[60,64,77,78] or markers of socioeconomic status (WHS and AAA).[60,66] Most included trials did not report these characteristics. Two trials (the Swedish Aspirin Low-Dose Trial [SALT] and ukCAP)[68,74] did not report results of their statistical significance testing for differences in baseline characteristics between groups. One trial (ASPREE) did not report information comparing age, gender, smoking, or other important characteristics between groups at baseline, however, this study is ongoing.[53]

Several trials reported differences in some baseline characteristics. In Asymptomatic Cervical Bruit Study (ACBS), the ASA group appeared to have a lower rate of current smoking (33% vs. 41%) and diabetes (19% vs. 28%; p-values NR).[79] In APACC, patients in the ASA group were more likely to have had advanced colon adenomas (79% vs. 68%).[82] Small, but statistically significant differences, were also reported between groups for Coronary Drug Project Aspirin Study (CDPA; physical activity and cigarette smoking),[59] JPAD (past smoking),[70] Persantine-Aspirin Reinfarction Study (PARIS; pulse rate, antiarrhythmic medications, beta-blockers, and electrocardiogram patterns),[71] and Aspirin Myocardial Infarction Study (AMIS; history of heart failure, angina, arrhythmias, CVD medications, and heart rate).[75] While most of the trials adjusted results for these baseline differences, we use the actual number of persons or events reported in our meta-analyses. These numbers are not adjusted values.

As most of the included trials were designed for CVD primary prevention, methods for ascertaining relevant non-CVD were generally less clearly reported. Of our included outcomes, ascertainment of total mortality and intracranial hemorrhage were the best described across these trials. Approximately half of these trials specified total mortality as either a primary[59,62,64,71,75] or secondary study outcome.[54,57,58,61,63,66,70,73,76,78,80] Intracranial bleeding was often part of the set of primary CVD outcomes. Four other trials also designated bleeding in general as a primary or secondary outcome.[53,58,76,78] In contrast, WHS and PHS were the only trials that specified total cancer as a primary or secondary outcome.[60,73] Trials that focused on adenoma prevention may have reported total cancers,[68,77] without describing how they ascertained non-colorectal cancer. In many cases, trials did not clearly report whether they continued to follow patients for any outcomes after primary endpoints were reached.

All included trials except four reported using double blinding. While many of these trials stated that ascertainment of primary outcomes were blinded, they were unclear about whether or not the assessment of non-primary outcomes was also blinded. In particular, few trials reported that blinding applied to ascertainment of nonfatal harms and only one trial[60] reported that it applied non-fatal cancers. Among four trials that were open-label,[61,70,72,81] only one specified that ascertainment of total mortality and adverse events were blinded.[70] Another trial specified that CVD outcome ascertainment was blinded.[81]

While cancer incidence and non-intracranial hemorrhage harms were not the focus of most trials, the approach to ascertaining outcomes was the similar for patients in both ASA and no ASA groups across trials. Studies generally followed up with patients with either questionnaire and/or clinic visits at regularly scheduled intervals. Studies often reported that medical records were reviewed for primary outcomes (often without specify if they were reviewed for other non-fatal outcomes). Several studies stated that CT or MRI imaging or necropsy were used to diagnose stroke.[58,61,65,73,74,79-81] Only two trials, however, reported that imaging was conducted for most or all cases of intracranial hemorrhage.[74,81]

Three of the included trials (rated as good quality for mortality or cancer incidence) used less stringent or unclear methods for ascertaining harms other than intracranial hemorrhage[60,73,77] or ARMD[60,73] For WHS, GI bleeding was self-reported and not confirmed by medical record review.[123] We included bleeding harms from the post-trial assessment as fair-quality. We excluded long-term data at the 18-year time point due to poor quality because data on GI bleeding were collected "intermittently", by self-report only, and without followup questionnaire as they were during the active trial period. The other two trials reported minimal information about how other harms were ascertained and we rated them as fair-quality for harms other than

intracranial hemorrhage and ARMD.[73,77] One trial did not report how non-colorectal cancers were ascertained and, because of this, we rated it as fair-quality for cancer incidence.[77]

Included trials generally followed an intention-to-treat approach in that patients were analyzed in the group to which they were assigned, regardless of compliance. Approximately half also specified that they attempted to followup and include all patients as they were originally allocated even after they discontinued treatment. Several to poor-quality trials censored patients from further analysis if they became noncompliant with treatment (**Appendix B**).

Completeness of followup for vital status was 99 to 100 percent in all trials that we rated as good quality and among eight trials that we rated as fair quality.[54,57,61,63,65,72,75,79] For the remaining fair-quality trials, followup for vital status was higher than 90 percent, except for one trial,[81] in which only 79 percent had followup for vital status. While completeness of ascertaining non-fatal outcomes was slightly lower for some trials, it was still greater than 90 percent for two trials[61,71] and was 97 to 99 percent for the other three trials.[59,60,73] The trials that had less than 99 percent followup dealt with missing data by carrying forward the status from the last time of contact or[70] excluding patients with unknown status.[51,67] Several trials did not report how they handled these missing data.[53,78,80,82]

The trials were generally all designed to assess differences in length of time-to-event. They enrolled participants and allocated them randomly to ASA and no ASA on an ongoing basis. The length of time that a patient was prescribed their intervention and the observation period varied depending on when the participant was enrolled. In most of the individual trial reports, the primary events are analyzed by creating survival curves and life table methods. In contrast, cancer, bleeding, and other adverse events are simply reported as the number of events out of the number randomized to the group. These trials did not necessarily report the total person-years of exposure for those in each group. Very few studies reported rates of adverse events that occurred over a constant period of time for all participants.

Description of Included Individual Patient Data Meta-Analyses

We identified three individual patient data meta analyses[8,10,87] and one study-level meta-analysis informed by individual patient data meta analysis[44] provided data complementary to that from our primary studies.

In two separate fair-quality individual patient data meta analyses (published in 2011 and 2012), Rothwell and colleagues reported multiple trial- and individual-patient-level meta-analyses of trials assessing the effect of daily ASA versus no ASA on multiple outcomes including cancer mortality, all-cause mortality, and cancer incidence.[8,10] Analyses in the two publications were different in terms of the studies focusing on CVD primary prevention or not, doses of ASA, minimum length of scheduled duration of treatment, and whether other antiplatelets or anticoagulant treatments could be co-administered. All of the analyses were restricted to trials of daily ASA, thus excluding WHS and PHS in which ASA was dosed every other day. The authors did not report any dual review process or assessment of methodological quality of individual trials.

In the 2011 publication, Rothwell and colleagues[8] reported an individual patient data meta-analysis of cancer mortality outcomes from the seven trials (BMD, UK-TIA, ETDRS, TPT, JPAD, POPADAD, AAA) in which the mean or median scheduled duration of daily ASA treatment was at least 4 years, with the range extending beyond 5 years (all regardless of adherence), and for which relevant individual-level data for cancer mortality were available from

the original trialists.[57,64-66,69,70,72] This publication included trials in which the ASA intervention was administered either alone or with another antiplatelet or antithrombotic agent if the other agent was administered the same way in ASA and no ASA groups. The authors made no distinction between trials focusing on primary and secondary prevention of CVD or dose of ASA. Additionally, the authors used the designation of death due to cancer that was made by the original trial's investigators in most cases. Using the individual-level data, Rothwell and colleagues estimated the cumulative effect of ASA on time to cancer death with Kaplan-Meier curves and log-rank tests stratified by trial and calculated hazard ratios from a Cox proportional hazards model, also stratified by trial. Analyses were intention-to-treat based on how patients were allocated in the original trials. They conducted stratified analyses looking at cancer subtypes, outcomes occurring during the first five years of treatment or afterwards. Analyses are not adjusted for other baseline characteristics.

In the same 2011 publication, Rothwell and colleagues[8] also reported long-term post-trial followup results on cancer mortality that were available for three of seven trials included in the main individual patient data analysis (TPT, UK-TIA, and BMD).[65,69,72] Post-trial followup had occurred using data from national death certificate and cancer registration systems. Fatal cancers were defined as those for which cancer was recorded as the primary underlying cause of death as described on the death certificate. Investigators blinded to treatment allocation coded deaths using ICD 9 or 10. Rothwell and colleagues assessed trials for underlying heterogeneity and then pooled results for analyses on the effect of allocation to ASA on risk of 20-year cancer mortality, also on an intention-to-treat basis.

In a 2012 publication, Rothwell and colleagues[10] conducted trial- and individual-patient-level meta-analysis of 51 trials of ASA versus no ASA, with mean or median scheduled duration of treatment of ≥ 90 days for which at least one non-vascular death was reported. They excluded trials targeting secondary cancer or individuals with colonic polyps and those in which non-ASA antiplatelet agents were administered in either group. This publication allowed trials with co-administration of anticoagulation agents. Data on vascular and non-vascular deaths during trials were abstracted from main and subsequent trial reports or from previous meta-analyses.[87] For cancer deaths, the authors obtained individual patient data from trialists, if available, and otherwise used data on cancer deaths from published reports. Analyses were intention-to-treat based on how patients were allocated in the original trials. For analyses of abstracted data on non-vascular death from 51 trials, they calculated pooled OR by fixed effects meta-analyses (Mantel-Haenszel-Peto method). Using the individual patient cancer mortality data, the authors stratified analyses by years from randomization to death (less than 3, 3 to 4.9, and ≥5 years), dose of ASA (less than 300 vs. ≥ 300 mg), and site of primary cancer.

For five of the six trials assessing daily ASA less than 300 mg/day in primary prevention of vascular events,[57,61,66,67,69] they also obtained individual patient data for all cancers (fatal and non-fatal) that occurred during the trials. They also assessed age, sex, and smoking status at baseline, major vascular events, major extracranial bleeds, and date and cause of all deaths during the trial. A sixth trial of low-dose ASA in primary prevention[70] used fatal cancers in their analyses. The author's conducted a meta-analysis of cancer incidence stratifying results by time to diagnosis or first notification (less than 3, 3 to 4.9, and ≥ 5 years). They then pooled individual patient data and generated Kaplan-Meier curves for time to diagnosis of first notification of cancer. They assessed the effect of treatment on cancer incidence using a Cox model with time expressed as a continuous variable. To assess the time course of risks and benefits, they conducted meta-analyses evaluating incident cancer, major vascular events (including

intracranial bleeds), major extracranial bleeds (fatal or requiring blood transfusion); the same analyses stratified by period of followup; pooled analyses of individual patient data (from a subset of six trials) to calculate the absolute number of events prevented per 1,000 patients per year for incident cancer, major vascular events, and major extracranial bleeds stratified by period of followup; pooled analyses on two composite outcomes including major vascular events, incident cancer, and extracranial bleeds with one analysis restricted to only the fatal extracranial bleeds.

A fair-to-good-quality individual patient data meta-analysis conducted by the Antithombotic Trialists' (ATT) Collaboration evaluated beneficial CVD and harmful bleeding outcomes in six trials of ASA in CVD primary prevention populations (n= 95,000 with 3,554 serious vascular events) and 16 trials of ASA in CVD secondary prevention (n=17,000 with 3,306 serious vascular events).[87] The primary prevention trials included at least 1,000 non-diabetic participants and 2 years of scheduled treatment with ASA and no other antiplatelet drugs in either group (BDS, PHS, TPT, HOT, PPP, WHS).[60,61,67,69,72,73] Dosages ranged from 100 mg every other day to 500 mg daily. Only 2 percent of the population was in a predicted 5-year CHD risk category of 10 percent or more. Secondary prevention trials represented individuals with previous stroke/TIA (10 trials) or MI (six trials). Serious vascular events were defined as MI, stroke, death from a vascular cause, and for secondary prevention trials only death from an unknown cause. Major coronary events included fatal and non-fatal events, while stroke included fatal and non-fatal hemorrhagic, ischemic, and unknown types. Extracranial bleeds were primary GI and usually required transfusion or were fatal.

A fair- quality study-level meta-analysis by Seshasai and colleagues analyzed nine placebo-controlled trials (with at least 1,000 participants and 1-year of followup) of ASA use (50 to 500 mg per day) for CVD primary prevention on CVD, nonvascular outcomes, or death.[44] This MA included the same trials as our companion systematic review,[41] except for one trial conducted in diabetics.[64] It also included all six trials in the individual patient data meta-analysis by the ATT Collaboration[87] and all six trials in individual patient data meta-analysis by Rothwell and colleagues,[10] although these two analyses overlapped for three trials (HOT, TPT, PPP) only.[61,67,69] Primary trial-reported data were supplemented by extracting information from another individual patient data meta-analysis on non-vascular outcomes,[8] by subsequent trial reporting and contacting authors for unpublished cancer data for two trials (HOT, PHS).[67,73] Thus, the data represented here are largely those already represented in previous individual patient data meta-analysis, but including additional published (or unpublished) outcomes for three trials and defining and reported on an "non-trivial bleeding" outcome that included fatal bleeding from any site, cerebrovascular or retinal bleeding, bleeding from a hollow viscus, bleeding requiring hospitalization or transfusion, or study-defined major bleeding. Event rates were approximated by dividing total numbers of events by mean (or median) followup time period and approximate control group event rates were pooled to estimate baseline risks. These estimates were used to construct number needed to harm (NNH) and number needed to treat (NNT) estimates for all statistically meaningful outcomes (only non-fatal MI, total CVD events, non-trivial bleeding and total bleeding). Study-level characteristics were explored through meta-regression examining the impact of period of publication (before or after 2000), study sample size (5,000 or above), event rates (at least 100 for nonfatal MI, at least 500 for total CVD events or non-trivial bleeds), average daily ASA dose, schedule of treatment on non-fatal MI, total CVD events, and non-trivial bleeding. The reviewers reported independent data abstraction with resolution by consensus, quality rating by at least one individual for included trials, and details of

statistical analyses. The reviewers did not report on reliability of the non-trivial bleeding categorization, on study screening, or on dual quality assessment.

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
AMIS, 1980 3083[75,124,125] Fair	RCT	United States	4745	Aged 30-69 years, documented MI (ECG criteria) ≥ 8 weeks (up to 5 years) before enrollment	ASA intolerance, severe ulcer disease, previous CV surgery, uncontrolled HTN, taking anticoagulants, ASA, dipyridamole or sulfinpyrazone; women capable of becoming pregnant, not willing to participate	3.2 (range, ≥ 3 years)
Baron, 2003 (AFPPS)[77] Good (KQ1); Fair (KQ2, KQ6)	RCT, 3x2 factorial	United States	1121	Aged 21-80 years; good health; either ≥ 1 histologically confirmed colorectal adenomas removed w/in 3 months before recruitment, ≥ 1 histologically confirmed adenomas removed w/in 16 months before recruitment, and lifetime history of ≥ 2 confirmed adenomas or a histologically confirmed adenoma ≥ 1 cm diameter removed w/in 16 months before recruitment; undergone complete colonoscopy w/in 3 months w/no known colorectal polyps remaining	History of familial CRC syndrome, invasive large-bowel cancer, malabsorption syndromes, any condition that could potentially be worsened by supplemental ASA or folic acid, any condition commonly treated with ASA, NSAIDs or folate (e.g., arthritis, atherosclerotic vascular disease)	2.7 (range, NR)
Becattini, 2012 (WARFASA)[78] Fair	RCT	Italy	403	Aged ≥ 18 years, treated for 6-18 months w/ vitamin K antagonists (target INR 2-3) for first ever, objectively confirmed, symptomatic, unprovoked DVT, PE, or both	Known cancer, major thrombophilia, other indication for long-term anticoagulant therapy (e.g. AF), previous symptomatic atherosclerosis complications requiring ASA or antiplatelet therapy, active bleeding, high-risk for bleeding, ASA allergy or intolerance, life expectancy < 6 months, pregnant, breast feeding, anticipated nonadherence, participation in other study in past 30 days, VTE associated with use of estro-progestin therapy; treatment w/ non-selective COX-1/2 NSAIDs	2.0 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
Belch, 2008 (POPADAD)[57] Fair	RCT, 2x2 factorial	Scotland	1276	Aged ≥ 40 years, type I or II DM, and asymptomatic PAD as detected by ABI ≤ 0.99	Evidence of symptomatic CVD (not further defined); using ASA or antioxidants on a regular basis; peptic ulceration; severe dyspepsia; bleeding disorders; intolerance to ASA; suspected physical illness which might shorten life expectancy (e.g., cancer); psychiatric illness; and congenital heart disease; not currently free from vascular disease symptoms	6.7 (range, 4.5-8.6)
Benamouzig, 2003 (APACC)[82] Fair	RCT	France	272	Aged 18-75 years, able to conform to protocol, ≥ 1 histologically confirmed colorectal adenomatous polyp, underwent a complete colonoscopy w/ polypectomy after adequate bowel preparation, no more than 3 months before initial consultation, confirmed free of polyps; ≥ 3 adenomas or ≥ 1 measuring ≥ 6 mm in diameter; no intentions to become pregnant, menopausal and/or using efficacious contraceptive methods	CRC, FAP (presence of > 50 polyps), chornic inflammatory disease in bowel, bowel resection excluding appendectomy, debilitating life-threatening disease	1 (range, 1)
Brighton, 2012 (ASPIRE)[58] Good	RCT	Multi-national (5 countries including Australia, New Zealand)	822	Aged ≥ 18 years, first unprovoked episode of objectively diagnosed symptomatic DVT involving the popliteal vein or more proximal leg veins or an acute PE; and completed initial anticoagulation w/ heparin followed by warfarin (or an effective alternative anticoagulant) for 1.5-24 months	Not unprovoked (transient risk factors during the preceding 2 months: bed confinement > 1 week, major surgery, trauma requiring a cast, pregnancy or puerperium, oral contraceptives or HRT), first unprovoked episode ≥ 2 years ago; indication or contraindication for ASA, other antiplatelet or NSAID therapy; indication for continuing oral anticoagulation; other medical conditions interfering w/ participation or would limit life expectancy	3.1 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
CDPRG, 1980 (CDPA)[59] Good	RCT	United States	1529	Men who had ≥ 1 ECG-documented MI prior to entry were in functional classes I, II or III of the NYHA and who discontinued from the treatment regimens of the Coronary Drug Project	Life-limiting diseases other than CHD (e.g., cancer, chronic renal disease, chronic hepatic disease, and pulmonary insufficiency), use of ASA or ASA-containing drug on regular basis and inability to be removed from ASA regimen; use of anticoagulants; ASA hypersensitivity or contraindication (e.g., peptic ulcer; history of GI bleeding)	1.83 (range, 0.83-2.33)
Cook, 2005 (WHS)[60] Good	RCT, 2x2x2 factorial	United States	39876	Women health professionals aged ≥ 45 years; post-menopausal or hand no intention of becoming pregnant	Participants in the Nurses' Health study; history of coronary heart disease, cerebrovascular disease, cancer (except NMSC), or other major chronic illness; history of side effects to any of the study medications; taking ASA or NSAIDs ≥ 1/week (or not willing to forego their use during the trial); taking anticoagulants or corticosteroids; and were taking individual supplements of vitamin A, E, or beta carotene ≥ 1/week	10.1 (range, 8.2-10.9)
Cook, 2013 (companion publication to Cook, 2005)[88] *Good*	*RCT, 2x2 factorial*	*United States*	*39876*	*Female health professionals aged ≥ 45 years*	*History of cancer (except NMSC), CVD, or other major chronic illnesses; not willing to forgo outside use of study medications*	*17.5 (range, 10.4-18.8)*
Cote, 1995 (ACBS)[79] Fair	RCT	Canada	372	Neurologically asymptomatic pts w/ an audible cervical bruit in whom duplex ultrasonography indicated the presence in ≥ 1 artery of a carotid lesion that reduced the diameter by ≥ 50%	History of symptomatic ischemic cerebrovascular disease, valvular heart disease other than mitral valve prolapse, nonvalvular AF, recent (< 3 months) MI or unstable angina, previous carotid endarterectomy, medically necessary use of ASA or regular use of NSAIDs, use of anticoagulants, life expectancy < 5 years, ASA allergy or intolerance	2.4 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
DAMAD, 1989[51] Fair	RCT	France, United Kingdom	314	Aged 17-67 years, type I or II DM, FBG > 6 mM and 2-hour postprandial blood glucose > 10 mM before treatment; presence of early diabetic retinopathy w/ ≥ 5 microaneurysms visualized by fluorescein angiograms of the field centered on the fovea	Other intercurrent diseases (e.g., CAD), HTN (DBP > 105 mm Hg on 3 successive exams), ASA contraindication (e.g., hemorrhagic tendency, history of peptic ulcer); macular edema, proliferative lesions, or previous photocoagulation, other eyes diseases (e.g., cataracts, glaucoma)	3 (range, NR)
de Berardis, 2012[85] Good	Cohort, Retrospective	Italy	NA	ASA users: New users of low-dose ASA (≤ 300 mg) during the index period; aged ≥ 30 years on index date w/ no prescription for ASA in the past year; current users those who had the last ASA prescription filled ≤ 75 days before hospitalization for major bleeding events or the end of followup. ASA nonusers: All pts not receiving ASA throughout study period.	ASA users and ASA nonusers: Aged <30 years or > 95 years, former ASA user (i.e., last ASA prescription ≥ 75 days before event) and those w/ diabetes w/out antidiabetic prescription during study period only	5.7 (range, 2.4-6.0)
de Gaetano, 2001 (PPP)[61] Fair	RCT, 2x2 factorial	Italy	4495	Aged ≥ 50 years w/ one of the following risk factors: age ≥ 65 years; HTN (SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg on at least 3 separate occasions); hypercholesterolemia (TC ≥ 6.4 mmol/L on ≥ 2 separate occasions); DM (FPG concentration ≥ 7.8 mmol/L on ≥ 2 separate occasions [chronic drug treatment for any of the 3 latter conditions was also a criterion for inclusion]); obesity (BMI ≥ 30 kg/m^2); and family history of MI before 55 years of age in ≥ 1 parent or sibling	Treatment w/ antiplatelet drugs (history of vascular events or diseases); chronic use of anti-inflammatory agents or anticoagulants; contraindications to ASA; diseases w/ predictable poor short-term prognosis; and predictable psychological or logistical difficulties affecting compliance with the trial requirements	3.6 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
Diener, 1997 (ESPS-2)[62] Good	RCT, 2x2 factorial	Europe (13 countries)	3298	Aged ≥ 18 years; experienced a recent (within 3 months) ischemic cerebrovascular event (TIA or stroke) diagnosed by clinical exam	Cerebral hemorrhage; brain tumor; cerebral disorders; ASA hypersensitivity; peptic ulceration; neurovascular surgery in past 6 weeks; uncontrolled HTN; chronic renal failure; bleeding disturbances; poor life expectancy; life-threatening disease; uncontrolled DM; conditions for anticoagulation; NSAIDs, anticoagulant or antiplatelet use; pregnancy; refusal to participate	2 (range, NR)
EAFT, 1993[63] Fair	RCT	Europe (13 countries), Israel	782	Aged > 25 years, had a TIA or minor ischemic stroke (≤ grade 3 on modified Rankin scale) in previous 3 months if AF had been proven by ECG or, in paroxysmal AF, in past 24 months and if echocardiography showed no evidence of rheumatic valvular disease	AF secondary to other disorders (e.g., hyperthyroidism), ASA contraindications, taking NSAIDs, other anti-platelet drugs or oral anticoagulants; other sources of cardiac emboli (e.g., prosthetic valves, cardiac aneurysms, atrial myxoma, cardiothoracic ration > 0.5, MI in past 3 months or blood coagulation disorders), scheduled for carotid endarterectomy or coronary surgery w/in next 3 months	2.3 (range, 1-4.6)
Ekstrom, 2013 (SNDR)[86] Fair	Cohort, Prospective	Sweden	NA	Aged 30-80 years, type 2 diabetics (treatment with diet only, oral hypoglycemics only or onset age of diabetes ≥ 40 years and insulin only or combined with oral agents) with data available in 2006 for all analyzed variables	History of CVD, cancer or bleeding; taking ASA dose other than 75 mg/day; BMI < 18 and/or plasma Cr > 150 umol/L; incomplete records; taking other anticoagulant drugs (except ASA), cardiac glycosides, or organic nitrates, history of CHD, CABG, PCI, stroke including cerebral bleeding, CHF, AF, PVD, amputation, renal failure, GI ulcer; ventricular, respiratory, other bleeding	3.9 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
ETDRS, 1992[64] Good	RCT, 2x2 factorial	United States	3711	Aged 18-70 years; clinical diagnosis of DM and one of the following categories of diabetic retinopathy: mild nonproliferative with macular edema, or moderate to severe nonproliferative or early proliferative (less severe than the high-risk proliferative stage, as defined by the Diabetic Retinopathy Study) with or without macular edema. Visual acuity was required to be better than 20/40 in each eye (or 20/400 if acuity was reduced as a result of diabetic macular edema)	SBP >210 mm Hg and/or DBP >110 mm Hg despite the use of HTN medication; history of GI hemorrhage or diagnosis of active GI ulcer in the past 2 years; inability or unwillingness to stop taking anticoagulants or antiplatelet drugs; allergy to ASA; pregnancy or lactation; or poor prognosis for 5 years of followup because of a prior major CV event, cancer, or another chronic disease	5 (range, 4-9)
Farrell, 1991 (UK-TIA)[65] Fair	RCT	United Kingdom	2449	Aged ≥ 40 years, had a recent TIA or minor ischemic stroke	Last cerebrovascular events occurred > 3 months earlier, previously experienced a disabling major stroke, attacks definitely due to something other than arterial thromboembolisms (e.g., migraine); likely to experience AEs from ASA (i.e., previous abnormal bleeding, alcoholism, chronic renal failure, peptic ulceration in previous 3 years); analysis likely to be confounded by ASA taken from 90 days or more pre-randomization, needed regular ASA (or any other antihemostatic medication), MI w/in 3 months before randomization, difficulty w/ followup, poor compliance, sever intercurrent non-vascular disease	4 (range, 1-7)
Fowkes, 2010 (AAA)[66] Good	RCT	United Kingdom	3350	Aged 50-75 years w/ no history of MI, CVA, angina or PAD and an ABI of ≤0.95 as determined by screening by trialist	History of MI, stroke, angina, or PAD; currently used ASA, other anti-platelets or anticoagulant agents; severe indigestion; chronic liver or kidney disease; receiving chemo-therapy; contraindications to ASA; or an abnormally high or low hematocrit value	8.2 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
Hansson, 1998 (HOT)[67] Fair	RCT, 2x2 factorial	International (Europe, North and South America, Asia)	19193	Hypertensives aged 50-80 years; DBP ≥100 and ≤115 mmHg on two occasions, ≥ 1 week apart	Malignant HTN; secondary HTN; DBP >115 mmHg; stroke or MI w/in past 12 months; decompensated CHF; other serious concomitant disease which could affect survival in the next 2-3 years; require a beta-blocker, ACE inhibitor or diuretic or reasons other than HTN; require antiplatelet or anticoagulant treatment; insulin-treated diabetics; hypersensitivity to felodipine; ASA contraindications	3.8 (range, 3.3-4.9)
Huang, 2010 (HPS)[83] Fair	Cohort, Prospective	United States	NA	Male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who returned a health questionnaire in 1986 who also returned the 1994 questionnaire on ASA use	Prior history of GI bleeding, cancer or peptic ulcer disease, bleeding related to cancer or post-polypectomy complications or w/out a known date of diagnosis	11.4 (range, ≤ 14)
Strate, 2011 (companion publication to Huang, 2010) 5585[126] *Fair*	*Cohort, Prospective*	*United States*	*NA*	*Male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists, aged 40-75 years in 1986*	*Diverticulitis, diverticulosis, or diverticular bleeding; cancer (except NMSC), or IBD; did not return the BL food frequency questionnaire or provided implausible dietary data*	*22 (range, NR)*
Huang, 2011 (NHS)[84] Fair	Cohort, Prospective	United States	NA	Female registered nurses aged 30-55 years, returned 1990 questionnaire	Prior history of GI bleeding, cancer, peptic ulcer disease, bleeding related to cancer or polypectomy, or w/out a date of bleeding diagnosis	12.5 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
Iso, 1999 (companion publication to Huang, 2011)[94] *Fair*	*Cohort, Prospective*	*United States*	*NR*	*Female registered nurses who responded to the 1980 questionnaire*	*Regular use of NSAIDs, cancer except NMSC, MI, angina, coronary revascularization, stroke, other CVD, RA in 1980*	*14 (range, NR)*
Manson, 1991 (companion publicaton to Huang, 2011)[127] *Fair*	*Cohort, Prospective*	*United States*	*NA*	*Female registered nurses aged 30-55 years, responded to 1980 questionnaire*	*CHD, stroke, cancer in 1980; regularly took non-ASA, non-steroidal anti-inflammatory analgesics; previous history of RA*	*6 (range, NR)*
Juul-Moller, 1992 (SAPAT)[54] Fair	RCT	Sweden	2035	Aged 30-80 years with a history of exertional chest pain (chronic stable angina pectoris) for ≥ 1 month; treated with increasing doses of sotalol until optimal symptom control and well tolerated for ≥ 3 weeks	Already on treatment w/ or requiring ASA, anticoagulants, verapamil or NSAIDs; pts needing ≥ 50 mg hydrochlorthiazide, ≥ 5 mg bendroflumethiazide or ≥ 40 mg frusemide qd; resting HR < 55 bpm, ongoing treatment w/ class I antiarrhytmic drugs, history of MI, A-V block II/III, symptoms of obstructive lung disease, active peptic ulcer, ASA hypersensitivity, juvenile DM, uncontrolled late-onset DM	4.2 (range, 1.9-6.3)
Logan, 2008 (ukCAP)[68] Fair	RCT, 2x2 factorial	United Kingdom, Denmark	945	Aged < 75 years, had colorectal adenoma ≥ 0.5 cm (after fixation) removed in the past 6 months or longer if then followed by removal ≥ 1 adenomas of any size in the past 6 months; clean colon as determined by a complete colonoscopy or barium enema if colonoscopy was incomplete at time of commencing trial medication	Serious medical conditions that might preclude successful completion of trial (e.g., hepatic cirrhosis, renal failure, unstable heart conditions), need for regular NSAID/ASA treatment, ASA intolerance or sensitivity, active ulcer disease, bleeding disorders or anticoagulant treatment; resection of large bowel or incomplete adenoma removal	3.4 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
MRC, 1998 (TPT)[69] Good	RCT, 2x2 factorial	United Kingdom	2540	Men aged 45-69 years, at the top 20% of the IHD risk score distribution, or 25% if from regions with high IHD rates. Risk score variables were weighted according to their association with IHD in the Northwick Park Heart Study and a risk score derived	Current or recent history of possible peptic ulceration, hiatus hernia, or esophagitis; a recent history of possible or definite MI or stroke, medication incompatible with trial treatment; history of bleeding tendency; actual or likely treatment w/ drugs interacting w/ Warfarin; history of cerebrovascular disease; already on antithrombotic drugs; likely inability to comply with trial; known or suspected alcohol abuse; a range of other conditions including liver disease, malignant disease, and other illnesses	6.8 (range, NR)
Nelson, 2008 (ASPREE)[53] Fair	RCT	Australia	209	GPs: Participated in second Australian National BP Study in Melbourne. Pts: Aged ≥ 70 years w/out overt CVD, compliant with placebo run-in	GPs: Did not have Medical Director clinical software. Pts: Deceased; GP considered unsuitable or not their usual pts; AAA, MI, angina, angioplasty, ASA/anticoagulants, CABG, CAD, cerebral aneurysm, coronary angiography, dementia, DM, gastric ulcer, HF, IHD, peptic ulcer, PAD, stroke, TIA	1 (range, NR)
Ogawa, 2008 (JPAD)[70] Fair	RCT	Japan	2539	Aged 30-85 years, type II DM, ability to provide informed consent	ECG changes consisting of ischemic ST-segment depression, ST-segment elevation, or pathologic Q waves; a history of CHD confirmed by coronary angiography; a history of cerebrovascular disease consisting of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and TIA; a history of arteriosclerotic disease necessitating medical treatment; AF; ASA, ticlopidine, cilostazol, dipyridamole, trapidil, warfarin, and argatroban; a history of severe gastric or duodenal ulcer; severe liver dysfunction; severe renal dysfunction, and ASA allergy; pregnancy	4.37 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
PARIS, 1980 [71] Good	RCT	United States, United Kingdom	1216	Aged 30-74 years w/ ≥ 1 ECG-documented MI w/in past 5 years, clinical history and cardiac enzymes, cardiac disease NYHA class I or II	MI thought to be due to coronary artery embolism, aortic dissection or prolonged arrhythmia; life-limiting diseases (e.g., cancer) or problems possibly affecting long-term followup (e.g., alcoholism); condition precluding regular ASA or dipyridamole use (e.g., hypersensitivity); previous cardiac or coronary surgery, prosthetic valve insertion or permanent pacemaker implantation; postural hypotension; SBP < 200 mm Hg, DBP < 115 mm Hg; child-bearing potential	3.4 (range,)
Petersen, 1989 (Copenhagen AFASAK)[80] Fair	RCT	Denmark	672	Aged ≥ 18 years, have an ECG-verified chronic AF	Previous anticoagulation therapy > 6 months; cerebrovascular events w/in past month; contraindications, side effects, or current treatment w/ ASA/warfarin therapy; pregnancy or breast-feeding; persistent BP > 180/100 mm Hg; psychiatric diseases (including alcoholism); heart surgery w/ valve replacement; sinus rhythm; rheumatic heart disease; refusal to participate	2 (range, NR)
Peto, 1988 (BMD)[72] Fair	RCT	United Kingdom	5139	Male physicians born in 20th century and listed in the 1977 Medical Directory who answered a 1951 smoking questionnaire	Already taking aspirin for various reasons; could not take aspirin; history of peptic ulcer, stroke, or definite MI	6 (range, NR)
PHS, 1989[73] Good (KQ1); Fair (KQ6)	RCT, 2x2 factorial	United States	22071	Male physicians residing in the US; aged 40-84 years; no history of cancer (except nonmelanoma skin cancer), MI, stroke, or transient cerebral ischemia	Current liver or renal disease, peptic ulcer, or gout; contraindications to aspirin consumption; current use of aspirin, other platelet-active drugs, or non-steroidal anti-inflammatory agents; current use of vitamin A supplement	5.0 (range, 3.8-6.4)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
SALT, 1991[74] Good	RCT	Sweden	1360	Aged 50-79 years, had had a TIA, minor ischemic stroke (i.e., by 3 weeks after onset, pts could be discharged home, walk w/out assistance, and cope unaided w/ self-care activities) or retinal artery occlusion w/in the previous 3 months	Potential cardiac source of emboli (chronic or intermittent AF, mitral valve disease, MI w/in preceding 3 months, prosthetic valve or other specified but less common sources), previous or planned carotid surgery, other causes of established symptoms (e.g., migraine, arteritis), other severe disorders that might affect prognosis or compliance; ASA contraindications (e.g., peptic ulcer); full cooperation unlikely; need for long-term anticoagulant or antiplatelet treatment	2.67 (range, NR)
Sato, 2006 (JAST)[81] Fair	RCT	Japan	871	Pts w/ chronic or intermittent AF documented by ECG ≥ twice w/in 12 months	Prosthetic heart valve, rheumatic HD, mitral valve disease, uncontrolled HTN, hyperthyroidism, severe HF (NYHA class IV), past history of symptomatic thromboembolic disease w/in a year, previous intracranial bleeding, GI hemorrhage w/in 6 months, other indications for anticoagulant therapy or antiplatelet agents (e.g., CAD, PE, VTE, other diseases), physicians considered inappropriate to participate	2.1 (range, 0.04-3.7)
Silagy, 1993[52] Fair	RCT	Australia	400	Aged ≥ 70 years	Clinical history of major preexisting CVD, ASA contraindication, receiving concomitant treatment w/ NSAIDs	1 (range, NR)

Appendix E Table 1. Study Design Characteristics of Included Studies

Study	Design	Country	N Rando-mized	Inclusion Criteria	Exclusion Criteria	Mean Followup and Range (years)
SPAF, 1991[76] Good	RCT	United States	1120	Pts w/ non-rheumatic AF (ECG-documented) w/in the past year including some who had a history of stroke or TIA > 2 years before entry	Unable to consent; transient, self-limited AF; successful electrical or chemical cardioversion; mitral stenosis; NYHA class IV CHF; mitral regurgitation w/ CHF and left atrial diameter > 5.5 cm; idiopathic cardiomyopathy w/ CHF; prosthetic heart valve; MI w/in past 3 months; coronary bypass surgery w/in past year; percutaneous transluminal coronary angioplasty w/in past 3 months; unstable angina w/in past year; stroke, TIA or carotid endarterectomy w/in past 2 years; life expectancy < 2 years (e.g., due to cancer); chronic renal failure (serum Cr > 3.0 mg/dL); warfarin for arterial embolism or other indication (e.g., PE, DVT); severe chronic alcohol habituation; NSAID treatment; "other"; physician referred anticoagulant therapy, thrombocyopenia or anemia	1.3 (range, NR)

Abbreviations: AAA = abdominal aortic aneurysm; ABI = ankle brachial index; ACE = angiotensin-converting enzyme; AE = adverse effect; AF = atrial fibrillation; ASA = acetylsalicylic acid; AV = atrioventricular; BMI = body mass index; BP = blood pressure; bpm = beats per minute; CABG = coronary artery bypass graft; CAD = coronary artery disease; CAD = coronary artery disease; CHD = coronary heart disease; CHF = coronary heart failure; COX = celecoxib; Cr = creatinine; CRC = colorectal cancer; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DBP = diastolic blood pressure; dL = deciliter; DM = diabetes mellitus; DVT = deep vein thrombosis; ECG = electrocardiogram; FAP = familial adenomatous polyposis; FBG = fasting blood glucose; GI = gastrointestinal; GP = general practitioner; HD = heart disease; HF = heart failure; HR = heart rate; HRT = hormone replacement therapy; HTN = hypertension; IBD = irritable bowel disease; IHD = ischemic heart disease; INR = international normalized ratio; kg = kilogram(s); KQ = key question; L = liter(s); LVA = left ventricular atrophy; m = meter(s); mg = milligram(s); MI = myocardial infarction; mM = millimolar; mm Hg = millimeters of mercury; mmol = millimole(s); NMSC = non-melanoma skin cancer; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; pt(s) = participant(s); PVD = peripheral vascular disease; qd = daily; RA = rheumatoid arthritis; RCT = randomized controlled trial; SBP = systolic blood pressure; TIA = transient ischemic attack; VTE = venous thromboembolism; w/ =with

Appendix E Table 2. Baseline Demographics of Participants in Included Studies

Study	N Baseline	Mean Age and Range (years)	% Female	% Non-White	% Current Smoker	BMI (kg/m^2)	% Diabetics	% Previous Stroke or MI	BL Exercise	Baseline Cancer History, n (%)
AMIS, 1980[75] Fair	4524	54.8 (range, 30-69)	11.1	8.4	27.3	NR	10.6	1.39 100	Sedentary, n (%), 814 (18.0)	Malignant neoplasm, 86 (1.9)
Baron, 2003 (AFPPS)[77] Good (KQ1), Fair (KQ2, KQ6)	1121	57.5 (range, 21-80)	36.5	14.5	14.9	27.4	NR	0 0	NR	CRC in first degree relative, 341 (30.4)
Becattini, 2012 (WARFASA)[78] Fair	402	62.0 (range, ≥ 18)	36.07	1	NR	27.3	NR	NR NR	NR	NR
Belch, 2008 (POPADAD)[57] Fair	1276	60.3 (range, ≥ 40)	55.9	NR	31.1	29.2	100	NR NR	NR	Cancer, 0 (0)
Brighton, 2012 (ASPIRE)[58] Good	822	54.5 (range, ≥ 18)	45.6	NR	NR	NR	NR	NR NR	NR	Active cancer (with NMSC not included), 16 (2)
CDPRG, 1980 (CDPA)[59] Good	1529	NR (range, NR)	0	6.1	NR	NR	NR	3.0 100	Light physical activity during leisure time, 917 (60.0)	Cancer, 0 (0)
Cook, 2005 (WHS) 273 [60] Good	39879	54.6 (range, ≥ 45)	100	5.2	13.1	26.0	2.6	0 0	≥ 1000 kcal/wk, n (%), 13383 (34.0)	Family history (parent, sibling) of cancer (breast, colorectal, or ovarian), 7046 (17.7)

Appendix E Table 2. Baseline Demographics of Participants in Included Studies

Study	N Baseline	Mean Age and Range (years)	% Female	% Non-White	% Current Smoker	BMI (kg/m^2)	% Diabetics	% Previous Stroke or MI	BL Exercise	Baseline Cancer History, n (%)
Cook, 2013 (companion publication to Cook, 2005)[88] *Good*	*33682*	*NR (range, ≥ 45)*	*100*	*NR*	*11.6*	*NR*	*NR*	*NR* *NR*	*≥ 1000 kcal/week, n (%), 11423 (31.1)*	*Family history of cancer, 5923 (17.6)*
Cote, 1995 (ACBS)[79] Fair	372	66.7 (range, NR)	53	NR	36.8	NR	23.7	NR NR	NR	NR
DAMAD, 1989[51] Fair	314	46.7 (range, 17-67)	35.4	NR	NR	24.6	100	NR 0	NR	NR
de Berardis, 2012[85] Good	372850	69.4 (range, 30-95)	53.1	NR	NR	NR	15	NR NR	NR	NR
de Gaetano, 2001 (PPP)[61] Fair	4495	64.4 (range, ≥ 50)	57.5	NR	14.8	27.6	16.5	0 0	NR	NR
Diener, 1997 (ESPS-2)[62] Good	3298	66.7 (range, ≥ 18)	42.2	NR	23.5	NR	14.5	76.6 NR	NR	NR
EAFT, 1993[63] Fair	782	73 (range, > 25)	44	NR	19.1	NR	13	78.4 7.9	NR	NR
Ekstrom, 2013 (SNDR)[86] Fair	18646	62.3 (range, 30-80)	44.7	NR	15.4	29.6	100	0 0	NR	NR
ETDRS, 1992[64] Good	3711	NR (range, 18-70)	43.5	24	NR	NR	100	1.8 5.7	NR	Cancer, 0 (0)
Farrell, 1991 (UK-TIA)[65] Fair	2435	59.8 (range, ≥ 40)	26.9	NR	53.1	25.3	4.4	3.3 9.9	NR	NR

Appendix E Table 2. Baseline Demographics of Participants in Included Studies

Study	N Baseline	Mean Age and Range (years)	% Female	% Non-White	% Current Smoker	BMI (kg/m^2)	% Diabetics	% Previous Stroke or MI	BL Exercise	Baseline Cancer History, n (%)
Fowkes, 2010 (AAA)[66] Good	3350	62.0 (range, 50-75)	71.5	NR	32.4	NR	2.6	NR NR	NR	NR
Hansson, 1998 (HOT)[67] Fair	18790	61.5 (range, 50-80)	47	NR	15.9	28.4	8	1.2 1.5	NR	NR
Huang, 2010 (HPS)[83] Fair	32989	60.9 (range, NR)	0	NR	5.2	26.0	5.4	NR NR	Metabolic equivalent of physical activity (hrs/week), mean, 36.7 (NR)	Cancer, 0 (0)
Strate, 2011 (companion publication to Huang, 2010)[126] *Fair*	*47210*	*53.9 (range, 40-75)*	*0*	*NR*	*9.3*	*25.0*	*NR*	*NR* *NR*	*Metabolic equivalent of physical activity (hrs/week), mean, 21 (NR)*	*Cancer (excluding NMSC), 0 (0)*
Huang, 2011 (NHS)[84] Fair	87680	56.6 (range, 30-55)	100	NR	17.6	25.2	5	NR NR	Physical actvitiy (mets/week), mean, 15.4 (NR)	Cancer, 0 (0)
Iso, 1999 (Companion publication to Huang, 2011)[94] *Fair*	*79319*	*NR (range, 34-59)*	*100*	*2*	*NR*	*NR*	*NR*	*0* *0*	*NR*	*Cancer (except NMSC), 0 (0)*
Manson, 1991 (Companion publication to Huang, 2011)[127] *Fair*	*87678*	*46.0 (range, 30-55)*	*100*	*2*	*28.8*	*NR*	*2.1*	*0* *0*	*Vigorous exercise ≥ 1/week, n (%), 39497 (45.0)*	*Cancer, 0 (0)*

Appendix E Table 2. Baseline Demographics of Participants in Included Studies

Study	N Baseline	Mean Age and Range (years)	% Female	% Non-White	% Current Smoker	BMI (kg/m^2)	% Diabetics	% Previous Stroke or MI	BL Exercise	Baseline Cancer History, n (%)
Juul-Moller, 1992 (SAPAT)[54] Fair	2035	67 (range, 30-80)	48	NR	16	NR	NR	NR 0	NR	NR
Logan, 2008 (ukCAP)[68] Fair	939	57.8 (range, 27.6-74.6)	43.1	NR	NR	NR	NR	NR NR	NR	CRC in first-degree relative, 132 (14.1)
MRC, 1998 (TPT)[69] Good	2540	57.5 (range, 45-69)	0	NR	41.3	27.4	NR	0 0	NR	Malignant disease, 0 (0)
Nelson, 2008 (ASPREE)[53] Fair	209	76.2 (range, ≥ 70)	59.3	NR	4.3	NR	0	0 0	Physically active in past 2 weeks, 147 (70.3)	NR
Ogawa, 2008 (JPAD)[70] Fair	2539	64.5 (range, 30-80)	45.4	100	21.2	24	100	0 0	NR	NR
PARIS, 1980[71] Good	1216	56.3 (range, 30-74)	13.2	2.6	26.8	25.8	NR	2.9 100	Sedentary, n (%), 357 (29.4)	Malignancy, 0 (0)
Petersen, 1989 (Copenhagen AFASAK)[77] Fair	672	74.9 (range, 38-91)	45.8	NR	35.9	NR	8.8	4.0 7.4	NR	NR
Peto, 1988 (BMD)[72] Fair	5139	NR (range, NR)	0	NR	12.9	NR	2	0 0	NR	NR
PHS, 1989[73] Good	22071	NR (range, 40-84)	0	NR	11	NR	2.4	0 0	Vigorous exercise ≥ 1/week, 15957 (72.3)	Cancer, 0 (0)
SALT, 1991[74] Good	1360	67 (range, 50-79)	34.2	NR	25.4	NR	12.9	9.1 11.3	NR	NR

Appendix E Table 2. Baseline Demographics of Participants in Included Studies

Study	N Baseline	Mean Age and Range (years)	% Female	% Non-White	% Current Smoker	BMI (kg/m^2)	% Diabetics	% Previous Stroke or MI	BL Exercise	Baseline Cancer History, n (%)
Sato, 2006 (JAST)[81] Fair	871	65.1 (range, NR)	29.6	100	30.4	NR	14	NR NR	NR	NR
Silagy, 1993[52] Fair	400	73 (range, 70-90)	51	NR	5.8	NR	NR	0 0	NR	NR
SPAF, 1991[76] Good	1120	67 (range, NR)	29.5	NR	16	NR	17.5	6.5 7.5	NR	Metastatic cancer, 0 (0)

Abbreviations: BL = baseline; BMI = body mass index; CRC = colorectal cancer; hr = hour(s); kcal = kilocalorie(s); kg = kilogram(s); m = meter(s); MI = myocardial infarction; NMSC = non-melanoma skin cancer; NR = not reported; wk = week(s)

Appendix E Table 3. Intervention Characteristics of Included Studies

Study	Intervention	N randomized	Dose and Frequency	Other Protocol Items
AMIS, 1980[75]	ASA	2267	0.5 g (1.0 g total per day) bid	Advised against using ASA drugs; given supply of acetaminophen
Fair	Placebo	2257	Placebo bid	Advised against using ASA drugs; given supply of acetaminophen
Baron, 2003 (AFPPS)[77]	ASA 325	372	325 mg qd	Oral route; distributed in calendar packs w/ each blister containing 3 tablets
	ASA 81	377	81 mg qd	Oral route; distributed in calendar packs w/ each blister containing 3 tablets
Good	Placebo	372	Placebo qd	Oral route; distributed in calendar packs w/ each blister containing 3 tablets
Becattini, 2012 (WARFASA)[78]	ASA	205	100 mg qd	NR
	Placebo	197	Placebo qd	Discouraged use of COX-2 inhibitors
Fair				
Belch, 2008 (POPADAD)[57]	ASA alone	318	100 mg qd	Taken with a placebo pill
	ASA + antioxidant	320	100 mg ASA; 200 mg vitamin E, 100 mg vitmain C, 25 mg vitamin B6, 10 mg zinc, 10 mg vitamin B3, 9.4 mg lechitin, 0.8 mg sodium selenite qd	NR
Fair	Antioxidant alone	320	200 mg vitamin E, 100 mg vitamin C, 25 mg vitamin B6, 10 mg zinc, 10 mg vitamin B3, 9.4 mg lechitin, 0.8 mg sodium selenite qd	Taken with a placebo pill
	Placebo alone	318	Placebo qd	Two placebo pills
Benamouzig, 2003 (APACC)[82]	ASA 300	67	300 mg qd	One sachet to be diluted in water
	ASA 160	73	160 mg qd	One sachet to be diluted in water
	Placebo	132	Placebo qd	Same appearance and taste as ASA
Fair				
Brighton, 2012 (ASPIRE)[58]	ASA	411	100 mg qd	With morning meal
	Placebo	411	Placebo qd	With morning meal
Good				
CDPRG, 1980 (CDPA)[59]	ASA	745	324 mg (972 mg total per day) tid	One tablet with a glass of water before the morning, mid-day and evening meals
	Placebo	755	Calcium phosphate (198 mg) and microcrystalline cellulose (200 mg) tid	One tablet with a glass of water before the morning, mid-day and evening meals
Good				
Cook, 2005 (WHS)[60]	ASA	19934	100 mg alone or with vitamin E or beta-carotene qod	NR
	No ASA	19942	Placebo with or without beta-carotene + vitamin E qod	Placebo alone, beta-carotene alone, vitamin E alone
Good (KQ1,KQ2); Fair (KQ6)				

Appendix E Table 3. Intervention Characteristics of Included Studies

Study	Intervention	N randomized	Dose and Frequency	Other Protocol Items
Cook, 2013 (companion publication to Cook, 2005)[88] *Good*	*ASA*	*19934*	*100 mg alone or with vitamin E or beta-carotene qod*	*NR*
	No ASA	*19942*	*Placebo with or without beta-carotene + vitamin E qod*	*Placebo alone, beta-carotene alone, vitamin E alone*
Cote, 1995 (ACBS)[79] Fair	ASA	188	325 mg qd	NR
	Placebo	184	Placebo qd	NR
DAMAD, 1989[51] Fair	ASA	157	330 mg (990 mg total per day) tid	NR
	Placebo	157	Placebo tid	NR
de Berardis, 2012[85] Good	ASA	186425	≤ 300 mg NR	NR
	No ASA	186425	Non-users NR	Pts not receiving ASA anytime during the study period
de Gaetano, 2001 (PPP)[61] Fair	ASA	2226	100 mg alone or with 300 mg vitamin E qd	Randomized to ASA alone or combination ASA + vitamin E
	No ASA	2269	Placebo with or without 300 mg vitamin E qd	Placebo alone or vitamin E alone
Diener, 1997 (ESPS-2)[62] Good	ASA alone	1649	25 mg (50 mg total per day) bid	Allowed temporary dose reduction if tolerating poorly; stopped trial medicaion if anticoagulation was indicated; recommended paracetamol for analgesia
	Placebo	1649	Placebo bid	Allowed temporary dose reduction if tolerating poorly; stopped trial medicaion if anticoagulation was indicated; recommended paracetamol for analgesia
EAFT, 1993[63] Fair	ASA	404	300 mg qd	NR
	Placebo	378	Placebo qd	NR
Ekstrom, 2013 (SNDR)[86] Fair	ASA	4608	75 mg qd	Filled ≥ 3 prescripton or 19 fills of multidose-dispensed drugs during the 12 month period (12 months continuous use at baseline)
	No ASA	14038	Non-users NR	NR
ETDRS, 1992[64] Good	ASA	1856	650 mg qd	NR
	Placebo	1855	Placebo bid	NR

Appendix E Table 3. Intervention Characteristics of Included Studies

Study	Intervention	N randomized	Dose and Frequency	Other Protocol Items
Farrell, 1991 (UK-TIA)[65] Fair	ASA 1200	815	300 mg bid (two tablets; 1200 mg total per day)	Two tablets in morning, two in evening (preferably with or after food); if indigestion, advised to omit evening tablets, one morning pill or changed to enteric-coated.
	ASA 300	806	150 mg bid (two tablets; 300 mg total per day)	Two tablets in morning, two placebo in evening (preferably with or after food); if indigestion, advised to omit evening tablets, one morning pill or changed to enteric-coated.
	Placebo	814	Placebo bid	Two tablets in morning, two in evening (preferably with or after food); if indigestion, advised to omit evening tablets, one morning pill or changed to enteric-coated.
Fowkes, 2010 (AAA)[66] Good	ASA	1675	100 mg qd	NR
	Placebo	1675	Placebo qd	NR
Hansson, 1998 (HOT)[67] Fair	ASA	9399	75 mg qd	NR
	Placebo	9391	Placebo qd	NR
Huang, 2010 (HPS)[83] Fair	ASA	30916	Any dose ≥ 2 times/week	
	No ASA	20613	Non-users < 2 times/week	"Non-regular users of ASA"
Strate, 2011 (Companion publication to Huang, 2010)[126] *Fair*	*ASA*	*13874*	*≥ 325 mg ≥ 2 times/week*	*Examples include Anacin, Bufferin, Alka-Seltzer; "regular users"*
	No ASA	*33336*	*Non-users < 2 times/week*	*"Non-regular users"*
Huang, 2011 (NHS)[84] Fair	ASA	32187	325 mg ≥ 2 tablets/week	"Regular users"; ranges from two tablets at once to one baby ASA qd
	No ASA	55493	Non-users < 2 tablets/week	"Non-regular users"
Iso, 1999 (Companion publication to Huang, 2011)[94] *Fair*	*ASA*	*48554*	*325 mg ≥ 1 tablet/week*	*NR*
	No ASA	*19233*	*Non-users*	*No ASA per week*

Appendix E Table 3. Intervention Characteristics of Included Studies

Study	Intervention	N randomized	Dose and Frequency	Other Protocol Items
Manson, 1991 (Companion publication to Huang, 2011)[127] *Fair*	*ASA*	*35048*	*325 mg ≥ 1 tablet/week*	*Tablets assumed to be 325 mg per week*
	No ASA	*52630*	*Non-users*	*No ASA per week*
Juul-Moller, 1992 (SAPAT)[54] Fair	ASA	1009	75 mg qd	Taken with sotalol
	Placebo	1026	Placebo qd	Taken with sotalol
Logan, 2008 (ukCAP)[68] Fair	ASA alone	236	300 mg qd	
	ASA + folic acid	236	300 mg ASA; 0.5 mg folic acid qd	
	Folic acid alone	234	0.5 mg qd	
	Placebo alone	233	Placebo qd	
MRC, 1998 (TPT)[69] Good	ASA alone	1268	75 mg qd	NR
	Placebo	1272	Placebo qd	Identical looking
Nelson, 2008 (ASPREE)[53] Fair	ASA	NR	100 mg qd	NR
	Placebo	NR	Placebo qd	NR
Ogawa, 2008 (JPAD)[70] Fair	ASA	1262	81 or 100 mg qd	NR
	No ASA	1277	Not prescribed ASA NR	NR
PARIS, 1980[71] Good	ASA	810	324 mg (972 mg total per day) tid	With a single placebo tablet; taken with a full glass of water at morning, noon and evening meals
	Placebo	406	Placebo tid	Two tablets taken with a full glass of water at morning, noon and evening meals
Petersen, 1989 (Copenhagen AFASAK)[80] Fair	ASA	336	75 mg qd	NR
	Placebo (citric acid)	336	Placebo qd	NR
Peto, 1988 (BMD)[72] Fair	ASA	3429	500 mg, or 300 mg if requested qd	NR
	No ASA	1710	Avoid ASA NA	Avoid ASA and ASA containing products uless some specific indication develops; use paracetamol if analgestics needed
PHS, 1989[73] Good (KQ1); Fair (KQ6)	ASA	11037	325 mg alone or with 50 mg beta-carotene qod	NR
	No ASA	11034	Placebo with or without 50 mg beta-carotene qod	Placebo alone or beta-carotene alone groups

Appendix E Table 3. Intervention Characteristics of Included Studies

Study	Intervention	N randomized	Dose and Frequency	Other Protocol Items
SALT, 1991[74] Good	ASA	676	75 mg qd	Swallowed without chewing ≥ 30 minutes before breakfast
	Placebo	684	Placebo qd	Swallowed without chewing ≥ 30 minutes before breakfast
Sato, 2006 (JAST)[81] Fair	ASA	426	150-200 mg qd (or qod if 330 mg preferred)	Dose selected by attending physician; instructed to take in morning after breakfast
	No ASA	445	Not prescribed ASA NA	Not prescribed ASA, antiplatelet or anticoagulant therapy
Silagy, 1993[52] Fair	ASA	200	100 mg qd	NR
	Placebo	200	Placebo qd	NR
SPAF, 1991[76] Good	ASA	552	325 mg qd	NR
	Placebo	568	Placebo qd	NR

Abbreviations: ASA = acetylsalcyclic acid; bid = twice daily; COX = celecoxib; g = gram(s); LDA = low-dose aspirin; mg = milligram(s); NR = not reported; qd = daily; tid = three times a day

Appendix E Table 4. Results of Included Studies, Total Cancer Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Differences
Belch, 2008 (POPADAD)[57] Fair	Cancer death (number of participants)	6.7	318	ASA alone	9 (2.8%)	ASA vs. No ASA: OR 0.80 (95% CI, 0.47 to 1.37)
			320	ASA + antioxidant	16 (5%)	
			320	Antioxidant alone	18 (5.6%)	
			318	Placebo alone	13 (4.1%)	
Brighton, 2012 (ASPIRE)[58] Good	Cancer death (number of participants)	3.1	411	ASA	6 (1.5%)	NR
			411	Placebo	4 (1.0%)	
CDPRG, 1980 (CDPA)[59] Good	Cancer death (number of participants)	1.8	758	ASA	1 (0.1%)	ASA vs. Placebo: Z-value -0.98, p=NR
			771	Placebo	3 (0.4%)	
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	Cancer death (number of participants)	10.1	19934	ASA	284 (1.4%)	ASA vs. No ASA: RR 0.95 (95% CI, 0.81 to 1.11), p=0.51*
			19942	No ASA	299 (1.5%)	
	Cancer death, lung (number of participants)	10.1	19934	ASA	58 (0.3%)	ASA vs. No ASA: HR 0.70 (95% CI, 0.50 to 0.99), p=0.04*
			19942	No ASA	82 (0.4%)	
Cook, 2013 (Companion publication to Cook, 2005)[88] *Good*	*Cancer death (number of participants)*	*18*	*19934*	*ASA*	*729 (3.7%)*	*ASA vs. No ASA: HR 0.97 (95% CI, 0.88 to 1.07), p=0.56**
			19942	*No ASA*	*748 (3.8%)*	
DAMAD, 1989[51] Fair	Cancer death, jaw (number of participants)	3	157	ASA	1 (0.6%)	NR
			157	Placebo	0 (0%)	
de Gaetano, 2001 (PPP)[61] Fair	Cancer death (data from Rothwell 2012[10]) (number of participants)	3.6	2226	ASA	31 (1.4%)	ASA vs. No ASA: OR 1.09 (95% CI, 0.66 to 1.82)
			2269	No ASA	29 (1.3%)	
Diener, 1997 (ESPS-2)[62] Good	Cancer death (number of participants)	2	1649	ASA	20 (1.2%)	NR
			1649	Placebo	24 (1.5%)	
	Cancer death (data from Rothwell 2012[10]) (number of participants)	2	1649	ASA	19 (1.2%)	ASA vs. Placebo: OR 0.79 (95% CI, 0.43 to 1.45)
			1649	Placebo	24 (1.5%)	
EAFT, 1993[63] Fair	Cancer death (data from Rothwell 2012[10]) (number of participants)	2.3	404	ASA	10 (2.5%)	ASA vs. Placebo: OR 0.77 (95% CI, 0.33 to 1.81)
			378	Placebo	12 (3.2%)	
ETDRS, 1992[64] Good	Cancer death (number of participants)	5	1856	ASA	16 (0.9%)	ASA vs. Placebo: Z-value 0.37, p=NR; OR 1.14 (95% CI, 0.56 to 2.35)
			1855	Placebo	14 (0.8%)	

Appendix E Table 4. Results of Included Studies, Total Cancer Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Differences
Farrell, 1991 (UK-TIA)[65] Fair	Cancer death (data from Rothwell 2012[10]) (number of participants)	4	1621	ASA	24 (1.5%)	ASA vs. Placebo: OR 0.47 (95% CI, 0.27 to 0.84)
			814	Placebo	25 (3.1%)	
	Cancer death (number of participants)	4	815	ASA 1200	12 (1.5%)	NR
			806	ASA 300	9 (1.1%)	
			814	Placebo	23 (2.8%)	
Fowkes, 2010 (AAA)[66] Good	Cancer death (data from Rothwell 2011[8]) (number of participants)	8.2	1675	ASA	78 (4.7%)	ASA vs. No ASA: OR 0.86 (95% CI, 0.63 to 1.17)
			1675	No ASA	90 (5.4%)	
Hansson, 1998 (HOT)[67] Fair	Cancer death (data from Rothwell 2012[10]) (number of participants)	3.8	9399	ASA	108 (1.1%)	ASA vs. Placebo: OR 1.03 (95% CI, 0.78 to 1.35)
			9391	Placebo	105 (1.1%)	
Logan, 2008 (ukCAP)[68] Fair	Carcinoma-related deaths (number of participants)	3.4	236	ASA alone	2 (0.8%)	NR
			236	ASA + folic acid	0 (0%)	
			234	Folic acid alone	1 (0.4%)	
			233	Placebo alone	2 (0.9%)	
	Intracerebral malignant tumor, death (number of participants)	3.4	236	ASA alone	0 (0%)	NR
			236	ASA + folic acid	0 (0%)	
			234	Folic acid alone	0 (0%)	
			233	Placebo alone	1 (0.4%)	
	Lung cancer, death (number of participants)	3.4	236	ASA alone	1 (0.4%)	NR
			236	ASA + folic acid	0 (0%)	
			234	Folic acid alone	1 (0.4%)	
			233	Placebo alone	1 (0.4%)	
	Pancreatic cancer, death (number of participants)	3.4	236	ASA + folic acid	0 (0%)	NR
			236	ASA alone	1 (0.4%)	
			234	Folic acid alone	0 (0%)	
			233	Placebo alone	0 (0%)	
MRC, 1998 (TPT)[69] Good	Cancer death (number of participants)	6.8	1268	ASA	49 (3.9%)	NR
			1272	Placebo	51 (4.0%)	
Ogawa, 2008 (JPAD)[70] Fair	Cancer death (number of participants)	4.37	1262	ASA	15 (1.2%)	ASA vs. No ASA: OR 0.80 (95% CI, 0.40 to 1.57)
			1277	No ASA	19 (1.5%)	
PARIS, 1980[71] Good	Cancer death (number of participants)	3.4	810	ASA	7 (0.9%)	ASA vs. Placebo: Difference 0.62; Z-value 1.10, p=NR†
			406	Placebo	1 (0.2%)	

Appendix E Table 4. Results of Included Studies, Total Cancer Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Differences
Peto, 1988 (BMD)[72] Fair	Cancer death, lung (per 10,000 person-years)	6	3429	ASA	7.4 (NR)	NR
			1710	No ASA	11.6 (NR)	
	Cancer death, other (per 10,000 person-years)	6	3429	ASA	26.6 (NR)	NR
			1710	No ASA	31.7 (NR)	
	Cancer death, upper digestive tract (per 10,000 person-years)	6	3429	ASA	5.8 (NR)	NR
			1710	No ASA	5.3 (NR)	
	Cancer death (data from Rothwell, 2012[10]) (number of participants)	6	3429	ASA	75 (2.2%)	ASA vs. No ASA: OR 0.79 (95% CI, 0.55 to 1.14)
			1710	No ASA	47 (2.7%)	
PHS, 1989[73] Good (KQ1); Fair (KQ6)	Cancer death (data from Seshasai 2012[44]) (number of participants)	5	11037	ASA	79 (0.7%)	ASA vs. No ASA: OR 1.16 (95% CI, 0.84 to 1.61), p=NR
			11034	No ASA	68 (0.6%)	
SALT, 1991[74] Good	Cancer deaths (data from Rothwell 2012[10]) (number of participants)	2.67	676	ASA	12 (1.8%)	ASA vs. Placebo: OR 0.75 (95% CI, 0.65 to 1.61)
			684	Placebo	16 (2.3%)	
	Death due to malignant disorders (number of participants)	2.67	676	ASA	10 (1.5%)	NR
			684	Placebo	15 (2.2%)	

*Adjusted by age, vitamin E and beta-carotene treatment assignment
†Adjustment for baseline differences across treatment groups

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; RR = relative risk; vs = versus

Appendix E Table 5. Results of Included Studies, All-Cause Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
AMIS, 1980[75] Fair	Total mortality (number of participants)	3	2267	ASA	218 (9.6%)	NR
			2257	Placebo	199 (8.8%)	
		3.2	2267	ASA	245 (10.8%)	ASA vs. Placebo: Z-score 1.27, p=NR
			2257	Placebo	219 (9.7%)	
			2267	ASA	238 (10.5%)*	ASA vs. Placebo: Cox Z-score 0.02, p=NR*
			2257	Placebo	226 (10.0%)*	
Baron, 2003 (AFPPS)[77] Good (KQ1); Fair (KQ2,KQ6)	Death (number of participants)	2.7	372	ASA 325	4 (1.1%)	All Groups: p=0.93
			377	ASA 81	3 (0.8%)	
			372	Placebo	3 (0.8%)	
Becattini, 2012 (WARFASA)[78] Fair	Death (number of participants)	2	205	ASA	6 (2.9%)	ASA vs. Placebo: HR 1.04 (95% CI, 0.32 to 3.42), p=0.95
			197	Placebo	5 (2.5%)	
	Death (percent per year)	2	205	ASA	1.4 (NR)	NR
			197	Placebo	1.3 (NR)	
Belch, 2008 (POPADAD)[57] Fair	Death (any cause) (number of participants)	6.7	318	ASA alone	38 (12%)	ASA vs. No ASA: HR 0.93 (95% CI, 0.71 to 1.24), p=0.63
			320	ASA + antioxidant	56 (18%)	
			320	Antioxidant alone	59 (18%)	
			318	Placebo alone	42 (13%)	
Brighton, 2012 (ASPIRE)[58] Good	Death (number of participants)	3.1	411	ASA	16 (3.9%)	NR
			411	Placebo	18 (4.4%)	
CDPRG, 1980 (CDPA)[59] Good	All-cause mortality (not cumulative) (number of participants)	1	745	ASA	25 (NR)	NR
			755	Placebo	31 (NR)	
		2	564	ASA	14 (NR)	
			562	Placebo	31 (NR	
		2.33	140	ASA	5 (NR)	
			138	Placebo	2 (NR)	
	All-cause mortality, cumulative (per 100 person-years)	1	745	ASA	3.30 (0.68)	ASA vs. Placebo: Z-value -0.75 (95% CI, -2.61 to 1.17), p=NR
			755	Placebo	4.02 (0.68)	
		2	564	ASA	5.63 (1.02)	ASA vs. Placebo: Z-value -2.51 (95% CI, -6.45 to -0.79), p=NR
			562	Placebo	9.25 (1.02)	
		2.33	140	ASA	6.74 (1.09)	ASA vs. Placebo: Z-value -1.91 (95% CI, -5.96 to 0.08), p=NR
			138	Placebo	9.68 (1.09)	
	Deaths (number of participants)	1.8	758	ASA	43 (5.7%)†	NR
		1.8	771	Placebo	65 (8.4%)†	
		1.8	758	ASA	44 (5.8%)	NR
		1.8	771	Placebo	64 (8.3%)	

Appendix E Table 5. Results of Included Studies, All-Cause Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	Any death (number of participants))	10.1	19934	ASA	609 (3.1%)	ASA vs. No ASA: RR 0.95 (95% CI, 0.85 to 1.06), p=0.32‡
			19942	No ASA	642 (3.2%)	
Cook, 2013 (Companion publication to Cook, 2005)[88] *Good*	*Any death (number of participants)*	*18*	*19934*	*ASA*	*1744 (8.7%)*	*ASA vs. No ASA: HR 1.00 (95% CI, 0.94 to 1.07), p≥0.99‡*
			19942	*No ASA*	*1728 (8.7%)*	
Cote, 1995 (ACBS)[79] Fair	Death (combined vascular and nonvascular) (number of participants)	2.4	188	ASA	11 (5.9%)	NR
			184	Placebo	13 (7.1%)	
de Gaetano, 2001 (PPP)[61] Fair	Total death (number of participants)	3.6	2226	ASA	62 (2.8%)	ASA vs. No ASA: RR 0.81 (95% CI, 0.58 to 1.13), p=NR
			2269	No ASA	78 (3.4%)	
Diener, 1997 (ESPS-2)[62] Good	Death (number of participants)	2	1649	ASA	182 (11.0%)	ASA vs. Placebo: Risk Reduction 10.9 (8.6), p=0.204; OR 0.88 (95% CI, 0.71 to 1.09), p=NR
			1649	Placebo	202 (12.2%)	
EAFT, 1993[63] Fair	All deaths (% per year)	838 p-y	404	ASA	11 (NR)	NR
		715 p-y	378	Placebo	12 (NR)	
	All deaths (number of participants)	2.3	404	ASA	102 (25.2%)	ASA vs. Placebo: HR 0.91 (95% CI, 0.69 to 1.20), p=0.48
			378	Placebo	99 (26.2%)	
ETDRS, 1992[64] Good	Death-all causes (5-year life table rate)	5	1855	ASA	14.9 (NR)	ASA vs. Placebo: RR 0.91 (99% CI, 0.75 to 1.11), p=0.24§
			1856	Placebo	12.1 (NR)	
	Death-all causes (number of participants)	5	1856	ASA	340 (18.3%)	ASA vs. Placebo: Z-value -1.10, p=NR
			1855	Placebo	366 (19.7%)	
Farrell, 1991 (UK-TIA)[65] Fair	All-cause mortality (number of participants)	4	815	ASA 1200	112 (13.7%)	NR
			806	ASA 300	109 (13.5%)	
			814	Placebo	122 (15.0%)	
Fowkes, 2010 (AAA)[66] Good	All-cause mortality (number of participants)	8.2	1675	ASA	176 (10.5%)	NR
			1675	Placebo	186 (11.1%)	
	All-cause mortality, incidence rate (per 1,000 person-years)	8.2	1675	ASA	12.8 (NR)	ASA vs. Placebo: HR 0.95 (95% CI, 0.77 to 1.16), p=NR
			1675	Placebo	13.5 (NR)	

Appendix E Table 5. Results of Included Studies, All-Cause Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Hansson, 1998 (HOT)[67]	Deaths (number of participants)	3.8	9399	ASA	284 (3.0%)	ASA vs. Placebo: RR 0.93 (95% CI, 0.79 to 1.09), p=0.36
			9391	Placebo	305 (3.2%)	
Fair	Deaths (per 1,000 patient-years)	3.8	9399	ASA	8.0 (NR)	NR
			9391	Placebo	8.6 (NR)	
Juul-Moller, 1992 (SAPAT)[54]	Deaths (number of participants)	4.2	1009	ASA	82 (8.1%)	ASA vs. Placebo: % Change -22, p=0.103
			1026	No ASA	106 (10.3%)	
Fair						
Logan, 2008 (ukCAP)[68]	Deaths, occurring while on study medication or w/in 6 months of completing treatment (number of participants)	3.4	472	ASA	3 (0.6%)	NR
			467	No ASA	5 (1.1%)	
Fair	Died (number of participants)	3.4	236	ASA alone	8 (3.4%)	NR
			236	ASA + folic acid	4 (1.7%)	
			234	Folic acid alone	4 (1.7%)	
			233	Placebo alone	7 (3.0%)	
MRC, 1998 (TPT)[69]	Death, all causes (number of participants)	6.8	1268	ASA	113 (8.9%)	NR
			1272	Placebo	110 (8.6%)	
Good	Death, all causes (per 1,000 person-years)	6.8	1268	ASA	13.6 (NR)	NR
			1272	Placebo	13.1 (NR)	
Nelson, 2008 (ASPREE)[53]	Death (number of participants)	1	NR	ASA	0 (0%)	NR
			NR	Placebo	0 (0%)	
Fair						
Ogawa, 2008 (JPAD)[70]	All-cause mortality (number of participants)	4.37	1262	ASA	34 (2.7%)	ASA vs. No ASA: HR 0.90 (95% CI, 0.57 to 1.14), p=0.67
			1277	No ASA	38 (3.0%)	
Fair						
PARIS, 1980[71]	All-cause mortality (number of participants)	3.4	810	ASA	85 (10.5%)	ASA vs. Placebo: Z-value -1.06, p=NR‖
			406	Placebo	52 (12.8%)	
Good	Total death (event rate)	1	810	ASA	3.2 (NR)	ASA vs. Placebo: % Reduction 5.9, p=Z-value: -0.23
			406	Placebo	3.4 (NR)	
		1.33	810	ASA	4.3 (NR)	ASA vs. Placebo: % Reduction 8.5, p=Z-value: -0.30
			406	Placebo	4.7 (NR)	
		1.67	810	ASA	5.4 (NR)	ASA vs. Placebo: % Reduction 23.9, p=Z-value: -1.25
			406	Placebo	7.1 (NR)	
		2	810	ASA	5.6 (NR)	ASA vs. Placebo: % Reduction 29.1, p=Z-value: -1.60
			406	Placebo	7.9 (NR)	
		3	810	ASA	9.0 (NR)	ASA vs. Placebo: % Reduction 21.1, p=Z-value: -1.31
			406	Placebo	11.4 (NR)	

Appendix E Table 5. Results of Included Studies, All-Cause Mortality

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Petersen, 1989 (Copenhagen AFASAK)[80] Fair	Death (number of participants)	2	336	ASA	NR (NR)	ASA vs. Placebo (citric acid): p=NSD
			336	Placebo (citric acid)	NR (NR)	
Peto, 1988 (BMD)[72] Fair	All-cause mortality (per 10,000 person-years)	6	3429	ASA	143.5 (NR)	NR
			1710	No ASA	159.5 (NR)	
PHS, 1989[73] Good (KQ1); Fair (KQ6)	All-cause mortality (number of participants)	5	11037	ASA	217 (2.0%)	ASA vs. Placebo: RR 0.96 (95% CI, 0.80 to 1.14), p=0.64¶
			11034	Placebo	227 (2.1%)	
	All-cause mortality, confirmed cause (number of participants)	5	11037	ASA	205 (1.9%)	ASA vs. Placebo: RR 0.95 (95% CI, 0.79 to 1.15), p=0.60¶
			11034	Placebo	216 (2.0%)	
SALT, 1991[74] Good	Total death (fatal stroke and non-stroke deaths) (number of participants)	2.67	676	ASA	61 (9.0%)	NR
			684	Placebo	69 (10.1%)	
Sato, 2006 (JAST)[81] Fair	Death (CV and non-CV combined) (number of participants)	2.1	426	ASA	10 (2.3%)	NR
			445	No ASA	9 (2.0%)	
SPAF, 1991[76] Good	Total mortality (number of participants)	1.3	552	ASA	39 (7.1%)	ASA vs. Placebo: Risk Reduction 0.20 (95% CI, -0.20 to 0.46), p=0.37; RR 0.80 (95% CI, 0.54 to 1.2), p=NR
			568	Placebo	50 (8.8%)	
	Total mortality (rate per year)	1.3	552	ASA	5.3 (NR)	NR
			568	Placebo	6.5 (NR)	

*Adjusted by HF, angina, arrhythmias, digitalis, nitrates, beta-blockers, ventricular conduction defcts, ST depression, MI, cardiomegaly, smoking, sex, diuretics, gout meds, antiarrhythmic agents
†Adjusted by 54 baseline characteristics
‡Adjusted by age, vitamin E and beta-carotene treatment assignment
§Adjusted by age > 30 years, age > 50 years, male, nonwhite, type I and type II DM, clinical center
‖Adjusted for baseline differences across the treatment groups
¶Adjusted for age and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; RR = relative risk; vs = versus

Appendix E Table 6. Results of Included Studies, Cancer Incidence

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
AMIS, 1980[75] Fair	Total cancer (malignant neoplasms) (number of participants)	3.2	2267	ASA	50 (2.2%)	ASA vs. Placebo: Z-score 0.73, p=NR
			2257	Placebo	43 (1.9%)	
Baron, 2003 (AFPPS)[77] Good (KQ1); Fair (KQ2,KQ6)	Colorectal cancer (number of events)	2.7	372	ASA 325	3 (0.8)	All Groups: p=0.71
			377	ASA 81	2 (0.5)	
			372	Placebo	1 (0.3)	
	Non-colorectal cancer (number of events)	2.7	372	ASA 325	9 (NR)	All Groups: p=0.21
			377	ASA 81	14 (NR)	
			372	Placebo	6 (NR)	
Belch, 2008 (POPADAD)[57] Fair	Cancer incidence (data from Rothwell 2012[10]) (number of participants)	6.7	638	ASA	45 (7.1%)	NR
			638	No ASA	60 (9.4%)	
	Total cancer (malignancy) (number of participants)	6.7	318	ASA alone	24 (8%)	ASA vs. No ASA: OR 0.76 (95% CI, 0.52 to 1.11), p=0.15
			320	ASA + antioxidant	29 (9%)	
			320	Antioxidant alone	36 (11%)	
			318	Placebo alone	32 (10%)	
Brighton, 2012 (ASPIRE)[58] Good	Cancer, leading to hospitalization (number of participants)	3.1	411	ASA	11 (2.7%)	NR
			411	Placebo	9 (2.2%)	
	Total cancer, after randomization (number of participants)	3.1	411	ASA	17 (1.3%)	ASA vs. Placebo: HR 0.92 (95% CI, 0.47 to 1.79), p=NSD*
			411	Placebo	18 (1.5%)	
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	Bladder cancer (number of events)	10.1	19934	ASA	27 (NR)	ASA vs. No ASA: RR 1.12 (95% CI, 0.65 to 1.94), p=0.69*
			19942	No ASA	24 (NR)	
	Brain cancer (number of events)	10.1	19934	ASA	17 (NR)	ASA vs. No ASA: RR 1.21 (95% CI, 0.60 to 2.46), p=0.59
			19942	No ASA	14 (NR)	
	Breast cancer (number of events)	10.1	19934	ASA	608 (NR)	ASA vs. No ASA: RR 0.98 (95% CI, 0.87 to 1.09), p=0.68*
			19942	No ASA	622 (NR)	
	Esophageal cancer (number of events)	10.1	19934	ASA	2 (NR)	NR
			19942	No ASA	5 (NR)	
	Hodgkin lymphoma (number of events)	10.1	19934	ASA	7 (NR)	NR
			19942	No ASA	4 (NR)	
	Kidney cancer (number of events)	10.1	19934	ASA	26 (NR)	ASA vs. No ASA: RR 0.74 (95% CI, 0.45 to 1.23), p=0.25*
			19942	No ASA	35 (NR)	
	Leukemia (number of events)	10.1	19934	ASA	37 (NR)	ASA vs. No ASA: RR 1.54 (95% CI, 0.92 to 2.57), p=0.10*
			19942	No ASA	24 (NR)	
	Leukemia/lymphoma (number of events)	10.1	19934	ASA	104 (NR)	ASA vs. No ASA: RR 1.15 (95% CI, 0.87 to 1.53), p=0.32*
			19942	No ASA	90 (NR)	
	Lung cancer (number of events)	10.1	19934	ASA	90 (NR)	ASA vs. No ASA: RR 0.78 (95% CI, 0.59 to 1.03), p=0.08*
			19942	No ASA	115 (NR)	
	Lymphoma (number of events)	10.1	19934	ASA	67 (NR)	ASA vs. No ASA: RR 1.01 (95% CI, 0.72 to 1.42), p=0.94*
			19942	No ASA	66 (NR)	
	Melanoma (number of events)	10.1	19934	ASA	68 (NR)	ASA vs. No ASA: RR 0.97 (95% CI, 0.70 to 1.36), p=0.87*
			19942	No ASA	70 (NR)	

Appendix E Table 6. Results of Included Studies, Cancer Incidence

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
	Multiple myeloma (number of events)	10.1	19934	ASA	18 (NR)	ASA vs. No ASA: RR 1.50 (95% CI, 0.72 to 3.11), p=0.28*
			19942	No ASA	12 (NR)	
	Ovarian cancer (number of events)	10.1	19934	ASA	63 (NR)	ASA vs. No ASA: RR 0.95 (95% CI, 0.68 to 1.35), p=0.79*
			19942	No ASA	66 (NR)	
	Pancreatic cancer (number of events)	10.1	19934	ASA	30 (NR)	ASA vs. No ASA: RR 1.42 (95% CI, 0.81 to 2.49), p=0.21*
			19942	No ASA	21 (NR)	
	Stomach cancer (number of events)	10.1	19934	ASA	10 (NR)	ASA vs. No ASA: RR 1.00 (95% CI, 0.42 to 2.40), p≥0.99*
			19942	No ASA	10 (NR)	
	Thyroid cancer (number of events)	10.1	19934	ASA	35 (NR)	ASA vs. No ASA: RR 1.40 (95% CI, 0.84 to 2.34), p=0.20*
			19942	No ASA	25 (NR)	
	Total cancer (excluding NMSC) (number of events)	10.1	19934	ASA	1438 (NR)	ASA vs. No ASA: RR 1.01 (95% CI, 0.94 to 1.08), p=0.87*
			19942	No ASA	1427 (NR)	
	Uterine cancer (number of events)	10.1	19934	ASA	123 (NR)	ASA vs. No ASA: RR 1.22 (95% CI, 0.94 to 1.58), p=0.14*
		10.1	19942	No ASA	101 (NR)	
Cook, 2013 (companion publication to Cook, 2005)[88] Good	Bladder cancer (number of cases)	18	19934	ASA	47 (0.2)	ASA vs. No ASA: HR 1.11 (95% CI, 0.73 to 1.68), p=0.63*
			19942	No ASA	42 (0.2)	
	Brain cancer (number of cases)	18	19934	ASA	33 (0.2)	ASA vs. No ASA: HR 1.56 (95% CI, 0.90 to 2.69), p=0.112*
			19942	No ASA	21 (0.1)	
	Breast cancer (number of cases)	10	19934	ASA	643 (3.2)	ASA vs. No ASA: HR 0.96 (95% CI, 0.86 to 1.07), p=0.43*
			19942	No ASA	671 (3.4)	
		11-18 (post-trial)	19934	ASA	385 (2.2)	ASA vs. No ASA: HR 1.02 (95% CI, 0.89 to 1.18), p=0.77*
			19942	No ASA	371 (2.2)	
		18	19934	ASA	1028 (5.2)	ASA vs. No ASA: HR 0.98 (95% CI, 0.90 to 1.07), p=0.65*
			19942	No ASA	1042 (5.2)	
	Esophageal cancer (number of cases)	18	19934	ASA	5 (0.03)	ASA vs. No ASA: HR 0.45 (95% CI, 0.16 to 1.29), p=0.138*
			19942	No ASA	11 (0.06)	
	Kidney cancer (number of cases)	18	19934	ASA	39 (0.2)	ASA vs. No ASA: HR 0.69 (95% CI, 0.46 to 1.04), p=0.077*
			19942	No ASA	56 (0.3)	
	Leukemia (number of cases)	18	19934	ASA	69 (0.3)	ASA vs. No ASA: HR 1.22 (95% CI, 0.86 to 1.74), p=0.27*
			19942	No ASA	56 (0.3)	
	Leukemia/lymphoma (number of cases)	18	19934	ASA	185 (0.9)	ASA vs. No ASA: HR 1.00 (95% CI, 0.81 to 1.22), p=0.97*
			19942	No ASA	184 (0.9)	
	Lung cancer (number of cases)	10	19934	ASA	117 (0.6)	ASA vs. No ASA: HR 0.87 (95% CI, 0.68 to 1.12), p=0.27*
			19942	No ASA	134 (0.7)	
		11-18 (post-trial)	19934	ASA	104 (0.6)	ASA vs. No ASA: HR 1.34 (95% CI, 1.00 to 1.80), p=0.052*
			19942	No ASA	76 (0.4)	
		18	19934	ASA	221 (1.1)	ASA vs. No ASA: HR 1.04 (95% CI, 0.86 to 1.26), p=0.67*
			19942	No ASA	210 (1.1)	
	Lymphoma (number of cases)	18	19934	ASA	116 (0.6)	ASA vs. No ASA: HR 0.90 (95% CI, 0.70 to 1.15), p=0.40*
			19942	No ASA	128 (0.6)	

Appendix E Table 6. Results of Included Studies, Cancer Incidence

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
	Melanoma (number of cases)	18	19934	ASA	127 (0.6)	ASA vs. No ASA: HR 0.94 (95% CI, 0.74 to 1.20), p=0.63*
			19942	No ASA	134 (0.7)	
	Multiple myeloma (number of cases)	18	19934	ASA	32 (0.2)	ASA vs. No ASA: HR 1.09 (95% CI, 0.66 to 1.80), p=0.73*
			19942	No ASA	29 (0.1)	
	Ovarian cancer (number of cases)	18	19934	ASA	95 (0.5)	ASA vs. No ASA: HR 0.85 (95% CI, 0.65 to 1.12), p=0.25*
			19942	No ASA	111 (0.6)	
	Pancreatic cancer (number of cases)	18	19934	ASA	48 (0.2)	ASA vs. No ASA: HR 1.19 (95% CI, 0.78 to 1.81), p=0.42*
			19942	No ASA	40 (0.2)	
	Stomach cancer (number of cases)	18	19934	ASA	16 (0.1)	ASA vs. No ASA: HR 0.75 (95% CI, 0.39 to 1.45), p=0.40*
			19942	No ASA	21 (0.1)	
	Thyroid cancer (number of cases)	18	19934	ASA	55 (0.3)	ASA vs. No ASA: HR 1.14 (95% CI, 0.77 to 1.68), p=0.50*
			19942	No ASA	48 (0.2)	
	Total cancer (excluding NMSC) (number of cases)	10	19934	ASA	1568 (7.9)	ASA vs. No ASA: HR 1.00 (95% CI, 0.93 to 1.07), p=0.96*
			19942	No ASA	1568 (7.9)	
		11-18 (post-trial)	19934	ASA	941 (5.4)	ASA vs. No ASA: HR 0.93 (95% CI, 0.85 to 1.02), p=0.113*
			19942	No ASA	995 (5.8)	
		18	19934	ASA	2509 (12.6)	ASA vs. No ASA: HR 0.97 (95% CI, 0.92 to 1.03), p=0.31*
			19942	No ASA	2562 (12.8)	
	Uterine cancer (number of cases)	18	19934	ASA	228 (1.1)	ASA vs. No ASA: HR 1.00 (95% CI, 0.83 to 1.20), p=0.98*
			19942	No ASA	227 (1.1)	
de Gaetano, 2001 (PPP)[61]	Cancer incidence (data from Rothwell 2012[10]) (number of participants)	3.6	2226	ASA	93 (4.2%)	NR
			2269	No ASA	89 (3.9%)	
Fair	Total cancer, non-fatal (number of participants)	3.6	2226	ASA	86 (3.9%)	ASA vs. No ASA: p=NSD
			2269	No ASA	80 (3.5%)	
Diener, 1997 (ESPS-2)[62]	Total cancer (number of events)	2	1649	ASA	32 (NR)	NR
			1649	Placebo	28 (NR)	
Good						
Fowkes, 2010 (AAA)[66]	Cancer incidence (data from Rothwell 2012[10]) (number of participants)	8.2	1675	ASA	166 (9.9%)	NR
			1675	Placebo	194 (11.6%)	
Good						
Hansson, 1998 (HOT)[67]	Cancer incidence (data from Rothwell 2012[10]) (number of participants)	3.8	9399	ASA	294 (3.1%)	NR
			9391	Placebo	311 (3.3%)	
Fair						
Juul-Moller, 1992 (SAPAT)[54]	Total cancer (malignant disease), reason for stopping early (number of participants)	4.2	1009	ASA	10 (1.0%)	NR
			1026	Placebo	19 (1.9%)	
Fair						

Appendix E Table 6. Results of Included Studies, Cancer Incidence

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Logan, 2008 (ukCAP)[68]	Colorectal cancer (number of participants)	3.4	472	ASA	3 (0.6%)	NR
			467	No ASA	7 (1.5%)	
Fair	Noncolorectal cancers (number of participants)	3.4	472	ASA	9 (1.9%)	NR
			467	No ASA	8 (1.7%)	
Peto, 1988 (BMD)[72]	Total cancer (malignant neoplasm), non-fatal (per 10,000 person-years)	6	3429	ASA	63.2 (NR)	NR
			1710	No ASA	61.2 (NR)	
Fair						

*Adjusted by age, vitamin E and beta-carotene treatment assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; NMSC = non-melanoma skin cancer; HR = hazard ratio; NR = not reported; NSD = no significant difference; OR = odds ratio; RR = relative risk; vs = versus

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
AMIS, 1980[75]	Black tarry stool (number of participants)	3.2	2267	ASA	61 (2.7%)	ASA vs. Placebo: Z-score 2.32, p=NR
			2257	Placebo	38 (1.7%)	
Fair	Bloody stool (number of participants)	3.2	2267	ASA	111 (4.9%)	ASA vs. Placebo: Z-score 3.38, p=NR
			2257	Placebo	65 (2.9%)	
	Peptic ulcer, fatal (number of participants)	3.2	2267	ASA	1 (0.04%)	NR
			2257	Placebo	0 (0%)	
Baron, 2003 (AFPPS)[77]	Serious GI bleeding, leading to hospitalization or surgical intervention (number of events)	2.7	372	ASA 325	4 (NR)	All Groups: p=0.65
			377	ASA 81	2 (NR)	
Good (KQ1); Fair (KQ2,KQ6)			372	Placebo	3 (NR)	
Belch, 2008 (POPADAD)[57]	GI bleeding (number of participants)	6.7	318	ASA alone	13 (4%)	ASA vs. No ASA: OR 0.90 (95% CI, 0.53 to 1.52), p=0.69
			320	ASA + antioxidant	15 (5%)	
			320	Antioxidant alone	13 (4%)	
Fair			318	Placebo alone	18 (6%)	
Brighton, 2012 (ASPIRE)[58]	GI adverse effects (toxicity and bleeding), leading to permanent discontinuation (number of participants)	3.1	411	ASA	14 (3.4%)	NR
			411	Placebo	2 (0.5%)	
Good						
CDPRG, 1980 (CDPA)[59]	Black tarry stool (number of participants)	1.8	727	ASA	20 (2.8%)	ASA vs. Placebo: Z-value 1.70, p=NR
			744	Placebo	11 (1.5%)	
	Bloody stools (number of participants)	1.8	727	ASA	22 (3.0%)	ASA vs. Placebo: Z-value 0.23, p=NR
Good			744	Placebo	21 (2.8%)	
Cook, 2005 (WHS)[60]	GI bleeding requiring transfusion (per 1,000 person-years)	10.1	19934	ASA	0.64 (NR)	ASA vs. No ASA: Rate Difference 0.18 (95% CI, 0.04 to 0.33), p=NR
			19942	No ASA	0.46 (NR)	
Good (KQ1,KQ2); Fair (KQ6)	GI bleeding requiring transfusion, any (number of events)	10.1	19934	ASA	127 (0.6)	ASA vs. No ASA: RR 1.40 (95% CI, 1.07 to 1.83), p=0.02*
			19942	No ASA	91 (0.5)	
	GI bleeding, any (number of events)	10.1	19934	ASA	910 (4.6)	ASA vs. No ASA: RR 1.22 (95% CI, 1.10 to 1.34), p≤0.001*
			19942	No ASA	751 (3.8)	
	GI bleeding, any (per 1,000 person-years)	10.1	19934	ASA	4.68 (NR)	ASA vs. No ASA: Rate Difference 0.83 (95% CI, 0.42 to 1.24), p=NR
			19942	No ASA	3.84 (NR)	
	GI hemorrhage, fatal (number of participants)	10.1	19934	ASA	2 (0.01%)	
			19942	No ASA	3 (0.02%)	
Cook, 2013 (Companion publication to Cook, 2005)[88]	*GI bleeding (number of cases)*	*10*	*19934*	*ASA*	*1489 (7.5)*	*ASA vs. No ASA: HR 1.15 (95% CI, 1.07 to 1.24), p≤0.001**
			19942	*No ASA*	*1301 (6.5)*	
		11-18 (post-trial)	*19934*	*ASA*	*156 (0.9)*	*ASA vs. No ASA: HR 1.03 (95% CI, 0.82 to 1.29), p=0.79**
Good			*19942*	*No ASA*	*151 (0.9)*	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		18	*19934*	*ASA*	*1645 (8.3)*	*ASA vs. No ASA: p=0.37; HR 1.14 (95% CI, 1.06 to 1.22), p≤0.001**
			19942	*No ASA*	*1452 (7.3)*	
	GI hemorrhage, fatal (number of participants)	*18*	*19934*	*ASA*	*3 (0.02%)*	*NR*
			19942	*No ASA*	*3 (0.02%)*	
Cote, 1995 (ACBS)[79] Fair	Nonfatal gastric hemorrhage requiring blood transfusion and hospitalization (number of participants)	2.4	188	ASA	1 (0.5%)	NR
			184	Placebo	1 (0.5%)	
DAMAD, 1989[51] Fair	GI bleeding, cause for discontinuation (number of participants)	3	157	ASA	0 (0%)	NR
			157	Placebo	1 (0.6%)	
de Berardis, 2012[85] Good	GI bleeding (number of events)	6	186425	ASA	2294 (NR)	ASA vs. No ASA: IRR 1.55 (95% CI, 1.46 to 1.65), p=NR
			186425	No ASA	2193 (NR)	
de Gaetano, 2001 (PPP)[61] Fair	GI bleeding, nonfatal (number of participants)	3.6	2226	ASA	17 (0.8%)	NR
			2269	No ASA	5 (0.2%)	
EAFT, 1993[63] Fair	GI bleeding, major and fatal (number of participants)	2.3	404	ASA	2 (0.5%)	NR
			378	Placebo	1 (0.3%)	
	GI bleeding, minor (number of participants)	2.3	404	ASA	8 (2.0%)	NR
			378	Placebo	5 (1.3%)	
Farrell, 1991 (UK-TIA)[65] Fair	GI bleeding associated w/ cancer (number of participants)	4	815	ASA 1200	2 (0.2%)	
			806	ASA 300	2 (0.2%)	
			814	Placebo	0 (0%)	
	GI bleeding, admitted to hospital (number of participants)	4	815	ASA 1200	11 (1.3%)	
			806	ASA 300	2 (0.2%)	
			814	Placebo	1 (0.1%)	
	GI bleeding, admitted to hospital and operated on (number of participants)	4	815	ASA 1200	4 (0.5%)	
			806	ASA 300	2 (0.2%)	
			814	Placebo	1 (0.1%)	
	GI bleeding, admitted to hospital and transfusion (number of participants)	4	815	ASA 1200	2 (0.2%)	
			806	ASA 300	6 (0.7%)	
			814	Placebo	0 (0%)	
	GI bleeding, lower (number of participants)	4	815	ASA 1200	6 (0.7%)	ASA 1200 vs. Placebo: OR 1.5 (95% CI, 0.4 to 5.3), p=NR ASA 300 vs. Placebo: OR 1.8 (95% CI, 0.5 to 6.1), p=NR
			806	ASA 300	7 (0.9%)	
			814	Placebo	4 (0.5%)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
	GI hemorrhage (number of participants)	4	815	ASA 1200	39 (5%)	ASA 1200 vs. placebo: OR 1.62 (95% CI, 0.94 to 2.79), p=NR ASA 300 vs. Placebo: OR 2.57 (95% CI, 1.20 to 5.53), p=NR
			806	ASA 300	25 (3%)	
			814	Placebo	9 (1%)	
	GI hemorrhage (per 1,000 person-years)	4	815	ASA 1200	11 (NR)	
			806	ASA 300	7 (NR)	
			814	Placebo	3 (NR)	
	GI hemorrhage, fatal (number of participants)	4	815	ASA 1200	2 (1%)	
			806	ASA 300	0 (0%)	
			814	Placebo	0 (0%)	
	Upper GI bleeding (number of participants)	4	815	ASA 1200	31 (3.8%)	ASA 1200 vs. Placebo: OR 6.4 (95% CI, 2.5 to 16.5), p=NR ASA 300 vs. Placebo: OR 3.3 (95% CI, 1.2 to 9.0), p=NR
			806	ASA 300	16 (2.0%)	
			814	Placebo	5 (0.6%)	
	Upper GI bleeding w/ hospitalization (number of participants)	4	815	ASA 1200	17 (2.1%)	ASA 1200 vs. Placebo: OR 8.7 (95% CI, 2.0 to 37.6), p=NR ASA 300 vs. Placebo: OR 3.6 (95% CI, 0.7 to 17.2), p=NR
			806	ASA 300	7 (0.9%)	
			814	Placebo	2 (0.2%)	
Fowkes, 2010 (AAA)[66] Good	GI hemorrhage, required admission to hospital (number of events)	8.2	65	ASA	13 (NR)	NR
			59	Placebo	14 (NR)	
	GI hemorrhage, required admission to hospital (number of participants)	8.2	1675	ASA	9 (0.5%)	NR
			1675	Placebo	8 (0.5%)	
Hansson, 1998 (HOT)[67] Fair	GI bleeding, fatal (number of events)	3.8	9399	ASA	5 (NR)	NR
			9391	Placebo	3 (NR)	
	Major GI bleeding, non-fatal (number of events)	3.8	9399	ASA	72 (NR)	NR
			9391	Placebo	34 (NR)	
	Minor GI bleeding (number of events)	3.8	9399	ASA	30 (NR)	NR
			9391	Placebo	18 (NR)	
Huang, 2010 (HPS)[83] Fair	GI bleeding (number of cases)	143386	NR	ASA ≥ 6 days/week	369 (NR)	<u>Age adjusted:</u> ASA ≥ 6 days/week vs. No ASA per week: RR 1.46 (95% CI, 1.20 to 1.77), p≤0.001 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.51 (95% CI, 1.09 to 2.07), p≤0.001 for trend <u>Multivariate adjusted†:</u> ASA ≥ 6 days/week vs. No ASA per week: RR 1.39 (95% CI, 1.14 to 1.69), p≤0.001 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.51 (95% CI, 1.09 to 2.07), p≤0.001 for trend
		24607	NR	ASA 4-5 days/week	52 (NR)	
		117552	NR	No ASA per week	163 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		200735	NR	ASA	463 (NR)	Age adjusted: ASA vs. No ASA: RR 1.36 (95% CI, 1.16 to 1.60), p≤0.001 Multivariate adjusted†: ASA vs. No ASA: RR 1.32 (95% CI, 1.12 to 1.55), p=0.001
		176496	NR	No ASA	244 (NR)	
	GI bleeding (per 1,000 person-years)	200735	NR	ASA	2.31 (NR)	NR
		176496	NR	No ASA	1.38 (NR)	
	GI bleeding, lower (number of cases)	143386	NR	ASA ≥ 6 days/week	153 (NR)	Age adjusted: ASA ≥ 6 days/week vs. No ASA per week: RR 1.34 (95% CI, 1.00 to 1.79), p=0.021 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.34 (95% CI, 0.83 to 2.18), p=0.021 for trend Multivariate adjusted†: ASA ≥ 6 days/week vs. No ASA per week: RR 1.34 (95% CI, 1.00 to 1.79), p=0.021 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.33 (95% CI, 0.82 to 2.17), p=0.055 for trend
		24607	NR	ASA 4-5 days/week	22 (NR)	
		117552	NR	No ASA per week	74 (NR)	
		200735	NR	ASA	193 (NR)	Age adjusted: ASA vs. No ASA: RR 1.26 (95% CI, 0.99 to 1.62), p=0.063 Multivariate adjusted†: ASA vs. No ASA: RR 1.22 (95% CI, 0.95 to 1.56), p=0.124
		176496	NR	No ASA	110 (NR)	
	Upper GI bleeding (number of cases)	143386	NR	ASA ≥ 6 days/week	161 (NR)	Age adjusted: ASA ≥ 6 days/week vs. No ASA per week: RR 1.63 (95% CI, 1.21 to 2.21), p≤0.001 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.55 (95% CI, 0.94 to 2.56), p≤0.001 for trend Multivariate adjusted†: ASA ≥ 6 days/week vs. No ASA per week: RR 1.56 (95% CI, 1.16 to 2.11), p≤0.001 for trend ASA 4-5 days/week vs. No ASA per week: RR 1.54 (95% CI, 0.93 to 2.55), p≤0.001 for trend
		24607	NR	ASA 4-5 days/week	21 (NR)	
		117552	NR	No ASA per week	66 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		200735	NR	ASA	204 (NR)	Age adjusted: ASA vs. No ASA: RR 1.53 (95% CI, 1.19 to 1.97), p≤0.001 Multivariate adjusted†: ASA vs. No ASA: RR 1.49 (95% CI, 1.16 to 1.92), p=0.002
		176496	NR	No ASA	99 (NR)	
Strate, 2011 (companion publication to Huang, 2010)[126] Fair	*Diverticular bleeding (number of cases)*	*273233*	*NR*	*ASA*	*93 (NR)*	*Age adjusted: ASA vs. No ASA/NSAIDs: HR 1.90 (95% CI, 1.36 to 2.65), p=NR* *Multivariate adjusted‡: ASA vs. No ASA/NSAIDs: HR 1.70 (95% CI, 1.21 to 2.39), p=NR*
		367223	*NR*	*No ASA/NSAIDs*	*58 (NR)*	
		107535	*NR*	*ASA 0.1-1.9 tablets/week*	*34 (NR)*	*Age adjusted:* *ASA 0.1-1.9 tablets/week vs. No ASA tablets: HR 1.81 (95% CI, 1.02 to 3.21), p=NR* *ASA 2.0-5.9 tablets/week vs. No ASA tablets: HR 2.75 (95% CI, 1.60 to 4.71), p=NR* *ASA ≥ 6.0 tablets/week vs. No ASA tablets: HR 2.02 (95% CI, 1.04 to 3.95), p=NR* *Multivariate adjusted‡:* *ASA 0.1-1.9 tablets/week vs. No ASA tablets: HR 1.58 (95% CI, 0.88 to 2.82), p=NR* *ASA 2.0-5.9 tablets/week vs. No ASA tablets: HR 2.32 (95% CI, 1.34 to 4.02), p=NR* *ASA ≥ 6.0 tablets/week vs. No ASA tablets: HR 1.65 (95% CI, 0.84 to 3.26), p=NR*
		98505	*NR*	*ASA 2.0-5.9 tablets/week*	*47 (NR)*	
		47467	*NR*	*ASA ≥ 6.0 tablets/week*	*16 (NR)*	
		127213	*NR*	*No ASA tablets*	*19 (NR)*	
		71418	*NR*	*ASA Daily*	*36 (NR)*	*Age adjusted:* *ASA Daily vs. No ASA per week: HR 1.87 (95% CI, 1.19 to 2.95), p=NR* *ASA 2.0-3.9 days/week vs. No ASA per week: HR 1.35 (95%*
		50674	*NR*	*ASA < 2 days/week*	*9 (NR)*	
		21787	*NR*	*ASA 2.0-3.9 days/week*	*5 (NR)*	
		40153	*NR*	*ASA 4.0-6.0 days/week*	*24 (NR)*	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		220303	*NR*	*No ASA per week*	*43 (NR)*	*CI, 0.53 to 3.46), p=NR* *ASA 4.0-6.0 days/week vs. No ASA per week: HR 3.49 (95% CI, 2.05 to 5.96), p=NR* *Multivariate adjusted‡:* *ASA Daily vs. No ASA per week: HR 1.57 (95% CI, 0.98 to 2.51), p=NR* *ASA 2.0-3.9 days/week vs. No ASA per week: HR 1.21 (95% CI, 0.47 to 3.11), p=NR* *ASA 4.0-6.0 days/week vs. No ASA per week: HR 3.13 (95% CI, 1.82 to 5.38), p=NR*
Huang, 2011 (NHS)[84] Fair	GI bleeding, all (number of cases)	424329	NR	ASA	818 (NR)	Age adjusted: ASA vs. No ASA: RR 1.56 (95% CI, 1.41 to 1.73), p≤0.001 Multivariate adjusted†: ASA vs. No ASA: RR 1.43 (95% CI, 1.29 to 1.59), p≤0.001
		670864	NR	No ASA	719 (NR)	
		495582	NR	ASA 0.5-1.5 tablets/week	578 (NR)	Age adjusted: ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 1.19 (95% CI, 0.99 to 1.43), p≤0.001 for trend ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.54 (95% CI, 1.27 to 1.86), p≤0.001 for trend
		242118	NR	ASA 2.0-5.0 tablets/week	405 (NR)	
		151224	NR	ASA 6.0-14.0 tablets/week	342 (NR)	
		30987	NR	ASA >14.0 tablets/week	71 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		175282	NR	No ASA tablets/week	141 (NR)	ASA 6.0-14.0 tablets/week vs. No ASA tablets: RR 2.09 (95% CI, 1.71 to 2.54), p≤0.001 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 2.57 (95% CI, 1.93 to 3.43), p≤0.001 for trend <u>Multivariate adjusted†:</u> ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 1.02 (95% CI, 0.85 to 1.23), p≤0.001 for trend ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.30 (95% CI, 1.07 to 1.58), p≤0.001 for trend ASA 6.0-14.0 tablets/week vs. No ASA tablets: RR 1.77 (95% CI, 1.44 to 2.18), p≤0.001 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 2.24 (95% CI, 1.66 to 3.03), p≤0.001 for trend
		186218	NR	ASA use 1-5 years	302 (NR)	<u>Age-adjusted:</u> ASA use 1-5 years vs. No ASA tablets: RR 1.08 (95% CI, 0.95 to 1.23), p=0.010 for trend
		64855	NR	ASA use 6-10 years	119 (NR)	
		29512	NR	ASA use 11-20 years	61 (NR)	
		26553	NR	ASA use > 20 years	40 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		788056	NR	No ASA use per year	1015 (NR)	ASA use 6-10 years vs. No ASA tablets: RR 1.19 (95% CI, 0.98 to 1.44), p=0.010 for trend ASA use 11-20 years vs. No ASA tablets: RR 1.33 (95% CI, 1.03 to 1.73), p=0.010 for trend ASA use > 20 years vs. No ASA tablets: RR 1.20 (95% CI, 0.87 to 1.65), p=0.010 for trend <u>Multivariate adjusted†:</u> ASA use 1-5 years vs. No ASA tablets: RR 0.99 (95% CI, 0.87 to 1.13), p=0.280 for trend ASA use 6-10 years vs. No ASA tablets: RR 0.98 (95% CI, 0.81 to 1.20), p=0.280 for trend ASA use 11-20 years vs. No ASA tablets: RR 0.98 (95% CI, 0.74 to 1.28), p=0.280 for trend ASA use > 20 years vs. No ASA tablets: RR 0.79 (95% CI, 0.57 to 1.11), p=0.280 for trend
	GI bleeding, all (per 1,000 person-years)	424329	NR	ASA	1.93 (NR)	NR
		670864	NR	No ASA	1.07 (NR)	
	GI bleeding, lower (number of cases)	424329	NR	ASA	319 (NR)	<u>Age adjusted</u>: ASA vs. No ASA: RR 1.29 (95% CI, 1.11 to 1.51), p=0.001 <u>Multivariate adjusted†</u>: ASA vs. No ASA: RR 1.21 (95% CI, 1.03 to 1.41), p=0.017
		670864	NR	No ASA	345 (NR)	
		495582	NR	ASA 0.5-1.5 tablets/week	276 (NR)	<u>Age adjusted</u>: ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 1.16 (95% CI, 0.89 to 1.52), p=0.003 for trend ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.40 (95% CI, 1.05 to 1.85), p=0.003 for trend ASA 6.0-14.0 tablets/week vs.
		242118	NR	ASA 2.0-5.0 tablets/week	178 (NR)	
		151224	NR	ASA 6.0-14.0 tablets/week	121 (NR)	
		30987	NR	ASA >14.0 tablets/week	20 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		175282	NR	No ASA tablets/week	69 (NR)	No ASA tablets: RR 1.55 (95% CI, 1.15 to 2.09), p=0.003 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 1.52 (95% CI, 0.92 to 2.50), p=0.003 for trend <u>Multivariate adjusted†</u>: ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 0.97 (95% CI, 0.74 to 1.26), p=0.004 for trend ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.18 (95% CI, 0.88 to 1.57), p=0.004 for trend ASA 6.0-14.0 tablets/week vs. No ASA tablets: RR 1.37 (95% CI, 1.00 to 1.87), p=0.004 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 1.45 (95% CI, 0.86 to 2.45), p=0.004 for trend
		186218	NR	ASA use 1-5 years	127 (NR)	<u>Age adjusted:</u> ASA use 1-5 years vs. No ASA tablets: RR 1.03 (95% CI, 0.85 to 1.26), p=0.952 for trend
		64855	NR	ASA use 6-10 years	41 (NR)	
		29512	NR	ASA use 11-20 years	23 (NR)	
		26553	NR	ASA use > 20 years	13 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		788056	NR	No ASA use per year	460 (NR)	ASA use 6-10 years vs. No ASA tablets: RR 0.93 (95% CI, 0.68 to 1.29), p=0.952 for trend ASA use 11-20 years vs. No ASA tablets: RR 1.17 (95% CI, 0.77 to 1.79), p=0.952 for trend ASA use > 20 years vs. No ASA tablets: RR 0.88 (95% CI, 0.51 to 1.53), p=0.952 for trend Multivariate adjusted†: ASA use 1-5 years vs. No ASA tablets: RR 0.98 (95% CI, 0.80 to 1.20), p=0.212 for trend ASA use 6-10 years vs. No ASA tablets: RR 0.82 (95% CI, 0.59 to 1.14), p=0.212 for trend ASA use 11-20 years vs. No ASA tablets: RR 1.11 (95% CI, 0.73 to 1.69), p=0.699 for trend ASA use > 20 years vs. No ASA tablets: RR 0.70 (95% CI, 0.39 to 1.26), p=0.212 for trend
	GI bleeding, lower (per 1,000 person-years)	424329	NR	ASA	0.75 (NR)	NR
		670864	NR	No ASA	0.51 (NR)	
	Small bowel bleeding (number of cases)	424329	NR	ASA	130 (NR)	Age adjusted: ASA vs. No ASA: RR 1.59 (95% CI, 1.23 to 2.06), p≤0.001 Multivariate adjusted†: ASA vs. No ASA: RR 1.45 (95% CI, 1.12 to 1.89), p=0.005
		670864	NR	No ASA	107 (NR)	
	Small bowel bleeding (per 1,000 person-years)	424329	NR	ASA	0.31 (NR)	NR
		670864	NR	No ASA	0.16 (NR)	
	Upper GI bleeding (number of cases)	424329	NR	ASA	369 (NR)	Age adjusted: ASA vs. No ASA: RR 1.89 (95% CI, 1.62 to 2.22), p≤0.001 Multivariate adjusted†: ASA vs. No ASA: RR 1.70 (95% CI, 1.45 to 2.00), p≤0.001
		670864	NR	No ASA	267 (NR)	
		495582	NR	ASA 0.5-1.5 tablets/week	219 (NR)	Age adjusted: ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 1.35 (95% CI, 0.99 to 1.85), p≤0.001 for trend
		242118	NR	ASA 2.0-5.0 tablets/week	169 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		151224	NR	ASA 6.0-14.0 tablets/week	160 (NR)	ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.92 (95% CI, 1.39 to 2.65), p≤0.001 for trend ASA 6.0-14.0 tablets/week vs. No ASA tablets: RR 2.87 (95% CI, 2.08 to 3.97), p≤0.001 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 4.20 (95% CI, 2.75 to 6.41), p≤0.001 for trend <u>Multivariate adjusted†:</u> ASA 0.5-1.5 tablets/week vs. No ASA tablets: RR 1.20 (95% CI, 0.87 to 1.65), p≤0.001 for trend ASA 2.0-5.0 tablets/week vs. No ASA tablets: RR 1.65 (95% CI, 1.19 to 2.30), p≤0.001 for trend ASA 6.0-14.0 tablets/week vs. No ASA tablets: RR 2.45 (95% CI, 1.74 to 3.44), p≤0.001 for trend ASA > 14.0 tablets/week vs. No ASA tablets: RR 3.61 (95% CI, 2.32 to 5.63), p≤0.001 for trend
		30987	NR	ASA >14.0 tablets/week	40 (NR)	
		175282	NR	No ASA tablets/week	48 (NR)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
		186218	NR	ASA use 1-5 years	123 (NR)	Age adjusted: ASA use 1-5 years vs. No ASA tablets: RR 1.10 (95% CI, 0.89 to 1.34), p=0.003 for trend ASA use 6-10 years vs. No ASA tablets: RR 1.44 (95% CI, 1.09 to 1.90), p=0.003 for trend ASA use 11-20 years vs. No ASA tablets: RR 1.61 (95% CI, 1.12 to 2.33), p=0.003 for trend ASA use > 20 years vs. No ASA tablets: RR 1.33 (95% CI, 0.83 to 2.14), p=0.003 for trend Multivariate adjusted†: ASA use 1-5 years vs. No ASA tablets: RR 0.97 (95% CI, 0.79 to 1.19), p=0.744 for trend ASA use 6-10 years vs. No ASA tablets: RR 1.13 (95% CI, 0.85 to 1.51), p=0.744 for trend ASA use 11-20 years vs. No ASA tablets: RR 1.09 (95% CI, 0.74 to 1.61), p=0.744 for trend ASA use > 20 years vs. No ASA tablets: RR 0.76 (95% CI, 0.46 to 1.26), p=0.744 for trend
		64855	NR	ASA use 6-10 years	58 (NR)	
		29512	NR	ASA use 11-20 years	31 (NR)	
		26553	NR	ASA use > 20 years	18 (NR)	
		788056	NR	No ASA use per year	406 (NR)	
	Upper GI bleeding (per 1,000 person-years)	424329	NR	ASA	0.87 (NR)	NR
		670864	NR	No ASA	0.40 (NR)	
Juul-Moller, 1992 (SAPAT)[54] Fair	GI bleeding, fatal (number of participants)	4.2	1009	ASA	2 (0.2%)	NR
			1026	Placebo	1 (0.1%)	
	GI bleeding, major fatal and nonfatal (number of participants)	4.2	1009	ASA	11 (1.1%)	NR
			1026	Placebo	6 (0.6%)	
Logan, 2008 (ukCAP)[68] Fair	GI bleeding, lower (number of participants)	3.4	472	ASA	3 (0.6%)	NR
			467	No ASA	5 (1.1%)	
	Upper GI bleeding (number of participants)	3.4	472	ASA	2 (0.4%)	NR
			467	No ASA	0 (0%)	
MRC, 1998 (TPT)[69] Good	Fatal major upper GI bleeding (number of participants)	6.8	1268	ASA	0 (0%)	NR
			1272	Placebo	1 (0.08%)	
	GI bleeding, intermediate (number of participants)	6.8	1268	ASA	16 (1.3%)	NR
			1272	Placebo	8 (0.6%)	
	Major GI bleeding, lower (number of participants)	6.8	1268	ASA	0 (0%)	NR
			1272	Placebo	1 (0.08%)	

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
	Major GI bleeding, upper (number of participants)	6.8	1268	ASA	5 (0.4%)	NR
			1272	Placebo	1 (0.08%)	
	Major indeterminate GI bleeding (number of participants)	6.8	1268	ASA	1 (0.08%)	NR
			1272	Placebo	0 (0%)	
	Rectal bleed, minor (number of participants)	6.8	1268	ASA	127 (10.0%)	ASA alone vs. Placebo: p≤0.05
			1272	Placebo	96 (7.5%)	
Ogawa, 2008 (JPAD)[70]	Bleeding from colon diverticula (number of participants)	4.37	1262	ASA	2 (0.2%)	NR
			1277	No ASA	0 (0%)	
Fair	Bleeding from esophageal varices (number of participants)	4.37	1262	ASA	1 (0.08%)	NR
			1277	No ASA	0 (0%)	
	GI bleeding (number of participants)	4.37	1262	ASA	12 (1.0%)	NR
			1277	No ASA	4 (0.3%)	
	GI bleeding due to cancer (number of participants)	4.37	1262	ASA	2 (0.2%)	NR
			1277	No ASA	0 (0%)	
	GI bleeding, cause unknown (number of participants)	4.37	1262	ASA	1 (0.08%)	NR
			1277	No ASA	1 (0.08%)	
	Hemorrhagic gastric ulcer (number of participants)	4.37	1262	ASA	5 (0.4%)	NR
			1277	No ASA	3 (0.2%)	
	Hemorrhoid bleeding (number of participants)	4.37	1262	ASA	1 (0.08%)	NR
			1277	No ASA	0 (0%)	
	Severe GI bleeding requiring transfusion (number of participants)	4.37	1262	ASA	4 (0.3%)	NR
			1277	No ASA	0 (0%)	
PARIS, 1980[71]	Hematemesis, bloody stool and/or black tarry stool (as reported by physician) (number of participants)	3.4	810	ASA	52 (6.4%)	ASA vs. Placebo: Z-value 2.81, p=NR
			406	Placebo	10 (2.5%)	
Good	Hematemesis, bloody stool and/or black tarry stool (number of participants)	3.4	810	ASA	33 (4.1%)	ASA vs. Placebo: Z-value 1.87, p=NR
			406	Placebo	8 (2.0%)	
	Hematemesis, bloody stools and/or black tarry stools, reason for permanent or temporary discontinuation of study drug (number of participants)	3.4	810	ASA	28 (3.4%)	ASA vs. Placebo: Z-value 1.53, p=NR
			406	Placebo	7 (1.7%)	
Petersen, 1989 (Copenhagen AFASAK)[80]	GI bleeding (number of participants)	2	336	ASA	1 (0.3%)	NR
			336	Placebo (citric acid)	0 (0%)	
Fair						

Appendix E Table 7. Results of Included Studies, GI Bleeding

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Difference Between Groups
Peto, 1988 (BMD)[72]	Hemorrhagic peptic ulcer, fatal (per 1,000 person-years)	6	3429	ASA	0 (NR)	NR
			1710	No ASA	3.2 (NR)	
Fair	Perforated peptic ulcer, fatal (per 10,000 person-years)	6	3429	ASA	1.1 (NR)	NR
			1710	No ASA	0 (NR)	
	Gastric hemorrhage, fatal (per 10,000 person-years)	6	3429	ASA	0.5 (NR)	NR
			1710	No ASA	0 (NR)	
	GI bleeding, reason for withdrawal (number of participants)	1	3429	ASA	39 (1.1%)	NR
		Year 2-6	2738	ASA	30 (1.1%)	
PHS, 1989[73]	Gastric hemorrhage, fatal (number of participants)	5	11037	ASA	1 (0.009%)	NR
			11034	Placebo	0 (0%)	
Good (KQ1); Fair (KQ6)	GI bleeding, required transfusion or fatal (number of participants)	5	11037	ASA	49 (0.4%)	NR
			11034	No ASA	28 (0.3%)	
	Nonspecific GI bleeding (number of participants)	5	11037	ASA	440 (4.0%)	ASA vs. Placebo: RR NR (95% CI, NR to NR), p=0.55‖
			11034	Placebo	422 (3.8%)	
SALT, 1991[74]	GI bleeding (number of participants)	2.67	676	ASA	11 (1.6%)	NR
			684	Placebo	4 (0.6%)	
Good	Severe GI bleeding, causing discontinuation of study drug (number of participants)	2.67	676	ASA	9 (1.3%)	NR
			684	Placebo	4 (0.6%)	
Sato, 2006 (JAST)[81]	Gastric bleeding (number of participants)	2.1	426	ASA	1 (0.2%)	NR
			445	No ASA	0 (0%)	
Fair	GI bleeding, reason for discontinuation (number of participants)	2.1	426	ASA	10 (2.3%)	ASA vs. No ASA: p=0.001
			445	No ASA	0 (0%)	
Silagy, 1993[52]	GI bleeding (number of participants)	1	200	ASA	6 (3%)	ASA vs. Placebo: RR ∞, p≤0.05
			200	Placebo	0 (0%)	
Fair	GI bleeding requiring hospitalization (number of participants)	1	200	ASA	1 (0.5%)	NR
			200	Placebo	0 (0%)	

*Adjusted for age, vitamin E and beta-carotene treatment assignment
†Adjusted for age, NSAID use, smoking status, BMI, exercise, alcohol intake
‡Adjusted for age, study period, BMI, dietary fat, fiber, red meat, nut, corn and total caloric intake, physical activity
§Adjusted for age, gender, smoking, alcohol, diabetes duration, retinopathy, sensory neuropathy, PVD, CV history, BMI, BP, lipid, HbA1c, albuminuria, Cr, BL usage of anti-HTN, anti-diabetics, anticoagulants, and lipid lowering drugs
‖Adjusted for age and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; IRR = incidence rate ratio; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; RR = relative risk; vs = versus

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Baron, 2003 (AFPPS)[77] Good (KQ1); Fair (KQ2,KQ6)	Hemorrhagic stroke, nonfatal (number of events)	2.7	372	ASA 325	0 (NR)	NR
			377	ASA 81	1 (NR)	
			372	Placebo	0 (NR)	
Belch, 2008 (POPADAD)[57] Fair	Hemorrhagic stroke, fatal (number of participants)	6.7	318	ASA alone	0 (0%)	NR
		6.7	320	ASA + antioxidant	2 (0.6%)	
		6.7	320	Antioxidant alone	1 (0.3%)	
		6.7	318	Placebo alone	2 (0.6%)	
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	Hemorrhagic stroke (per 1,000 person-years)	10.1	19934	ASA	0.26 (NR)	ASA vs. No ASA: Rate Difference 0.05 (95% CI, -0.04 to 0.14), p=NR
			19942	No ASA	0.21 (NR)	
	Hemorrhagic stroke, fatal and nonfatal (number of participants)	10.1	19934	ASA	51 (NR%)	ASA vs. No ASA: HR 1.24 (95% CI, 0.82 to 1.87), p=0.31*
			19942	No ASA	41 (NR%)	
Cook, 2013 (Companion publication to Cook, 2005)[88] *Good*	*Hemorrhagic stroke (number of cases)*	*10*	*19934*	*ASA*	*56 (0.3)*	*ASA vs. No ASA: HR 1.36 (95% CI, 0.91 to 2.03), p=0.135**
			19942	*No ASA*	*41 (0.2)*	
		11-18 (post-trial)	*19934*	*ASA*	*29 (0.2)*	*ASA vs. No ASA: HR 1.36 (95% CI, 0.77 to 2.38), p=0.29**
			19942	*No ASA*	*21 (0.1)*	
		18	*19934*	*ASA*	*85 (0.4)*	*ASA vs. No ASA: HR 1.36 (95% CI, 0.98 to 1.88), p=0.066**
			19942	*No ASA*	*62 (0.3)*	
Cote, 1995 (ACBS)[79] Fair	Intracranial hemorrhage, nonfatal (number of participants)	2.4	188	ASA	0 (0%)	NR
			184	Placebo	0 (0%)	
de Berardis, 2012[85] Good	Intracranial bleeding, nonfatal (number of events)	6	186425	ASA	1267 (NR)	ASA vs. No ASA: IRR 1.54 (95% CI, 1.43 to 1.67), p=NR
			186425	No ASA	1197 (NR)	
de Gaetano, 2001 (PPP)[61] Fair	Hemorrhagic stroke, fatal and nonfatal (number of participants)	3.6	2226	ASA	2 (0.09%)	ASA vs. No ASA: p=NSD
			2269	No ASA	3 (0.1%)	
	Intracranial bleeding (not parenchymal), nonfatal (number of participants)	3.6	2226	ASA	2 (0.09%)	NR
			2269	No ASA	0 (0%)	
EAFT, 1993[63] Fair	Cerebral bleeding, fatal and nonfatal (number of participants)	2.3	404	ASA	1 (0.2%)	NR
			378	Placebo	0 (0%)	
Ekstrom, 2013 (SNDR)[86] Fair	Cerebral hemorrhage, fatal (number of events)	4	18646	All Participants	14 (0.1)	ASA vs. No ASA: HR 1.60 (95% CI, 0.51 to 6.05), p=0.4
	Cerebral hemorrhage, fatal (per 1,000 person-years)	4	18646	All Participants	0.2 (NR)	NR
	Cerebral hemorrhage, fatal and nonfatal (number of events)	4	18646	All Participants	59 (0.3)	ASA vs. No ASA: HR 1.26 (95% CI, 0.70 to 2.25), p=0.4

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
	Cerebral hemorrhage, fatal and nonfatal (per 1,000 person-years)	4	18646	All Participants	0.9 (NR)	NR
	Ventricular hemorrhage, fatal and nonfatal (number of events)	4	18646	All Participants	79 (0.4)	ASA vs. No ASA: HR 1.27 (95% CI, 0.77 to 2.09), p=0.4
	Ventricular hemorrhage, fatal and nonfatal (per 1,000 person-years)	4	18646	All Participants	1.2 (NR)	NR
Farrell, 1991 (UK-TIA)[65]	Definite hemorrhagic stroke, fatal (number of participants)	4	815	ASA 1200	6 (0.7%)	NR
			806	ASA 300	4 (0.5%)	
Fair			814	Placebo	1 (0.1%)	
	Hemorrhagic stroke (definite), fatal and/or major (number of participants)	4	815	ASA 1200	7 (0.9%)	NR
			806	ASA 300	7 (0.9%)	
			814	Placebo	2 (0.2%)	
Fowkes, 2010 (AAA)[66]	Hemorrhagic stroke, fatal (number of events)	8.2	65	ASA	3 (NR)	NR
			59	Placebo	4 (NR)	
Good	Hemorrhagic stroke, fatal (number of participants)	8.2	1675	ASA	3 (0.2%)	NR
			1675	Placebo	3 (0.2%)	
	Hemorrhagic stroke, nonfatal (number of events)	8.2	65	ASA	2 (NR)	NR
			59	Placebo	1 (NR)	
	Hemorrhagic stroke, nonfatal (number of participants)	8.2	1675	ASA	2 (0.1%)	NR
			1675	Placebo	1 (0.1%)	
	Subarachnoid/subdural hemorrhage, fatal (number of events)	8.2	65	ASA	3 (NR)	NR
			59	Placebo	0 (NR)	
	Subarachnoid/subdural hemorrhage, fatal (number of participants)	8.2	1675	ASA	3 (0.2%)	NR
			1675	Placebo	0 (0%)	
	Subarachoid/subdural hemorrhage, nonfatal (number of events)	8.2	65	ASA	3 (NR)	NR
			59	Placebo	4 (NR)	
	Subarachoid/subdural hemorrhage, nonfatal (number of participants)	8.2	1675	ASA	3 (0.2%)	NR
			1675	Placebo	3 (0.2%)	
Hansson, 1998 (HOT)[67]	Cerebral bleeding, fatal (number of events)	3.8	9399	ASA	2 (NR)	NR
			9391	Placebo	3 (NR)	
Fair	Major cerebral bleeding, nonfatal (number of events)	3.8	9399	ASA	12 (NR)	NR
			9391	Placebo	12 (NR)	

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Iso, 1999 (Companion publication to Huang, 2011)[94] *Fair*	*Hemorrhagic stroke (number of cases)*	*53304*	*NR*	*ASA ≥15 tablets/week*	*16 (NR)*	*Age-adjusted:* *ASA 1-2 tablets/week vs. No ASA: RR 0.69 (95% CI, 0.45 to 1.07), p=0.01 for trend* *ASA 3-6 tablets/week vs. No ASA: RR 0.97 (95% CI, 0.60 to 1.58), p=0.01 for trend* *ASA 7-14 tablets/week vs. No ASA: RR 1.19 (95% CI, 0.73 to 1.95), p=0.01 for trend* *ASA ≥ 15 tablets/week vs. No ASA: RR 1.68 (95% CI, 0.96 to 2.92), p=0.01 for trend* *Multivariate-adjusted‖:* *ASA 1-2 tablets/week vs. No ASA: RR 0.76 (95% CI, 0.49 to 1.19), p=0.02 for trend* *ASA 3-6 tablets/week vs. No ASA: RR 1.04 (95% CI, 0.64 to 1.71), p=0.02 for trend* *ASA 7-14 tablets/week vs. No ASA: RR 1.25 (95% CI, 0.76 to 2.05), p=0.02 for trend* *ASA ≥ 15 tablets/week vs. No ASA: RR 1.63 (95% CI, 0.93 to 2.86), p=0.02 for trend*
		102659	*NR*	*ASA 7-14 tablets/week*	*22 (NR)*	
		137649	*NR*	*ASA 3-6 tablets/week*	*22 (NR)*	
		263428	*NR*	*ASA 1-2 tablets/week*	*31 (NR)*	
		387138	*NR*	*No ASA*	*61 (NR)*	
	Intraparenchymal hemorrhage, nonfatal (number of cases)	*53304*	*NR*	*ASA ≥15 tablets/week*	*4 (NR)*	*NR*
		102659	*NR*	*ASA 7-14 tablets/week*	*9 (NR)*	
		137649	*NR*	*ASA 3-6 tablets/week*	*7 (NR)*	
		263428	*NR*	*ASA 1-2 tablets/week*	*8 (NR)*	
		387138	*NR*	*No ASA*	*24 (NR)*	
	Subarachnoid hemorrhage, nonfatal (number of cases)	*53304*	*NR*	*ASA ≥15 tablets/week*	*12 (NR)*	*NR*
		102659	*NR*	*ASA 7-14 tablets/week*	*13 (NR)*	
		137649	*NR*	*ASA 3-6 tablets/week*	*15 (NR)*	
		263428	*NR*	*ASA 1-2 tablets/week*	*23 (NR)*	
		387138	NR	No ASA	37 (NR)	

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Juul-Moller, 1992 (SAPAT)[54] Fair	Hemorrhagic stroke, fatal (number of participants)	4.2	1009	ASA	4 (0.4)	NR
			1026	Placebo	1 (0.1)	
	Hemorrhagic stroke, fatal and nonfatal (number of participants)	4.2	1009	ASA	5 (0.5%)	NR
			1026	Placebo	2 (0.2%)	
	Major subdural hematoma (number of participants)	4.2	1009	ASA	1 (0.1%)	NR
			1026	Placebo	0 (0%)	
Logan, 2008 (ukCAP)[68] Fair	Subarachnoid hemorrhage, nonfatal (number of participants)	3.4	472	ASA	2 (0.4%)	NR
			467	No ASA	0 (0%)	
Manson, 1991 (Companion publication to Huang, 2011)[127] *Fair*	*Hemorrhagic stroke (number of cases)*	*6*	*4998*	*ASA ≥ 15 tablets/week*	*12 (NR)*	*Age-adjusted: ASA ≥ 15 tablets/week vs. No ASA: RR 1.65 (95% CI, 0.83 to 3.27), p=NR ASA 7-14 tablets/week vs. No ASA: RR 0.76 (95% CI, 0.27 to 2.13), p=NR ASA 1-6 tablets/week vs. No ASA: RR 1.04 (95% CI, 0.58 to 1.86), p=NR Multivariate-adjusted‡: ASA ≥ 15 tablets/week vs. No ASA: RR 1.71 (95% CI, 0.84 to 3.47), p=NR ASA 7-14 tablets/week vs. No ASA: RR 0.69 (95% CI, 0.24 to 1.95), p=NR ASA 1-6 tablets/week vs. No ASA: RR 1.07 (95% CI, 0.60 to 1.90), p=NR*
			22698	*ASA 1-6 tablets/week*	*20 (NR)*	
			7352	*ASA 7-14 tablets/week*	*4 (NR)*	
			52630	*No ASA*	*26 (NR)*	
MRC, 1998 (TPT)[69] Good	Hemorrhagic stroke (number of events)	6.8	1268	ASA	2 (NR)	NR
			1272	Placebo	0 (NR)	
	Hemorrhagic stroke (per 1,000 person-years)	6.8	1268	ASA	0.2 (NR)	NR
			1272	Placebo	0 (NR)	
	Subarachnoid stroke (number of events)	6.8	1268	ASA	1 (NR)	NR
			1272	Placebo	2 (NR)	
	Subarachnoid stroke (per 1,000 person-years)	6.8	1268	ASA	0.1 (NR)	NR
			1272	Placebo	0.2 (NR)	

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Ogawa, 2008 (JPAD)[70]	Chronic subdural hematoma, nonfatal (number of participants)	4.37	1262	ASA	2 (0.2%)	NR
			1277	No ASA	0 (0%)	
Fair	Hemorrhagic stroke, fatal (number of participants)	4.37	1262	ASA	1 (0.08%)	NR
			1277	No ASA	4 (0.3%)	
	Hemorrhagic stroke, fatal and nonfatal (number of participants)	4.37	1262	ASA	6 (0.5%)	NR
			1277	No ASA	7 (0.6%)	
	Hemorrhagic stroke, nonfatal (number of participants)	4.37	1262	ASA	5 (0.4%)	ASA vs. No ASA: HR 1.68 (95% CI, 0.40 to 7.04), p=0.48
			1277	No ASA	3 (0.2%)	
	Hemorrhagic stroke, nonfatal (per 1,000 person years)	4.37	1262	ASA	1.0 (NR)	NR
			1277	No ASA	0.6 (NR)	
Petersen, 1989 (Copenhagen AFASAK)[80]	Cerebral hemorrhage (according to CT), nonfatal (number of participants)	2	336	ASA	0 (0%)	NR
			336	Placebo (citric acid)	0 (0%)	
Fair						
Peto, 1988 (BMD)[72]	Hemorrhagic stroke (probably), nonfatal (number of participants)	6	3429	ASA	3 (0.09%)	NR
			1710	No ASA	2 (0.12%)	
Fair	Hemorrhagic stroke (probably), nonfatal (per 10,000 person-years)	6	3429	ASA	1.6 (NR)	NR
			1710	No ASA	2.1 (NR)	
	Hemorrhagic stroke, fatal (number of participants)	6	2429	ASA	10 (0.3%)	NR
			1710	No ASA	4 (0.2%)	
	Hemorrhagic stroke, fatal (per 10,000 person-years)	6	3429	ASA	5.3 (NR)	NR
			1710	No ASA	4.2 (NR)	
PHS, 1989[73]	Hemorrhagic stroke, fatal (number of participants)	5	11037	ASA	7 (0.06%)	ASA vs. No ASA: HR 1.68 (95% CI, 0.40 to 7.04), p=0.48§
			11034	No ASA	2 (0.02%)	
Good (KQ1); Fair (KQ6)	Hemorrhagic stroke, fatal and nonfatal (number of events)	5	11037	ASA	23 (NR)	ASA vs. Placebo: RR 2.14 (95% CI, 0.96 to 4.77), p=0.06§
			11034	Placebo	12 (NR)	
	Hemorrhagic stroke, mild (number of events)	5	11037	ASA	10 (NR)	ASA vs. Placebo: RR 1.67 (95% CI, 0.61 to 4.57), p=0.32§
			11034	Placebo	6 (NR)	
	Hemorrhagic stroke, moderate, severe or fatal (number of events)	5	11037	ASA	13 (NR)	ASA vs. Placebo: RR 2.19 (95% CI, 0.84 to 5.69), p=0.11§
			11034	Placebo	6 (NR)	
	Hemorrhagic stroke, nonfatal (number of events)	5	11037	ASA	16 (NR)	NR
			11034	No ASA	10 (NR)	
SALT, 1991[74]	Intracerebral hemorrhage, fatal (number of participants)	2.67	676	ASA	4 (0.6%)	NR
			684	Placebo	0 (0%)	
Good	Intracerebral hemorrhage, nonfatal (number of participants)	2.67	676	ASA	4 (0.6%)	NR
			684	Placebo	3 (0.4%)	
	Intracranial stroke, fatal and nonfatal (number of participants)	2.67	676	ASA	11 (1.6%)	NR
			684	Placebo	4 (0.6%)	
	Intracranial stroke, nonfatal (number of participants)	2.67	676	ASA	5 (0.7%)	NR
			684	Placebo	4 (0.6%)	

Appendix E Table 8. Results of Included Studies, Intracranial Bleeding, Including Hemorrhagic Stroke

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
	Severe intracranial bleeding, causing discontinuation of study drug, nonfatal (number of participants)	2.67	676	ASA	10 (1.5%)	NR
			684	Placebo	3 (0.4%)	
	Subarachnoid hemorrhage, fatal (number of participants)	2.67	676	ASA	2 (0.3%)	NR
			684	Placebo	0 (0%)	
	Subarachnoid hemorrhage, nonfatal (number of participants)	2.67	676	ASA	1 (0.1%)	NR
			684	Placebo	1 (0.1%)	
Sato, 2006 (JAST)[81] Fair	Intracranial bleeding, fatal and nonfatal (number of participants)	2.1	426	ASA	4 (0.9%)	NR
			445	No ASA	2 (0.4%)	
SPAF, 1991[76] Good	Any CNS bleeding (number of events)	1.3	552	ASA	2 (NR)	NR
			568	Placebo	2 (NR)	
	Intracerebral hemorrhage, fatal (number of participants)	1.3	552	ASA	1 (0.2%)	NR
			568	Placebo	0 (0%)	
	Intracerebral hemorrhage, nonfatal (number of participants)	1.3	552	ASA	1 (0.2%)	NR
			568	Placebo	0 (0%)	
	Subdural hematoma (full recovery), nonfatal (number of events)	1.3	552	ASA	0 (NR)	NR
			568	Placebo	2 (NR)	
	Subdural hematoma, fatal (number of participants)	1.3	552	ASA	1 (0.2%)	NR
			568	Placebo	0 (0%)	

*Adjusted by age, vitamin E and beta-carotene treatment assignment
†Adjusted by SBP, time walk and LV mass
‡Adjusted by age, smoking status, HTN, DM, high cholesterol, parental MI history, BMI, menopause status, hormone use, oral contraceptive use, followup period, alcohol intake, physical activity, vigorous exercise, multivitamin use, dietary sat/unsaturated fat, dietary cholesterol, physician visit in previous year
§Adjusted by age and beta-carotene assignment
‖Adjusted by age, smoking, BMI, alcohol, menopausal status, hormone use, vigorous exercise, multivitamin use, vitamin E use, HTN, DM, cholesterol, intake of SF, protein, Ca, PFA, and dietary vitamin C

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; CNS = central nervous system; HR = hazard ratio; NR = not reported; NSD = no significant difference; RR = relative risk

Appendix E Table 9. Results of Included Studies, Ulcers

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
AMIS, 1980[75] Fair	Duodenal ulcer, hospitalization (number of participants)	3.2	2267	ASA	21 (0.9%)	ASA vs. Placebo: RR 10.5 (95% CI, 2.9 to 66.4), p=NR
			2257	Placebo	2 (0.09%)	
	Gastric ulcer, hospitalization (number of participants)	3.2	2267	ASA	12 (0.5%)	ASA vs. Placebo: RR 6.0 (95% CI, 1.5 to 39.6), p=NR
			2257	Placebo	2 (0.09%)	
	Peptic ulcer (number of participants)	3.2	2267	ASA	NR (NR)	ASA vs. Placebo: RR 7.7 (95% CI, 2.7 to 21.7), p≤0.0001*
			2257	Placebo	NR (NR)	
	Peptic ulcer, gastritis, erosion of gastric mucosa symptoms (number of participants)	3.2	2267	ASA	537 (23.7%)	ASA vs. Placebo: Z-score 7.52, p=NR
			2257	Placebo	336 (14.9%)	
	Ulcer diagnosis during hospitalization for GI problems (number of participants)	3.2	2267	ASA	29 (1.3%)	NR
			2257	Placebo	5 (0.2%)	
CDPRG, 1980 (CDPA)[59] Good	Ulcer, peptic (number of participants)	1.8	727	ASA	20 (2.8%)	ASA vs. Placebo: Z-value 0.75, p=NR
			744	Placebo	16 (2.2%)	
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	Ulcer, peptic (number of events)	10.1	19934	ASA	542 (2.7)	ASA vs. No ASA: RR 1.32 (95% CI, 1.16 to 1.50), p≤0.001†
			19942	No ASA	413 (2.1)	
	Ulcer, peptic (per 1,000 person-years)	10.1	19934	ASA	2.76 (NR)	ASA vs. No ASA: Rate Difference 0.66 (95% CI, 0.35 to 0.97), p=NR
			19942	No ASA	2.10 (NR)	
Cook, 2013 (Companion publication to Cook, 2005) 980[88] *Good*	*Ulcer, peptic (number of cases)*	*10*	*19934*	*ASA*	*1115 (5.6)*	*ASA vs. No ASA: HR 1.20 (95% CI, 1.10 to 1.31), p≤0.001†*
			19942	*No ASA*	*931 (4.7)*	
	Ulcer, peptic (number of cases)	*11-18 (post-trial)*	*19934*	*ASA*	*341 (2.0)*	*ASA vs. No ASA: HR 1.09 (95% CI, 0.94 to 1.28), p=0.26†*
			19942	*No ASA*	*311 (1.8)*	
	Ulcer, peptic (number of cases)	*18*	*19934*	*ASA*	*1456 (7.3)*	*ASA vs. No ASA: HR 1.17 (95% CI, 1.09 to 1.27), p≤0.001†*
			19942	*No ASA*	*1242 (6.2)*	
DAMAD, 1989[51] Fair	Ulcer, cause for discontinuation (number of participants)	3	157	ASA	5 (3.2%)	NR
			157	Placebo	1 (0.6%)	
Diener, 1997 (ESPS-2)[62] Good	Duodenal ulcer bleeding, hospitalization and transfusion (number of participants)	2	1649	ASA	1 (0.06%)	NR
			1649	Placebo	0 (0%)	
	Ulcer, gastro-duodenal (number of events)	2	1649	ASA	1 (NR)	NR
			1649	Placebo	2 (NR)	
Ekstrom, 2013 (SNDR)[86] Fair	Ulcer, ventricular (number of events)	4	18646	All Participants	93 (0.5)	ASA vs. No ASA: HR 1.64 (95% CI, 1.06 to 2.53), p=0.02‡
			18646	All Participants	1.4 (NR)	

Appendix E Table 9. Results of Included Studies, Ulcers

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Fowkes, 2010 (AAA)[66]	Ulcer, GI (number of events)	8.2	65	ASA	15 (NR)	NR
			59	Placebo	11 (NR)	
Good	Ulcer, GI (number of participants)	8.2	1675	ASA	14 (0.8%)	NR
			1675	Placebo	8 (0.5%)	
Logan, 2008 (ukCAP)[68]	Ulcer, peptic (number of participants)	3.4	472	ASA	3 (0.6%)	NR
			467	No ASA	1 (0.2%)	
Fair						
PARIS, 1980 [71]	Symptoms suggestive of peptic ulcer, gastritis, or gastric mucosa erosion (as reported by physician) (number of participants)	3.4	810	ASA	147 (18.1%)	ASA vs. Placebo: Z-value 2.09, p=NR
			406	Placebo	54 (13.2%)	
Good						
Peto, 1988 (BMD)[72]	Ulcer, peptic (per 10,000 person-years)	6	3429	ASA	46.8 (NR)	ASA vs. No ASA: p≤0.05
			1710	No ASA	29.6 (NR)	
Fair						
PHS, 1989 843 [73]	Ulcer, duodenal (number of participants)	5	11037	ASA	46 (0.4%)	ASA vs. Placebo: p=0.03§
			11034	Placebo	27 (0.2%)	
Good (KQ1); Fair (KQ6)	Ulcer, esophageal (number of participants)	5	11037	ASA	11 (0.1%)	ASA vs. Placebo: p=0.23§
			11034	Placebo	6 (0.05%)	
	Ulcer, gastric (number of participants)	5	11037	ASA	25 (0.2%)	ASA vs. Placebo: p=0.11§
			11034	Placebo	15 (0.1%)	
	Ulcer, gastrojejunal (number of participants)	5	11037	ASA	3 (0.03%)	ASA vs. Placebo: p=0.70§
			11034	Placebo	4 (0.04%)	
	Ulcer, peptic (number of participants)	5	11037	ASA	156 (1.4%)	ASA vs. Placebo: p=0.11§
			11034	Placebo	129 (1.2%)	
	Ulcer, some hemorrhage (number of participants)	5	11037	ASA	38 (0.3%)	ASA vs. Placebo: RR 1.77 (95% CI, 1.07 to 2.94), p=0.04§
			11034	Placebo	22 (0.2%)	
	Ulcer, upper GI (number of participants)	5	11037	ASA	169 (1.5%)	ASA vs. Placebo: RR 1.22 (95% CI, 0.98 to 1.53), p=0.08§
			11034	Placebo	138 (1.3%)	

*Multivariate adjusted

†Adjusted by age, vitamin E and beta-carotene treatment assignment

‡Stratification w/ propensity score decile, age, sex, DM duration, hospitalization, hypoglycemic treatment, HbA1c, smoking, BMI, SBP, ratio TC:HDL, albuminuria > 20ug/min, anti-HTN, statins, other lipid-lowering drugs, estrogen, multidose

§Adjusted by age and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; NR = not reported; RR = relative risk

Appendix E Table 10. Results of Included Studies, ARMD

Study	Outcome (unit)	Followup (years)	N Analyzed	Group	Results	Between Group Difference
Cook, 2005 (WHS)[60] Good (KQ1,KQ2); Fair (KQ6)	ARMD, visually significant (number of events)	10	19716	ASA	111 (NR)	ASA vs. No ASA: HR 0.82 (95% CI, 0.64 to 1.06), p=NR*
			19705	No ASA	134 (NR)	
	ARMD, advanced (number of events)	10	19716	ASA	26 (NR)	ASA vs. No ASA: HR 0.90 (95% CI, 0.53 to 1.52), p=NR*
			19705	No ASA	29 (NR)	
	ARMD, w/ or w/out vision loss (number of events)	10	19716	ASA	302 (NR)	ASA vs. No ASA: HR 1.03 (95% CI, 0.88 to 1.21), p=NR*
			19705	No ASA	391 (NR)	
PHS, 1989[73] Good (KQ1); Fair (KQ6)	ARMD, w/ or w/out vision loss (number of cases)	5	10617	ASA	51 (NR)	ASA vs. No ASA: RR 0.77 (95% CI, 0.54 to 1.11), p=0.16†
			10599	No ASA	66 (NR)	
	ARMD, w/ vision loss (number of cases)	5	10617	ASA	25 (NR)	ASA vs. No ASA: RR 0.78 (95% CI, 0.46 to 1.32), p=0.36†
			10599	No ASA	32 (NR)	

*Adjusted by age, vitamin E and beta-carotene treatment assignment
†Adjusted by age and vitamin E assignment

Abbreviations: ARMD = age-related macular degeneration; ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; NR = not reported; RR = relative risk

Appendix F Table 1. Cancer Mortality by Subgroup (KQ 1)

Subgroup	Study				
Sex	Farrell, 1991 (UK-TIA)[65]	Group	Women	Men	Between Group Difference
		ASA 1200 mg	3/214 (1.4%)	9/601 (1.5%)	NR
		ASA 300 mg	0/203 (0%)	9/603 (1.5%)	
		Placebo	6/239 (2.5%)	17/575 (3.0%)	
	Cook, 2005 (WHS)[60]	ASA	284/19934 (1.4%)	NA	ASA vs. No ASA: RR 0.95 (95% CI, 0.81 to 1.11), p=0.51*
		No ASA	299/19942 (1.5%)		
	PHS, 1989[73]	ASA	NA	79/11037 (0.7%)	ASA vs. No ASA: OR 1.16 (95% CI, 0.84 to 0.61), p=NR
		No ASA		68/11034 (0.6%)	
	Peto, 1988 (BMD)[72]	ASA	NA	75/3429 (2.2%)	ASA vs. No ASA: OR 0.79 (95% CI, 0.55 to 1.14), p=NR
		No ASA		47/1710 (2.7%)	
Race/Ethnicity	Ogawa, 2008 (JPAD)[70]	Group	Japanese	--	Between Group Difference
		ASA	15/1262 (1.2%)	NA	ASA vs. No ASA: OR 0.80 (95% CI, 0.40 to 1.57), p=NR
		No ASA	19/1277 (1.5%)		
Baseline Cancer Risk	Logan, 2008 (ukCAP)[68]	Group	Prior Colon Adenoma	--	Between Group Difference
		ASA	2/472 (0.4%)	NA	ASA vs. No ASA: RR 0.66 (95% CI, 0.11 to 3.93), p=NR
		No ASA	3/467 (0.6%)		
Diabetes	Belch, 2008 (POPADAD)[57]	Group	Diabetic	--	Between Group Difference
		ASA	25/638 (3.9%)	NA	ASA vs. No ASA: OR 0.80 (95% CI, 0.47 to 1.37), p=NR
		No ASA	31/638 (4.9%)		
	Ogawa, 2008 (JPAD)[70]	ASA	15/1262 (1.2%)	NA	ASA vs. No ASA: OR 0.80 (95% CI, 0.40 to 1.57), p=NR
		No ASA	19/1277 (1.5%)		
	DAMAD, 1989[51]	ASA	1/157 (0.6%)	NA	ASA vs. Placebo: NR
		Placebo	0/157 (0%)		
	ETDRS, 1992[64]	ASA	16/1856 (0.9%)	NA	ASA vs. No ASA: OR 1.14 (95% CI, 0.56 to 2.35), Z-value 0.37, p=NR
		No ASA	14/1855 (0.8%)		

Note: No studies reported cancer mortality specific to age subgroups
*Adjusted by age, vitamin E and beta-carotene treatment assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; mg = milligram(s); NA = not applicable; NR = not reported; OR = odds ratio; RR = relative risk

Appendix F Table 2. All-Cause Mortality by Subgroup (KQ 1)

Subgroup	Study				
Age	AMIS, 1980[75]	Group	Age <55 years	Age ≥55 years	Between Group Difference
		ASA	NR (8.8%)	NR (12.0%)	Age <55 years: ASA vs. Placebo: Z-value: 1.52, p=NR Age ≤55 years: ASA vs. Placebo Z-value: 0.13, p=NR
		Placebo	NR (7.0%)	NR (11.9%)	
	Hansson, 1998 (HOT)[67]	Group	Age <65 years	Age ≤65 years	Between Group Difference
		ASA	4.9 (NR)*	14.7 (NR)*	Age < 65 years: ASA vs. Placebo: RR 0.90 (95% CI, 0.70 to 1.15), p=0.40 Age ≤ 65 years: ASA vs. Placebo: RR 0.96 (95% CI, 0.77 to 1.19), p=0.72
		Placebo	5.5 (NR)*	15.3 (NR)*	
Sex	AMIS, 1980[75]	Group	Women	Men	Between Group Difference
		ASA	21/2267 (8.0%)	218/2004 (10.9%)	Women: ASA vs. Placebo: Z-value 1.33, p=NR Men: ASA vs. Placebo: Z-value 0.80, p=NR
		Placebo	12/239 (5.0%)	204/2018 (10.1%)	
	ETDRS, 1992[64]	ASA	11.6 (NR)†	12.4 (NR)†	Women: ASA vs. Placebo: RR 0.88 (99% CI, 0.65 to 1.17), p=NR‡ Men: ASA vs. Placebo: RR 0.94 (99% CI, 0.73 to 1.22), p=NR‡
		Placebo	16.2 (NR)†	13.8 (NR)†	
	Farrell, 1991 (UK-TIA)[65]	ASA 1200 mg	25/214 (11.7%)	87/601 (14.5%)	NR
		ASA 300 mg	20/203 (9.9%)	89/603 (14.8%)	
		Placebo	24/239 (10.0%)	98/575 (17.0%)	
	Hansson, 1998 (HOT)[67]	ASA	6.6 (NR)*	9.2 (NR)*	Women: ASA vs. Placebo: RR 1.12 (95% CI, 0.86 to 1.47), p=0.41 Men: ASA vs. Placebo: RR 0.83 (95% CI, 0.68 to 1.02), p=0.08
		Placebo	5.9 (NR)*	11.1 (NR)*	
	Cook, 2005 (WHS)[60]	ASA	609/19934 (3.1%)	NA	ASA vs. No ASA: RR 0.95 (95% CI, 0.85 to 1.06), p=0.32§
		No ASA	642/19942 (3.2%)		
	PHS, 1989[73]	ASA	NA	217/11037 (2.0%)	ASA vs. No ASA: RR 0.96 (95% CI, 0.80 to 1.14), p=0.64‖
		No ASA		227/11034 (2.1%)	
	Peto, 1988 (BMD)[72]	ASA	NA	270/3429 (7.9%)	NR
		No ASA		151/1710 (8.8%)	
Race/Ethnicity	Ogawa, 2008 (JPAD)[70]	Group	Japanese	--	Between Group Difference
		ASA	34/1262 (2.7%)	NA	ASA vs. No ASA: HR 0.90 (95% CI, 0.57 to 1.14), p=0.67
		No ASA	38/1277 (3.0%)		
	Sato, 2006 (JAST)[81]	ASA	10/426 (2.3%)	NA	NR
		No ASA	9/445 (2.0%)		
Baseline Cancer Risk	Logan, 2008 (ukCAP)[68]	Group	Prior Colon Adenoma	--	Between Group Difference
		ASA	12/472 (2.5%)	NA	NR
		No ASA	11/467 (2.4%)		
	Baron, 2003 (AFPPS)[77]	ASA 325 mg	4/372 (1.1%)	NA	ASA vs. No ASA: p=0.93 (all groups)
		ASA 81 mg	3/377 (0.8%)		
		No ASA	3/372 (0.8%)		

Appendix F Table 2. All-Cause Mortality by Subgroup (KQ 1)

Subgroup	Study				
Diabetes	de Gaetano, 2001 (PPP)[61]	Group	Diabetic	Non-Diabetic	Between Group Difference
		ASA	25/519 (4.8%)	42/1826 (2.3%)	Diabetic: ASA vs. No ASA: RR 1.23 (95% CI, 0.69 to 2.19), p=NR Non-Diabetic: ASA vs. No ASA: RR 0.70 (95% CI, 0.47 to 1.04), p=NR
		No ASA	20/512 (3.9%)	61/1906 (3.2%)	
	Ogawa, 2008 (JPAD)[70]	ASA	34 (2.7%)	NA	ASA vs. No ASA: HR 0.90 (95% CI, 0.57 to 1.14), p=0.67
		No ASA	38 (3.0%)		
	Belch, 2008 (POPADAD)[57]	ASA	94/638 (14.7%)	NA	ASA vs. No ASA: HR 0.93 (95% CI, 0.71 to 1.24), p=0.63
		No ASA	101/638 (15.8%)		
	ETDRS, 1992[64]	ASA	12.1 (NR)†	NA	ASA vs. No ASA: RR 0.91 (99% CI, 0.75 to 1.11), p=0.24‡
		No ASA	14.9 (NR)†		

*Rate per 1,000 patient-years
†5-year life table rate
‡Adjusted by age > 30 years, age > 50 years, nonwhite, type I or II diabetes mellitus, and clinical center
§Adjusted by age, vitamin E and beta-carotene treatment
‖Adjusted for age and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; mg = milligram(s); NA = not applicable; NR = not reported; OR = odds ratio; RR = relative risk

Appendix F Table 3. Cancer Incidence by Subgroup (KQ 2)

Subgroup	Study					
Age	Cook, 2005 (WHS)[60]*	Group	45-54 years	55-64 years	≥65 years	Between Group Difference
		ASA	671/12010 (6%)	515/5876 (9%)	252/2048 (12%)	45-54 years: ASA vs. No ASA: RR 1.04 (95% CI, 0.93 to 1.16), p=0.49‡ 55-64 years: ASA vs. No ASA: RR 1.00 (95% CI, 0.89 to 1.14), p=0.94‡ ≥ 65 years: ASA vs. No ASA: RR 0.93 (95% CI, 0.78 to 1.11), p=0.42‡
		No ASA	647/12015 (5%)	512/5878 (9%)	268/2049 (13%)	
	Rothwell, 2012[10] (IPD MA) Cancer <3 years	Group	Age <60 years	Age ≥60 years	--	Between Group Difference
		ASA	115/NR (NR)	330/NR (NR)	--	Age < 60 years: ASA vs. No ASA: OR 0.83 (95% CI, 0.65 to 1.07), p=0.14 Age ≥ 60 years: ASA vs. No ASA: OR 1.08 (95% CI, 0.92 to 1.27), p=0.32
		No ASA	141/NR (NR)	301/NR (NR)		
	Rothwell, 2012[10] (IPD MA) Cancer ≥3 years	ASA	105/NR (NR)	219/NR (NR)	--	Age < 60 years: ASA vs. No ASA: OR 0.72 (95% CI, 0.56 to 0.93), p=0.01 Age ≥ 60 years: ASA vs. No ASA: OR 0.77 (95% CI, 0.65 to 0.93), p=0.006
		No ASA	149/NR (NR)	272/NR (NR)		
Sex	Peto, 1988 (BMD)[72]	Group	Women	Men	--	Between Group Difference
		ASA	NA	119/3429 (3.5%)	--	NR
		No ASA		58/1710 (3.4%)		
	Cook, 2005 (WHS)[60]	ASA	1438/19934 (7.2%)	NA	--	ASA vs. No ASA: RR (95% CI): 1.01 (0.94, 1.08), p=0.87‡
		No ASA	1427/19942 (7.2%)			
	Rothwell, 2012[10] (IPD MA) Cancer <3 years	ASA	176/NR (NR)	269/NR (NR)	--	Women: ASA vs. No ASA: OR 1.13 (95% CI, 0.91 to 1.40), p=0.28 Men: ASA vs. No ASA: OR 0.94 (95% CI, 0.80, 1.12), p=0.49
		No ASA	158/NR (NR)	284/NR (NR)		
	Rothwell, 2012[10] (IPD MA) Cancer ≥3 years	ASA	132/NR (NR)	192/NR (NR)	--	Women: ASA vs. No ASA: OR 0.75 (95% CI, 0.59 to 0.94), p=0.01 Men: ASA vs. No ASA: OR 0.77 (95% CI, 0.63 to 0.93), p=0.008
		No ASA	176/NR (NR)	245/NR (NR)		
Baseline Cancer Risk	Cook, 2005 (WHS)[60]†	Group	Family History of Cancer	No Family History of Cancer	--	Between Group Difference
		ASA	264/3529 (7%)	1174/16405 (7%)	--	Family History of Cancer: RR 0.94 (95% CI, 0.79 to 1.11), p=0.46‡ No Family History of Cancer: RR 1.02 (95% CI, 0.94 to 1.11), p=0.59‡
		No ASA	280/3517 (8%)	1147/16425 (7%)		
	Baron, 2003 (AFPPS)[77]	Group	Prior Colon Adenoma	--	--	Between Group Difference
		ASA 325 mg	12/372 (3.2%)	NA	--	NR
		ASA 81 mg	16/377 (4.2%)			
		Placebo	7/372 (1.9%)			
	Logan, 2008 (ukCAP)[68]	ASA	12/472 (2.5%)	NA	--	NR
		No ASA	15/367 (4.1%)			

Appendix F Table 3. Cancer Incidence by Subgroup (KQ 2)

Subgroup	Study					
Diabetes	Belch, 2008 (POPADAD)[57]	Group	Diabetic	--	--	Between Group Difference
		ASA	45/638 (7.1%)	NA	--	NR
		No ASA	60/638 (9.4%)			
	de Gaetano, 2001 (PPP)[61]	ASA	93/2226 (4.2%)	NR	--	NR
		No ASA	89/2269 (3.9%)			

Note: Studies reported cancer incidence specific to race/ethnicity subgroups
*Interaction testing, p=0.32
†Interaction testing, p=0.37
‡Adjusted by age, vitamin E and beta-carotene assignment

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio; mg = milligram(s); NA = not applicable; NR = not reported; OR = odds ratio; RR = relative risk

We identified 20 relevant meta-analyses on the use of ASA to prevent cancer. The majority of included studies in these reviews and meta-analyses were originally meant to study the cardioprotective effects of ASA or the primary prevention of colorectal cancer.

Cancer Mortality

We identified four meta-analyses of trials examining the effect of ASA on cancer-related mortality. All examined cancer deaths in general, only one examined cancer deaths by site (e.g., gastrointestinal [colorectal, esophageal, pancreatic and stomach], prostate, kidney/bladder, and other solid tumors). [8,10,44,128] Two were conducted by the same first author and suggested that daily aspirin for 5 years or more might reduce risk of cancer-related mortality.[8,10]

A 2012 meta-analysis of 34 trials comparing daily ASA to no ASA found ASA was associated with a reduced risk of cancer-related mortality (OR, 0.85 [95% CI, 0.76 to 0.96]).[10] When combined with non-vascular mortality data from an additional 17 trials (i.e., trials that did not specify cancer deaths), the association was still significant (p=0.005). The most beneficial effect occurred after 5 years of followup (OR, 0.63 [95% CI, 0.49 to 0.82]). In the same meta-analysis, pooled individual patient data showed that ASA reduced the risk of incident cancers in six trials after at least 3 years of followup.

Another 2012 meta-analysis of 23 trials comparing daily low-dose aspirin to placebo or no treatment found that ASA after at least 2.5 years of followup may reduce risk of non-vascular (RR 0.88 [95% CI, 0.81 to 0.96]) and cancer-related mortality (in 11 trials; RR, 0.77 [95% CI, 0.63 to 0.95]).[128] Included studies demonstrated a significant treatment effect after approximately 4 years of followup. Another 2012 meta-analysis, however, did not find a statistically significant reduction in cancer-related mortality (OR, 0.93 [95% CI, 0.84 to 1.03]) as reported in eight primary prevention (of vascular and/or nonvascular outcomes) trials.[44]

A 2011 meta-analysis of eight trials (all designed to compare the use of ASA vs. placebo in the primary or secondary prevention of vascular disease) found that ASA use was associated with a reduced risk of cancer-related mortality (OR, 0.79 [95% CI, 0.68 to 0.92]).[8] Individual patient data was available in seven trials; a significant effect on cancer-related mortality was seen only after 5 or more years of followup (HR, 0.62 [95% CI, 0.47 to 0.82]). There was no effect, however, on non-gastrointestinal (e.g., lung, prostate), stomach or esophageal cancers. Three trials provided data beyond 20 years of followup and also found a statistically significant reduce risk of cancer-related mortality (HR, 0.78 [95% CI, 0.70 to 0.87]) including non-gastrointestinal, cancers. The greatest absolute risk reduction occurred in patients aged 65 years or older after 20 years.

Cancer Incidence

With regards to cancer incidence, only one trial (the Women's Health Study[60]) was included in a handful of the meta-analyses summarized below; otherwise the majority of data comes from case-control and cohort studies. Many investigators recommend additional research (i.e., trials) before making definitive conclusions about the protective effects of ASA, the size and timing of the chemopreventive benefit, any dose-response relationships and trends in subgroups analyses.

A 2012 meta-analysis of ASA chemoprevention on 12 selected cancer sites included 139 observational studies.[129] It demonstrated that regular ASA use is associated with a statistically significant reduced risk of colorectal cancer, esophageal cancer (RR, 0.61 [95% CI, 0.50 to 0.76]), esophageal and gastric cardia adenocarcinoma (RR, 0.64 [95% CI, 0.52 to 0.78]), gastric

cancer (RR, 0.67 [95% CI, 0.54 to 0.83]), lung cancer (RR, 0.91 [95% CI, 0.84 to 0.99]), breast cancer (RR, 0.90 [95% CI, 0.85 to 0.95]), and prostate cancer (RR, 0.90 [95% CI, 0.85 to 0.96]). No statistically significant reductions in risk were seen in other cancer sites (i.e., pancreatic, endometrial, ovarian, bladder, and kidney). Although the observational data indicate a beneficial role of ASA on some cancer sites, results are heterogeneous across studies and unclear relationships exist between risk and dose and duration.

Another review examined the effects of regular ASA use on long-term cancer incidence and metastasis and compared the evidence from observational studies versus trials.[130] The authors aimed to assess the reliability of estimates of the effect of ASA use on risk and outcome of all types of cancer in 150 case-control and 45 cohort studies. For other cancers, they found that case-control and cohort studies yielded associations that were also consistent with those from trials, with reductions in risk of biliary, esophageal, and gastric cancer. Lastly, this study showed a reduction in risk of breast cancer with regular use of ASA, which was not seen in the trials.

Three meta-analyses examined the association between ASA use and lung cancer risk.[131-133] A 2011 meta-analysis found that regular ASA use (i.e., seven or more tablets per week) can significantly reduce lung cancer risk (OR, 0.80 [95% CI, 0.67 to 0.95]), however, when all 19 studies were pooled there was no significant effect.[133] A 2012 meta-analysis of 15 observational studies found a statistically significant decreased lung cancer risk (OR, 0.86 [95% CI, 0.76 to 0.98]); subgroup analyses by study type, study quality, and sex showed mixed results (e.g., protective effect in men but not women).[131] A 2011 meta-analysis of individual patient level data from eight observational studies in the International Lung Cancer Consortium also found a statistically significant protective effect of any ASA use against lung cancer in men (RR, 0.73 [95% CI, 0.57 to 0.92]) but not women (RR, 1.02 [95% CI, 0.87 to 1.19]).[132]

Four meta-analyses examined the association between regular ASA use and breast cancer risk.[134-137] A 2012 meta-analysis of 32 observational studies and one RCT[60] found that ASA use was associated with a statistically significant reduction in breast cancer risk (OR, 0.86 [95% CI, 0.81 to 0.92]).[137] The RCT, however, did not find a statistically significant effect (OR, 0.98 [95% CI, 0.87 to 1.09]).[60] A 2008 meta-analysis also found a reduced risk for breast cancer in 37 observational studies and one RCT[60] (RR, 0.87 [95% CI, 0.82 to 0.92]).[134] Two other meta-analyses of observational studies also found statistically significant reduction in breast cancer risk with ASA use: RR, 0.75 (95% CI, 0.64 to 0.88) in ten studies[136] and RR, 0.91 (95% CI, 0.83 to 0.98) in 26 studies.[135]

A 2010 meta-analysis of 24 observational studies found a statistically significant reduced risk of prostate cancer in older adults (OR, 0.83 [95% CI, 0.77 to 0.89]).[138] It also found a statistically significant effect on advanced cancer (OR, 0.81 [95% CI, 0.72 to 0.92]).

Three meta-analyses examining the association between ASA use and gastric cancer risk showed mixed results.[139-141] One 2010 meta-analysis of 13 observational studies and one RCT showed there was no statistically significant effect of ASA use on gastric cancer risk (OR, 0.80 [95% CI, 0.54 to 1.19]).[140] while another 2010 meta-analysis of 21 observational studies showed a statistically significant effect (adjusted risk ratio, 0.81 [95% CI, 0.73 to 0.89]).[141] A cohort study that also included a meta-analysis of 17 studies also showed a statistically significant protective effect against gastric (OR, 0.74 [95% CI, 0.64 to 0.87]).[139]

Three meta-analyses examined the association between ASA use and esophageal cancer.[142-144] A 2012 meta-analysis of six observational studies, ever use of ASA had significantly reduced the risk of esophageal adenocarcinoma (OR, 0.68 [95% CI, 0.56 to 0.83]).[144] A 2011 meta-analysis also found a reduced risk of esophageal adenocarcinoma in 14 observational studies

with ASA use (OR, 0.73 [95% CI, 0.65 to 0.83]).[142] Another 2011 meta-analysis pooled seven case-control studies of ASA use found a statistically significant effect on esophageal squamous cell carcinoma (OR, 0.60 [95% CI, 0.48 to 0.76]).[143]

Appendix H. Ongoing Studies

We identified six relevant ongoing or recently completed studies through searches of clinicaltrials.gov, the Current Controlled Trials (http://www.controlled-trials.com), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au), and the World Health Organization's International Clinical Trials Registry Platform (http://www.who.int/ictrp/en). Additional individual patient data meta-analyses by the Non-Vascular Outcomes (NOVA) Collaboration (Rothwell and colleagues) are currently underway incorporating data from the WHS and PHS as well as evaluating long-term cancer incidence and mortality.

Study	Aim	Population	Intervention	Control	Relevant Outcomes	Status
A Study of Cardiovascular Event iN Diabetes (ASCEND)[145]	Determine whether ASA prevent serious vascular events	Diabetics aged ≥ 40 years	100 mg ASA with or without 1 gram omega-3-Ethyl esters	Placebo with or without 1 gram omega-3-Ethyl esters	Cerebral hemorrhage	Anticipated completion date, December 2016
Aspirin and simvastatin Combination for Cardiovascular Events Prevent Trial in Diabetes (ACCEPT-D)[118]	Study the efficacy of low-dose ASA in the prevention of CV events	Diabetics aged ≥ 50 years without clinically manifest vascular disease and treated with simvastatin (n=5,170)	100 mg ASA	Simvastatin alone	Total and cause-specific mortality, major hemorrhagic episodes	Anticipated completion date, December 2013
ASPirin in Reducing Events in the Elderly (ASPREE)[146,147]	Assess whether daily ASA extends the duration of disability-and dementia-free life	Healthy older adults aged ≥ 65 years (n=19,000)	100 mg enteric-coated ASA for 5 years	Placebo	All-cause mortality, fatal and non-fatal cancer, clinically significant bleeding	Anticipated completion date, August 2016
Aspirin to Reduce the Risk of Initial Vascular Events (ARRIVE)[148]	Assess the efficacy of ASA	Older adults with moderate risk CVD (n=12,590)	Enteric-coated ASA for 5 years	Placebo	All-cause mortality, treatment-emergent AEs	Anticipated completion date, May 2014
IMProving Adherence using Combination Therapy (IMPACT)[149]	Assess whether polypill improves adherences and CVD risk factors	Patients at high-risk of CVD in primary care settings (n=600)	Polypill containing 75 mg ASA, 40 mg simvastatin, 10 mg lisinopril and either 12.5 mg hydrochlorothiazide or 50 mg atenolol for 12 months	Usual care	Serious AEs	Ongoing
Japanese Primary Prevention Project (JPPP)[150]	Evaluate the primary prevention of low-dose ASA	Older adults aged 60-85 years with hypertension, dyslipidemia, or DM (n-14,466)	100 mg enteric-coated ASA for 4 years	No ASA	All-cause mortality, extracranial hemorrhage	Recently published

Abbreviations: AE = adverse event; ASA = aceylysalycyclic acid; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; mg = milligram(s); PAH = pulmonary arterial hypertension