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Comparative Effectiveness Review
Number 135

Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

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

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease

Structured Abstract

Objectives. To systematically review the literature on the use of cardiac troponin levels in patients with chronic kidney disease (CKD) regarding four Key Questions (KQ): (1) diagnosis of acute coronary syndrome (ACS), (2) management decisions for ACS, (3) prognosis after presenting with ACS, and (4) risk stratification in patients without symptoms of ACS.

Data sources. MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1990 through September 2013.

Review methods. We included studies that compared a cardiac troponin elevation with a nonelevation in terms of diagnostic accuracy, mortality, or cardiovascular events among patients with CKD. Two reviewers evaluated studies for eligibility; abstracted data using standardized forms; and independently evaluated study quality and graded strength of evidence (SOE). We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous.

Results. We included 124 studies (130 articles). **KQ 1:** Fourteen studies evaluated diagnostic accuracy. The sensitivity of troponin T for ACS diagnosis in CKD patients ranged from 71 to 100 percent, and specificity from 31 to 86 percent (6 studies; low SOE). The sensitivity of troponin I for ACS diagnosis ranged from 43 to 94 percent, and specificity from 48 to 100 percent (8 studies; low SOE). **KQ 2:** One study indirectly addressed management decisions. We could not draw any conclusions about whether troponin levels affect management strategies, such as timing of intervention, in CKD patients with ACS (SOE: insufficient). **KQ 3:** Twelve studies examined the prognostic value of troponin in CKD patients. Elevated troponin I and T were associated with higher risk of short-term mortality and cardiac outcomes (low SOE). A similar trend was observed for long-term mortality with troponin I (low SOE), but less evidence was found for long-term cardiac events for troponin I and long-term outcomes for troponin T (insufficient SOE). Patients with advanced stages of CKD tended to have worse prognosis with elevated troponin I than those without elevation (moderate SOE). **KQ 4:** Ninety-eight studies met inclusion criteria. Elevated troponin was associated with all-cause and cardiovascular mortality among dialysis patients with moderate SOE. Hazard ratios (HR) adjusted at least for age and coronary artery disease or risk equivalents were pooled: All-cause mortality, troponin T (HR 3.0 [95% CI 2.4 to 4.3]), troponin I (HR 2.7 [1.9 to 4.6]); Cardiovascular mortality, troponin T (HR 3.3 [95% CI 1.8 to 5.4]), troponin I (HR 4.2 [2.0 to 9.2]). Findings were similar for non-dialysis CKD patients, with fewer studies. No study tested management strategies by troponin cut-points. **KQs 1–4:** Few studies evaluated high-sensitivity troponin T and I assays in CKD patients. **KQs 1–4:** We found substantial heterogeneity across studies in terms of study design, troponin assays, troponin cutpoints, patient populations, and adjustment for potential confounders. For ACS populations, the studies varied in the pretest probability descriptions and ACS definitions and adjudication. We found no studies that carried out direct a priori comparisons of troponin testing in patients with CKD versus patients with normal renal function.

Conclusions. Cardiac troponin elevations are associated with a worse prognosis for CKD patients with and without suspected ACS. However, the wide variation in assays and cutoffs, along with the lack of comparative studies, prevents clear conclusions about how this association should change management, compared with management based on clinical factors or evidence derived from the non-CKD population. Future research should compare various management strategies that incorporate measuring cardiac troponins in their algorithms, including using different cutoffs or assays. For this research to be effective, troponin assays and cutpoints need to be standardized and harmonized so that results can be pooled, compared, and applied in practice.

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Background

Cardiac Troponin Assays

Troponin Detection in Normal and Disease States

Troponin is a protein complex of three subunits (T, I, and C) that is involved in the contractile process of skeletal and cardiac muscle. Both cardiac and skeletal muscle express troponin C; whereas troponin T and I are generally thought to be cardiac-specific.[*1] When cardiac injury occurs (from ischemia or various other causes), cardiomyocytes release cardiac troponin into the blood in proportion to the degree of damage.[2] Troponin levels increase within 3 to 4 hours after the onset of damage and remain high for up to 4 to 7 days (troponin I) or 10 to 14 days (troponin T). However, blood from healthy individuals with no evidence of cardiac disease also contains very low amounts of cardiac troponin.[3] Some of the newer high-sensitivity assays may be able to measure troponin in normal individuals; although many of the commercially available assays cannot detect troponin at all or cannot quantify it at levels below the measuring range of the assay.

Clinically, the most important use of troponin testing is to identify patients suspected of having an acute coronary syndrome (ACS). ACS is defined as a spectrum of conditions caused by insufficient supply of oxygen to the myocardium by the coronary arteries. However, elevated cardiac troponin levels are not specific for the diagnosis of ACS or acute spontaneous myocardial infarction (MI) (type 1 MI). Individuals with non-ACS conditions can also have elevated cardiac troponin.[4] Non-ACS conditions can include noncoronary causes (e.g., sepsis, congestive heart failure, myocarditis, drug toxicity, pulmonary embolism, hypoxia, and global hypoperfusion) and coronary causes from ischemic imbalance [i.e., increased demand in the setting of stable coronary artery disease (CAD) lesions] classified as type 2 MI. Many symptoms associated with non-ACS conditions may overlap with symptoms of ACS (e.g., chest pain or dyspnea).This presents a diagnostic dilemma to the clinician and often requires an extended evaluation before the clinician can make an accurate diagnosis.

The 99th Percentile Cutpoint—Challenges

Because we can detect troponin even among presumably healthy adults, we must set guidelines regarding what is considered an "elevated" level. The joint European Society of Cardiology/American College of Cardiology guidelines define a clinically relevant increase in troponin levels as a level that exceeds the 99th percentile of a normal reference population.[5] However, because using a statistical cut-off means that some normal individuals will have a higher value, and because other clinical causes can cause an elevation, we must interpret elevated troponin levels in the context of an intermediate to high pre-test probability of suspected ACS.[6]

Currently, there is no universally adopted 99th percentile value because there is no reference standard for detecting either troponin T or I, as each test manufacturer independently develops its own assays. Additionally, no consensus exists on how to define a reference population for the assays (in terms of age, gender, race/ethnicity, comorbidities, or number of participants), and many of the 99th percentile values come from diverse and poorly defined study participants.[7]

[*] Note: A recent study has challenged whether troponin T is exclusively cardiac-specific.[1]

When studies compare troponin T and I assays in the same population, assays can differ regarding troponin concentrations at the 99th percentile by as much as five-fold. Recommendations call for cardiac troponin assays to have a coefficient of variation less than or equal to 10 percent at the 99th percentile cutpoint. However, many current assays have a coefficient of variation between 10 and 20 percent at the 99th percentile.[8]

High-Sensitivity Troponin Assays

Troponin assays have evolved over time, becoming ever more sensitive with detection limits 10 to 100 times lower than currently available commercial troponin assays. This also challenges the precision guidelines for acceptable coefficient of variation.[9] For example, a contemporary sensitive cardiac troponin I (such as TnI-Ultra) can detect concentrations as low as 0.006 mcg/L, and the high-sensitive cardiac troponin T assay (Roche, approved in Europe but not the United States) can detect as low as 0.005 mcg/L.[6] Manufacturers are continuing to develop new generations of high-sensitivity assays that are more precise at even lower concentrations, such as less than 1 ng/L (0.001 mcg/L).

Thus, the high-sensitivity assays detect measurable troponin levels in a larger percentage of presumably healthy people—redefining what is "normal."[7] For patients with suspected ACS, this means potentially earlier detection for the diagnosis of ACS which may aid management in emergency room departments. On the other hand, this increased sensitivity comes at a cost of reduced specificity for ACS. High-sensitivity assays may also aid in our ability to detect increases in cardiac troponin, which will help distinguish patients with acute disease from more chronic disease—where levels, while elevated, are more static.

With constantly evolving and newer assays, there is a need to define how these new high-sensitivity assays compare with contemporary and older generations of troponin assays. In 2009, Apple et al. proposed a "scorecard" based on imprecisions (coefficient of variation percent) of each assay at the 99th percentile and how many samples from normal individuals are measurable below the 99th percentile.[8]

Troponin Elevation in Chronic Kidney Disease

Given that the prevalence of chronic kidney disease (CKD) in the United States reached 15 percent in 2008, how to interpret troponin levels in this population is an important issue.[10, 11] We listed a description of the stages of CKD in Table A. Of note, even more recently, there are new guidelines for classifying CKD that incorporate albuminuria: http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

Table A. Stages of chronic kidney disease

Stage	Description	GFR, mL/min/ 1.73 m2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 or dialysis

GFR = glomerular filtration rate; mL/min/1.73 m2 = milliliters per minute for 1.73 meters squared

Patients with CKD (particularly those with end-stage renal disease [ESRD]) have a greater prevalence of persistently-elevated cardiac troponin when compared with patients who do not have CKD. Current thinking, although somewhat controversial, is that this troponin elevation is not due to reduced renal clearance, but rather represents a marker of myocardial injury.[12, 13] The

intact troponin molecule is large and it is unlikely that the kidneys are primarily responsible for clearance from serum. However, work by Diris et al. suggests that the troponin molecule is degraded into smaller fragments, which can be detected by the assays and are small enough to be filtered by the kidneys. This mechanism may contribute to the elevation of troponin in severe renal failure.[14] Despite this, Ellis et al.[15] did not observe a statistically significant difference in the half-life and the elimination rate constant of troponin I in patients with MI and ESRD when compared with patients with MI and normal kidney function.

As with non-CKD patients, we must interpret elevated troponin levels in patients with CKD in the context of one's pre-test probability for suspecting an ACS event. Elevated levels may also be due to cardiac injury associated with chronic structural heart disease (e.g., CAD, heart failure, etc.), which is highly prevalent among CKD patients, rather than from acute ischemia, especially when the levels do not change rapidly over time.[16] Among patients without suspected ACS, potential reasons for detectable small increases in troponin include micro-infarctions, microvascular disease, subendocardial ischemia associated with left ventricular hypertrophy and diastolic dysfunction, and nonischemic cardiomyopathic processes, all of which are more common in patients with CKD.

Use of Troponin for the Diagnosis of Acute Coronary Syndrome in Patients With Chronic Kidney Disease (Background for Key Question 1)

In patients with symptoms of ACS, without other causes for increased troponin, clinicians use elevated troponin levels (along with clinical factors) to diagnosis MI as outlined by the Global Task Force's Third Universal Definition of MI (Table B).[17]

Table B. Definition of myocardial infarction according to 2012 Third Universal Definition

Both are required for a diagnosis of myocardial infarction: (1) Rise and/or fall of troponin (or another cardiac biomarker) with at least one value above the 99th percentile reference limit (2) Evidence of myocardial ischemia from symptoms, electrocardiogram, or cardiac imaging

The diagnosis of ACS among patients with CKD (especially those with ESRD) can be particularly challenging. Electrocardiograms (ECGs) are frequently abnormal in CKD patients (indicating left ventricular hypertrophy, intraventricular conduction delay, etc.), which can reduce the sensitivity/specificity of detecting ischemia.[18] Also, baseline troponin levels are often not known in patients with CKD on initial presentation, making it hard to define elevated troponin levels (increased troponin is considered, along with symptoms and other clinical factors, in diagnosing ACS, as per the global definition of MI). Whether clinicians should use an alternative threshold, other than the 99th percentile, of elevated cardiac troponin when assessing patients with CKD is unknown. Furthermore, since not all CKD patients will have elevated levels, high cut-off values will disadvantage those who do not have elevated levels. Therefore, using alternate cutpoints may not be preferable.

On the other hand, the patterns of changes in troponin levels (rise, fall, and magnitude of change) can also be very helpful for clinicians in distinguishing ACS from non-ACS in symptomatic patients. The National Academy of Clinical Biochemistry[19] has recommended that for patients with ESRD and suspected ACS, a diagnosis of acute MI (Type I) should require a dynamic change in troponin levels of greater than 20 percent within 9 hours (with at least one value above the 99th percentile).[13] However, clinicians should also consider the timing of

presentation from the onset of symptoms. If the patient presents late in the course of ACS, testing could take place during the "plateau phase," and clinicians may miss the rise/fall pattern. Although widely applied in the guidelines, researchers have not yet studied this 20 percent rule in a vigorous evidence-based fashion and compared it with other degrees of change or the use of a single elevated value in the context of high pre-test probability.

No consensus exists about whether the diagnostic criteria for MI using troponin levels should be different for patients with CKD and those without CKD. It's also unclear whether elevated baseline troponin levels make it more difficult to diagnose ACS in patients with ESRD than in patients with milder forms of CKD.

The following clinical vignette highlights some of the clinical diagnostic dilemmas: The patient is a 68-year-old man with a history of diabetes and CAD who has had remote coronary artery bypass surgery. He has CKD (creatinine 1.8 mg/dL) and previously had a troponin I level of 0.06 mcg/L on his last admission. He is admitted to the hospital with pneumonia but repeated tests of troponin indicate a level of 0.24 mcg/L. He is short of breath but has no chest pain and his ECG shows a left bundle branch block (old). What is the clinical significance of his newly elevated troponin? Should he additionally be managed for ACS?

Use of Troponin Level as a Management Strategy for Patients With Chronic Kidney Disease and Acute Coronary Syndrome (Background for Key Question 2)

Frequently, clinicians use troponin levels, along with clinical factors, to stratify patients according to risk when a diagnosis of non-ST-elevation MI (NSTEMI)/unstable angina is likely. Clinicians usually treat patients at high risk for ACS with an "early invasive" strategy (i.e., diagnostic angiography with the intent of revascularization), while clinicians may treat patients with low-to-intermediate risk of ACS with an "initially conservative" (i.e., selectively invasive) management strategy.[20]

The "troponin hypothesis" suggests that patients with elevated troponin levels (troponin-positive) are likely to have more thrombus burden, complex lesions, and be at higher risk for worse outcomes than patients with normal troponin levels (troponin-negative). Therefore, it stands to reason that clinicians should treat troponin-positive patients more aggressively. Results from a general population of patients presenting with ACS (not exclusively CKD), found that even minor troponin elevations identify patients who benefit from an early invasive strategy (compared with initially conservative management).[21] In addition to an early invasive strategy, the use of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparin also appear more beneficial in troponin-positive versus troponin-negative patients with suspected ACS.[13] However, in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) clinical trial of ACS patients, clopidogrel use did not confer a preferential benefit in troponin-positive versus troponin-negative patients.[13] Therefore, the troponin hypothesis may not be applicable to all therapeutic management in ACS.

As with the initial diagnosis of ACS, elevated background troponin levels in patients with CKD call into question the applicability of treatment algorithms that are based on troponin levels in non-CKD populations. Whether elevated background troponin levels in patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies is unknown.

Use of Troponin Level as a Prognostic Indicator in Patients With Chronic Kidney Disease Following Acute Coronary Syndrome (Background for Key Question 3)

In addition to their use in diagnosing and managing ACS, studies have examined troponin assays as potential independent risk predictors of morbidity and mortality in populations following an acute ischemic event. Previous reviews and meta-analyses have investigated the prognostic performance of troponin testing in patients with kidney failure, but often excluded studies on patients with ACS.[22, 23] Therefore, the prognostic significance of elevated cardiac troponin levels with regard to short- and long-term major adverse cardiovascular events (MACE) for patients with both CKD and ACS remains uncertain.

Use of Troponins in Adults With Chronic Kidney Disease Who Do Not Have Symptoms of Acute Coronary Syndrome: A Role for Risk Stratification (Background for Key Question 4)

Patients with CKD are known to be at increased risk for cardiovascular morbidity and mortality. Despite established guidelines for primary and secondary cardiovascular disease prevention (i.e., blood pressure, lipid, and glucose targets), cardiovascular disease remains the number one cause of death for CKD patients. Among asymptomatic CKD patients without suspected ACS, prior studies have shown that chronic elevated cardiac troponin is associated with increased risk of cardiovascular morbidity and mortality.[23-26] For this reason, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). However, it is unknown whether measuring troponins improves risk prediction when compared with (or used in conjunction with) existing models that are based on traditional clinical and laboratory risk factors. Whether troponin testing improves metrics of discrimination and re-classification of patients into higher or lower risk groups is unknown.

It is also unclear whether clinicians should manage asymptomatic patients with CKD and chronically-elevated cardiac troponin levels differently than patients with CKD who have normal troponin levels.

Types of Troponin Assays and Special Subgroups of Patients With Chronic Kidney Disease (Key Questions 1–4)

There are multiple commercially available troponin assays including cardiac troponin T, troponin I, high-sensitivity troponin T, and high-sensitivity troponin I. Whether all of these troponin assays are equal in distinguishing ACS from non-ACS conditions and prognosticating and risk-stratifying CKD patients (with and without ACS) is unclear.

Furthermore, whether troponin testing leads to changes in management and outcomes among certain subgroups of patients with CKD is also unknown (e.g., categories of CKD stages, dialysis status, age, race, gender, and those with prior history of CAD).

Scope and Key Questions

The purpose of this comparative effectiveness review will be to present information for the appropriate use of troponin levels to guide evidence-based management decisions for patients

with CKD. These findings should be useful for a diverse set of contingents including cardiologists, nephrologists, emergency room physicians, and laboratory medicine scientists who use and interpret troponin testing in the clinical management of patients. Findings may also be useful for epidemiologists in tackling research gaps for further studies. We addressed the following Key Questions (KQs) in this review:

KQ 1: Diagnosis of ACS

What is the diagnostic performance of a troponin elevation (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) >99th percentile (compared to no elevation) for the detection of ACS in adult patients with CKD (including those with ESRD)?

1.1 What are the operating characteristics of a troponin elevation (compared with no elevation) in distinguishing between ACS and non-ACS, including sensitivity, specificity, and positive and negative predictive values?

1.1a How do the positive predictive value and the negative predictive value vary with the population's pre-test probability for ACS?

1.1b Does a significant delta of change (such as greater than 20 percent within 9 hours) better discriminate between ACS and non-ACS compared with a single troponin elevation?

1.2 What are the operating characteristics of troponin elevation for distinguishing ACS from non-ACS among the following subgroups?

1.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

1.3 What are the harms associated with a false-positive diagnosis of ACS based on an elevated troponin level?

1.4 Among studies that directly compared one type of troponin assay (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, do the operating characteristics of a certain type of troponin test perform better for diagnosis of ACS?

1.5 Among studies that directly compared troponin testing in patients with CKD versus patients with normal renal function, do the operating characteristics of a troponin elevation perform similarly?

KQ 2: Management in ACS

In adults with CKD (including ESRD), do troponin levels improve management of ACS?

2.1 Does a troponin elevation modify the comparative effectiveness of interventions or management strategies for ACS (e.g., Is an aggressive strategy better than a initially conservative strategy for high troponin levels, but not for low/normal troponin levels)?

2.2 Among adults with CKD with suspected ACS, how does a troponin elevation change the effects of interventions or management strategies according to the following characteristics?

2.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

KQ 3: Prognosis in ACS

In adult patients with CKD (including those with ESRD) and suspected ACS, does an elevated troponin level help to estimate prognosis?

3.1 Do troponin results relate to:

3.1a Long-term outcomes (all-cause mortality and major adverse cardiovascular events [MACE] such as subsequent MI, stroke or cardiovascular death, over at least 1 year of followup)?

3.1b Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of followup)?

3.2 Does a troponin elevation help to estimate prognosis after ACS in the following subgroups?

3.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

3.3 Among studies that directly compared one type of troponin assay (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, does a certain type of troponin test estimate prognosis better after ACS?

KQ 4: Risk Stratification in non-ACS

Does an elevated troponin level (compared with no elevation) help with risk stratification in adults with CKD (including those with ESRD) who do not have symptoms of ACS?

4.1 In clinically stable adults with CKD (including those with ESRD) who do not have symptoms of ACS, what is the distribution of troponin values?

4.1a What is the distribution by CKD stages I-IV and in ESRD?

4.2 Do troponin threshold levels or patterns of troponin change in this population improve prediction for MACE or all-cause mortality, compared with or supplementing existing models?

4.3 Does troponin elevation improve CHD risk prediction for the following subgroups:

4.3a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD on dialysis), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

4.4 Among studies that directly compared one type of troponin assay (troponin I, troponin T, hs troponin T, or hs troponin I) against another type of troponin assay, does a certain type of troponin test predict risk better?

Methods

Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1990 through September 2013. We further updated the MEDLINE® search through May 2014. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text from key articles we identified a priori. We conducted the search according to a prespecified protocol, which can be found on the Agency for Healthcare Research and Quality's Effective Health Care Program's Web site (http://effectivehealthcare.ahrq.gov).

To identify additional studies, the Evidence-based Practice Center Program's Scientific Resource Center submitted requests to troponin assay manufacturers for any published or unpublished randomized controlled trials (RCTs) or observational studies.

Study Selection

Two independent reviewers evaluated the titles, abstracts, and full articles. For an abstract or an article to be excluded, both reviewers had to agree that the article met one or more of the exclusion criteria (Table C). We tracked and resolved the differences regarding inclusion through consensus adjudication. For articles that were not in English, we tried to find at least two people (either an investigator or a person with a medical or public health background) who were fluent in the language to review the article.

Table C. Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Population and condition of interest	• All studies included human subjects exclusively. • We included studies of adult patients with CKD including ESRD. o For KQs 1, 2, and 3, we included patients who also are clinically suspected of having ACS. o For KQ 1.5, we only included patients with normal renal function if the studies made a direct comparison with CKD. o For KQ 4, we included patients who are clinically stable and asymptomatic for ACS.	
Interventions	• We included studies that evaluated troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I.	
Comparisons of interest	• We included studies that compared troponin elevation versus no elevation. • We included studies that *directly* compared different types of troponin assays with each other (KQs 1.4, 3.3, and 4.4). • We included studies that directly compared the utility of troponin elevation for diagnosing ACS in patients with or without CKD (KQ 1.5).	• We excluded studies that did not have a comparison group.
Outcomes	• For KQ 1, we included studies that evaluated sensitivity, specificity, and positive and negative predictive values compared with clinical diagnosis of ACS (adjudicated using strict criteria according to guidelines). • For KQ 2a, we included studies that evaluated differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds. • For KQs 3 and 4, we included studies that evaluated: o All-cause mortality o Cardiovascular mortality o MACE o Hospitalizations o Other major adverse events	
Type of study	• We included randomized controlled trials and observational studies with a comparison group. • We did not place any restrictions based on sample size or language.	• We excluded articles with no original data (reviews, editorials, and commentaries). • We excluded studies published before 1990 because troponin started being used a cardiac marker in the early 1990s.
Timing and setting	• We included studies regardless of the followup length. • We included all study settings.	

ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; KQ = Key Question; MACE = major adverse cardiovascular event

Data Abstraction

We created standardized forms for data extraction, which we pilot tested. The study investigators double-reviewed each article for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy.

For all articles, the reviewers extracted information on general study characteristics and

participants; characteristics of the troponin assays; and outcome measures, definitions, and results, including measures of variability. For KQs 1, 2, and 3, we collected information on how the studies defined ACS outcome. We collected the number with elevated versus nonelevated troponin values and the number of events in each arm. If studies presented regression models with various degrees of covariate adjustment, we abstracted results from the most-adjusted model.

Quality Assessment

Two reviewers independently assessed study quality. We used the Downs and Black quality assessment tool to assess the quality of all included studies.[27] We supplemented this tool with additional quality-assessment questions based on recommendations in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (Methods Guide).[28] Our quality assessment tool included items on the reporting, external validity, internal validity, power, and conflicts of interest. We assessed the overall study quality in terms of good, fair, and poor.[28] A third-party adjudicator resolved differences between reviewers.

Data Analysis and Synthesis

We conducted meta-analyses when at least 2 studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For KQ 1, we followed the meta-analytic methods for studies that had an imperfect reference standard.[29] We constructed 2×2 tables and calculated sensitivity, specificity, and positive and negative predictive values where possible. If we found at least five studies that were sufficiently homogenous, we conducted a hierarchical summary receiver operator curve meta-analysis to analyze sensitivity and specificity.

For KQ 3, there was insufficient data for conducting meta-analyses. For KQ 4, we conducted two types of meta-analyses. For studies that reported a hazards ratio (HR) with a confidence interval, we pooled the hazards ratios by using the profile likelihood estimate for calculating between-study variance.[30] This method provides better accounting of uncertainty in estimation of between-study variance than the DerSimonian and Laird formula.[30]

Pooled HR meta-analyses were stratified by levels of adjustment. We considered the highest level of adjustment to be models that adjusted for age and CAD and/or similar risk equivalent (cerebrovascular disease, peripheral vascular disease, reduced left ventricular ejection fraction, heart failure, and/or diabetes).

If a study reported HRs by tertiles or quartiles of troponin levels, we selected the HR that compared the highest with the lowest group. Studies that only presented results by troponin as a continuous variable, rather than a cutpoint, could not be included in meta-analyses. For studies that reported the incidence of events, we pooled the unadjusted odds ratios (ORs) using a profile likelihood estimate.[30] Depending on the type of results reported in the individual study, it could be included in the HR meta-analysis, OR meta-analysis, or both. If a study reported more than one troponin assay, we included in the meta-analysis the assay that was most commonly used. If several articles were published using the same patient cohort, we included only the most adjusted and/or most recent results, to avoid double-counting the same study population.

We tested heterogeneity among the trials in all the meta-analyses using a standard chi-squared test with a significance level of alpha less than or equal to 0.10. We examined heterogeneity among studies using an I^2 statistic, which describes the variability in effect

estimates that is due to heterogeneity rather than random chance.[31] We considered a value greater than 50 percent an indication of substantial variability.

We examined publication bias using Begg's test[32] and Egger's test[33] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which we conducted meta-analyses.

We used STATA statistical software (Intercooled, Version 12.1, StataCorp, College Station, TX) for all meta-analyses.

We summarize studies that were not amenable to pooling qualitatively.

Strength of the Body of Evidence

At the completion of our review, at least two reviewers independently rated the strength of the body of evidence on each of the troponin assays. We graded the strength of evidence addressing KQs 1, 2, 3, and 4 by adapting an evidence grading scheme recommended in the Methods Guide.[34] We applied evidence grades to the bodies of evidence about each troponin assay for each outcome. We rated the strength of the evidence in terms of the risk of bias, consistency, directness, and precision.

We classified the strength of evidence pertaining to the KQs into four basic grades: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Results

Results of Literature Searches

We retrieved 6,809 unique citations from our searches. After reviewing titles, abstracts, and full articles, 124 studies (in 130 publications) met inclusion criteria. Clinically, the utility of troponin was felt to be distinct between patients presenting with suspected ACS where troponin may be potentially used for diagnosis, management, and prognosis (most often in the acute care setting) versus the use of troponin in patients without suspected ACS where the troponin biomarker would be used for risk stratification (generally in the outpatient or dialysis clinic setting). Therefore, results for KQ 1-3 were considered together (23 total studies), while results for KQ 4 were considered separately (98 studies). The number of studies relevant to each KQ is presented below in the respective sections.

KQ 1: Use of Troponin for Diagnosis of Acute Coronary Syndrome Among Patients With Chronic Kidney Disease

Among CKD patients presenting with ACS symptoms, 14 studies reported operating characteristics (sensitivity, specificity, positive predictive value [PPV], and/or negative predictive value [NPV]) of troponin elevation compared with a final clinical diagnosis of ACS.

The studies had low SOE on diagnostic accuracy for both troponin T and I, largely due to incomplete information on adjudication of ACS and a lack of blinding (Table D).

ACS diagnosis was made by the European Society for Cardiology standards in five studies (one also used the American College of Cardiology standards), and five studies did not report diagnostic criteria used. Troponin assay manufacturer varied among studies.

Six studies of troponin T and eight of troponin I examined sensitivity and specificity for ACS diagnosis (Figures A and B). Three of these assessed more than one assay cutoff value. The sensitivity for ACS diagnosis ranged from 71% to 100% for troponin T and 43% to 94% for troponin I. Specificity ranged from 31% to 86% for troponin T and 48% to 100% for troponin I. Given heterogeneity of troponin cutoffs and assay manufacturers used in these studies, it was not possible to identify a trend relating assay cutoff value to these characteristics.

SOE was insufficient regarding the diagnostic accuracy of a change in troponin value. The magnitude of change in troponin T in the first 24 hours after admission did not differ between the control and ACS groups (n=46). Similarly, the rate of change from 0-6 or 6-12 hours after admission was not different between groups.

Subgroups by age and creatinine level were used to report on sensitivity and specificity of troponin T elevation in the diagnosis of ACS. The findings could not be directly compared except to note that the operating characteristics varied by both age and creatinine level (SOE: insufficient). Regarding troponin I, one study reported areas under the curve for ACS diagnosis across groups of CKD patients classified by creatinine clearance (CrCl). Although the study suggested comparable diagnostic performance in all subgroups, the evidence was insufficient to support a definitive conclusion. We did not find evidence on either troponin T or I for other relevant subgroups such as dialysis status, history of CAD, presence of ischemic symptoms, ECG changes, diabetes mellitus, other comorbidity, or race/ethnicity.

One study directly compared troponin T and I. The troponin T Elecsys assay (Roche Diagnostics, Basel, Switzerland) with 0.1 mcg/L cutoff was associated with 100% sensitivity and 42% specificity for ACS. In contrast, the Troponin I Immulite assay (DPC, Inc., Los Angeles, California) with 1.0 mcg/L cutoff had 45% sensitivity and 100% specificity.

One study compared troponin testing in CKD patients to those without CKD for ACS diagnosis and found a higher sensitivity for troponin T in patients with moderate to severe renal failure than for those with normal function, however, they also found lower specificity, PPV, and NPV, as well as an area under the curve of 0.54 for CKD. This study is limited by a heterogeneous population, a relaxed diagnosis of renal function, and a lack of long-term outcomes.

No study addressed harms associated with a false positive diagnosis.

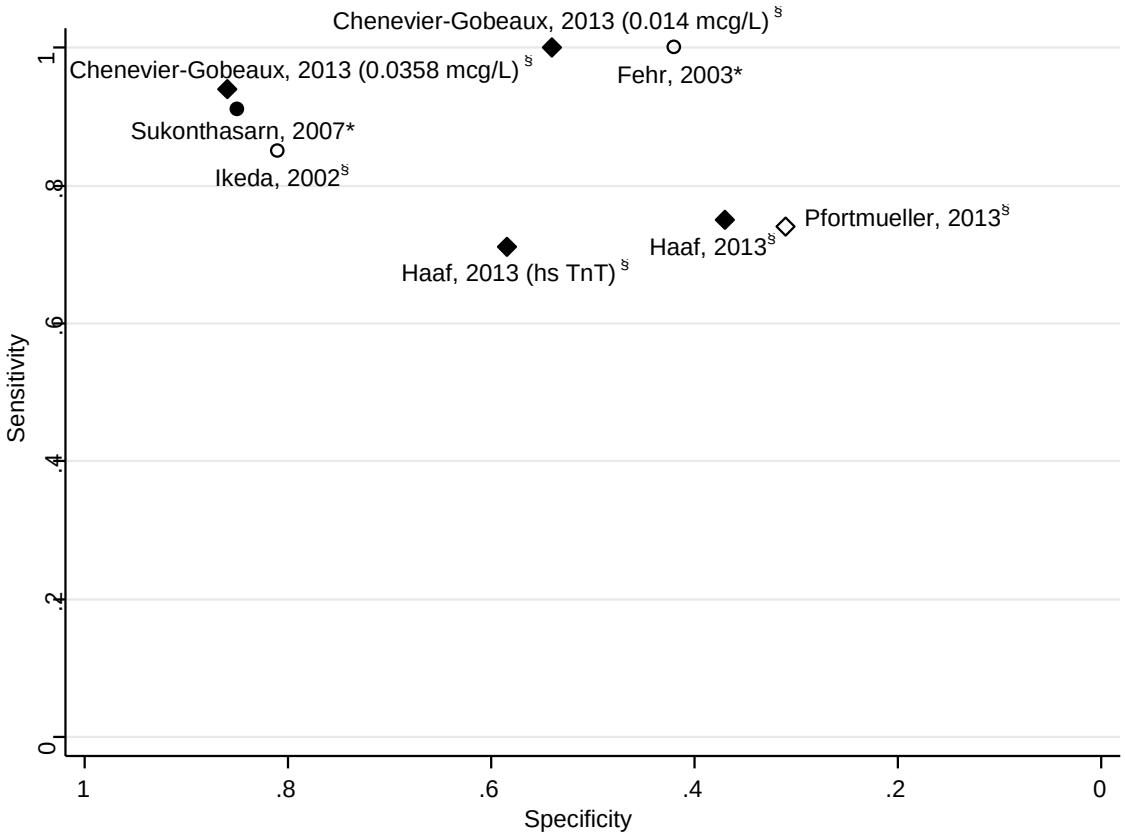
Table D. Summary of the strength of evidence and conclusions for the use of troponin for the diagnosis of acute coronary syndrome among chronic kidney disease patients*

Key Question	Troponin Assay	Strength of Evidence (# of studies)	Summary and Conclusions
1.1, 1.1a: Operating characteristics (sensitivity, specificity, PPV, NPV) of a troponin elevation in diagnosing ACS	Troponin T	Low (6)	The sensitivity of the troponin T assay for ACS in patients with CKD ranged from 71 to 100%, and its specificity ranged from 31 to 86%. Three studies reported a PPV and NPV for troponin T for the diagnosis of ACS. The PPV for troponin T ranged from 6 to 77; the NPV ranged from 71 to 98. In one study, the assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. The strength of evidence was low because of the medium risk of bias and imprecise results. With low strength of evidence, we can conclude that troponin T assays have limited sensitivity and specificity to diagnose ACS in populations with CKD.
1.1, 1.1a: Operating characteristics (sensitivity, specificity, PPV, NPV) of a troponin elevation in diagnosing ACS	Troponin I	Low (8)	There were six studies reporting seven troponin I cutpoints (one study reported two cutpoints). The sensitivity of the troponin I assay for ACS ranged from 43 to 94%, and its specificity ranged from 48 to 100%. In the five studies estimating PPV and NPV, the PPV ranged from 7 to 100; the NPV ranged from 93 to 98%. The assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years. The broad range of these findings can be attributed to the heterogeneity among the studies in study population, definition of ACS, assays used, and assay cut-points used. The strength of evidence was low because of the medium risk of bias and imprecise results. With low strength of evidence, we can conclude that troponin I assays have limited sensitivity and specificity to diagnose ACS in populations with CKD.
1.b: Change in troponin values vs. single troponin elevation	Troponin T	Insufficient (1)	We cannot draw a conclusion about the diagnostic accuracy of a change in troponin levels. This was addressed by a single fair quality study with a small sample size and imprecise results.
1.2: Operating characteristics of a troponin elevation by subgroups	Troponin I or T	Insufficient (4)	Although a few studies have looked at how age and CKD stage affect the operating characteristics of troponin, they are small, poor quality, and use different cutpoints for different categories. Therefore, we are unable to draw any conclusions.
1.2: Operating characteristics of a troponin elevation by subgroups	Troponin I or T	Insufficient (0)	Evidence is lacking on the operating characteristics of troponin assays for diagnosing ACS for subgroups of patients with regard to history of coronary artery disease, electrocardiogram abnormalities, other comorbidity, and race or ethnicity.
1.3: Harms associated with a false-positive diagnosis	Troponin I or T	Insufficient (0)	We found no studies addressing this KQ.
1.4: Direct comparisons between troponin assays	Troponin I vs. troponin T	Insufficient (1)	We are unable to draw conclusions about the diagnostic accuracy of troponin T vs. troponin I. We found a single, poor quality study, which is indirect, lacks consistency, and is imprecise.
1.5: Comparisons with non-CKD patients	Troponin I or T	Insufficient (0)	We found no studies that carried out direct a priori comparisons of troponin testing in patients with CKD vs. patients with normal renal function.

ACS = acute coronary syndrome; CKD = chronic kidney disease; mcg/L = micrograms per liter; NPV = negative predictive value; PPV = positive predictive value

* We graded the strength of evidence for all comparisons not listed here as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

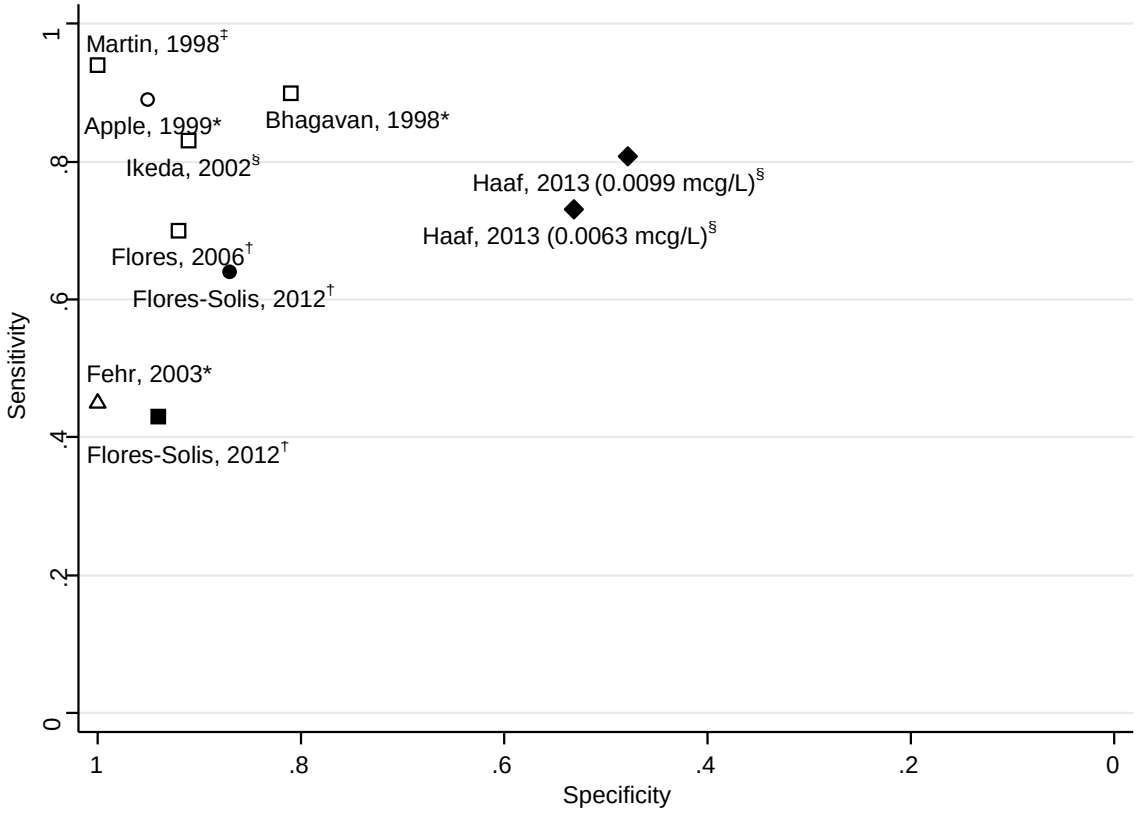
Figure A. Sensitivity and specificity of troponin T elevation in the diagnosis of acute coronary syndrome (ACS) versus non-ACS among patients with chronic kidney disease



Closed markers represent studies that adjudicated acute coronary syndrome, open markers represent studies that either did not adjudicate or did not report adjudicating acute coronary syndrome. Diamond markers indicate a troponin T cutoff of less than 0.1 mcg/L. Round markers indicate a troponin T cutoff of 0.1 mcg/L or higher.
* Indicates a dialysis population.
† Indicates a non-dialysis population.
‡ Indicates a mixed population

§ Does not specify if the population is on dialysis or not.

Figure B. Sensitivity and specificity of troponin I elevation in the diagnosis of acute coronary syndrome (ACS) versus non-ACS among patients with chronic kidney disease



Closed markers represent studies that adjudicated acute coronary syndrome, open markers represent studies that either did not adjudicate or did not report adjudicating acute coronary syndrome. Diamond markers indicate a troponin I cutoff of less than 0.1 mcg/L. Round markers indicate a troponin I cutoff between 0.1 mcg/L and 0.5 mcg/L. Square markers indicate a troponin I cutoff between 0.5 and 1.0 mcg/L. Triangular markers indicate a troponin I cutoff greater than or equal to 1.0 mcg/L.

* Indicates a dialysis population.

† Indicates a non-dialysis population.

‡ Indicates a mixed population

§ Does not specify if the population is on dialysis or not.

KQ 2: Do Troponin Levels Help Guide Management Decisions in Acute Coronary Syndrome for Patients With Chronic Kidney Disease?

We did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., no studies randomized patients to any management strategy by troponin levels).

The one study evaluating management of non-ST elevation ACS in CKD patients found that peak cardiac troponin I values were similar between the two management groups (immediate vs. delayed invasive strategy). Because this study did not compare cutpoints of troponin elevation, and because it did not randomize patients to their management groups on the basis of their troponin levels, we could not draw conclusions to answer whether measuring troponin improves outcomes (strength of evidence: insufficient).

KQ 3: Do Troponin Levels Predict Short- and Long-Term Prognosis in Patients With Chronic Kidney Disease Presenting With Suspected Acute Coronary Syndrome?

Twelve studies assessed troponin T or I in establishing short- or long-term prognosis for CKD patients following a presentation suggestive of ACS. The studies used heterogeneous methodology for ACS diagnosis, comparators, and outcomes, precluding pooled analyses. While several studies required the presence of symptoms, ECG and enzymatic changes for ACS diagnosis, one defined its patients only by the presence of clinical symptoms, two categorized patients as low, moderate, or high risk ACS, one based it on medical records, and three studies did not specify any criteria for diagnosis. Only three studies reported how the diagnosis was adjudicated, and whether there was a cardiologist involved.

Definition of CKD also varied, with five studies using CrCl, four using serum creatinine, and three not specifying a definition. Three studies used the Cockcroft-Gault equation to calculate glomerular filtration rate (GFR), three used the Modification of Diet in Renal Disease equation, and six did not specify. Stages of CKD differed, with one study noting exclusion of dialysis patients, and two including only dialysis patients.

Mortality and MACE for Elevated Troponin T

Six studies analyzed elevated troponin T in predicting adverse outcomes following a suspected ACS event.

Of the three evaluating troponin T with all-cause mortality, one did not specify length of follow-up. We found low SOE that patients with elevated troponin T was associated with increased short-term mortality, but insufficient SOE regarding long-term mortality due to a high risk of bias.

Studies with short-term follow-up demonstrated that risk of other outcomes (cardiac mortality, acute MI, cardiac ischemia, revascularization, dysrhythmia, congestive heart failure, and composites of these endpoints) was increased with elevated troponin T. The assay cutoff ranged from 0.01 to 0.1 mcg/L. SOE for the prognostic value of elevated troponin T was low, as one study found higher rates of the composite outcome with troponin elevation, yet another found no difference between groups. In a comparison of patients with and without events, an

increase in troponin T of 0.11 mcg/L from baseline had 27% sensitivity and 96% specificity for MACE (positive likelihood ratio 7.2).

Two analyses of outcomes by severity of CKD were insufficient to assign a SOE grading due to differences in defining CKD stages, followup period, and outcomes assessed. One found no difference in in-hospital mortality between those with elevated troponin T and those with non-elevated troponin T based on the hospital's upper limit cutpoint for any renal function subgroup, while the other found a greater risk of 30-day MACE in patients with elevated troponin who had more severe CKD. Additionally, there were no differences in outcome when dialysis patients were analyzed separately from those with severe CKD.

Mortality and MACE for Elevated Troponin I

Seven studies (nine publications) investigated the prognostic value of elevated troponin I.

We found a low SOE for elevated troponin I as a predictor of long-term mortality in CKD patients with ACS. Cutpoints ranged from 0.15 to 1 mcg/L, with two studies not reporting a threshold. Two studies found a higher mortality with elevated troponin I after adjustment for age and multiple clinical factors; however, a third study that did not adjust for covariates found no difference.

Short-term mortality as an independent outcome was limited to a single investigation with low SOE. Following adjustment for clinical factors, the only association between in-hospital mortality and troponin I elevation was in patients with moderate CKD with estimated GFR of 30-60 mL/min/1.73m^2. Another study found an association with troponin and mortality at 30 days but did not specify between troponin T or troponin I.

Studies of troponin I reporting MACE included cutpoints ranging from 0.0001 to 1 mcg/L. The SOE was insufficient, with a medium risk of bias for long-term prognostic value, with one study reporting more cardiac deaths within 1 year and a second reporting no differences between groups for acute MI, revascularization, or composite MACE. In comparison of assays, the rate of death or acute MI was higher in those with elevated levels for three types of troponin I assay.

Elevated troponin I in CKD patients predicted short-term MACE with low SOE based on an analysis of acute MI as primary diagnosis on discharge and of a composite endpoint including cardiac death, acute MI, revascularization, or congestive heart failure.

In dialysis patients with ACS, elevated troponin I was associated with a higher risk of short-term adverse cardiac outcome.

A large (n=2179) study of good quality evaluated both troponin T and I, but did not distinguish between the two in its analysis. When comparing patients with elevated versus non-elevated troponin levels, differences in composite death or acute MI remained significant after adjusting for baseline clinical characteristics, ECG, and laboratory findings at 30 days (HR 2.1; 95% CI 1.5-2.8) and 1 year (HR 1.7; 1.4-2.2). Troponin elevation was associated with increased risk of cardiovascular outcomes in moderate (CrCl 30-60 mL/min) but not advanced (<30ml/min) CKD, but sample size limited the power to detect differences across troponin groups.

Sensitivity and Specificity

A troponin T assay with cutpoint of 0.1 mcg/L predicted MACE with sensitivity and specificity of 43% and 46% during hospitalization, 45% and 72% within 6 months, and 57% and 88% within 2 years, respectively. A troponin I assay with 0.6 mcg/L cutoff predicted MACE with 28% sensitivity and 80% specificity during hospitalization and 27% sensitivity and 83%

specificity within 6 months. With a 0.4 mcg/L cutoff and -2 year followup, sensitivity and specificity were 57% and 67%, respectively.

Table E presents a summary of the strength of evidence and conclusions for using troponin levels in the prognosis of patients with CKD presenting with symptoms suggestive of ACS.

Table E. Summary of the strength of evidence and conclusions for using troponin levels in the prognosis of patients with chronic kidney disease presenting with symptoms suggestive of acute coronary syndrome

Key Question and Outcome	Troponin Assay	Strength of Evidence* (# of studies)	Summary and Conclusions
3.1: Prognosis after ACS in terms of all-cause mortality (long-term ≥1 year)	Troponin T	Insufficient (1)	We were unable to draw conclusions about the ability of troponin T elevation to predict long-term (≥1 year) all-cause mortality in CKD patients following ACS based on a single small study.
3.1: Prognosis after ACS in terms of all-cause mortality (long-term ≥1 year)	Troponin I	Low (3)	The studies investigating the ability of troponin I elevation in CKD patients presenting with ACS, showed a trend toward increased risk of long term all-cause mortality (≥1 year) for patients with elevated troponin. However, conclusions may be limited due to population included (asymptomatic patients).
3.1: Prognosis after ACS in terms of all-cause mortality (< 1 year)	Troponin T	Low (3)	One study was not statistically significant. One study found that Troponin T was most prognostic in patients with moderate CKD. One study found troponin associated with increased risk of death in CKD patients but did not specify between troponin T or I.
3.1: Prognosis after ACS in terms of all-cause mortality (< 1 year)	Troponin I	Low (2)	One study found that Troponin T was most prognostic in patients with moderate CKD. One study found troponin associated with increased risk of death in CKD patients but did not specify between troponin T or I.
3.1 Prognosis after ACS in terms of MACE (long-term ≥1 year)	Troponin I	Insufficient (2)	We could not draw definitive conclusions of the ability of troponin elevation (T or I) to estimate long-term (≥1 year) MACE in CKD patients with ACS based on two studies with inconsistent and imprecise estimates.
3.1: Prognosis after ACS in terms of MACE (< 1 year)	Troponin T	Low (3)	The studies investigating the ability of troponin T elevation in CKD patients presenting with ACS, showed a trend toward increased risk of MACE within 1 year for patients with elevated troponin. However, conclusions may be limited due to the imprecision of the results.
3.1: Prognosis after ACS in terms of MACE (< 1 year)	Troponin I	Low (3)	The studies investigating the ability of troponin I elevation in CKD patients presenting with ACS showed a trend toward increased risk of MACE within 1 year for patients with elevated troponin. However, conclusions may be limited due to the imprecision of the results.
3.2: Prognosis after ACS by stage of CKD	Troponin T	Insufficient (2)	We could not draw definitive conclusions of the ability of troponin T to estimate prognosis after ACS by stage of CKD due to the inconsistency and imprecision of the studies included.
3.2: Prognosis after ACS by stage of CKD	Troponin I	Moderate (2)	The studies investigating the ability of troponin I to estimate prognosis after ACS by stage of CKD showed that patients with advanced stages of CKD and elevated troponin I are likely to have worse prognosis.
3.2: Prognosis after ACS by dialysis status	Troponin I or T	Low (3)	The studies investigating the ability of troponin T or I to estimate prognosis after ACS by dialysis status showed a trend towards a higher risk of adverse cardiac outcome in dialysis patients with ACS and elevated troponin. However, generalizability is lost due to inclusion of non-ACS patients in one of the studies.
3.2: Prognosis after ACS by other subgroups	Troponin I or T	Insufficient (0)	We did not find any studies that evaluated the ability of troponin elevation to estimate prognosis after ACS in subgroups of CKD patients based on sex, age, status after renal transplant, presence of previously elevated troponin, ECG changes, comorbidities, smoking status, 10-year CAD risk, or history of CAD.
3.3: Prognosis after ACS comparing troponin I with troponin T in same population	Troponin I vs. troponin T	Insufficient (3)	We are unable to determine if there is a difference in the performance of troponin T vs. troponin I assays to estimate prognosis after ACS in patients with CKD due to the heterogeneity and imprecision of the studies.

ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; ECG = electrocardiogram; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; OR = odds ratio

* We graded the strength of evidence for all comparisons not listed here as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence. None of the studies presented used high-sensitivity troponin assays.

KQ 4: Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

We included 98 studies (in 105 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4). All studies were observational cohort studies. The median followup time ranged from 30 days to 5 years. The overall study quality was rated fair to good.

Given the marked heterogeneity, we presented the results separately for dialysis and nondialysis CKD patients.

Results for Patients on Dialysis

KQ 4.1: Prevalence of Elevated Baseline Troponin Among Patients on Dialysis

Depending on cutpoints used, the prevalence of elevated troponin T among dialysis patients ranged from 12 to 82 percent across studies and the prevalence of elevated troponin I ranged from 45 to 82 percent. Cutpoints for troponin T ranged from 0.01 to 0.2 mcg/L with the majority of studies using the 0.1 mcg/L cutpoint. The cutpoints for troponin I ranged from 0 to 2.3 mcg/L. Given the differences in study populations, even with the same cutpoint, the prevalences varied widely. For example, for a cutpoint of troponin T greater than 0.1 mcg/L the prevalence of elevated troponin ranged from 12 to 50 percent across studies.

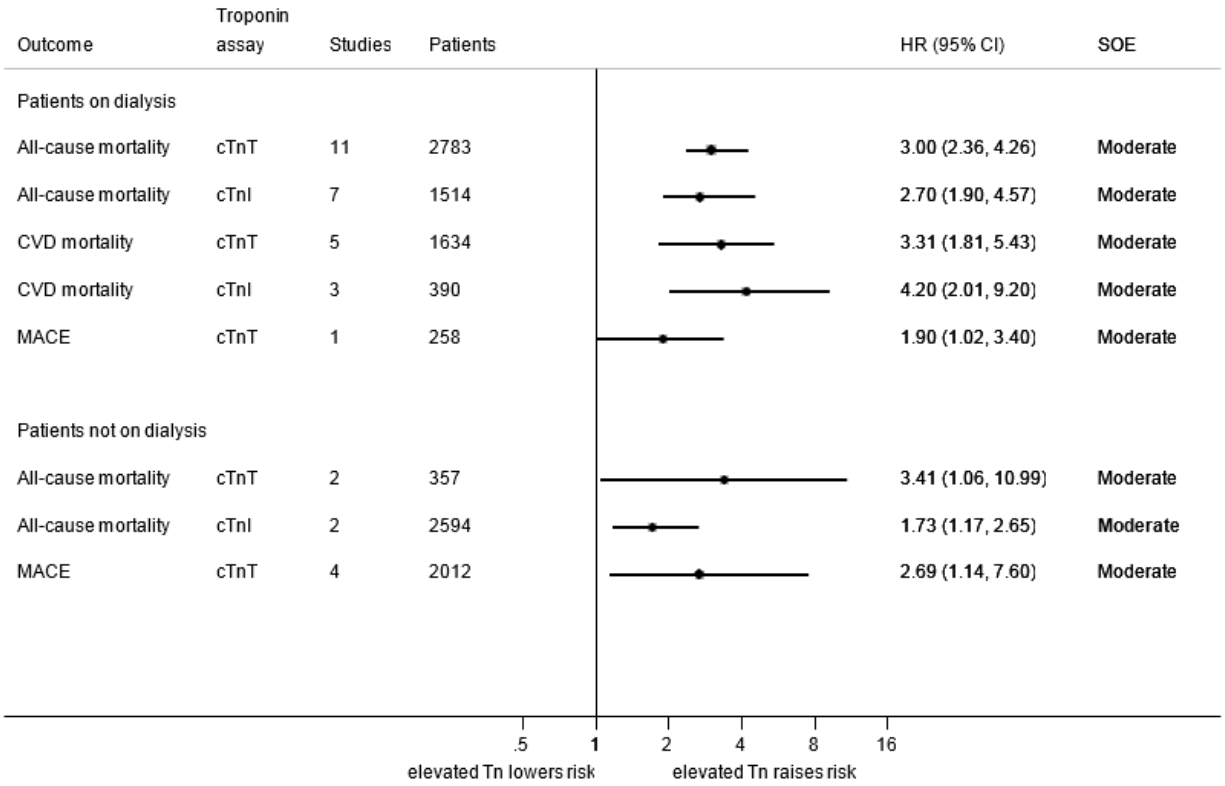
KQ 4.2: Risk Stratification Among Patients on Dialysis Without Symptoms of Acute Coronary Syndrome

Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin is associated with a higher risk (~2-4 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (i.e., "composite" outcome of MI, cardiovascular death, and/or revascularization). We summarized the strength of evidence for these findings along with the meta-analysis results from studies that adjusted at least for age and CAD (or risk equivalent) in Figure C. Table F presents a summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of CKD patients on dialysis without symptoms suggestive of ACS.

Results for Nondialysis Patients

Of the publications meeting criteria for KQ 4 , 26 included nondialysis CKD patients as part or all of the study population. Table G presents a summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of nondialysis CKD patients without symptoms suggestive of ACS. Figure C also includes the meta-analysis results for nondialysis patients for the outcomes where there was sufficient data to perform meta-analyses.

Figure C. Overall summary of the meta-analysis results of the pooled hazard ratios from studies that adjusted for at least age and CAD (or risk equivalent) for the association of an elevated troponin among dialysis and nondialysis patients*



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CVD = cardiovascular disease; HR = hazard ratio; MACE = major adverse cardiovascular events; SOE = strength of evidence; Tn = troponin

* The strength of evidence for other outcomes not listed here was graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Table F. Summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of CKD patients on dialysis without symptoms suggestive of ACS

Outcome	Troponin Assay	No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence*
All-cause mortality	Troponin T	43 observational studies overall; 11 in HR meta-analysis adjusting for at least age and CAD; 5 adjusting for at least age; 24 in unadjusted OR meta-analysis	Medium (23 fair quality and 20 good quality studies)	Direct	Consistent*	Precise	Adjusted HR 3.00; unadjusted OR 4.69	Moderate
All-cause mortality	Troponin I	30 observational studies overall; 7 in HR meta-analysis adjusting for at least age and CAD; 2 adjusting for at least age; 19 in unadjusted OR meta-analysis	Medium (13 good, 16 fair, and 1 poor quality studies)	Direct	Consistent*	Precise	Adjusted HR 2.70; unadjusted OR 2.55	Moderate
All-cause mortality	hs Troponin T	1 observational study with adjusted results	Medium (1 fair quality study	Direct	NA	Precise	One study reported HR 1.4	Low
All-cause mortality	hs Troponin I	1 observational study without adjusted results	High (1 fair quality study)	No	NA	Imprecise	Per 10 ng/L increase, no association found.	Insufficient
Cardiovascular-specific mortality	Troponin T	20 observational studies overall; 5 in HR meta-analysis adjusting for at least age and CAD; 1 adjusting for age 9 in OR meta-analysis	Medium (9 fair, 10 good and 1 poor quality studies)	Direct	Consistent*	Precise	Adjusted HR 3.31; unadjusted OR 4.26	Moderate
Cardiovascular-specific mortality	Troponin I	13 observational studies overall; 3 in HR meta-analysis adjusting for at least age and CAD; 9 in unadjusted OR meta-analysis	Medium (8 fair and 5 good quality studies)	Direct	Consistent	Precise	Adjusted HR 4.20; unadjusted OR 5.18	Moderate

Table F. Summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of CKD patients on dialysis without symptoms suggestive of ACS (continued)

Outcome	Troponin Assay	No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence*
MACE	Troponin T	12 observational studies overall; 1 adjusting for at least age and CAD; 1 adjusting for at least age; 9 in unadjusted OR meta-analysis	Medium (6 fair and 6 good quality studies)	Direct	Consistent	Precise	Adjusted HR 1.90; unadjusted OR 5.96	Moderate
MACE	Troponin I	12 observational studies overall; 9 in unadjusted OR meta-analysis; only 1 study reported adjusted results	High (6 fair, 5 good, and 1 poor quality studies)	Direct	Consistent	Precise	Unadjusted OR 6.29	Low
MACE	hs Troponin I	1 observational study with adjusted results	Medium (1 fair quality study)	Direct	NA	Imprecise	6 cases [24%] versus 0, P = 0.022	Insufficient

ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; HR = hazard ratio; hs = high sensitivity; MACE = major adverse cardiovascular events; NA = not applicable; ng/L = nanograms per liter; OR = odds ratio

* We graded the strength of evidence for all comparisons not listed here as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

Table G. Summary of the strength of evidence and conclusions for the use of troponin levels in risk stratification of nondialysis CKD patients without symptoms suggestive of ACS

Outcome	Troponin Assay	Study Design: No. Studies	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence*
All-cause mortality	Troponin T	9 observational studies overall; 2 in HR meta-analysis R adjusting for at least age and CAD; 5 in OR meta-analysis	Medium (6 fair and 3 good quality studies)	Direct	Consistent	Precise	Adjusted HR 3.41; unadjusted OR 2.98	Moderate
All-cause mortality	Troponin I	4 observational studies overall; 2 in HR meta-analysis adjusting for at least age and CAD	Medium (2 fair quality and 2 good quality studies)	Direct	Consistent	Precise	Adjusted HR 1.73; OR range 1.4 to 3.80	Moderate
MACE	Troponin T	9 observational studies overall; 4 in HR meta-analysis adjusted for at least age and CAD	Medium (6 fair quality and 3 good quality studies)	Direct	Consistent	Precise	Adjusted HR 2.69	Moderate
MACE	Troponin I	2 observational studies overall including both dialysis and non-dialysis patients	High (2 fair quality studies)	Indirect	Consistent	Imprecise	N/A (combined dialysis and non-dialysis)	Insufficient
MACE	hs Troponin T	1 observational study (unadjusted analysis)	High (1 fair quality study)	Direct	NA	Precise	OR 2.08	Insufficient

ACS = acute coronary syndrome; CAD = coronary artery disease; CKD = chronic kidney disease; HR = hazard ratio; hs = high sensitivity; MACE = major adverse cardiac events; OR = odds ratio

* We graded the strength of evidence for all comparisons not listed here as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

KQ 4.3: Troponin Associations With Short- and Long-Term Outcomes by Subgroups

We presented results for dialysis, nondialysis, and kidney transplant subgroups of CKD patients separately, as indicated in previous sections. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Studies were too few to generate meta-analyses for subgroup type. We described subgroups in the main report.

KQ 4.4: Comparisons Between Troponin Assays To Predict Risk

While many studies evaluated multiple troponin assays in the same population (troponin T vs. troponin I, or multiple troponin I assays by different manufacturers compared with each other), no studies presented formal interaction testing. No studies included troponin T and I levels in the same multivariate model adjusted for the other cardiac biomarkers. Some studies hinted at a stronger association with troponin T than with I among dialysis patients. However, in our pooled meta-analyses, the effect sizes of the association of adverse events for cardiac troponin elevation were similar for both T and I overall. Therefore, we are unable to draw any specific conclusion about which biomarker is better in the CKD patient. Both cardiac troponin markers T and I were similarly associated with an increased risk for adverse outcomes.

Discussion

Key Findings

KQ 1: Use of Troponin for Diagnosis of Acute Coronary Syndrome Among Patients With Chronic Kidney Disease

We systematically reviewed the available evidence regarding the utility of troponin testing with final (usually adjudicated) ACS diagnosis. However, we only found low-quality or insufficient evidence regarding the use troponin T and I assays to diagnose ACS in CKD patients. Troponin levels were associated with a wide range of sensitivity and specificity compared with final ACS diagnosis.

Studies addressing these operating characteristics were markedly heterogeneous in setting, population, and completeness of reporting regarding adjudication of ACS. In addition, there is also heterogeneity between studies regarding the assay manufacturer and cutpoints used for diagnosing ACS. We found limited evidence directly comparing the use of troponin T and I assays to diagnose ACS in a comparable population of CKD patients, and limited evidence examining the operating characteristics among relevant subgroups. We were unable to perform a meta-analysis of the summary statistics due to insufficient data.

The National Academy of Clinical Biochemistry recommends that ESRD patients with suspected ACS have a dynamic change in troponin levels of greater than 20 percent within 9 hours (with at least one value above the 99th percentile) to warrant diagnosis of acute MI.[19] We did not find any studies that tested this guideline in terms of operating characteristics (sensitivity, specificity, PPV, and NPV).

Overall, we were struck by the paucity of evidence for this KQ, and thus could not establish a clear cutpoint that maximizes sensitivity and specificity. The lack of direct comparison to patients without CKD in the same population cohort is another major limitation to understanding how troponin elevations in patients with CKD should be interpreted.

The sensitivities and specificities for diagnosing MI, among patients with CKD that we identified in our review may seem problematically low or too variable to draw conclusions (sensitivities ranging from 43 to 100 percent and specificities ranging from 42 to 100 percent).

However, one must keep in mind that using troponin levels to diagnose ACS can be problematic even in a general population of patients, not only in CKD patients. In a study of patients presenting to an emergency room with positive troponin I at a threshold of 0.04 mcg/L, clinicians diagnosed 20.4 percent with type I MI, 9.1 percent with type II MI, but the majority (65.8 percent) did not meet criteria for acute MI.[35] In another study of patients presenting to an emergency room with positive troponin, clinicians ultimately diagnosed only 55 percent with MI.[36] Furthermore, a recent study evaluating four new point-of-care assays for troponin I among patients with suspected ACS found that at the 99th percentile for each assay, sensitivities varied from 26 to 68 percent and specificities varied from 81 to 93 percent for diagnosing MI, versus the gold standard of the Universal Guidelines for MI.[37]

Thus, our findings must be put in context of what we already know about using troponin to diagnose ACS in the general population—that the utility of the diagnostic test is dependent on the pre-test probability for suspected ACS (i.e., Bayes Theorem). Newby et al., in a review on troponins for a consensus document on behalf of the American College of Cardiology Foundation (ACCF),[13] cites this following example: If the pre-test probability for ACS is high, such as 90 percent, based on classic symptoms and ECG changes, the post-test probability for a positive troponin above the 99th percentile is still 95 percent even if the false positive rate is 40 percent. Conversely, if the pre-test probability is very low, such as 10 percent (due to atypical symptoms or symptoms suggestive of other cause), the post-test probability for ACS is only 50 percent even if false positive rate is only 10 percent. Even with lab evidence suggestive of myocardial necrosis, the post-test probability for ACS for positive troponin is still low if the pre-test probability is low. Conversely, low values do not exclude ACS if the pre-test probability is high. Therefore, it is difficult to interpret the sensitivities and specificities of troponin testing for diagnosing ACS for studies included in our report that do not specifically state the pre-test probability of the population. Furthermore, relying on a single value should be avoided, especially those from a high-sensitivity assay, in favor of serial values.

Newby et al. stress that the problem with troponin testing, like any laboratory test, is inappropriate testing (when not indicated) or inappropriate interpretation of results, not the marker itself, and that clinicians should only test for troponin when appropriate (i.e., clinically indicated).[13] In patients with non-ST elevation ACS, global risk assessment rather than any single marker should be used for diagnosis and to guide therapy.

Therefore, to directly compare the utility of troponin testing in CKD and non-CKD populations, the pre-test probabilities should be similar in order to draw conclusions about comparisons. Although we found no studies that directly compared the use of troponin for diagnosing ACS in CKD versus non-CKD in the same population, our indirect comparison does not suggest that troponin is less effective in diagnosing ACS in CKD.

KQ 2: Do Troponin Levels Help Guide Management Decisions in Acute Coronary Syndrome for Patients With Chronic Kidney Disease?

As described in the background section, frequently, clinicians use troponin levels, along with clinical factors, to further risk-stratify patients presenting with suspected ACS. In regard to ACS management, glycoprotein IIb/IIIA inhibitors, low-molecular-weight heparin, and an early invasive strategy may have a better effect for troponin-positive patients than for troponin-

negative patients. Patients with CKD also have a worse prognosis when presenting with ACS compared with non-CKD patients.[38] Furthermore, many RCTs that tested therapeutic agents for ACS management excluded patients with advanced CKD.

Unfortunately, since elevated cardiac biomarkers are such an integral component of the diagnosis and risk-assessment in ACS, it is difficult to study this question in an evidence-based way. It may not be ethical to randomize or withhold therapy based on troponin values alone, as ACS treatment algorithms depend on a whole host of clinical factors and timing of presentation.

As was anticipated, we did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., no studies randomized patients to any management strategy by troponin levels). Therefore we cannot draw conclusions to directly answer this question. We recommend further study in this area, such as carefully-designed post hoc analyses of clinical trials testing ACS management strategies, comparing gradations of troponin elevation across treatment groups with a highlighted focus on CKD patients.

KQ 3: Do Troponin Levels Facilitate Short- and Long-Term Prognosis in Patients With Chronic Kidney Disease Presenting With Suspected Acute Coronary Syndrome?

As described in the background section, studies have examined elevated troponin as an independent predictor of morbidity and mortality in populations following an acute ischemic event but data is limited in CKD.

Overall, evidence is limited for the prognostic significance of elevated cardiac troponin with regard to short-term and long-term MACE, as well as for the mortality of patients with both CKD and ACS. Our review lends support toward higher rates of MACE within 1 year in CKD patients with ACS who have elevated (vs. nonelevated) troponins for both troponin T and I, with more available evidence linking an association of troponin I with MACE within 1 year than for troponin T. Regarding the outcome of all-cause mortality following a suspected ACS event, we also found limited data for troponin T (two insignificant studies), but did find a generally positive association of troponin I with all-cause mortality. However, few studies met our inclusion criteria for KQ 3, and many studies were small and/or at risk of bias.

Overall, our findings suggest that elevated cardiac troponin (particularly troponin I) compared with nonelevated cardiac troponin, does appear to identify CKD patients who are at higher risk for subsequent MACE (following a presentation for ACS). However, all studies were observational in design. And no studies evaluated changes in management decision. Clinicians treat all patients with suspected ACS based on the guideline-recommended treatment for acute ACS interventions, and then prescribe subsequent secondary prevention management (antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, etc.). Thus, although elevated troponin can identify a CKD patient as being a higher prognostic risk, the available evidence does not indicate how to lower a patient's risk (based on elevated troponin), beyond usual guideline-directed therapy.

KQ 4: Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

Risk Prediction

The results from our systematic review found that in observational data, elevated troponin (defined by varying cutpoints across studies) strongly and fairly consistently identifies CKD patients at higher risk for subsequent adverse events, compared with patients with nonelevated troponin. Among dialysis patients without suspected ACS, a baseline elevated cardiac troponin is associated with a higher risk (~2-4 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (e.g., "composite" outcome of MI, cardiovascular death, and/or revascularization) in models adjusted at least for age and CAD or risk equivalent.

A substantial number of observational studies confirmed this association among patients on dialysis, and results were largely consistent (in terms of direction of a positive association). More of the studies included in the pooled meta-analyses reported outcomes for all-cause mortality than for other outcomes. Thus, the evidence from the pooled meta-analysis is strongest for the association of elevated cardiac troponin with all-cause mortality; an approximately 3-fold increased risk was found, which was highly significant. The evidence from meta-analyses for the association of elevated cardiac troponin with cardiovascular-specific mortality and MACE showed similar effect sizes but with wider confidence intervals due to fewer studies.

The association of elevated troponin with adverse outcomes among dialysis patients was generally similar for troponin T versus I. Few studies reported results for high-sensitivity troponin T and I assays, so less is known about how well these assays predict risk. Studies that used a sensitive assay identified more patients as having elevated troponin.

While almost all studies of dialysis patients supported a positive association for elevated cardiac troponin with adverse cardiovascular outcomes (particularly mortality), we noted heterogeneity in several of the pooled meta-analyses results (as defined by the I-squared statistic >50%), even though we analyzed troponin T and I separately. We performed sensitivity analyses, such as only including studies that adjusted for age or age and CAD, but we were unable to eliminate all of the heterogeneity in the meta-analyses. Generally, the direction of association was similar (indicating increased risk for elevated troponin levels), but the magnitude of risk varied substantially across studies.

Previous to our report, Khan et al. published the largest meta-analysis of the use of cardiac troponin for risk prediction among dialysis patients in 2005.[23] The authors reviewed studies through December 2004, and found 17 studies evaluating troponin T for all-cause mortality (pooled relative risk 2.6; 95% confidence interval, 2.2 to 3.2, also with high heterogeneity). Of note, this pooled meta-analysis used a relatively high troponin T cutpoint of >0.1 mcg/L, almost 10-fold higher than the lower limit of detection. They found 12 studies for troponin I for all-cause mortality (pooled relative risk, 1.7; 95% confidence interval, 1.3 to 2.4). Many of the individual studies identified for troponin I were not statistically significant, but their pooled relative risk was significant.

We have now updated the literature by performing a comprehensive review through May 2014. We found 43 studies for troponin T and 30 studies for troponin I for all-cause mortality. We were able to perform meta-analyses for both HRs (time to event) and ORs (relative risk) as available, whereas Khan et al. only performed relative risk analyses. We used all cut-points available in literature (and did not limit studies to troponin T >0.1 mcg/L as per Khan's study). We stratified results by levels of covariate adjustment. In our meta-analyses, we found similar (if

not stronger) effect sizes for both troponin T and I with all-cause mortality compared with the previous results by Khan et al. We similarly noted heterogeneity across studies. We also performed meta-analyses for the other outcomes of cardiovascular-specific mortality and MACE.

Researchers have previously questioned troponin I as not being an important prognostic marker for risk prediction among dialysis patients given null results from several of the individual studies. However, the results from our meta-analyses do not clearly support this conclusion, as our pooled results showed a similarly strong association.. Differences may be due to more heterogeneity of the troponin I assays (multiple manufacturers) compared with troponin T (largely handled by one manufacturer).

We can conclude that both elevated troponin T levels and troponin I levels, are both strongly associated with increased risk of mortality among dialysis patients (strength of evidence: moderate). Therefore, elevated baseline troponin among CKD and dialysis patients is not "spurious" but portends a worse prognosis. Of note, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). The findings of our updated review lend continuing support for this recommendation for risk prediction. However, how to manage patients based on the results from risk prediction (i.e., whether dialysis patients with elevated troponin should be treated differently than dialysis patients with nonelevated level beyond usual clinical risk-factor guided care), remains an important clinical question that this review did not answer.

Troponin Testing Versus Clinical Risk Markers

Almost all of the studies found by our review determined the "prognostic" value of troponin by its associations with outcomes in regression models. However, while one must critically examine the utility of a biomarker for "prediction," the more clinically relevant question is how the marker stacks up in metrics of discrimination and re-classification. Discrimination (which is most often measured by the area under the curve [AUC] of a receiver operating characteristics [ROC]) is a measure of how well a model can distinguish those who and who do not have the disease of interest. Net reclassification index (NRI) is a newer statistical measure that quantifies the number of people correctly reclassified to higher and lower risk categories. We found very few studies that used AUC results and no studies that used NRI.

The meta-analyses performed for the pooled ORs were unadjusted results using number of events in each arm. For the meta-analyses for HRs, we selected the most-adjusted regression model. However, many studies only reported an unadjusted HR. While many studies adjusted for age, fewer studies adjusted for a history of CAD or CAD risk equivalent, such as diabetes mellitus, or adjusted for other cause of elevated troponin, such as heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors, such as systolic blood pressure, dyslipidemia, and smoking. Therefore, elevated troponin levels may simply be a surrogate marker of someone with underlying CAD (i.e., a person already known to be at predicted higher risk). The studies presenting adjusted HRs did generally show a positive association of elevated troponin levels with adverse outcomes even in progressively adjusted models, but because this was not generally assessed by more rigorous methods of discrimination and reclassification, it is hard to have confidence in the results.

The most robust evidence after adjustment for clinical factors was for the association of elevated troponin T and all-cause mortality among dialysis patients (strength of evidence: moderate). Of 21 studies available for HR analyses, 6 were unadjusted, 15 adjusted at least for

age, and 11 adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes. For the HR analyses for troponin I, all of these studies at least adjusted for age, and six out of nine additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, and diabetes). These studies predominantly used traditional regression models to show that the associations persisted after adjustment for clinical factors, but most did not use a more rigorous method of comparing C-statistics (area under the curve) against clinical models.

Havekes et al.[39] was one of the largest studies (847 dialysis patients) to rigorously examine whether troponin testing adds incremental prognosis over routine clinical factors. While a troponin T level greater than 0.1 mcg/L was a potent predictor of mortality in their study (adjusted HR, 2.2; 95% confidence interval, 1.5 to 3.3), it did not improve prediction over clinical factors. A survival model with clinical factors and routine laboratory markers predicted mortality with an area under the curve of 0.81, but adding troponin T to this model did not change this estimate. The area under the curve for predicting mortality for troponin T alone was 0.67. This data suggests that the troponin T biomarker is a potent predictor of mortality on its own, however, it may have little prognostic utility over clinical factors when more rigorously assessed (i.e., change in the C-statistic). We did not find any studies that evaluated a NRI for troponin in CKD patients without ACS.

Thus, whether measuring this biomarker of cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables is still uncertain.

Management of Nonacute Coronary Syndrome Patients Based on Troponin Testing

The National Kidney Foundation already endorses that all patients with CKD should be considered in the "highest risk" group for cardiovascular disease risk prediction, irrespective of levels of traditional cardiovascular risk factors (i.e., that CKD should be considered a CAD risk equivalent).[40] Therefore, if patients with CKD are already candidates for intensive management of their cardiovascular risk factors for prevention, what, if any, is the additive role of measuring troponin?

All of the studies we found that related to KQ 4 were observational cohort studies. We did not find any intervention studies that compared management strategies of dialysis patients (without suspected ACS) on the basis of elevated troponin. Thus, while elevated cardiac troponin is clearly a marker of a patient at increased risk for subsequent cardiac events, it is unknown whether changing or altering patient management (such as implementing more intensified preventive efforts) on the basis of elevated troponin can reduce/prevent cardiovascular events and mortality. This is even a greater concern with the introduction of high-sensitivity assays, as more patients are labeled as having elevated troponin.

In the absence of MI, there are no specific interventions recommended to reduce cardiovascular disease risk in patients with CKD based solely on elevated troponin. Therefore the role of screening asymptomatic individuals, or how to use the prognostic information from the results in a way that affects patient management and outcomes is not clear.

KQs 1-4: Heterogeneity With Assays Platforms, Cutpoints, and 99th Percentile Considerations

Much heterogeneity across results for KQs 1–4 stemmed from differences between studies in the types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing over time, and newer generations of assays can detect lower and lower concentrations of cardiac troponin. Many of the papers did not report which generation of assay they used; and this was a significant limitation of our analyses. For troponin T, there was generally only one manufacturer (Roche, or Boehringer Mannheim which was acquired by Roche Diagnostics in 1997). However, there were multiple manufacturers of the troponin I assay. The studies were also heterogeneous regarding what cutpoints they considered elevated. Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold also changed depending on the reference population and assay generation that the study used. The reference populations for the 99th percentiles were largely unclear, and were most likely not from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported with the lowest for consistency. All of our findings in this systematic review must be interpreted with this important caveat in mind.

The European Society of Cardiology/American College of Cardiology guidelines support a 99th percentile cutpoint, and studies that have used the 99th percentile cutpoint did confirm its utility in predicting risk. However, most studies presented results using higher cutpoints. For example, the Roche Elecsys assay lists a 99th percentile of 0.014 mcg/L, but most studies presented the 0.1 mcg/L cutpoint, which is 10-fold higher. A current list (as of 2012) of the 99th percentile for commercial and research assays is on the Web site for the International Federation of Clinical Chemistry and Laboratory Medicine (see http://www.ifcc.org/ifcc-scientific-division/documents-of-the-sd/troponinassayanalyticalcharacteristics2012/).

Applicability

Chronic Kidney Disease Stages

We found the largest body of evidence relating to dialysis patients without suspected ACS. Whereas these findings are most likely generalizable to the typical cohort of dialysis patients treated in clinical practice, these findings cannot necessarily be extrapolated to other stages of CKD I-IV. We did find limited data for nondialysis patients with CKD with strength of evidence ranging from low to moderate, suggesting a positive association for all-cause mortality, but results were not stratified by CKD stages.

Other Subgroups

We found limited data regarding subgroups classified by gender, history of CAD, and pre-or post-renal transplantation, but data were insufficient to generate pooled meta-analyses results by these subgroups or to make conclusive statements about generalizability to apply findings across these select groups. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Subgroups described were as follows: persistently elevated troponin levels (one study), history of CAD (four studies), gender (two studies), pro-brain natriuretic peptide levels (one study), diabetes (one study), hypotension-prone (one study), and hemodialysis versus peritoneal dialysis (one study). We did not find any data in regard to subgroups of ECG changes or 10-year CAD risk status.

Limitations

We identified over 6,000 titles on this topic, narrowing it down to 130 publications that met our inclusion criteria. All of these studies were observational in design and have at least a moderate risk of bias due to known confounding associations. Patients with elevated troponin levels are more likely to have underlying CAD, heart failure, or comorbidities that place them at higher risk of mortality. As described further in the above sections, we were limited by the fact that most studies were either unadjusted or minimally adjusted for other risk factors. Studies determined the use of troponin for "prognosis" by its association with outcomes in regression models, which is not the most clinically useful way to evaluate a biomarker. None of the studies evaluated the utility of troponin as a predictor by metrics of net reclassification index (i.e., its ability to re-classify patients into higher or lower risk groups). Only one study compared discrimination against a model of clinical factors.

As described above, studies were very heterogeneous in the assays (particularly for troponin I), troponin cutpoints, and definitions of ACS they used. This limited our ability to pool data and perform meta-analyses. Many studies failed to report any rigorous adjudication for ACS diagnosis. Therefore, without a "gold standard" outcome to gauge troponin testing, we were limited in our ability to draw conclusions about the operating characteristics of the troponin biomarker for diagnosing ACS in CKD patients.

Our inclusion criteria deliberately selected only studies that reported clinical outcomes. This is because evidence-based guidelines are largely directed by studies with clinical outcomes, as there are many examples where findings in surrogate outcome studies do not translate into clinical benefits. Thus we did not evaluate elevated troponin with any surrogate markers (echocardiography, stress testing, left ventricular hypertrophy, etc.), only hard clinical outcomes. Therefore, our review is unable to explore potential mediating mechanisms for the associations presented, for which therapeutic strategies could be devised.

We did not explore the prevalence of elevated baseline troponin across all potential studies, but only for studies that also reported hard outcomes (i.e., we did not include cross-sectional studies). Thus, our assessment of the prevalence of elevated baseline troponin may be incomplete (KQ 4.1).

We only reviewed studies that included results for patients with CKD by troponin levels. To keep the scope of our review specific to the topic at hand, we did not review all studies relevant to troponin testing and did not report results for general populations that did not specifically stratify by CKD subgroups. As further described above, 99th percentiles for troponin vary across study populations as well as pre-test probabilities for ACS; this makes indirect comparisons across studies very problematic. Therefore, we were unable to make any indirect comparisons of our results to non-CKD patients. There were no studies that directly compared troponin testing for non-CKD and CKD in the same population.

Research Gaps

Issues Related to Troponin Assays (KQs 1-4)

Need for Harmonization

Standardization of the troponin assays (particularly troponin I, where assays vary between numerous manufacturers), would facilitate interpretation across future studies. This is currently one of the goals of the International Federation of Clinical Chemistry Working Group on

Standardization of Cardiac Troponin I. This goal is challenging given the complexity of troponin I (multiple isoforms), and that the antibodies used in the various immunoassays recognize different epitopes with variable reactivity.[41] In spite of these challenges, the need for harmonization, so that results can be compared across studies, is paramount. This need is only further emphasized by our review.

Need to Rigorously Standardize and Test the 99th Percentile

As further described above, we need to standardize the 99th percentile threshold in a unifying reference population. While universal guidelines have endorsed the 99th percentile threshold, studies are still being published using higher cutpoints, sometimes 10-fold higher. Thus, we need more studies that actually test the 99th percentile cutpoint for diagnosis and prognosis. Future studies should focus on using guideline-established cutpoints for consistency in the literature and relevance to clinical practice.

Timing of Measurement

Some studies involving only dialysis patients imply that the timing of troponin measurement (before vs. after a dialysis session) may be important. If clinicians are going to use troponin for risk stratification, studies recommend that troponin be measured prior to dialysis as dialysis can affect cardiac troponin levels. This review did not consider this, and it may be a research gap.

Diagnosis of Acute Coronary Syndrome (KQ 1)

Future work should seek to compare the operating characteristics of troponin T and I as an a priori objective of a well-designed series of studies using standardized assays and cutoffs. These studies should consider, in their design, testing the use of troponin among different subgroups of patients with CKD (such as stages 1 to 5) among which the operating characteristics of a troponin assay for ACS diagnosis might vary. Therapeutic options and likelihood of impact on outcomes may vary across stages of CKD. Studies also need to include a direct comparison to non-CKD patients to assess the assay head-to-head among the same reference population with the same pre-test probability. Furthermore, future studies should emphasize the pre-test probability of their population for suspected ACS using global risk assessment criteria in their reports, as the interpretation of troponin post-testing is largely driven by the pre-test probabilities.

The 20 percent rise/fall guideline (with at least one value above the 99th percentile) for acute MI diagnosis should be vetted against other potential diagnostic criteria such as single absolute thresholds or other delta of change in CKD patients.

Since RCTs are unlikely to be done, well-designed retrospective and post hoc analyses could potentially address this question. Such studies would provide highly useful information to clinicians as to the use of troponin assays in the real-world care of CKD patients.

Management of Acute Coronary Syndrome (KQ 2)

Whether the results from troponin testing for patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies remains uncertain. This is an area for potential further investigation. Since RCTs likely will never be done, future research should focus on post hoc analyses of pre-existing clinical trials of ACS management.

Prognosis After Acute Coronary Syndromes (KQ 3)

The articles included for this study focused mainly on troponin values measured at the time of ACS presentation. Baseline, or previous values, of troponin are largely unknown. Thus, there is limited data supporting that a change in troponin from baseline is associated or not associated with different prognosis for adverse cardiac events in CKD patients with ACS.

It is unclear from this review if major increases in troponin levels in CKD patients with ACS should carry more weight than minor increases, as the studies we identified generally evaluated above and below a diagnostic cutpoint (of modest elevation) and not gradations of more significant increases in troponin. However prior literature among general populations supports that a large increase of troponin (evidence of more myocardial damage) portends a worse prognosis.[2]

There are current guidelines already in existence for management of ACS.[20] Areas of future research should focus on management to reduce the risk of both short and long term events in CKD patients with suspected ACS who have elevated troponins. Future studies should address whether management in CKD patients is different than non-CKD patients with similar degrees of elevated troponins. And if more elevated troponin levels in ACS are associated with worse outcomes, should these patients be managed differently (i.e., subjected to different medications and interventions) than CKD patients with ACS who have absent or lower degrees of troponin elevation? A prognostic biomarker by itself is insufficient without guidance of how to use this biomarker to guide or alter therapy.

Risk Prediction in Non-Acute Coronary Syndrome Chronic Kidney Disease Patients (KQ 4)

What is the Pathophysiological Mechanism for the Association?

Elevated cardiac troponin levels indicate that a patient is at higher risk for adverse outcomes, particularly all-cause mortality among patients without suspected ACS. Cardiovascular mortality and MACE were also higher in patients with elevated troponin. But what is the precise cause of death? Is elevated cardiac troponin simply a marker of underlying CAD or a marker of silent ischemia? Are patients dying from MIs, heart failure, arrhythmias, or other causes? Once we clearly define the cause of death associated with elevated troponin, we can test and implement potential interventional strategies.

Need To Compare Troponin Testing Against Conventional Risk Prediction/Clinical Factors

As described above, a CKD patient with elevated troponin is at higher risk of adverse outcomes (the evidence being strongest for dialysis patients). It is less clear whether troponin testing offers incremental prognostic value over assessing risk based on clinical factors alone. Any future studies published on this topic should vigorously test troponin against other clinical models (i.e., whether troponin testing changes the area under the curve compared with other traditional clinical and laboratory risk markers). Studies should focus on metrics of net reclassification to determine whether this biomarker can appropriately re-classify CKD patients into higher and lower risk groups.

Need for Guidance for Management—Next Step Beyond Risk Prediction

Once a patient is identified at higher risk on the basis of an elevated serum troponin level, what is the next step? Should cardiac troponin testing include other diagnostic tests, such as stress testing or echocardiography? Should clinicians prescribe additional preventive medications such as aspirin, statins, or beta-blockers to CKD patients with elevated troponin levels? Many patients may already have indications for these therapies; what additional treatment should clinicians prescribe in these cases?

The next area of investigation should be large-scale clinical trials or carefully designed post hoc analyses to determine the next steps in therapeutic intervention and clinical management.

Conclusion

In summary, we conclude that even relatively minor elevations of cardiac troponin are associated with a worse prognosis for patients with and without suspected ACS. In particular, for dialysis patients without suspected ACS, increased troponin T or I is a potent predictor of subsequent mortality. However, whether elevated troponin provides incremental prognostic value over and above carefully assessed clinical risk factors for CAD and mortality, is not conclusive.

Regarding troponin testing, until there is harmonization and standardization of the troponin assay (similar to other laboratory markers), comparison of results from study to study and from population to population remains problematic.

Regarding patients with suspected ACS, troponin is already the gold standard for diagnosing MI and it is measured routinely in patients with suspected ACS. Established guidelines for ACS diagnosis and management are already in existence for the general population based on pre-test probability based on symptoms, ECG changes, and clinical factors.

Our findings do not dispute the utility of troponin for diagnosis or prognosis among CKD patients, with findings generally similar to studies reported for general populations of patients (indirect comparison); however we found very limited evidence for guiding disease management based on troponin levels alone.

Regarding CKD patients without suspected ACS, our findings support the current Food and Drug Administration and National Kidney Foundation recommendations that measuring troponin levels may be reasonable for additional risk stratification. Further work in this area should focus on improving our knowledge of the utility of this biomarker in regard to discrimination and the ability to appropriately reclassify CKD patients into higher and lower risk groups. However, unless we can identify the next steps regarding how best to manage these patients with elevated troponin levels (how and if treatments would vary from those treatments indicated by clinical factors alone), the applicability of this screening recommendation is incomplete. Thus it is difficult to endorse the routine risk stratification measurement of cardiac troponin in clinical practice because of the uncertainty regarding appropriate clinical strategies that may use this information. New research should focus on testing patient management strategies that incorporate measuring this biomarker in their prevention algorithms.

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Background

Cardiac Troponin Assays

Troponin Detection in Normal and Disease States

Troponin is a protein complex of three subunits (T, I, and C) that's involved in the contractile process of skeletal and cardiac muscle. Both cardiac and skeletal muscle express troponin C; whereas troponin T and I are generally thought to be cardiac-specific. (However, a recent study has challenged whether troponin T is exclusively cardiac-specific.[1]) Blood from healthy individuals with no evidence of cardiac disease contains very low amounts of cardiac troponin.[2] Some of the newer high-sensitivity assays may be able to measure troponin in normal individuals; although many of the commercially available assays cannot detect troponin at all or cannot quantify it at levels below the measuring range of the assay.

When cardiac injury occurs (from ischemia or various other causes), cardiomyocytes release cardiac troponin into the blood in proportion to the degree of damage.[3] Troponin levels increase within 3 to 4 hours after the onset of damage and remain high for up to 4 to 7 days (troponin I) or 10 to 14 days (troponin T).

Clinically, the most important use of troponin testing is to detect elevated troponin levels so as to identify patients suspected of having an acute coronary syndrome (ACS). ACS is defined as a spectrum of conditions caused by insufficient supply of oxygen to the myocardium by the coronary arteries. However, elevated cardiac troponin levels are not specific for the diagnosis of ACS or acute spontaneous myocardial infarction (MI) [type 1 MI]. Individuals with non-ACS conditions can also have elevated cardiac troponin.[4] Non-ACS conditions can include noncoronary causes (e.g., sepsis, congestive heart failure, myocarditis, drug toxicity, pulmonary embolism, hypoxia, and global hypoperfusion) and coronary causes from ischemic imbalance [i.e., increased demand in the setting of stable coronary artery disease (CAD) lesions] classified as type 2 MI. Many symptoms associated with non-ACS conditions may overlap with symptoms of ACS (e.g., chest pain or dyspnea). This presents a diagnostic dilemma to the clinician and often requires an extended evaluation before the clinician can make an accurate diagnosis.

The 99th Percentile Cutpoint—Challenges

Because we can detect troponin even among presumably healthy adults, we must set guidelines regarding what is considered an "elevated" level. The joint European Society of Cardiology/American College of Cardiology guidelines define a clinically relevant increase in troponin levels as a level that exceeds the 99th percentile of a normal reference population.[5] However, we must interpret elevated troponin levels in the context of a intermediate to high pre-test probability of suspected ACS.[6]

Currently, there is no universally adopted 99th percentile value because there is no reference standard for detecting either troponin T or I, as each test manufacturer independently develops its own assays. Additionally, no consensus exists on how to define a reference population for the assays (in terms of age, gender, race/ethnicity, comorbidities, or number of participants), and many of the 99th percentile values come from diverse and poorly defined study participants.[7] When studies compare troponin T and I assays in the same population, assays can differ regarding troponin concentrations at the 99th percentile by as much as five-fold. Recommendations call for cardiac troponin assays to have a coefficient of variation less than or

equal to 10 percent at the 99th percentile cutpoint. However, many current assays have a coefficient of variation between 10 and 20 percent at the 99th percentile.[8]

High-Sensitivity Troponin Assays

Troponin assays have evolved over time, becoming ever more sensitive with detection limits 10 to 100 times lower than currently available commercial troponin assays. This also challenges the precision guidelines for acceptable coefficient of variation.[9] For example, a contemporary sensitive cardiac troponin I (such as TnI-Ultra) can detect concentrations as low as 0.006 mcg/L, and the high-sensitive cardiac troponin T assay (Roche, approved in Europe but not the United States) can detect as low as 0.005 mcg/L.[6] Manufacturers are continuing to develop new generations of high-sensitivity assays that are more precise at even lower concentrations, such as less than 1 ng/L (0.001 mcg/L).

Thus, the high-sensitivity assays detect measurable troponin levels in a larger percentage of presumably healthy people—redefining what is "normal".[7] For patients with suspected ACS, this means potentially earlier detection for the diagnosis of ACS which may aid management in emergency room departments. On the other hand, this increased sensitivity comes at a cost of reduced specificity for ACS. High-sensitivity assays may also aid in our ability to detect increases in cardiac troponin, which will help distinguish patients with acute disease from more chronic disease—where levels, while elevated, are more static.

With constantly evolving and newer assays, there is a need to define how these new high-sensitivity assays compare with contemporary and older generations of troponin assays. In 2009, Apple et al. proposed a "scorecard" based on imprecisions (coefficient of variation percent) of each assay at the 99th percentile and how many samples from normal individuals are measurable below the 99th percentile.[8]

Troponin Elevation in Chronic Kidney Disease

Given that the prevalence of chronic kidney disease (CKD) in the United States reached 15 percent in 2008, how to interpret troponin levels in this population is an important issue.[10, 11] We listed a description of the stages of CKD in Table 1. Of note, even more recently, there are new guidelines for classifying CKD that incorporate albuminuria: http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf

Table 1. Stages of chronic kidney disease

Stage	Description	GFR, mL/min/ 1.73 m2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 or dialysis

GFR = glomerular filtration rate; mL/min/1.73 m2 = milliliters per minute for 1.73 meters squared

Patients with CKD (particularly those with end-stage renal disease [ESRD]) have a greater prevalence of persistently-elevated cardiac troponin when compared with patients who do not have CKD. Although somewhat controversial, reduced renal clearance most likely is not the primary mechanism for troponin elevation in CKD, but rather it represents a marker of myocardial injury.[12, 13] The intact troponin molecule is large and it is unlikely that the kidneys are primarily responsible for clearance from serum. However, work by Diris et al. suggests that the troponin molecule is degraded into smaller fragments, which can be detected by the assays

and are small enough to be filtered by the kidneys. This mechanism may contribute to the elevation of troponin in severe renal failure.[14] Despite this, Ellis et al.[15] did not observe a statistically significant difference in the half-life and the elimination rate constant of troponin I in patients with myocardial infarction (MI) and ESRD when compared with patients with MI and normal kidney function.

As with non-CKD patients, we must interpret elevated troponin levels in patients with CKD in the context of one's pre-test probability for suspecting an ACS event. Elevated levels may also be due to cardiac injury associated with chronic structural heart disease (e.g., CAD, heart failure, etc.), which is highly prevalent among CKD patients, rather than from acute ischemia, especially when the levels do not change rapidly over time.[16] Among patients without suspected ACS, potential reasons for detectable small increases in troponin include micro-infarctions, microvascular disease, subendocardial ischemia associated with left ventricular hypertrophy and diastolic dysfunction, and nonischemic cardiomyopathic processes, all of which are more common in patients with CKD.

Use of Troponin for the Diagnosis of Acute Coronary Syndrome in Patients With Chronic Kidney Disease (Background for Key Question 1)

In patients with symptoms of ACS, without other causes for increased troponin, clinicians use elevated troponin levels (along with clinical factors) to diagnosis MI as outlined by the Global Task Force's Third Universal Definition of MI (Table 2).[17]

Table 2. Definition of myocardial infarction according to 2012 Third Universal Definition

Both are required for a diagnosis of myocardial infarction: (3) Rise and/or fall of troponin (or another cardiac biomarker) with at least one value above the 99th percentile reference limit (4) Evidence of myocardial ischemia from symptoms, electrocardiogram, or cardiac imaging

The diagnosis of ACS among patients with CKD (especially those with ESRD) can be particularly challenging. Electrocardiograms (ECGs) are frequently abnormal in CKD patients (indicating left ventricular hypertrophy, intraventricular conduction delay, wide QRS, etc.), which can reduce the sensitivity/specificity of detecting ischemia.[18] Also, baseline troponin levels are often not known in patients with CKD on initial presentation, making it hard to define elevated troponin levels (increased troponin is considered, along with symptoms and other clinical factors, in diagnosing ACS, as per the global definition of MI). Whether clinicians should use an alternative threshold, other than the 99th percentile, of elevated cardiac troponin when assessing patients with CKD is unknown. Since not all CKD patients will have elevated levels, high cut-off values will disadvantage those who do not have elevated levels. Therefore, using alternate cutpoints may not be preferable.

On the other hand, the patterns of changes in troponin levels (rise, fall, and magnitude of change) can also be very helpful for clinicians in distinguishing ACS from non-ACS in symptomatic patients. The National Academy of Clinical Biochemistry[19] has recommended that for patients with ESRD and suspected ACS, a diagnosis of acute MI (Type I) should require a dynamic change in troponin levels of greater than 20 percent within 9 hours (with at least one value above the 99th percentile).[13] However, clinicians should also consider the timing of presentation from the onset of symptoms. If the patient presents late in the course of ACS, testing could take place during the "plateau phase," and clinicians may miss the rise/fall pattern.

Although widely applied in the guidelines, researchers have not yet studied this 20 percent rule in a vigorous evidence-based fashion and compared it with other degrees of change or the use of a single elevated value in the context of high pre-test probability.

No consensus exists about whether the diagnostic criteria for MI using troponin levels should be different for patients with CKD and those without CKD. It's also unclear whether elevated baseline troponin levels make it more difficult to diagnose ACS in patients with ESRD than in patients with milder forms of CKD.

The following clinical vignette highlights some of the clinical diagnostic dilemmas: The patient is a 68-year-old man with a history of diabetes and CAD who has had remote coronary artery bypass surgery. He has CKD (creatinine 1.8 mg/dL) and previously had a troponin I level of 0.06 mcg/L on his last admission. He is admitted to the hospital with pneumonia but repeated tests of troponin indicate a level of 0.24 mcg/L. He is short of breath but has no chest pain and his ECG shows a left bundle branch block (old). What is the clinical significance of his newly elevated troponin? Should he additionally be managed for ACS?

Use of Troponin Level as a Management Strategy for Patients With Chronic Kidney Disease and Acute Coronary Syndrome (Background for Key Question 2)

Frequently, clinicians use troponin levels, along with clinical factors, to stratify patients according to risk when a diagnosis of non-ST-elevation MI (NSTEMI)/unstable angina is likely. Clinicians usually treat patients at high risk for ACS with an "early invasive" strategy (i.e., diagnostic angiography with the intent of revascularization), while clinicians may treat patients with low-to-intermediate risk of ACS with an "initially conservative" (i.e., selectively invasive) management strategy.[20]

The "troponin hypothesis" suggests that patients with elevated troponin levels (troponin-positive) are likely to have more thrombus burden, complex lesions, and be at higher risk for worse outcomes than patients with normal troponin levels (troponin-negative). Therefore, it stands to reason that clinicians should treat troponin-positive patients more aggressively. Results from a general population of patients presenting with ACS (not exclusively CKD), found that even minor troponin elevations identify patients who benefit from an early invasive strategy (compared with initially conservative management).[21] In addition to an early invasive strategy, the use of glycoprotein IIb/IIIa inhibitors and low-molecular-weight heparin also appear more beneficial in troponin-positive versus troponin-negative patients with suspected ACS.[13] However, in the Clopidogrel in Unstable Angina to prevent Recurrent Events (CURE) clinical trial of ACS patients, clopidogrel use did not confer a preferential benefit in troponin-positive versus troponin-negative patients. Therefore, the troponin hypothesis may not be applicable to all therapeutic management in ACS.

As with the initial diagnosis of ACS, elevated background troponin levels in patients with CKD may limit the applicability of treatment algorithms that are based on troponin levels in non-CKD populations. Whether elevated background troponin levels in patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies is unknown.

Use of Troponin Level as a Prognostic Indicator in Patients With Chronic Kidney Disease Following Acute Coronary Syndrome (Background for Key Question 3)

In addition to their use in diagnosing and managing ACS, studies have examined troponin assays as potential independent risk predictors of morbidity and mortality in populations following an acute ischemic event. Previous reviews and meta-analyses have investigated the prognostic performance of troponin testing in patients with kidney failure, but often excluded studies on patients with ACS.[22, 23] Therefore, the prognostic significance of elevated cardiac troponin levels with regard to short- and long-term major adverse cardiovascular events (MACE) for patients with both CKD and ACS remains uncertain.

Use of Troponins in Adults With Chronic Kidney Disease Who Do Not Have Symptoms of Acute Coronary Syndrome: A Role for Risk Stratification (Background for Key Question 4)

Patients with CKD are known to be at increased risk for cardiovascular morbidity and mortality. Despite established guidelines for primary and secondary cardiovascular disease prevention (i.e., blood pressure, lipid, and glucose targets), cardiovascular disease remains the number one cause of death for CKD patients. Among asymptomatic CKD patients without suspected ACS, prior studies have shown that chronic elevated cardiac troponin is associated with increased risk of cardiovascular morbidity and mortality.[23-26] For this reason, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). However, it is unknown whether measuring troponins improves risk prediction when compared with (or used in conjunction with) existing models that are based on traditional clinical and laboratory risk factors. Whether troponin testing improves metrics of discrimination and re-classification of patients into higher or lower risk groups is unknown.

It is also unclear whether clinicians should manage asymptomatic patients with CKD and chronically-elevated cardiac troponin levels differently than patients with CKD who have normal troponin levels.

Types of Troponin Assays and Special Subgroups of Patients With Chronic Kidney Disease (Key Questions 1–4)

There are multiple commercially available troponin assays including cardiac troponin T, troponin I, high-sensitivity troponin T, and high-sensitivity troponin I. Whether all of these troponin assays are equal in distinguishing ACS from non-ACS conditions and prognosticating and risk-stratifying CKD patients (with and without ACS) is unclear.

Furthermore, whether troponin testing leads to changes in management and outcomes among certain subgroups of patients with CKD is also unknown (e.g., categories of CKD stages, dialysis status, age, race, gender, and those with prior history of CAD).

Scope and Key Questions

The purpose of this comparative effectiveness review will be to present information for the appropriate use of troponin levels to guide evidence-based management decisions for patients with CKD. These findings should be useful for a diverse set of contingents including cardiologists, nephrologists, emergency room physicians, and laboratory medicine scientists who use and interpret troponin testing in the clinical management of patients. Findings may also be useful for epidemiologists in tackling research gaps for further studies. We addressed the following Key Questions (KQs) in this review (Figures 1 and 2):

KQ 1: Diagnosis of ACS

What is the diagnostic performance of a troponin elevation (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) >99th percentile (compared to no elevation) for the detection of ACS in adult patients with CKD (including those with ESRD)?

1.1 What are the operating characteristics of a troponin elevation (compared with no elevation) in distinguishing between ACS and non-ACS, including sensitivity, specificity, and positive and negative predictive values?

1.1a How do the positive predictive value and the negative predictive value vary with the population's pre-test probability for ACS?

1.1b Does a significant delta of change (such as greater than 20 percent within 9 hours) better discriminate between ACS and non-ACS compared with a single troponin elevation?

1.2 What are the operating characteristics of troponin elevation for distinguishing ACS from non-ACS among the following subgroups?

1.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD.

1.3 What are the harms associated with a false-positive diagnosis of ACS based on an elevated troponin level?

1.4 Among studies that <u>directly</u> compared one type of troponin assay (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, do the operating characteristics of a certain type of troponin test perform better for diagnosis of ACS?

1.5 Among studies that directly compared troponin testing in patients with CKD versus patients with normal renal function, do the operating characteristics of a troponin elevation perform similarly?

KQ 2: Management in ACS

In adults with CKD (including ESRD), do troponin levels improve management of ACS?

2.1 Does a troponin elevation modify the comparative effectiveness of interventions or management strategies for ACS (e.g., is an aggressive strategy better than a initially conservative strategy for high troponin levels, but not for low/normal troponin levels)?

2.2 Among adults with CKD with suspected ACS, how does a troponin elevation change the effects of interventions or management strategies according to the following characteristics?

2.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

KQ 3: Prognosis in ACS

In adult patients with CKD (including those with ESRD) and suspected ACS, does an elevated troponin level help to estimate prognosis?

3.1 Do troponin results relate to:

3.1a Long-term outcomes (all-cause mortality and major adverse cardiovascular events [MACE] such as subsequent MI, stroke or cardiovascular death, over at least 1 year of followup)?

3.1b Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of followup)?

3.2 Does a troponin elevation help to estimate prognosis after ACS in the following subgroups?

3.2a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD), dialysis status (for ESRD), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

3.3 Among studies that directly compared one type of troponin assay (troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I) against another type of troponin assay, does a certain type of troponin test estimate prognosis better after ACS?

KQ 4: Risk Stratification in non-ACS

Does an elevated troponin level (compared with no elevation) help with risk stratification in adults with CKD (including those with ESRD) who do not have symptoms of ACS?

4.1 In clinically stable adults with CKD (including those with ESRD) who do not have symptoms of ACS, what is the distribution of troponin values?

4.1a What is the distribution by CKD stages I-IV and in ESRD?

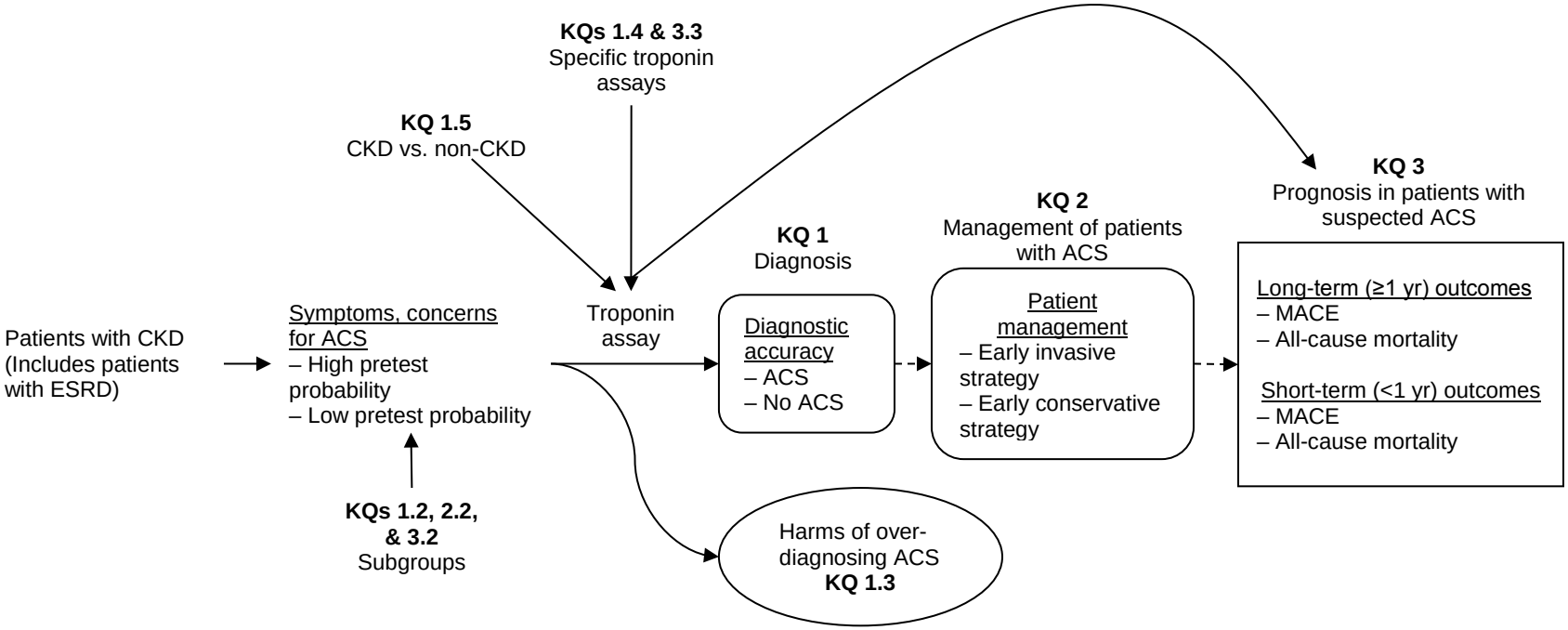
4.2 Do troponin threshold levels or patterns of troponin change in this population improve prediction for MACE or all-cause mortality, compared with or supplementing existing models?

4.3 Does troponin elevation improve CHD risk prediction for the following subgroups:

4.3a Gender, age, ethnicity, stage of kidney disease (CKD stages I-IV or ESRD on dialysis), status post-renal transplant, presence of baseline or prior elevated troponins, presence of ischemic ECG changes, comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD predicted risk, or history of CAD

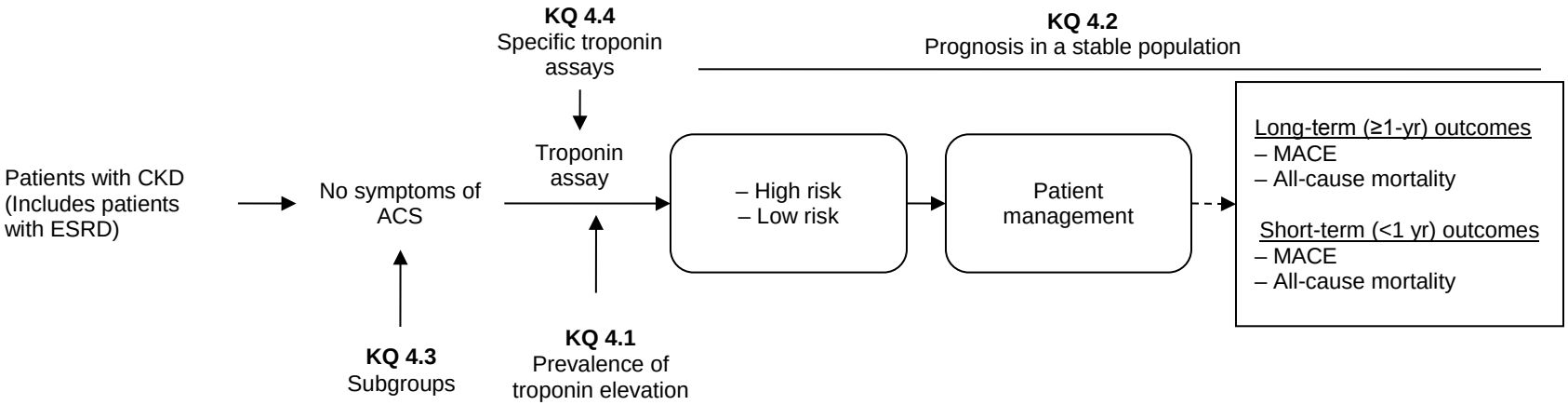
4.4 Among studies that directly compared one type of troponin assay (troponin I, troponin T, hs troponin T, or hs troponin I) against another type of troponin assay, does a certain type of troponin test predict risk better?

Figure 1. Analytic framework for interpreting troponin as a cardiac marker among patients with chronic kidney disease and suspected acute coronary syndrome



Abbreviations: ACS = acute coronary syndrome; CKD = chronic kidney disease; ESRD = end-stage renal disease; KQ = key question; MACE = major adverse cardiovascular event

Figure 2. Analytic framework for interpreting troponin as a cardiac marker during renal function impairment among patients with chronic kidney disease without symptoms of acute coronary syndrome



Abbreviations: ACS = acute coronary syndrome; CKD = chronic kidney disease; ESRD = end-stage renal disease; KQ = key question; MACE = major adverse cardiovascular event

Methods

This topic was nominated via the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program's Web site. Our Evidence-based Practice Center established a team and a protocol to develop the evidence report. The project involved formulating and refining the questions, developing a protocol with input from selected technical experts, performing a comprehensive literature search, summarizing the state of the literature, constructing evidence tables, synthesizing the evidence, and submitting the report for peer review.

Topic Refinement

A panel of Key Informants was recruited to provide input on the selection and refinement of the questions to be examined. We posted our draft Key Questions (KQs) on the AHRQ Effective Health Care Program's Web site in March 2012 for public comment. With input from the Key Informants, representatives of AHRQ, and public comments, we developed the KQs that we presented in the Scope of Review and KQs section of the Introduction.

Technical Expert Panel

We recruited a Technical Expert Panel (TEP) to review a draft of the protocol for preparing this evidence report. The TEP included clinical chemists, cardiologists, nephrologists, emergency medicine physicians, and a representative from the Food and Drug Administration. The TEP reviewed our protocol and provided feedback on the proposed methods for addressing the KQs. With the feedback from the TEP and AHRQ representatives, we finalized the protocol and posted it on AHRQ Effective Health Care Program's Web site (www.effectivehealthcare.ahrq.gov).

Search Strategy

We searched the following databases for primary studies: MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials from January 1990 through September 2013. We updated our MEDLINE search in May 2014. We developed a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text from key articles we identified a priori (Appendix A).

To identify additional studies, the Evidence-based Practice Center Program's Scientific Resource Center submitted requests to troponin assay manufacturers for any published or unpublished randomized controlled trials or observational studies.

Study Selection

Two independent reviewers conducted title scans. For a title to be eliminated at this level, both reviewers must indicate that the study was ineligible. If the reviewers disagreed, we advanced the article to the next level (Appendix B, Title Review Form).

We designed the abstract review phase to identify studies that could potentially report on the use of troponin levels to guide management decisions for patients with chronic kidney disease. Two investigators independently reviewed abstracts and excluded them if both investigators agreed that the article met one or more of the exclusion criteria (Appendix B, Abstract Review Form). At this phase, we excluded articles that (1) had no original data; (2) were conference

abstracts; (3) included only patients with normal renal function; (4) were a case report; (5) did not apply to the key questions; (6) did not include human adult subjects; and (7) were published prior to 1990. We excluded studies published prior to 1990 because troponin started to be used as a cardiac marker in the early 1990s. We tracked and resolved differences between investigators regarding the inclusion or exclusion of abstracts through consensus adjudication.

Two independent investigators reviewed articles that we promoted on the basis of the abstract review to determine if they should be included in the final systematic review. Two investigators independently reviewed articles and excluded them if both investigators agreed that the article met one or more of the exclusion criteria (Table 3 and Appendix B, Article Review Form). We tracked and resolved the differences regarding article inclusion through consensus adjudication. For articles that were not in English, we tried to find at least two people (either an investigator or a person with a medical or public health background) who was fluent in the language to review the article.

Table 3. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Population and condition of interest	• All studies included human subjects exclusively. • We included studies of adult patients with CKD including ESRD. o For KQs 1, 2, and 3, we included patients who also are clinically suspected of having ACS o For KQ 1.5, we only included patients with normal renal function if the studies made a direct comparison with CKD. o For KQ 4, we included patients who are clinically stable and asymptomatic for ACS.	
Interventions	• We included studies that evaluated troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I.	
Comparisons of interest	• We included studies that compared troponin elevation versus no elevation. • We included studies that *directly* compared different types of troponin assays with each other (KQs 1.4, 3.3, and 4.4). • We included studies that directly compared the utility of troponin elevation for diagnosing ACS in patients with or without CKD (KQ 1.5).	• We excluded studies that did not have a comparison group.
Outcomes	• For KQ 1, we included studies that evaluated sensitivity, specificity, and positive and negative predictive values compared with clinical diagnosis of ACS (adjudicated using strict criteria according to guidelines). • For KQ 2a, we included studies that evaluated differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds. • For KQs 3 and 4, we included studies that evaluated: o All-cause mortality o Cardiovascular mortality o MACE o Hospitalizations o Other major adverse events	

Table 3. Inclusion and exclusion criteria (continued)

	Inclusion criteria	Exclusion criteria
Type of study	• We included randomized controlled trials and observational studies with a comparison group. • We did not place any restrictions based on sample size or language.	• We excluded articles with no original data (reviews, editorials, and commentaries). • We excluded studies published before 1990 because troponin started being used a cardiac marker in the early 1990s.
Timing and setting	• We included studies regardless of the followup length. • We included all study settings.	

Abbreviations: ACS = acute coronary syndrome; CAD = coronary artery disease; CHD = coronary heart disease; CKD = chronic kidney disease; ECG = electrocardiogram; ESRD = end-stage renal disease; MACE = major adverse cardiovascular event

Data Abstraction

We used a systematic approach to extract all data to minimize the risk of bias in this process. We created standardized forms for data extraction (Appendix B, Study Design Form, Population Characteristics Form, Interventions Form, and Outcomes Form), which we pilot tested.

The study investigators double-reviewed each article for data abstraction. The second reviewer confirmed the first reviewer's abstracted data for completeness and accuracy. We formed reviewer pairs to include personnel with both clinical and methodological expertise. We did not mask reviewers to the authors of the articles, their respective institutions, nor the journals that published the articles.

For all articles, the reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, dialysis status, history of coronary artery disease (CAD), stage of kidney disease, glomerular filtration rates (GFR), and race/ethnicity), characteristics of the troponin assays (assay type, manufacturer, brand of assay, troponin cut-off level), outcome measures, definitions, and the results of each outcome, including measures of variability. For KQs 1, 2, and 3, we collected information on how the ACS outcome was defined in the studies. We collected data on prespecified subgroups of interest, including sex, age, ethnicity, stage of kidney disease, dialysis status, pre/post dialysis (in patients receiving dialysis), status after renal transplant, presence of baseline or previously elevated troponins, presence of ischemic ECG changes (for patients with clinically suspected ACS only), comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CAD risk, and history of CAD. We collected the number with elevated versus nonelevated troponin values and the number of events in each arm. If regression models were presented with various degrees of covariate adjustment, we abstracted results from the most-adjusted model.

The individual completing the review entered all information from the article review process into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada). Reviewers entered comments into the system whenever applicable. We used the DistillerSR database to maintain the data and to create detailed evidence tables and summary tables.

Quality Assessment

Two reviewers independently assessed study quality. We used the Downs and Black quality assessment tool to assess the quality of all included studies.[27] We supplemented this tool with additional quality assessment questions based on recommendations in the Methods Guide for

Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide).[28] Our quality assessment tool included items on the reporting, external validity, internal validity, power, and conflicts of interest (Appendix B, Study Quality Form). The reporting questions evaluated clear descriptions of the objectives, main outcomes, subject characteristics, tests of interest, distribution of principal confounders, main findings, estimates of random variability, characteristics of subjects lost to followup, and actual p-values. External validity questions assessed the representativeness of those asked to participate in the study, the representativeness of those willing to participate in the study, and the representativeness of the staff, places, and facilities. Internal validity questions assessed the blinding of the outcome assessors, a priori specification of the results, adjustment for different lengths of followup, appropriateness of the statistical tests, accuracy of the main outcome measures, selection of patients in the different intervention groups, adequate adjustment for confounding, and accounting for loss to followup. We assessed the overall study quality in terms of:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Differences between reviewers were resolved by a third party adjudicator.

Applicability

We assessed the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings are typical for adult patients with CKD or ESRD. Factors that may limit applicability include sex, age, ethnicity, stage of kidney disease, dialysis status, status after renal transplant, presence of baseline or previously elevated troponins, presence of ischemic ECG changes (for patients with suspected ACS only), comorbidity, smoking status, 10-year CAD risk, and history of CAD.

Data Analysis and Synthesis

We conducted meta-analyses when there were sufficient data and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For KQ 1, we followed the meta-analytic methods for studies that had an imperfect reference standard.[29] We constructed 2×2 tables and calculated sensitivity, specificity, and positive and negative predictive values where possible. If we found at least five studies that were sufficiently homogenous, we conducted a hierarchical summary receiver operator curve meta-analysis to analyze sensitivity and specificity.

For KQ 3, there was insufficient data to conduct meta-analyses. For KQ 4, meta-analyses were performed separately for time to event data (hazard ratios) and for regression models (odds ratios) as it is inappropriate to combine data from hazard ratios and odds ratios in the same meta-analysis. We conducted a meta-analysis if we found at least two studies that reported on these measures and were sufficiently homogenous.

For studies that reported a hazards ratio with a confidence interval, we pooled the hazards ratios by using the profile likelihood estimate for calculating between-study variance.[30] This method is felt to provide better accounting of uncertainty in estimation of between-study variance than the DerSimonian-Laird estimator.[31] Pooled hazard ratio meta-analyses were stratified by level of adjustment. We considered the highest level of adjustment to be models tht adjusted for age and CAD and/or similar risk equivalent (cerebrovascular disease, peripheral vascular disease, reduced left ventricular ejection fraction, heart failure, and/or diabetes). If a study reported hazard ratios by tertiles or quartiles of troponin levels, then we selected the hazard ratio that compared the highest group with the lowest group. For studies that presented a hazard ratio but no confidence intervals, if enough information was provided (such as total events and the number randomized on each arm), we derived confidence intervals using the methods provided by Tierney et al.[32] Studies that presented results by troponin only as a continuous variable, rather than a cutpoint, could not be included in meta-analyses.

For studies that reported the incidence of events, we pooled the odds ratios by using the profile likelihood estimate.[30] Sometimes, if the number of events in each group was not directly provided by the authors, that information was abstracted from a Kaplan-Meier survival figure in the published article using the DigitizeIt software program (DigitizeIt, Braunschweig, Germany). If a study reported on more than one troponin assay, we selected the assay that was most commonly used to include in the meta-analysis. Most of the odds ratios were derived from the number of events in the elevated and non-elevated troponin groups. These are all unadjusted odds ratios.

If the authors reported a hazard ratio and the number of events, that study was included in both meta-analyses. If the authors reported a hazard ratio and not the number of events, then it was only included in the hazard meta-analysis.

For studies that had two or more publications presenting outcome results from the same patient population, only one result per one unique cohort was presented. We typically selected the publication with the longest followup, unless the cutpoints for troponin elevation were not clear, and then the study with the clearest reporting of results was selected.

For studies that presented outcome results at multiple time points, the longest followup time point was abstracted. For studies that presented both unadjusted and adjusted measures of association, the results from the most adjusted regression model were abstracted.

Heterogeneity among the trials in all the meta-analyses was tested by using a standard chi-squared test with a significance level of alpha ≤ 0.10. Heterogeneity was also examined among studies by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[33] A value greater than 50 percent was considered to connote substantial variability.

Publication bias was examined by using Begg's test[34] and Egger's test[35] including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.

We used STATA statistical software (Intercooled, Version 12.1, StataCorp, College Station, TX) for all meta-analyses. Studies that were not amenable to pooling were summarized qualitatively.

For studies that presented multiple cut-points for troponin elevation (such as tertiles or quartiles rather than dichotomous cut-points), the results comparing the highest cut-point compared with the lowest cut-point was reported.

We report troponin levels in terms of mcg/L, because most studies used this unit. However, some of the newer high sensitivity troponin assays report troponin levels in terms of ng/L. To convert from mcg/L to ng/L, multiply by 1000.

Data Entry and Quality Control

A second reviewer checked the data that had been entered into DistillerSR. Second reviewers were generally more experienced members of the research team. We discussed any problems with a reviewer's data abstraction at a meeting with the reviewers.

Rating the Strength of the Body of Evidence

At the completion of our review, at least two reviewers independently rated the strength of the body of evidence on each of the troponin assays. We graded the strength of evidence addressing KQs 1, 2, 3, and 4 by adapting an evidence grading scheme recommended in the Methods Guide.[36] We applied evidence grades to the bodies of evidence about each troponin assay for each outcome.

We assessed the study limitations of individual studies according to internal validity measures described in the Quality Assessment section. Since most of the studies addressing these questions would be observational studied, we started with the assumption of a low level of study limitations. The study limitations domain was downgraded to medium or high if there was one or more than one concern about study quality.

We rated the body of evidence as "consistent" if most of the studies showed the same direction of effect. We rated the consistency of a single study as "not applicable," without downgrading the strength of evidence.

We rated the body of the evidence as "direct" if most of the studies directly addressed the question. Since we included only clinical outcomes and allowed for only direct comparisons, most evidence bodies were graded as direct.

We based our rating of precision on the magnitude and the width of the confidence intervals of the hazard ratios. If the hazard ratio was greater than 1.5 and its confidence interval did not cross 1, then we graded it as precise.

We classified the strength of evidence pertaining to the KQs into four basic grades: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect), (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate), (3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate), and (4) "insufficient" grade (evidence is unavailable or does not permit a conclusion).

Peer Review and Public Commentary

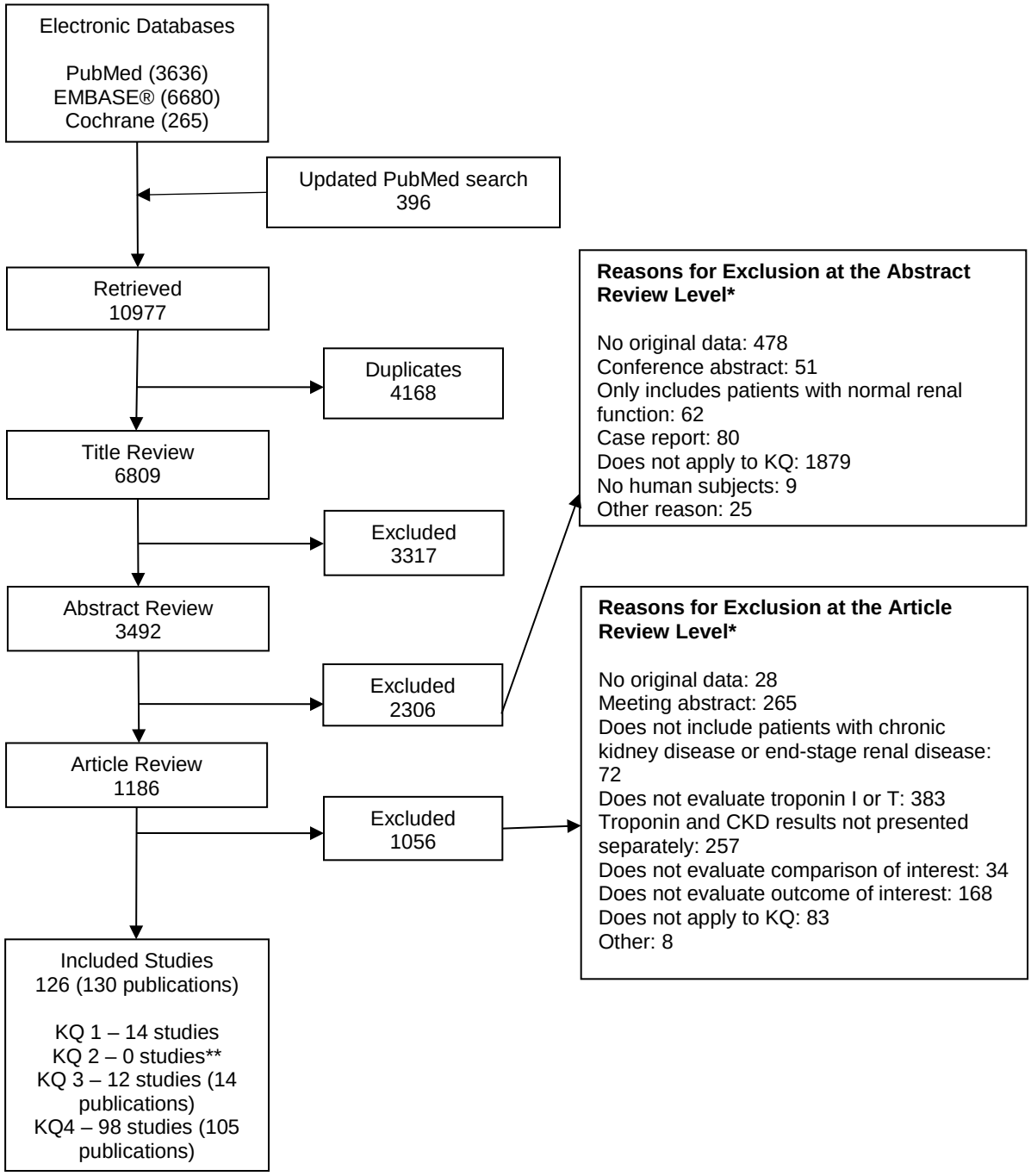
Experts in nephrology, cardiology, emergency medicine, and clinical chemistry and representatives from other government agencies were invited to provide external peer review of this CER; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a "disposition of comments report" that will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

Search Results

After removing duplicate citations from our searches, we retrieved 6,809 unique citations (Figure 3). After reviewing titles, abstracts, and full articles, we included 126 studies (in 130 publications). We included 14 studies that evaluated the diagnostic accuracy of a troponin elevation in the diagnosis of acute coronary syndrome (ACS) in patients with chronic kidney disease (CKD) (Key Question [KQ] 1).[37-50] We did not find any studies that directly assessed how troponin levels affect management strategies of ACS in patients with CKD (KQ 2). However, we discuss one study that reported troponin levels by management strategies in patients with CKD and symptoms of ACS.[51] We found 12 studies in 14 publications that addressed short- and long-term prognosis in patients with CKD after presentation with ACS by troponin levels (KQ 3).[40, 52-64] We included 98 studies (in 105 publications) that evaluated use of troponin levels for risk stratification among patients with CKD without ACS symptoms (KQ 4).[9, 11, 25, 26, 47, 65-163] One study reported on both KQ 1 and KQ 3.[40] One study reported on both KQ 3 and KQ 4.[47]

Figure 3. Summary of the literature search



* Total may exceed number in corresponding box, as articles could be excluded for more than one reason at this level.
** One study indirectly addressed this Key Question
CKD = chronic kidney disease; KQ = Key Question

KQ 1: Use of Troponin for Diagnosis of Acute Coronary Syndrome Among Chronic Kidney Disease Patients

Study Design Characteristics

We included 14 studies for this KQ. Of these, six used a prospective cohort design, five used a retrospective design, two used a cross-sectional design, and one used a prospective case-control design. All studies took place in the acute care setting, and all but two took place in the hospital setting. Of these two, one took place in a mixed setting, including the emergency department, intensive care unit, and internal medicine wards;[40] and the setting for the second was unknown.[42] Five studies took place in the United States,[41, 43, 45-47] six in Europe,[37, 40, 42, 48-50] two in Asia,[38, 44] and one in the Middle East.[39]

Seven studies did not explicitly give dates of enrollment. For those seven studies which did report enrollment, start dates ranged from 1999 to 2009 and end dates ranged from 1999 to 2010.[37-40, 43, 49, 50] Seven studies did not report mean length of followup. For those studies that did report length of followup, it ranged from 30 days to 2 years.[37, 41-43, 47, 49]

Of the 14 studies included for this KQ, different numbers of studies addressed various operating characteristics; some studies addressed more than one type of operating characteristic. Table 4, below, presents the number of unique studies addressing each type of operating characteristic, and the relevant KQ to which they apply.

Table 4. Number of unique studies addressing each type of operating characteristic

Key Question	Type of Operating Characteristic Presented	Number of Unique Studies
1.1	Sensitivity and specificity	11
1.1a	Negative and positive predictive value	6
1.1b	Change in troponin values vs. single value	1
1.2	Operating characteristic by subgroup	3
1.4	Direct comparison of troponin assays	1
All of Key Question 1		14 unique studies

Study Population Characteristics

The total number of patients enrolled ranged from 31 to 1,601. Five studies reported explicit adjudication of an acute coronary syndrome (ACS) diagnosis, all with panels; two included cardiologists;[39, 43] and three did not include cardiologists.[46, 48, 49] Table 5 summarizes the adjudication criteria the studies used.

Table 5. Adjudication criteria researchers used to define acute coronary syndromes in studies that evaluated the use of troponin to diagnosis acute coronary syndromes among patients with chronic kidney disease

Author, Year	ACS Definition	Adjudication
Flores-Solis, 2012[37]	European Society of Cardiology [164]	No
Sukonthasarn, 2007[38]	European Society of Cardiology[164]	No
Alcalai, 2007[39]	Not explicitly reported	Yes (including cardiologist)
Flores, 2006[40]	European Society of Cardiology/American College of Cardiology "AMI definition of 2000"[165]	No
Noeller, 2003[41]	STEMI: ECG changes plus chest pain or CK-MB increase; NSTEMI: ECG changes and either chest pain or ECG changes; UA: anginal change/at rest/ECG changes [no reference given]	No
Fehr, 2003[42]	"MI: angiography; UA: typical symptoms, ECG changes and positive cTnT test" [no reference given]	No
McCullough, 2002[43]	Not explicitly reported	Yes (including cardiologist)
Ikeda, 2002[44]	Not explicitly reported	No
Apple, 1999[45]	Not explicitly reported	Yes
Bhagavan, 1998[46]	"WHO criteria were used for diagnosing MI, which included presenting symptoms, ECG, and cardiac enzymes. Physical exam findings and various diagnostic imaging studies were also taken into consideration." [no reference]	No
Martin, 1998[47]	"History, physical examination, ECG, and CK-MB measurements" [no reference]	No
Chenevier-Gobeaux, 2013[48]	Global Consensus on MI	Yes (including cardiologist)
Haaf, 2013[49]	Global Consensus on MI	Yes (including cardiologist)
Pfortmueller, 2013[50]	Patint history, physical examination, electrocardiogram, and laboratory values [no reference given]	No

AMI = acute myocardial infarction; CK-MB = creatine kinase-MB; cTnT = cardiac troponin T; ECG = electrocardiogram; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; WHO = World Health Organization

The studies included patients with various stages of CKD. Four studies included patients on dialysis.[38, 42-44] One study included patients in stages 1-4 of CKD.[40] Another study included patients in stages 1-5 of chronic kidney disease (CKD) but did not include patients on dialysis.[48] No studies exclusively included patients in stage 1 or 2. Two studies included only patients in stage 3 or 4.[37, 50]

The mean age of those enrolled ranged from 48 to 80 years. Three studies did not provide this information.[44-46] The percentage of men among those enrolled ranged from 35 to 76; three studies did not report gender distribution.[44-46] Five of the studies reported distribution of race or ethnicity. The percentage of African American patients ranged from 48 to 86, and the percentage of White patients ranged from 12 to 65.[41, 43, 47]

Study Quality

The quality of the included studies varied. Three studies were of good quality.[37-39] One study was of poor quality.[40] The remainder of the studies were of fair quality.

KQ 1.1: Operating Characteristics of a Troponin Elevation (Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value)

Key Points

- In six studies, the sensitivity of the troponin T assay for ACS in patients with CKD ranged from 71 to 100 percent, and its specificity ranged from 31 to 86 percent. Three studies reported a positive predictive value (PPV) and negative predictive value (NPV) for troponin T for the diagnosis of ACS. The PPV for troponin T ranged from 66 to 77; the NPV ranged from 71 to 98. In one study, the assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years (strength of evidence: low).
- In eight studies, the sensitivity of the troponin I assay for ACS ranged from 43 to 94 percent, and its specificity ranged from 48 to 100 percent. In five studies, that reported PPV and NPV, PPV ranged from 74 to 100; the NPV ranged from 93 to 98 percent. The broad range of these findings can be attributed to heterogeneity in regard to study populations, definitions of ACS, assays used, and assay cutoffs used (strength of evidence: low).
- One study found that the magnitude of change in the troponin T assay did not differ between patients with ACS and a control group, during 24 hours after admission. The rate of change did differ but this rate displayed marked variability during the 24 hours. This was a single study with a small sample size and imprecise results, and thus not conclusive (strength of evidence: insufficient).
- One study, which included details of ACS adjudication, reported sensitivity and specificity for troponin I elevation which appeared roughly comparable to that of other studies, though direct comparison is impossible.

Results

Ten unique studies reported on the sensitivity or specificity of a troponin assay to diagnose ACS.[37, 38, 40, 42, 44-47, 49, 50] Three studies reported explicit adjudication of an ACS diagnosis, all included panels, two including cardiologists,[39, 43] and three did not include cardiologists.[46, 48, 49] Two studies reported other diagnostic criteria of ACS; two used criteria from the European Society of Cardiology,[37, 38] and two electrocardiogram and clinical criteria.[41, 50] We were unable to conduct a meta-analysis because the number of studies was too small, and thus we do not have an aggregate estimate of the sensitivity and specificity. We presented the results for troponin T and troponin I separately below.

Troponin T

Six studies examined the operating characteristics of the troponin T assay in their entire study population (Table 6).[38, 42, 44, 48-50] Two studies used a cutoff of 0.1 mcg/L, both used the Roche Elecsys assay.[38, 42] One study used a cutoff of 0.16 mcg/L and did not specify the manufacture or assay.[44] Another study used multiple cutoffs, including 0.014 mcg/L and 0.0358 mcg/L and the high-sensitivity Roche Elecsys assay.[48] One study reported a cutoff of 0.009 mcg/L for the Roche Elecsys assay, and a cutoff of 0.0194 mcg/L for the high-sensitivity Roche Elecsys assay.[49] One study used a cutoff of 0.014 mcg/L for the Roche Modular E170 assay.[50] The sample size of those studies using the troponin T assay ranged from 31 to 382. The sensitivity in these studies ranged from 71 to 100 percent, and the specificity ranged from 31 to 86 percent

(Figure 4). The heterogeneity of these results using the same cutoff and assay can potentially be understood in the light of the different geographic settings of the studies; moreover, while one study adjudicated ACS according to the standards of the European Society of Cardiology;[38] and two others did so with cardiologist adjudication, according to the criteria of the Global Consensus on MI;[48, 49] two other studies did not explicitly report adjudication standards.[42, 44]

Troponin I

Eight studies examined the operating characteristics of the troponin I assay in their entire study population (Table 6).[37, 40, 42, 44-47, 49] The cutoff values they used for the diagnosis of ACS differed (with some studies evaluating multiple different cutoffs). One study used a cutoff of 0.11 mcg/L,[37] one study used 0.4 mcg/L,[45] two studies used 0.5 mcg/L,[37, 40] one study used 0.6 mcg/L,[46]one study used 1.0 mcg/L[42] and two studies used 0.8 mcg/L.[44, 47] One study used two cutoffs, 0.0063 mcg/L and 0.0099 mcg/L.[49] The sample size of these studies ranged from 31 to 1,601.

The troponin I assays in these studies were of a variety of types from a range of manufacturers. Three studies used an assay from the same manufacturer, Beckman.[37, 40, 49] Other studies used the manufacturers Vidas, Biosite, Baxter, Dade, DPC, and Siemens. One study did not report a manufacturer.[44]

One study[46] that reported details of ACS adjudication, showed values of sensitivity and specificity, which did not appear to differ markedly from those of the other studies using troponin I; however, we can make no conclusions due to the heterogeneity of cutpoints.

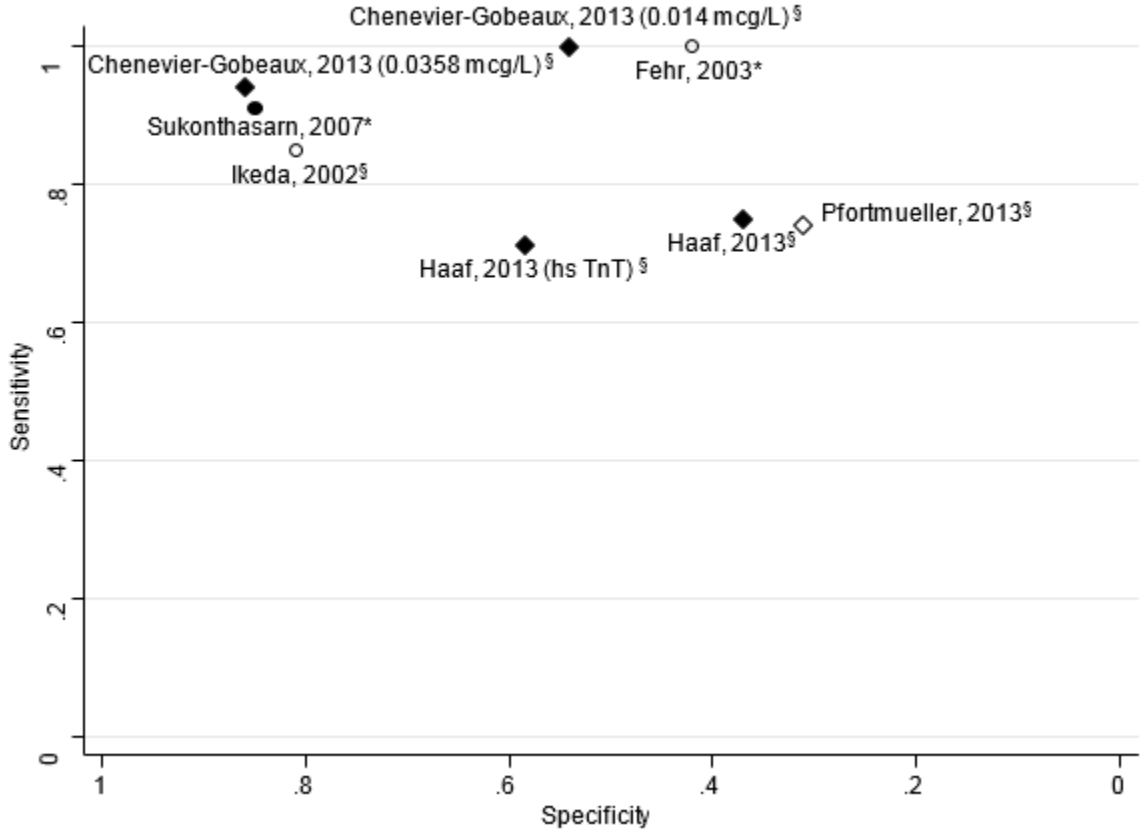
The sensitivity in these studies ranged from 43 to 94 percent, and the specificity ranged from 48 to 100 percent (Figure 5).

Table 6. Operating characteristics of elevated troponin in the diagnosis of acute coronary syndrome among patients with chronic kidney disease

Author, Year	Troponin Assay	Cutoff (mcg/L)	ACS Diagnosis	Total N	Sensitivity	Specificity
Flores-Solis, 2012[37]	Troponin I, Beckman	0.5	Adjudication according to European Society for Cardiology 2007 standards	484	0.43	0.94
Flores, 2006[40]	Troponin I, Beckman Access AccuTnI	0.5	European Society of Cardiology/American College of Cardiology 2000 standards	467	0.70 (95% CI, 0.57 to 0.83)	0.92 (95% CI 0.90 to 0.95)
Flores-Solis, 2012[37]	Troponin I, Vidas	0.11	Adjudication according to European Society for Cardiology 2007 standards	484	0.64	0.87
Apple, 1999[45]	Troponin I, BioSite	0.4	Modified WHO criteria	1,601	>0.89	0.95 to 1.00
Bhagavan, 1998[46]	Troponin I, Baxter	0.6	WHO criteria	155	0.90	0.81
Martin, 1998[47]	Troponin I, Dade Stratus	0.8	None given	56	0.94 (95% CI, 0.82 to 1.06)	1.00
Ikeda, 2002[44]	Troponin I, manufacturer not given	0.8	None given	173	0.83	0.91
Fehr, 2003[42]	Troponin I, DPC Immulite	1.0	None given	31	0.45	1.00
Haaf, 2013[49]	High-sensitivity troponin I, Siemens	0.0063	Global Consensus on MI (JACC)	1,117	0.73	0.53
Haaf, 2013[49]	High-sensitivity troponin I, Beckman Access	0.0099	Global Consensus on MI (JACC)	1,117	0.81	0.48
Sukonthasarn, 2007[38]	Troponin T, Roche	0.1	Adjudication according to European Society of Cardiology standards	46	0.91	0.85
Fehr, 2003[42]	Troponin T, Roche Elecsys	0.1	None given	31	1.00	0.42
Ikeda, 2002[44]	Troponin T, manufacturer not given	0.16	None given	173	0.85	0.81
Chenevier-Gobeaux, 2013[48]	High sensitivity troponin T, Roche Elecsys	0.014	Global Consensus on MI (JACC)	375	1.00 (95% CI, 0.76 to 1.00)	0.54 (95% CI 0.40 to 0.67)
Chenevier-Gobeaux, 2013[48]	High sensitivity troponin T, Roche Elecsys	0.0358	Global Consensus on MI (JACC)	375	0.94 (95% CI, 0.68 to 1.00)	0.86 (95% CI 0.74 to 0.94)
Haaf, 2013[49]	Troponin T Roche Elecsys	0.009	Global Consensus on MI (JACC)	1,117	0.75	0.37
Haaf, 2013[49]	High sensitivity troponin T Roche Elecsys	0.0194	Global Consensus on MI (JACC)	1,117	0.71	0.58
Pfortmueller, 2013[50]	High sensitivity troponin T, Roche Modular E170	0.014	Patient history, signs and symptoms, electrocardiogram changes, positive TnT test	382	0.74 (95% CI, 0.60 to 0.88)	0.31 (95% CI, 0.21 to 0.41)

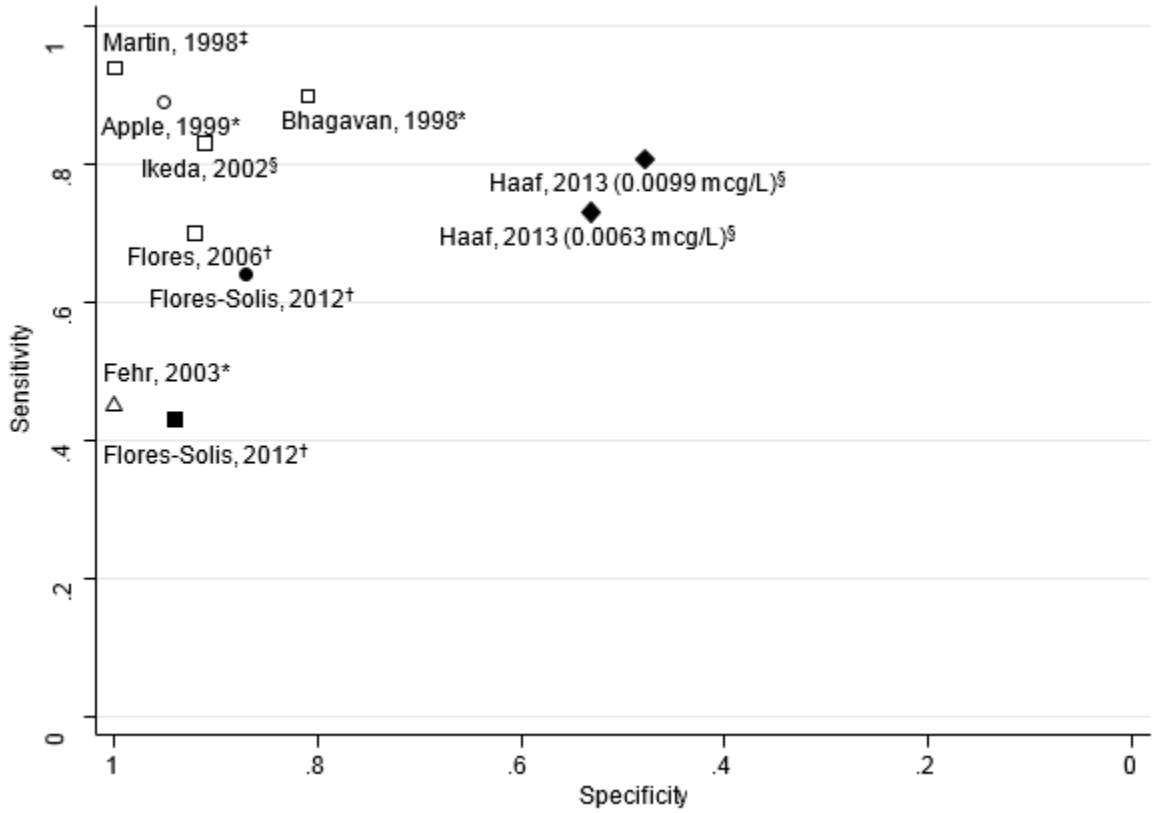
ACS = acute coronary syndrome; CI = confidence interval; JACC = Journal of the American College of Cardiology; mcg/L = micrograms per liter; WHO = World Health Organization

Figure 4. Sensitivity and specificity of elevated troponin T in the diagnosis of acute coronary syndrome among patients with chronic kidney disease



Closed markers represent studies that adjudicated acute coronary syndrome, open markers represent studies that either did not adjudicate or did not report adjudicating acute coronary syndrome. Diamond markers indicate a troponin T cutoff of less than 0.1 mcg/L. Round markers indicate a troponin T cutoff of 0.1 mcg/L or higher.
* Indicates a dialysis population.
† Indicates a non-dialysis population.
‡ Indicates a mixed population
§ Does not specify if the population is on dialysis or not.

Figure 5. Sensitivity and specificity of elevated troponin I in the diagnosis of acute coronary syndrome among patients with chronic kidney disease



Closed markers represent studies that adjudicated acute coronary syndrome, open markers represent studies that either did not adjudicate or did not report adjudicating acute coronary syndrome. Diamond markers indicate a troponin I cutoff of less than 0.1 mcg/L. Round markers indicate a troponin I cutoff between 0.1 mcg/L and 0.5 mcg/L. Square markers indicate a troponin I cutoff between 0.5 and 1.0 mcg/L. Triangular markers indicate a troponin I cutoff greater than or equal to 1.0 mcg/L.
* Indicates a dialysis population.
† Indicates a non-dialysis population.
‡ Indicates a mixed population
§ Does not specify if the population is on dialysis or not.

KQ 1.1.a: Positive and Negative Predictive Values

Results

Five studies estimated the positive and negative predictive values for troponin I in the assessment of ACS in their entire study population.[37, 40, 46, 47, 49] They used multiple cutoffs. One used 0.11 mcg/L,[37] two used 0.5 mcg/L,[37, 40] one used 0.6 mcg/L,[46] one used 0.8 mcg/L,[47] and one used two cutoffs, 0.0063 mcg/L and 0.0099 mcg/L. For troponin I in the diagnosis of ACS, the PPV ranged from 7 to 100 percent; the NPV ranged from 93 to 98 percent. Given the heterogeneity of the cutoffs and manufacturers used in these studies, it was not possible to identify a trend relating the cutoff value to NPV or PPV. We were unable to conduct a meta-analysis because the studies were insufficient in number, and thus cannot provide an aggregate estimate of PPV or NPV.

One study estimated the NPV or PPV of troponin T for the diagnosis of ACS for two subgroups[41] (Table 7); two studies did so for the entire study population.[48, 49] The PPV for troponin T ranged from 6 to 77 percent; the NPV ranged from 71 to 98 percent. In one study, the assay was associated with a greater PPV and NPV for the subgroup of patients with age less than 65 years.

Table 7. Operating characteristics of elevated troponin in the diagnosis of acute coronary syndrome among patients with chronic kidney disease

Author, Year	Troponin Assay	Cutoff (mcg/L)	PPV	NPV
Flores-Solis, 2012[37]	Troponin I, Vidas	0.1	40	95
Flores-Solis, 2012[37]	Troponin I, Beckman	0.5	50	93
Flores, 2006[40]	Troponin I, Beckman Access AccuTnI	0.5	51 (95% CI, 39 to 63)	97 (95% CI, 95 to 98)
Bhagavan, 1998[46]	Troponin I, manufacturer and assay not given	0.6		98
Martin, 1998[47]	Troponin I, Dade International Stratus	0.8	100	94
Haaf, 2013[49]	High-sensitivity troponin I, Siemens	0.0063	7	98
Haaf, 2013[49]	High-sensitivity troponin I, Beckman Access	0.0099	7	98
Noeller, 2003[41] Age < 65 years	Troponin T, Roche-Boehringer-Mannheim CARDIAC-T ELISA	0.1	77	78
Noeller, 2003[41] Age > 65 years	Troponin T, Roche-Boehringer-Mannheim CARDIAC-T ELISA	0.1	62	71
Chenevier-Gobeaux, 2013[48]	High-sensitivity troponin T, Roche Elecsys	0.014	37 (95% CI, 23 to 53)	100 (95% CI, 96 to 100)
Chenevier-Gobeaux, 2013[48]	High-sensitivity troponin T, Roche Elecsys	0.0358	65 (95% CI, 43 to 83)	98 (95% CI, 89 to 100)
Haaf, 2013[49]	Troponin T, Roche Elecsys	0.009	6	97
Haaf, 2013[49]	High-sensitivity troponin T, Roche Elecsys	0.0194	8	98

CI = confidence interval; mcg/L = micrograms per liter; NPV = negative predictive value; PPV = positive predictive value

KQ 1.1.b: Change in Troponin Values Versus Single Troponin Elevation

Results

One study addressed this KQ, with a total sample size of 46.[38] This study was performed in CKD patients in stages 3, 4, and 5, including nine patients on hemodialysis. The authors found that the magnitude of change in the troponin T assay in the first 24 hours after admission did not

significantly differ between the control group and the group with ACS; neither did the rate of change from 0 to 6, or 6 to 12 hours after admission. While the rate of change from 0 to 24 hours after admission was greater in the group with ACS, there was great variability in this rate of change.

Strength of Evidence

The strength of evidence for the body of literature addressing KQ1.1, 1.1a, and 1.1b is explained in Tables 8 and 9.

Table 8. Elevated troponin T or I versus nonelevated troponin T or I in terms of diagnostic accuracy among patients with chronic kidney disease: Strength of evidence domains for KQ 1.1, 1.1a, and 1.1b

Comparison	Number of Studies (subjects)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Diagnostic accuracy of troponin T elevation	6 (2,738)	Medium	Consistent	Direct	Imprecise	Low
Diagnostic accuracy of troponin I elevation	8 (5,008)	Medium	Consistent	Direct	Imprecise	Low
Change in troponin T values	1 (46)	High	NA (single study)	Direct	Imprecise	Insufficient

NA = not applicable

Table 9. Elevated troponin T or I versus nonelevated troponin T or I in terms of diagnostic accuracy among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Diagnostic accuracy of troponin T elevation	1 study poor quality, 5 fair quality, and 1 good quality	Some studies did not provide complete information on adjudication of outcomes, and assessors were generally not blinded to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise.
Diagnostic accuracy of troponin I elevation	4 studies poor quality, and 5 fair quality	One study did not report information on assay type and reported incomplete operating characteristics. Two studies provided no information on adjudication of ACS. Other studies did not provide complete information on adjudication of outcomes, and generally did not blind assessors to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise.
Change in troponin T values	1 study fair quality	There was one study of fair quality. The study was too small to provide precise estimates.

ACS = acute coronary syndrome

KQ 1.2: Operating Characteristics of a Troponin Elevation by Subgroups

Key Points

- Although a few studies have looked at how age and CKD stage affect the operating characteristics of troponin, they are small, of poor quality, and use different cutoffs for different categories. Therefore we were unable to draw any conclusions.

- There were no studies of troponin operating characteristics for ACS diagnosis in CKD patients with regard to history of coronary artery disease, electrocardiogram abnormalities, other comorbidities, or race and ethnicity.

Results

Two studies reported the operating characteristics of elevated troponin in diagnosing ACS among subgroups of patients with CKD. These studies reported one or more of sensitivity, specificity, PPV, or NPV by subgroups of age or CKD.[39, 41]

While these studies both examined the operating characteristics of the troponin T assay, they did so using different values of age and creatinine in their subgroups; thus their results cannot be directly compared except to say that the operating characteristics of troponin T appeared to vary by age and creatinine level (Table 10). Another study reported values of the area under the curve for subgroups (Table 11).[43]

Two of the studies reporting results for subgroups[39, 43] reported details of ACS adjudication, in contrast to other studies in this KQ. However, we can draw no conclusions about the operating characteristics of troponin assays in these studies compared with others, owing to heterogeneity in the type of operating characteristics reported.

This literature did not report many other subgroup characteristics that might be relevant to understanding the operating characteristics of a troponin assay in diagnosing ACS, including history of coronary artery disease, presence or absence of ischemic or other electrocardiogram changes, diabetes or other comorbidities, or race or ethnicity.

Table 10. Operating characteristics of elevated troponin in the diagnosis of acute coronary syndrome among subgroups of patients with chronic kidney disease

Author, Year	Subpopulation	Troponin Assay	Cutoff (mcg/L)	Sensitivity	Specificity	PPV	NPV
Alcalai, 2007[39]	Age < 70 years and creatinine < 1.13 mg/dL	Troponin T	Any positive result	NR	NR	78 (95% CI, 72 to 84)	NR
Alcalai, 2007[39]	Age < 70 years and creatinine < 1.13 mg/dL	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[39]	Age < 70 years and creatinine < 1.13 mg/dL	Troponin T	> 1.0	NR	NR	89 (95% CI, 79 to 95)	NR
Alcalai, 2007[39]	Age < 70 years and creatinine > 1.13 mg/dL	Troponin T	Any positive result	NR	NR	44 (95% CI, 35 to 55)	NR
Alcalai, 2007[39]	Age < 70 years and creatinine > 1.13 mg/dL	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[39]	Age < 70 years and creatinine > 1.13 mg/dL	Troponin T	> 1.0	NR	NR	59 (95% CI, 36 to 79)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine < 1.13 mg/dL	Troponin T	Any positive result	NR	NR	52 (95% CI, 42 to 63)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine < 1.13 mg/dL	Troponin T	0.1 to 1.0	NR	NR	42 (95% CI 31 to 54)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine < 1.13 mg/dL	Troponin T	> 1.0	NR	NR	90 (95% CI, 68 to 99)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine > 1.13 mg/dL	Troponin T	Any positive result	NR	NR	37 (95% CI, 29 to 45)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine > 1.13 mg/dL	Troponin T	0.1 to 1.0	NR	NR	73 (95% CI, 65 to 80)	NR
Alcalai, 2007[39]	Age > 70 years and creatinine > 1.13 mg/dL	Troponin T	> 1.0	NR	NR	59 (95% CI, 43 to 73)	NR
Noeller, 2003[41]	Age < 65 years	Troponin T	> 0.1	45	94	77	78
Noeller, 2003[41]	Age > 65 years	Troponin T	> 0.1	44	83	62	71
Noeller, 2003[41]	Age < 65 years, creatinine < 1.5 mg/dL	Troponin T	> 0.1	45	96	78	83
Noeller, 2003[41]	Age > 65 years, creatinine < 1.5 mg/dL	Troponin T	> 0.1	41	89	69	71
Noeller, 2003[41]	Age < 65 years, creatinine > 1.5 mg/dL	Troponin T	> 0.1	43	69	38	73
Noeller, 2003[41]	Age > 65 years, creatinine > 1.5 mg/dL	Troponin T	> 0.1	52	66	48	69

CI = confidence interval; mcg/L = micrograms per liter; mg/dL = miligrams per deciliter; NPV = negative predictive value; NR = not reported; PPV = positive predictive value

Table 11. Area under the curve for elevated troponin in the diagnosis of acute coronary syndrome among subgroups of patients with chronic kidney disease

Author, Year	Creatinine clearance or ESRD	Troponin Assay	Cut point (mcg/L)	AUC
McCullough, 2002[43]	>99.4 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	1
McCullough, 2002[43]	99.3-72.7 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	0.94 (SD 0.02)
McCullough, 2002[43]	72.8-47.0 mL/min/72 kg	Troponin I, Biosite Incorporated	0.4	0.97 (SD 0.01)
McCullough, 2002[43]	ESRD, on dialysis	Troponin I, Biosite Incorporated	0.4	0.99 (SD 0 .01)

AUC = area under the curve; ESRD = end-stage renal disease; mcg/L = micrograms per liter; mL/min/72 kg = milliliters per minute per 72 kilograms; SD = standard deviation

Strength of Evidence

We described the strength of the evidence addressing KQ1.2 in Tables 12 and 13.

Table 12. Numbers of studies and subjects, strength of evidence domains, magnitude of effect, and strength of evidence for the operating characteristics of elevated troponin among subgroups of patients with chronic kidney disease

Comparison	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Operating characteristics in subgroups	3	Medium	Inconsistent	Direct	Imprecise	Insufficient

Table 13. Elevated troponin T versus nonelevated troponin T in terms of diagnostic accuracy in subgroups of age and chronic kidney disease stage among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Operating characteristics in subgroups	3 studies fair quality	Studies did not provide complete information on adjudication of outcomes, and generally did not blind assessors to the results of troponin assays on adjudicating ACS diagnoses. Some results were imprecise. In addition, the direction of the relationship between the operating characteristics and subgroups of age and CKD stage was inconsistent.

ACS = acute coronary syndrome; CKD = chronic kidney disease

KQ 1.3: Harms Associated with a False-Positive Diagnosis

Results

We found no studies addressing this KQ.

KQ 1.4: Direct Comparisons Between Troponin Assays

Results

Troponin T Versus Troponin I

One study addressed this question.[42] The troponin T, Roche Elecsys assay using a cutoff of 0.1 mcg/L, was associated with a 100 percent sensitivity for ACS and a 42 percent specificity. By contrast, the Troponin I, DPC Immulite assay, using a cutoff of 1.0 mcg/L, had a sensitivity of 45 percent and a specificity of 100 percent. Both troponin assays predicted an increased risk

of ACS, with area under the curve ranging from 0.7 to 0.8. We found no studies performing direct comparisons between troponin assays from the same manufacturer or using the same cutoff for the assay to diagnose ACS.

Troponin T Versus High-Sensitivity Troponin T

We found no studies addressing this comparison.

Troponin I Versus High-Sensitivity Troponin I

We found no studies addressing this comparison.

Strength of Evidence

The strength of evidence for KQ1.4 is insufficient given that it is based on one study of poor quality that is indirect, imprecise, and lacks consistency (since it is a single study).

KQ 1.5: Direct Comparisons of Troponin Testing in Patients with Chronic Kidney Disease Versus Patients with Normal Renal Function

Results

Although the studies reviewed in the previous section did include patients with normal renal function, we were not able to draw conclusions because of the size and quality of the studies. We found no studies that carried out direct a priori comparisons of troponin testing in patients with CKD versus patients with normal renal function.

KQ 2: Management of Acute Coronary Syndrome by Troponin Levels

We did not find any study that directly addressed the question of whether troponin levels can affect management strategies in chronic kidney disease (CKD) patients with acute coronary syndrome (ACS) symptoms. We identified one study by Barthelemy et al. that did not directly address this question since the study did not treat patients according to troponin levels, but they reported on troponin levels.[51] This study did not answer KQ 2 as we defined it, but we discussed it here since it is the only study found that addressed troponin levels and management options in CKD patients with ACS symptoms.

Barthelemy et al. included patients with non-ST elevation ACS (diagnosis based on symptoms, ECG changes, and elevated troponin) scheduled for percutaneous coronary intervention and divided them according to those with and without renal failure. The study randomized ACS patients presenting to the emergency department to receive immediate or next working-day invasive management. In patients with a creatinine clearance less than 60 mL/min (n = 75), the peak cardiac troponin I level during hospitalization was not significantly different between those receiving immediate or next-day ACS management ($P = 0.36$). The study did not present a composite outcome of death, acute myocardial infarction (MI), urgent revascularization, or recurrent ischemia at 1 month separately based on elevated cardiac troponin I in the reported results; however, the authors stated in the discussion that "there was no increase in MI as evaluated by troponin I release."[51]

We did not identify any additional studies meeting the criteria for KQ2.

KQ 2.1: Modification of a Troponin Elevation on Comparative Effectiveness of Interventions or Management Strategies for Acute Coronary Syndrome

Key Points

- The one study evaluating management of ACS in CKD patients did not find a significant difference in peak cardiac troponin I between the management groups (immediate vs. delayed invasive strategy) (strength of evidence: insufficient).

KQ 2.2: Modification of a Troponin Elevation on Comparative Effectiveness of Interventions or Management Strategies for Acute Coronary Syndrome by Subgroups

Barthelemy et al. did not do any subgroup analysis.

KQ 3: Short- and Long-Term Prognosis After Presentation with Acute Coronary Syndrome by Troponin Levels

Study Design Characteristics

We found 12 unique studies in 14 publications assessing the value of troponin in establishing prognosis for patients with CKD who presented with signs/symptoms of suspected ACS.[40, 52-64]

These studies included seven prospective studies,[54, 56, 58, 59, 62-64] four retrospective studies,[40, 53, 57, 60] and three post hoc analyses[52, 55, 61] of previously published large randomized controlled trials (RCTs). The studies were published between 1999 and 2012 and enrolled patients from 1994 to 2008 with followups ranging from 1 month to 2 years. Three of the studies did not report the dates of enrollment[52, 56, 63] and four of the studies did not specify the length of followup.[40, 53, 55, 59] Studies did not report relevant details of study design uniformly.

The studies originated from the United States (nine studies),[52, 54-56, 58-60, 62, 64] Europe (two studies, one from Germany[63] and one from Spain[40]), one from Canada,[57] one from Asia (Singapore)[53]), and one was a multinational study that recruited patients from 24 countries.[61] Six studies enrolled the patients from the hospital,[52-55, 61, 62] four from the emergency department,[56, 57, 60, 64] two from the coronary care unit,[58, 59] one from the dialysis unit,[63] and one from two outpatient clinics as well as patients from the emergency department and the intensive care unit[40] (Tables 14 through 17).

Table 14. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin T levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Chew, 2008[53] Asia (Singapore)	2002 - 2005	NR	Retrospective cross sectional	Hospital	CKD + chest pain (unstable angina, STEMI, non-STEMI)	Death	Normal vs. abnormal Tn levels in CKD patients
Han, 2005[60] U.S.	1999 - 2003	6 months	Retrospective	ED	Patients presenting to the ED with chest pain	Cardiac events at 6 months (acute MI, unstable angina, revascularization, cardiac dysrhythmias, all-cause mortality, congestive heart failure exacerbation)	ACS vs. No ACS
Aviles, 2002[61] Multinational	1998 - 2000	1 month	Post hoc analysis sub study GUSTO IV	Hospital	Patients with high risk ACS with no revascularization	Death MI	Normal vs. abnormal CrCl with Normal vs. abnormal Tn levels

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; ED = emergency department; GUSTO IV = Global Use of Strategies to Open Occluded Coronary Arteries IV in Acute Coronary Syndromes; MI= myocardial infarction; STEMI = ST-elevation myocardial infarction; Tn = troponin; U.S. = United States

Table 15. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin I levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Melloni, 2008[55] U.S.	2003 - 2005	NR	Post hoc analysis sub-study CRUSADE	Hospital	Patients with high risk NSTE-ACS admitted for exclusion of MI	Short-term mortality	Normal vs. abnormal Tn levels
Flores, 2006[40] Europe (Spain)	2004 - 2004	NR	Retrospective	ED-ICU-Outpatient	Patients with CKD and chest pain	Cardiac events (MI) Death	AMI vs. Angina vs. Other chest pain
Bueti, 2006[57]	2001 - 2002	1 month	Retrospective cohort	ED	Dialysis patients presenting to the ED with chest pain	MACE (cardiovascular death, MI, coronary revascularization, de novo congestive heart failure) within 30 days	Chest pain followup at 30 days
Kontos, 2008[54] U.S.	1996 - 2000	1 year	Prospective	Hospital	Patients with chest pain	30 day and 1 year mortality	Cockcroft-Gault (C-G) vs. Modification of Diet in Renal Disease (MDRD) equation
Kontos, 2005[58] U.S.	1996 - 2000	1 year	Prospective	Hospital (CCU)	Patients with chest pain admitted for exclusion of MI	Cardiac mortality All-cause mortality Revascularization	Severe renal failure Moderate renal failure Normal renal function
Kontos, 2005[59] U.S.	1996 - 2000	NR	Prospective	Hospital (CCU)	Patients with chest pain admitted for exclusion of MI	30 day and 1 year: Cardiac mortality All-cause mortality	Severe renal failure Moderate renal failure Normal renal function
Gruberg, 2002[62] U.S.	1994 - 1999	1 year	Prospective	Hospital	CKD patients post PCI	In-hospital and 1 year: MI, Cardiac mortality All-cause mortality Repeat revascularization	Normal vs. abnormal Tn levels

ACS = acute coronary syndrome; CCU = critical care unit; CKD = chronic kidney disease; CrCl = creatinine clearance; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines Initiative; ED = emergency department; ICU = intensive care unit; MACE = major adverse cardiovascular events; MI= myocardial infarction; NR = not reported; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; Tn = troponin; U.S. = United States

Table 16. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin T and I levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations Compared
Apple, 2007[56] U.S.	NR	6 months	Prospective	ED	Patients presenting to the ED with symptoms suggestive of ACS	Cardiac events (MI) Death	Dade cTnI Roche cTnT Beckman cTnI Tosoh cTnI
Wayand, 2000[63] Europe (Germany)	NR	2 year	Prospective	Dialysis center	Dialysis patients	Cardiac events (MI) Death	ACS vs. No ACS
Van Lente, 1999[64] U.S.	1995 - 1997	6 months	Prospective	ED	CKD patients presenting to the ED with chest pain	In-hospital and 6 months: MI All-cause mortality Recurrent ischemia Revascularization/Bypass surgery Congestive heart failure Stroke	Troponin T and I in renal and nonrenal patients

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; ED = emergency department; MI= myocardial infarction; Tn = troponin; U.S. = United States

Table 17. Study design characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by unspecified troponin levels

Author, Year	Enrollment	Followup	Study Design	Setting	Inclusion Diagnosis	Outcomes Measured	Populations compared
Acharji, 2012[52] U.S.	NR	1 year	Post hoc analysis Substudy ACUITY	Hospital	CKD patients with ACS	MACE Death MI Revascularization Major bleeding	Positive vs. negative Tn

ACS = acute coronary syndrome; ACUITY = Acute Catheterization and Urgent Intervention Triage strategy; CKD = chronic kidney disease; MACE = major adverse cardiovascular events; MI= myocardial infarction; NR = not reported; Tn = troponin; U.S. = United States

Study Population Characteristics

These 12 studies included 46,988 subjects and varied widely in size. Two studies included less than 100 patients,[60, 63] six studies included between 100 and 1,000 patients,[40, 53, 56, 57, 62, 64] five studies included between 1,000 and 10,000 patients,[52, 54, 58, 59, 61] and one study included 31,586 patients.[55]

Three studies by Kontos et al.[54, 58, 59] recruited patients during the same time period, in the same institution, and under the same protocol, but aimed to predict mortality in patients admitted for exclusion of myocardial ischemia in different ways; Cockcroft-Gault equation versus Modification of Diet in Renal Disease equation,[54] specific short-term and long-term prognostic value of troponin I for patients with and without CKD,[58] and short-term and long-term outcomes and prognostic value of multiple variables (troponin, ejection fraction, and renal function).[59] Even if the total population for these studies is not the same, some of the patients may recur from study to study.

All the studies included patients older than 40 years, with means ranging between 56 and 71 and medians ranging between 63 and 80. All studies included similar proportions of men and women. One study included many more men (72 percent) than women[62] and one study did not report gender of participants.[63] Only five studies reported race.[53-56, 60] Han et al.[60] recruited 83 percent African Americans, Melloni et al.[55] recruited 82 percent Whites, Apple et al.[56] and Kontos et al.[54] recruited a more balanced population, and Chew et al.[53] recruited a prevalently Chinese population (Singapore).

We included studies with very heterogeneous baseline diagnosis, comparators, and aims. All studies had the presentation of suspected ACS at enrollment, but the definition of ACS varied among them. Apple et al., defined its patients only by the presence of clinical symptoms.[56] While other studies required the presence of symptoms and ECG and enzymatic changes,[53, 55, 59, 61, 64] two studies categorized the patients as low, moderate, or high risk ACS,[52, 54] one based it on medical records,[60] and five studies did not specify any criteria for diagnosis.[40, 57, 58, 62, 63] Only three studies reported how the diagnosis was adjudicated[52, 53, 64] and whether there was a cardiologist involved.[53] Only 50 percent of studies reported presence of CAD, which ranged from 14 to 68 percent in those studies that did report this variable.[40, 53, 54, 57, 60-62]

All studies included patients with renal failure but again, the definition of renal failure varied amongst them. Seven studies defined renal failure as a creatinine clearance less than 60 mL/min,[40, 52, 54-56, 58, 59] three studies used serum creatinine to set the cutoff,[60, 62, 64] one study classified patients per quartiles of creatinine clearance,[61] and three studies did not specify definition or cutoffs.[53, 57, 63] Four studies used the Cockcroft-Gault equation to calculate glomerular filtration rate,[52, 58, 59, 62] three studies used the Modification of Diet in Renal Disease equation,[40, 55, 56] one used both since its purpose was to compare them,[54] and six studies did not specify the equation used.[53, 57, 60, 61, 63, 64] Three studies included patients in all renal failure stages including end-stage patients requiring dialysis.[53, 55, 64] Two studies included patients in all renal failure stages but excluded patients on dialysis[54, 62] and four studies included patients in all CKD stages and did not specify if dialysis patients were included or not.[56, 58, 59, 166] Two studies included only dialysis patients,[57, 63] one study included only patients with severe stage patients (including patients both in medical treatment and dialysis),[60] and one study included only patients with moderate renal failure.[52]

Seven studies evaluated troponin I,[40, 54, 55, 57-59, 62] three studies evaluated troponin T,[53, 60, 61] and three studies evaluated both types of troponin assay.[56, 63, 64] One study did not specify which troponin it measured (Table 18 and Table 19).[52]

Table 18. Study population characteristics of studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels

Author, Year	Patients Enrolled	Exclusion Criteria	Age (Years)	Male %	Race %
Acharji, 2012[52]	2179	Patients with CrCl <30 mL/min	Median 76	53	NR
Chew, 2008[53]	227	NR	Median 66	54	Chinese 75 Malay 23 Indian 2
Kontos, 2008[54]	4343	STEMI, missing data (8-hour troponin, weight)	58	51	AA 64 W 36
Melloni, 2008[55]	31586	Patients transferred, missing data (troponin and data needed to calculate eGFR)	Median 70	59	W 82 Other 18
Apple, 2007[56]	510	NR	58	57	W 48 AA 35 Native Am 8 Other 9
Flores, 2006[40]	467	Patients transferred, missing data	Median 80	67	NR
Bueti, 2006[57]	149	NR	Median 63	49	NR
Kontos, 2005[58]	3774	ST-segment elevation that met criteria for fibrinolytic therapy, missing data (8-hour cardiac troponin I)	58	50	NR
Kontos, 2005[59]	3074	ST-segment elevation, missing data (8-hour troponin I, ejection fraction)	62	50	NR
Han, 2005[60]	64	Kidney transplant, trauma, terminal cancer	56	52	W 16 AA 83 Unknown 1
Aviles, 2002[61]	7033	Early revascularization	53% over age 65 years	62	NR
Gruberg, 2002[62]	116	Patients on dialysis, baseline cardiac troponin I > 0.15 mcg/L, AMI within 72 hours (NSTEMI/STEMI)	71	72	NR
Wayand, 2000[63]	59	NR	Range 40-77	NR	NR
Van Lente, 1999[64]	255	Cardiopulmonary resuscitation within 7 days, angiography or thrombolytic therapy within 3 weeks patients on vasopressors	65	58	NR

AA = African American; AMI = acute myocardial infarction; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; mcg/L = micrograms per liter; Native Am = Native American; NR = not reported; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; W = White

Table 19. Definitions used to define cardiac and renal populations in studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels

Author, Year	ACS Diagnosis Parameters	ACS Diagnosis Adjudi-cated	% Population With Known CAD	CKD Definition	Formula Used for eGFR	CKD Stage Included /Dialysis	GFR Mean ml/min/m^2
Acharji, 2012[52]	Patients with moderate- and high-risk NSTE ACS	Panel adjudicated	NR	CrCl <60 ml/min	C-G	Included patients with and without impaired renal function CrCl 30-59 mL/min	48.1
Chew, 2008[53]	Symptoms, serial ECG, cardiac enzymes, and cardiac catheterization, or noninvasive cardiac imaging	Panel adjudicated with cardiologist	63%	NR	NR	CKD patients Medical therapy (52%) Hemodialysis (32%) Peritoneal dialysis (16%)	NR
Kontos, 2008[54]	High risk: Ischemic ECG changes or known coronary disease and typical symptoms Low risk: confirmed with markers and perfusion imaging	NR	14-22%	eGFR <60 ml/min/1.73 m^2	MDRD and C-G	All stages (No dialysis) Percentages vary depending of the formula used >60 ml/min/1.73m2 (73% C-G – 77% MDRD) 30-69 ml/min/1.73m2 (18% C-G – 15% MDRD) <30 ml/min/1.73m2 (8.9% C-G – 8.2% MDRD)	C-G 85 MDRD 82
Melloni, 2008[55]	High-risk NSTE ACS: ACS Symptoms ST depression or elevation Positive cardiac markers	NR	NR	eGFR <60 ml/min/1.73 m^2	MDRD	1-2- eGFR >60 ml/min/1.73m2 (56%) 3- 30-60 ml/min/1.73m2 (32%) 4-5- <30 ml/min/1.73m2 (15%) Dialysis (2.8%)	NR
Apple, 2007[56]	Clinical features considered indicative of ACS	NR	NR	eGFR<60 ml/min/1.73 m^2	MDRD	eGFR ≥60 ml/min/1.73m2 (68%) 41-59 ml/min/1.73m2 (17%) ≤40 ml/min/1.73m2 (12%)	77
Flores, 2006[40]	Patients with ACS 1. AMI 2. Angina 3. Other diagnosis	NR	19%	eGFR <60 ml/min/1.73 m^2	MDRD	eGFR <60 ml/min/1.73m2 30-59 (34%) 15-29 (50%) <15 (16%)	NR
Bueti, 2006[57]	NR	NR	43%	NR	NR	All dialysis patients	NR
Kontos, 2005[58]	NR	NR	NR	CrCl <60 ml/min	C-G	CrCl >60 ml/min (71%) 30-59 (20%) <30 (8%)	NR

Table 19. Definitions used to define cardiac and renal populations in studies evaluating the short- or long-term prognosis of patients with chronic kidney disease after presentation of acute coronary syndrome by troponin levels (continued)

Author, Year	ACS Diagnosis Parameters	ACS Diagnosis Adjudi-cated	% Population With Known CAD	CKD Definition	Formula Used for eGFR	CKD Stage Included /Dialysis	GFR Mean ml/min/m^2
Kontos, 2005[59]	ECG changes, known coronary disease with typical symptoms, or MPI with positive results	NR	NR	CrCl <60 ml/min	C-G	CrCl >60 ml/min (73%) 30-59 (19%) <30 (8%)	CrCl >60; 92 CrCl 30-59; 47 CrCl <30; 16
Han, 2005[60]	Medical record and social security death index	NR	40.6%	Serum creatinine >2.0 mg/dL	NR	CKD-Estimated CrCl <30 mL/min Medical therapy (60%) Hemodialysis (37%) Peritoneal dialysis (3%)	NR
Aviles, 2002[61]	One or more episodes of angina, new ST-segment depression, abnormal result on a cardiac troponin	NR	Up to 68% (% given by features; MI-angina, previous interventions)	CrCl NS Patients grouped by quartiles	NR	Median CrCl 76 ml/min Severe <10 (11 patients)	76 (median)
Gruberg, 2002[62]	All patients post PCI—this was not exclusively an ACS population—could include patients with stable angina	NR	100%	Serum creatinine ≥ 1.8 mg/dL	C-G	All stages but dialysis	NR
Wayand, 2000[63]	ACS criteria not specified, Included patients with stable cardiac disease	NR	NR	NR	NR	All dialysis patients	NR
Van Lente, 1999[64]	WHO criteria at least 2 of the following: chest pain, ECG changes or changes in CK and CK-MB	Single adjudicator	NR	Serum creatinine > 2 mg/dL	NR	Non CKD CKD all stages (9% in dialysis)	NR

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; C-G = Cockroft-Gault formula; CK = creatine kinase; CKD = chronic kidney disease; CK-MB = creatine kinase MB; CrCl = creatinine clearance; ECG = electrocardiogram; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; mL/min/m2 = millimeters per minute per meters squared; MPI = myocardial perfusion imaging; NR = not reported; NSTE ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; WHO = World Health Organization

Study Quality

The overall quality in the 14 studies evaluating the value of troponin in establishing prognosis for patients with renal failure who presented with signs/symptoms of suspected ACS was generally fair (three were good,[52, 55, 57] eight were of fair quality,[54, 56, 58-62, 64] and three were poor).[40, 53, 63] All studies appropriately described their objective, interventions, outcomes and findings. Only one study did not describe the characteristics of the patients included.[64] We felt that the included populations were representative of the general population in nine studies[52, 55-58, 60-62, 64] and the setting (staff and facilities) was representative of a normal setting in eight studies.[55, 57-59, 61-64] All the studies recruited their intervention groups from the same population and at the same time.

All the studies described the statistical methods used; none of the studies reported calculation of power (we found the power calculation for one study in the original RCT but not in the study we included[52]), seven studies reported on withdrawals,[40, 57, 60-64] but all the studies took into account the losses to followup for the analyses. The authors described an adequate adjustment for confounding in the analyses in six studies,[52, 55, 57, 58, 60, 64] only 21 percent of the studies (n=3)[61, 63, 64] reported blinding the personnel who measured outcomes—43 percent (n=6)[54-57, 59, 62] did not blind, and in 43 percent (n=6)[40, 52, 53, 58, 60] blinding was not feasible due to the study design. Only one study did not do data dredging.[62] All the studies reported accurate outcomes measures. Three studies did not report random variability estimates,[40, 53, 55] and four studies did not report actual probability values.[40, 54, 55, 60]

In regard to funding, industry sponsored four studies[52, 55, 61, 64] and government sponsored one.[56] One study reported having no sponsorship[57] and in eight studies this information was unclear.[40, 53, 54, 58-60, 62, 63]

KQ 3.1: Troponin Associations With Long-Term and Short-Term Outcomes

Key Points

- Elevated troponin I or T were associated with higher risk of short-term mortality (<1 year) and cardiac outcomes (strength of evidence: low).
- A similar trend was observed for long-term mortality (≥1 year) with troponin I (strength of evidence: low), but less evidence was found for long-term cardiac events for troponin I and long-term outcomes for troponin T (strength of evidence: insufficient).
- Patients with advanced stages of CKD tend to have worse prognosis with elevated troponin I than those without elevation (strength of evidence: moderate).

All-Cause Mortality

Troponin T

Four studies evaluated all-cause mortality, following a presentation for suspected ACS, in the context of troponin T levels: one with a long-term followup period (greater than 1 year),[63] one with an unreported followup period,[53] and two with short-term followup periods (Table 20).[52, 55] The long-term study and one short-term study used a troponin T cutoff of 0.1 mcg/L, while the others did not specify the upper limits of normal.

Wayand et al. conducted a small prospective cohort study that followed dialysis patients for 2 years and included 28 patients with myocardial discomfort or evidence of myocardial injury. The study analyzed both cardiac troponin T and I. Three patients with elevated cardiac troponin T values (>0.1 mcg/L) (n = 9) and one patient with a nonelevated cardiac troponin T died during followup (odds ratio [OR], 6.3; 95% confidence interval [CI], 0.6 to 69.7; *P* = 0.13). The study did not report the timing of these deaths.[63]

In the second study, Chew et al. found no significant difference in all-cause mortality between those with elevated (≥ 0.1 mcg/L) and nonelevated troponin T levels (*P* = 0.614). This was a retrospective study of 227 CKD patients with unstable angina pectoris, although the study did not report the number of patients in each group. Additionally, it did not give the duration of followup.[53]

The largest study of troponin T with an all-cause mortality outcome used data from an observational registry of patients admitted with ACS. A total of 13,843 patients had an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on creatinine clearance. The study analyzed patients with mild CKD and normal kidney function jointly, so we did not consider data for stages 1 and 2 CKD for this review. Melloni et al. found an association between increases in troponin levels and death during initial hospitalization, though the study did not report the durations of hospital stays. The study grouped cardiac troponin T measurements by multiples of the assay's upper limits of normal. The study saw a trend toward death in those with higher troponin values assays. In those with an estimated GFR of 30-60 mL/min/1.73m^2, the study saw mortality in 3.7, 5.3, and 7.3 percent of those with a troponin T value less than 1, 1 to 3, and greater than 3 times the upper limit of normal, respectively. For those with more severe CKD, these percentages were 7, 5.7, and 14 percent, respectively. However, after adjustment, troponin T elevation did not remain a significant predictor of mortality.[55]

Acharji et al. evaluated both cardiac troponin T and I, but did not distinguish between the two in the results or analysis, and therefore we did not include it in the strength of evidence analysis. This was a post hoc analysis of a large RCT reporting all-cause mortality in patients that had troponin measured prior to undergoing cardiac catheterization and revascularization after presenting with ACS. They analyzed data from the subjects in the RCT who had both CKD and baseline troponin T or I levels. The study did not list cutoff values for an elevated versus nonelevated test. They evaluated all-cause mortality at both 30 days and 1 year after presentation with ACS. Death within 30 days occurred in 4.7 percent (n = 60) of those with an elevated troponin versus only 1.0 percent (n = 9) with a non-elevated troponin (*P* < 0.0001). Similarly, 10.7 percent (n = 127) of those with an elevated troponin were dead at 1 year compared with 6.8 percent (n = 51) of those with non-elevated troponins (*P* = 0.0005). The study did not perform adjustment for this individual outcome.[52]

Table 20. Association of an elevated troponin T level with all-cause mortality among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Followup	n with Elevated Troponin	n (%) with Outcome (death)	n with Nonelevated Troponin	n (%) with Outcome (death)	Quality	Summary of Results
Chew, 2008[53]	NR; 0.1 mcg/L	NR	121	NR	106	NR	Poor	*P* = 0.614
Wayand, 2000*[63]	Roche Enzymum; 0.1 mcg/L	2 years	9	3 (33.3%)	19	1 (5.3%)	Poor	OR, 6.3; 95% CI, 0.6 to 69.7; *P*= 0.13
Melloni 2008[55]	NR 1, 2 and 3x ULN	In-hospital	NR	NR	NR	NR	Good	Incidence of death increased with severity of renal damage but relationship disappeared after adjustment
Acharji 2012[52]	Unspecified troponin defined as positive or negative	30 days 1 year	1,291	60 (4.7%) 127 (10.7%)	888	9 (1%) 51 (6.8%)	Good	*P* <0.0001 *P* =0.0005

CI = confidence interval; mcg/L = micrograms per liter; NR = Not reported; OR = odds ratio; ULN = upper limit of normal
*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Troponin I

Seven studies investigated cardiac troponin I with an outcome of all-cause mortality.[52, 54, 55, 58, 59, 62, 63] Because of overlap in patient cohorts and populations that were not exclusively ACS patients, we could not perform a pooled analysis (Table 21). The troponin I cutoff values ranged from 0.15 mcg/L to 1 mcg/L; two studies did not report a threshold.

The only study we identified that reported on troponin I with a long-term outcome was the same study identified for troponin T that we described above. Out of a total of 28 patients, 14 had elevated cardiac troponin I values (≥ 0.4 mcg/L), and four of these patients died, whereas no patients with non-elevated cardiac troponin I died (OR, 9.0; 95% CI, 0.44 to 182.8; $P = 0.15$).[63]

A large study by Melloni et al., that used both troponin T and I (described above), grouped troponin values by multiples of the upper limit of normal, but do not specify the number of patients studied for each marker. After adjusting for patient characteristics and clinical factors, the only remaining significant association they found was between in-hospital mortality and elevated troponin I greater than 3-times the upper limit of normal in patients with an estimated GFR of 30-60 mL/min/1.73m^2 (OR, 1.8; 95% CI, 1.3 to 2.5).[55]

Kontos et al. evaluated all-cause mortality in patients admitted to a large hospital after presenting to the emergency department with chest pain. This included 1,084 patients with creatinine clearance less than 60 mL/min; however, those with mild kidney dysfunction (creatinine clearance greater than 60 mL/min) and patients with normal kidney function were analyzed as a single group and therefore not appropriate for evaluation in this review. A significantly larger number of patients with creatinine clearance less than 60 mL/min who presented with elevated troponin levels died within 1 year, (12.6 percent) compared with those with non-elevated troponin I levels (6.8 percent; OR, 1.9; 95% CI, 1.4 to 2.5; $P = 0.0001$). Notably, this population excluded patients with ST elevation acute MI and was not exclusively ACS, as it may have included those with stable angina.[58]

Two additional studies by the same author meeting inclusion criteria for this review also included all-cause mortality as an outcome in ACS patients with CKD.[54, 59]

Acharji et al. evaluated both cardiac troponin T and I, but did not distinguish between the two in the results or analysis. We described the results above.[52]

Table 21. Association of an elevated troponin I level with all-cause mortality among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Followup	n with Elevated Troponin	n (%) with Outcome (death)	n with Nonelevated Troponin	n (%) with Outcome (death)	Quality	Summary of Results
Wayand, 2000*[63]	Dade Stratus; 0.4 mcg/L	2 years	14	4 (28.6%)	14	0 (0%)	Poor	OR, 9.0; 95% CI, 0.4 to 182.8; *P* = 0.15
Melloni, 2008[55]	NR; 3 x ULN	In-hospital	NR	NR	NR	NR	Good	Incidence of death increased with severity of renal damage but after adjustment was significant only for moderate CKD and TnI 3XULN OR, 1.8; 95% CI, 1.3 to 2.5 (adjusted)
Gruberg, 2002*[62]	Beckman Chemiluscent; 0.15 mcg/L	1 year	50	14	66	7	Fair	OR, 2.3; 95% CI, 1.1 to 4.8, adjusted for age, diabetes, CAD
Kontos, 2005a[58]	Behring Opus Magnum and Bayer ImmunoOne; 1.0 mcg/L	1 year	494	62 (12.6%)	2951	200 (6.8%)	Fair	OR, 1.9; 95% CI, 1.4 to 2.5; *P* = 0.0001
Acharji 2012[52]	Unspecified troponin Defined as positive or negative	30 days 1 year	1291	60 (4.7%) 127 (10.7%)	888	9 (1%) 51 (6.8%)	Good	*P* <0.0001 *P* =0.0005

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; mcg/L = micrograms per liter; NR = Not reported; OR = odds ratio; ULN = upper limit of normal

*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Major Adverse Cardiovascular Events

Troponin T

In addition to the outcome of all-cause mortality, we also considered composite cardiac mortality, acute MI, cardiac ischemia, revascularization, dysrhythmia, and congestive heart failure exacerbation, as well as various composites of these endpoints. We did not identify any studies of cardiac troponin T that met inclusion criteria and evaluated MACE with a followup period of greater than 1 year.

We identified four studies of troponin T using short-term MACE outcomes following a presentation of suspected ACS (Table 22).[52, 56, 60, 61] Troponin T cutoff values ranged from 0.01 mcg/L to 0.1 mcg/L. One report justified using a 0.1 mcg/L threshold by noting that the 99th percentile in the reference population was below the lower limit of detection of 0.01 mcg/L.[61]

A post hoc analysis of an RCT with a composite outcome of 30-day acute MI or death found significant differences between patients with elevated and nonelevated troponin T. This study included patients with and without kidney dysfunction and presented results by quartile of creatinine clearance. There was a higher percentage of events in those with an elevated versus nonelevated troponin T when using a cutoff value of either 0.1 mcg/L (12.4 percent vs. 6.9 percent, respectively) or 0.03 mcg/L (12.2 percent vs. 5.3 percent). We presented results of the higher cutoff in Table 22. The results of the first two quartiles were significant after adjusting for sex, older age, ST-segment depression, and a history of angina, acute MI, stroke, diabetes, bypass surgery, and angioplasty. We provide an analysis of the quartiles separately below.[61]

Apple et al. reported a 6-month composite outcome of acute MI or death in 135 CKD patients with estimated glomerular filtration rates of less than 60 mL/min/1.73m^2. The difference in event rate in those with elevated versus nonelevated troponin T was not statistically significant. (OR, 2.5; 95% CI, 1.0 to 6.3; $P = 0.06$).[56]

The study by Acharji et al. (described above) presented several outcomes for patients with measured troponin T or I, although the analysis did not distinguished the type of troponin. These outcomes included rate of cardiac death, which was significantly higher in the elevated troponin group than in the nonelevated troponin group at 30 days ($P < 0.001$) and 1 year ($P = 0.0001$). At both 30 days and 1 year, rates of ischemia and acute MI were higher in those with elevated troponin values than non-elevated troponin values ($P < 0.05$ for both). Differences in rates of unplanned revascularization were not significant. The only outcome presented as adjusted data was composite death or acute MI. Death or MI remained statistically significant after adjusting for baseline clinical characteristics and ECG and laboratory findings. This was true at 30 days (HR, 2.1; 95% CI, 1.5 to 2.8; $P < 0.0001$) and 1 year (HR, 1.7; 95% CI, 1.4 to 2.2; $P < 0.0001$).[52]

A study of 90 CKD patients presenting to the emergency department with symptoms of ACS by Han et al. used a composite endpoint of acute MI, unstable angina, revascularization, cardiac dysrhythmias, all-cause mortality, or congestive heart failure exacerbation. Using receiver operating curve analysis, the authors found that an increase in troponin T of 0.11 mcg/L compared with a prior non-ACS measure had a sensitivity of 27 percent and a specificity of 96 percent for the composite outcome at 6 months (positive likelihood ratio 7.2). The study did not provide the rate of events in groups with and without an elevated troponin T.[60]

Troponin I

Three of the studies reporting on short-term MACE outcomes for troponin I by the same author included substantial overlap in patient populations;[54, 58, 59] therefore, we presented the most relevant results here. We identified five additional studies of troponin I.[40, 52, 56, 57, 62] These included a wide range of troponin I cutoff values, from 0.0001 mcg/L to 1 mcg/L, although one study did not specify the threshold used (Table 23).

Apple et al. reported a 6-month composite outcome of acute MI or death in CKD patients with estimated glomerular filtration rates less than 60 mL/min/1.73m^2 for three troponin I assays. All assays resulted in a statistically significant higher event rate in those with elevated troponin levels (Dade: OR, 3.0; 95% CI, 1.3 to 6.8, *P* = 0.01; Beckman: OR, 3.0; 95% CI, 1.2 to 7.1, *P* = 0.01; Tosoh: OR, 3.6; 95% CI, 1.1 to 11.4; *P* = 0.03); however, there was some variation between assays. In the Tosoh and Beckman studies, respectively, event rates ranged from 9.6 to 15.6 percent in those with non-elevated troponin levels, and from 34.4 to 42.6 percent in those with elevated troponin values.[56]

Kontos et al. recruited patients who presented to an emergency department with chest pain, although the study excluded those with ST-segment elevation. The study defined cardiac death as death caused by acute MI, CAD, or arrhythmia. In 1,084 patients with creatinine clearance less than 60 mL/min, there were significantly fewer cardiac deaths in those with non-elevated troponin I levels (3.2%) than in those with elevated troponin I levels (9.3%).[58]

Flores et al. presented results of a retrospective study of 467 patients with creatinine clearance less than 60 mL/min and with suspected myocardial injury. They found an increased incidence of acute MI as primary diagnosis on discharge in those with troponin I between 0.05 and 0.5 mcg/L (8.3 percent, n = 14) and over 0.5 mcg/L (50.8 percent, n = 33) compared with those with a non-elevated troponin I (n = 0).[40]

A study of 149 chronic dialysis patients used a composite endpoint that included cardiac death, acute MI, revascularization, or de novo congestive heart failure within 30 days of presentation. Bueti et al. found that a troponin I greater than 0.0001 mcg/L had a strong association with the outcome (OR, 15.2; 95% CI, 5.3 to 43.6; *P* = 0.0000004). This remained strongly significant when adjusting separately for sex, blood pressure, and prior cardiovascular disease. This study included patients presenting to the emergency department for any reason who had a troponin I value recorded: 29 percent presented with chest pain and 20 percent presented with symptoms that were noted to be clearly non-cardiac. The association between clinical presentation and troponin I was not significant (*P* = 0.7), suggesting that the ability of troponin I to predict the outcome was similar in those presenting with cardiac and non-cardiac complaints.[57]

Although Gruberg et al. found 1-year all-cause mortality different between those with elevated versus non-elevated troponin I (as described above), there were no significant differences between troponin I groups for 1-year acute MI (*P* = 0.06), revascularization (*P* = 0.88), or composite MACE (death, acute MI, or revascularization) (*P* = 0.16).[62]

We presented results above of a study by Acharji et al., which did not distinguish between troponin T and I values.[52]

Table 22. Association of elevated troponin T with major adverse cardiac events among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Quality	Summary of Results
Apple, 2007[56]	Roche Elecsys; 0.01 mcg/L	Death or MI	6 months	69	18 (26.1%)	66	7 (10.6%)	Fair	OR, 2.5, 95% CI, 1.0 to 6.3; *P* = 0.06
Aviles, 2002[61]	Roche Elecsys; 0.1 mcg/L	Death or MI	30 days	2715	338 (12.4%)	2583	177 (6.9%)	Fair	By quartile of CrCl: 1st; OR, 2.5; 95% CI, 1.8 to 3.3; 2nd; OR, 1.8; 95% CI, 1.3 to 2.6; 3rd; OR, 1.4; 95% CI, 0.9 to 2.1; 4th; OR, 2.3, 95% CI, 1.3 to 4.1; adjusted for sex, age, CAD
Han, 2005[60]	Roche Elecsys; 0.1 mcg/L	MI, Angina, Revascularization, cardiac disrrhythmia, death	In-Hospital 30 days 6 months	NR	NR	NR	NR	Fair	AUC for changes in TnT and ACE at timepoints 0.63 (95% CI 0.48-0.78), 0.58 (95% CI 0.43-0.73) 0.60 (95% CI0.45-0.74)
Acharji, 2012[52]	Unspecified troponin, defined as positive or negative	Cardiac death, MI Revascularization,	30 days 1 year 30 days 1 year 30 days 1 year	1291	51 (4.0%) 79 (6.8%) 106 (8.3%) 165 (13.3%) 45 (3.6%) 117 (10.0%)	888	6 (0.7%) 23 (2.7%) 44 (5.0%) 63 (7.3%) 25 (2.8%) 89 (11.2%)	Good	*P* <0.0001 *P* =0.0001 *P* =0.003 *P* <0.0001 *P* =0.33 *P* =0.65

CI = confidence interval; CrCl = creatinine clearance; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio; TnT = troponin T

Table 23. Association of an elevated troponin I level with major adverse cardiac events among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Quality	Summary of Results
Apple, 2007[56]	Dade Dimension; 0.06 mcg/L	Death or MI	6 months	41	14 (34.1%)	113	13 (11.5%)	Fair	OR, 3.0, 95% CI, 1.3 to 6.8, *P* = 0.01
Apple, 2007[56]	Beckman Access; 0.1 mcg/L male, 0.04 mcg/L female	Death or MI	6 months	31	12 (38.7%)	107	14 (13.1%)	Fair	OR, 3.0; 95% CI, 1.2 to 7.1, *P* = 0.01
Apple, 2007[56]	Tosoh AIA; 0.07 mcg/L males, 0.06 females	Death or MI	6 months	35	10 (28.6%)	63	5 (7.9%)	Fair	OR, 3.6; 95% CI, 1.1 to 11.4; *P* = 0.03
Bueti, 2006[57]	Bayer ImmunoOne; 0.0001 mcg/L	Cardiac death, MI, revascu-larization, de novo CHF	30 days	NR	NR	NR	NR	Good	OR, 15.2; 95% CI, 5.3 to 43.6
Flores, 2006[40]	Beckman Access; 0.05 mcg/L	MI	In-hospital	233	47 (20.2%)	234	0 (0%)	Poor	OR, 95.4; 95% CI, 5.9 to 1556.9; *P* = 0.001
Kontos, 2005a[58]	Behring Opus Magnum 1.0 mcg/L and Bayer ImmunoOne; 0.3 mcg/L	Cardiac mortality	1 year	494	46 (9.3%)	2951	95 (3.2%)	Fair	OR, 2.9; 95% CI, 2.0 to 4.2; *P* < 0.0001

Table 23. Association of an elevated troponin I level with major adverse cardiac events among patients with chronic kidney disease presenting with symptoms of acute coronary syndrome (continued)

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Quality	Summary of Results
Gruberg, 2002*[62]	Beckman Chemiluscent; 0.15 mcg/L	Death, MI, or revascu-larization	1 year	50	20	66	20	Fair	*P* = 0.16
Acharji, 2012[52] Unspecified cTn	NR, defined as positive or negative	Cardiac death MI Revascu-larization	30 days 1 year 30 days 1 year 30 days 1 year	1291	51 (4.0%) 79 (6.8%) 106 (8.3%) 165 (13.3%) 45 (3.6%) 117 (10.0%)	888	6 (0.7%) 23 (2.7%) 44 (5.0%) 63 (7.3%) 25 (2.8%) 89 (11.2%)	Good	*P* <0.0001 *P* =0.0001 *P* =0.003 *P* <0.0001 *P* =0.33 *P* =0.65

CHF = congestive heart failure; CI = confidence interval; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio
*Not exclusively a population presenting with symptoms of acute coronary syndrome.

Strength of Evidence

We list the strength of evidence for the body of literature addressing KQ3.1 in Tables 24 and 25.

Table 24. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of prognosis after acute coronary syndrome among patients with chronic kidney disease: Strength of evidence domains

Outcome	Troponin Assay	Number of Studies	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
All-cause mortality (≥ 1 year)	Troponin T	1	High	NA (single study)	Direct	Imprecise	OR 6.3	Insufficient
All-cause mortality (≥ 1 year)	Troponin I	3	Medium	Consistent	Indirect	Precise	OR range 1.9 to 9.0	Low
All-cause mortality (< 1 year)	Troponin T	1	Low	NA (single study)	Direct	Imprecise	NA	Low
All-cause mortality (< 1 year)	Troponin I	1	Low	NA (single study)	Direct	Precise	OR 1.8	Low
MACE (≥1 year)	Troponin I	2	Medium	Inconsistent	Direct	Imprecise	OR 2.9 1 study NR	Insufficient
MACE (< 1 year)	Troponin T	3	Medium	Consistent	Direct	Imprecise	OR range 1.4 to 2.5 AUC 0.60	Low
MACE (<1 year)	Troponin I	3	Medium	Consistent	Direct	Imprecise	OR range 3.6 to 95	Low

AUC = area under the curve; HR = hazard ratio; MACE = major adverse cardiac event; NA = not applicable; NR = not reported; OR = odds ratio

Table 25. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of prognosis after acute coronary syndrome among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains- Comments About How Overall Strength of Evidence Derived
All-cause mortality (≥ 1 year)	Troponin T	Prospective cohort	1 observational study of poor quality that was not adjusted for confounders	We were unable to draw conclusions based on one study with poor description of patient characteristics and imprecise estimates.
All-cause mortality (≥ 1 year)	Troponin I	Prospective cohorts	3 observational studies, 1 of poor quality and 2 with fair quality, only 1 study adjusted for confounders	All the studies suggested an increased risk of mortality associated with elevated troponin, although one of the studies did not meet statistical significance. However, the results are indirect because two studies included asymptomatic patients.
All-cause mortality (< 1 year)	Troponin T and Troponin I	Prospective cohort	1 observational study of good quality that adjusted for confounders, number with elevated values in each group not reported	The study suggested Troponin T and I were both associated with in-hospital mortality but the association disappeared when adjusted to confounders.
MACE (≥1 year)	Troponin I	2 prospective	2 studies of fair quality, 1 adjusted for confounders.	The results were inconsistent and imprecise. One study found significant results for TnI and the other found no significant difference.
MACE (< 1 year)	Troponin T	1 prospective, 1 post hoc and 1 retrospective	3 observational studies of fair quality, 1 study adjusted for confounders, another study blinded outcome assessors	Differences in study design limit our ability to combine data. Effect estimates suggested an association, but were imprecise with wide confidence intervals crossing 1.
MACE (<1 year)	Troponin I	1 prospective, and 2 retrospective	3 observational studies of fair quality, 1 study adjusted for confounders	Effect estimates consistently suggested an association, but were imprecise with wide confidence intervals crossing 1.

ACS = acute coronary syndrome; CKD = chronic kidney disease; MACE = major adverse cardiac events; OR = odds ratio; TnI = troponin I; TnT = troponin T

KQ 3.2: Troponin Associations with Long-Term and Short-Term Outcomes by Subgroups

Key Points

- Patients with more advanced stages of CKD and elevated troponin I seem to be at higher risk of adverse outcomes than those with nonelevated troponin I (strength of evidence: moderate).
- Elevated troponin was associated with a higher risk of adverse cardiac outcome in dialysis patients with ACS compared with normal troponin levels, although the quality and heterogeneity of study designs limits the strength of this finding (strength of evidence: low).
- We did not find any studies that reported on the ability of elevated troponin to estimate prognosis after ACS in subgroups of CKD patients based on sex, age, status after renal transplant, presence of previously elevated troponin, ECG changes, comorbidities, smoking status, 10-year CAD risk, or history of CAD (strength of evidence: insufficient).

Results

The only subgroups presented in the studies meeting criteria for KQ3 were extent of kidney disease and utilization of dialysis.

Stage of Chronic Kidney Disease or Creatinine Clearance

Troponin T

Aviles et al. presented their study results by quartile of creatinine clearance, rather than standard stage of CKD. The authors found a significantly higher rate of death or MI in those with a troponin T greater than 0.1 mcg/L in creatinine clearance groups less than 58.4 mL/min and 58.4 to 76.9 mL/min ($P < 0.001$ for both). The difference for creatinine clearance 77.0 to 98.6 mL/min was insignificant ($P = 0.16$); however, this result became significant when they used a lower troponin T cutoff value of 0.03 mcg/L for analysis ($P < 0.001$).[61]

Melloni et al. did not find a significant difference in in-hospital mortality between those with elevated and nonelevated troponin T based on the hospital's upper limit of normal value when they considered stages of CKD separately.[55]

In a post hoc analysis of an RCT, Acharji et al. considered patients with creatinine clearance less than 30 mL/min separately from those with creatinine clearance 30 to 60 mL/min. Types of troponin included both T and I (threshold not specified) but they did not distinguish between the two in the analysis. The only statistically significant difference in outcomes between troponin groups that the study saw were in the creatinine clearance 30 to 60 mL/min subgroup. These included all-cause mortality, cardiac death, acute MI, and composite death or acute MI ($P \leq 0.001$ for all) at both 30 days and 1 year.[52]

Troponin I

In their large analysis of registry data, Melloni et al. grouped patients by estimated glomerular filtration calculated via the Modification of Diet in Renal Failure method. After adjusting for patient characteristics and other factors known to be associated with in-hospital mortality, the only association that remained statistically significant was death in stage 3 CKD patients with elevated troponin I at more than 3-times the hospital-specified upper limit of

normal (OR, 1.8; 95% CI, 1.3 to 2.5; $P < 0.0012$). They did not report ORs for insignificant adjusted analyses.[55]

One multivariate analysis, Kontos et al., that adjusted for age, sex, hypertension, prior revascularization or acute MI, left ventricular hypertrophy, and ischemic ECG changes, reported that an elevated troponin I (>1 mcg/L for Opus assay and >0.3 mcg/L for Bayer assay) was a predictor of 1-year all-cause mortality in patients with creatinine clearance 30 to 60 mL/min (HR, 1.7; 95% CI, 1.1 to 2.6) and creatinine clearance less than 30 mL/min (HR, 3.0; 95% CI, 1.8 to 5.0). Additionally, elevated troponin I was a predictor of 1-year cardiac mortality in patients with creatinine clearance 30 to 60 mL/min (HR, 2.2; 95% CI, 1.3 to 3.8) and with creatinine clearance less than 30 mL/min (HR, 3.3; 95% CI, 1.8 to 6.1). Thirty-day all-cause mortality was higher in those with an elevated versus nonelevated troponin I by CKD subgroup (10 vs. 3.8 percent in those with creatinine clearance 30 to 60 mL/min and 26 vs. 9.7 percent in those with creatinine clearance less than 30 mL/min).[58]

We presented the results of a CKD subgroup analysis for a study considering troponins T and I jointly above.[52]

Dialysis Status

Melloni et al. analyzed a nondialysis subgroup from a large cohort of CKD patients and did not demonstrate a significant difference from the results for the entire population of CKD patients. The study saw a trend toward death in those with higher troponin values for both troponin T and I in those with CKD not undergoing dialysis.[55]

Two studies only included those undergoing chronic dialysis (described above), and these have limitations.[57, 63] The former was a small cohort of 28 patients and, although it reported long-term mortality as an outcome, it did not report timing of patient deaths. The latter study found an elevated troponin I had a strong association with a composite 30-day outcome including cardiac death, acute MI, revascularization, or de novo congestive heart failure (OR, 15.2; 95 percent CI, 5.3 to 43.6; $P = 0.0000004$). Limitations of this study included a low cutoff value for elevated troponin I (0.0001 mcg/L) and that it included all dialysis patients presenting to the emergency department (i.e., not strictly an ACS population).

Strength of Evidence

We listed the strength of evidence for the body of literature addressing KQ3.2 in Tables 26 and 27.

Table 26. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of prognosis after acute coronary syndrome by subgroups of patients with chronic kidney disease: Strength of evidence domains*

Subgroup	Troponin Assay	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
Stage of CKD or creatinine clearance	Troponin T	2 (40798)[55, 61]	Medium	Inconsistent	Direct	Imprecise	OR Not given	Insufficient
Stage of CKD or creatinine clearance	Troponin I	2 (37539)[55, 58]	Medium	Consistent	Direct	Precise	OR 1.8 HR range 1.7 to 3.0	Moderate
Dialysis status	Troponin T or I	3 (31794)[55, 57, 63]	Medium	Consistent	Indirect	Precise	OR range 1.8 to 15.2	Low

CKD = chronic kidney disease; HR = hazards ratio; OR = odds ratio.
*None of the studies included high-sensitivity troponin T or I

Table 27. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of prognosis after acute coronary syndrome by subgroups of patients with chronic kidney disease: Details regarding strength of evidence domains*

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains- Comments About How Overall Strength of Evidence Derived
Stage of CKD or creatinine clearance	Troponin T	2 post hoc analyses	2 observational studies, 1 of fair and 1 of good quality	The effect of association was inconsistent and imprecise. One study did not find an association, while the other one found an association when using a higher cutoff. Magnitude of effect was not given as OR or HR in any study.
Stage of CKD or creatinine clearance	Troponin I	1 post hoc and 1 prospective	2 observational studies, 1 of fair and 1 of good quality	Effect estimates were consistent, direct, and precise for an association of troponin with the outcome. While one of the studies found the association in all stages, the other one found it only for severe CKD.
Dialysis status	Troponin T or I	1 post hoc, 1 prospective, 1 retrospective	3 observational studies, 1 of poor and 2 of good quality	One study included only nondialysis patients while the other two studies included dialysis patients only. Effect estimates consistently and precisely suggested an association of Tn with the outcome, but directness is lost due to inclusion of non-ACS patients in one of the studies.

ACS = acute coronary syndrome; CKD = chronic kidney disease; CrCl = creatinine clearance; HR = hazards ratio; OR = odds ratio; TnI = troponin I; TnT = troponin T
*None of the studies included high-sensitivity troponin T or I

KQ 3.3: Direct Comparisons Between Troponin Assays to Estimate Prognosis After Acute Coronary Syndrome

Key Points

- We are unable to determine if there is a difference in the performance of troponin assays to estimate prognosis after ACS in patients with kidney disease based on three very heterogeneous studies with indirect and imprecise estimates (strength of evidence: insufficient).
- We did not identify any studies that included high sensitivity troponin I or T.

Results

Troponin T Versus Troponin I

Two studies directly compared troponin T and I by measuring performance in the prediction of composite cardiac ischemic endpoints; however they used different cutoff values and there were differences in the cardiac events comprising the outcome (Table 28).[63, 64] From these results, it is difficult to determine the extent to which differences in predicting prognosis are due to the type of troponin or to the cutoff the studies used. One of these studies also compared receiver operating curve characteristics and found the difference between the area under the curve for troponin T and I to be insignificant ($P = 0.213$).[63]

A study by Apple et al. compared four troponin assays in ACS patients with an estimated glomerular filtration rate less than 60 mL/min/1.73m^2 for a composite outcome of acute MI or death. These included troponin I by Beckman, Dade, and Tosoh, and troponin T by Roche. Six-month event rates were significantly different in elevated versus nonelevated troponin groups for all assays ($P < 0.05$ for all). Although there were differences in exact event rates between the assays, the study reported no measures of significance for these differences.[56]

Table 28. Results from studies directly comparing troponin T with troponin I to estimate prognosis after acute coronary syndrome

Troponin T Cutoff	Sensitivity	Specificity
0.01*	57%	88%
0.02†	75%	44%
0.10†	45%	72%
Troponin I Cutoff	**Sensitivity**	**Specificity**
0.35†	33%	78%
0.4*	57%	67%
0.6†	27%	83%
1.0†	21%	89%

*Results from Wayand, 2000[63]
†Results from Van Lente, 1999[64]

Troponin T Versus High-Sensitivity Troponin T

We did not identify any studies that met inclusion criteria and evaluated troponin T versus high-sensitivity troponin T.

Troponin I Versus High-Sensitivity Troponin I

We did not identify any studies that met inclusion criteria and evaluated troponin I versus high-sensitivity troponin I.

Strength of Evidence

We listed the strength of evidence for the body of literature addressing KQ3.3 in Tables 29 and 30. The strength of evidence is insufficient to compare the performance of troponin subclasses because the effects were not consistent; the precision could not be determined; the magnitude of effect was weak; and the rating is limited by the heterogeneity of the overall risk of bias of the assays the studies used, and the populations the studies included.

Table 29. Comparisons between troponin assays to estimate prognosis after acute coronary syndrome among patients with chronic kidney disease: Strength of evidence domains

Troponin Assay	Number of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Strength of Association	Strength of Evidence
Troponin T vs. troponin I	3 (824)	Medium	Consistent	Indirect	Imprecise	ROC 0.56 vs. 0.54 (p=0.7) 0.73 vs. 0.47 (p=0.2)	Insufficient

ROC = receiver operator curve

Table 30. Comparisons between troponin assays to estimate prognosis after acute coronary syndrome among patients with chronic kidney disease: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains-Comments About How Overall Strength of Evidence Derived
All-cause mortality	Troponin T vs. troponin I	3 prospective	1 poor quality, 1 fair quality, and 1 good quality study	Two studies directly compared TnT with TnI and found no significant difference, however, they used different assays and cutoffs and measured different endpoints.

TnI = troponin I; TnT = troponin T

KQ 4: Use of Troponin for Risk Stratification Among Chronic Kidney Disease Patients Without Acute Coronary Syndrome

Study Design Characteristics

We included 98 studies (in 105 publications) that evaluated the use of troponin levels for risk stratification among patients with chronic kidney disease (CKD) without acute coronary syndrome (ACS) symptoms, KQ 4.[9, 11, 25, 26, 47, 65-163]

The studies took place in diverse countries, including 18 in the United States, 8 in Canada, 60 in Europe, 10 in Asia, 3 in Middle-East, 1 in Mexico, 6 in Australia, and 1 in multiple countries.

Studies varied in their sources of support. Twenty-four received industry funding, 26 reported no industry support, and the remainder did not report on support.

All studies were observational cohort studies. Enrollment into 21 studies started and ended before or in 2000,[26, 89, 94, 98, 100, 104, 114, 118, 121, 122, 124, 127, 133, 138, 140, 142-144, 151, 152, 167] while 45 studies did not report the dates of enrollment period.[11, 47, 69, 70, 75-77, 79, 81, 82, 87, 91, 93, 102, 103, 106, 110-113, 116, 117, 120, 123, 125, 126, 128-132, 134-137, 139, 141, 145-150, 153, 155]

The median study followup time ranged from 30 days to 5 years.

Forty-six studies recruited patients in the outpatient setting, 50 took place in hospital setting, and 36 in dialysis centers.

Study Population Characteristics

The characteristics of studies included in KQ4 are outlined in Table 31. The study sample size ranged from 16[151] to 8,121.[69] Five studies did not report the age distributions.[65, 70, 76, 121, 140] Among others, the mean/median age of study populations ranged from 32[115] to 77 years.[25] Six studies did not report gender distribution.[65, 76, 116, 126, 129, 146] Two studies included only men.[93, 148] Among other studies, the percentage of men ranged from 14 percent[154] to about 80 percent.[121]

Sixty-five studies specifically excluded ACS patients, while 38 studies did not report ACS inclusion/exclusions. Seven studies included patients with CKD stage 1 to 4; one included patients with CKD stage 3 to 4; eight included patients with CKD stage 5; 75 included dialysis patients; and six studies included kidney transplant patients. Eight used the Modification of Diet in Renal Disease equation; two used the CKD-Epi equation; and five used the Cockcroft-Gault formula.

Table 31. Population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Mockel, 1999[147]	Both	40	Europe	Range: 28 to 78	NR	55	NR
Musso, 1999[148]	Both	Total: 166 CKD: 49	Europe	NR	NR	NR	0
Farshid, 2013[160]	Both	153	Australia	66	NR	58	NR
Hickman, 2009[77]	Dialysis	143	Australia	60	W, 89 AA, 4 Other, 7	63	NR
McGill, 2010[76]	Dialysis	143	Australia	NR	NR	NR	NR
Roberts, 2009[85]	Dialysis	81	Australia	NR	NR	55	NR
Choy, 2003[126]	Dialysis	113	Canada	Median: 63	NR	NR	NR
Holden, 2012[72]	Dialysis	103	Canada	63	NR	69	47
Morton, 1998[150]	Dialysis	112	Canada	61	NR	62	47
Ooi, 2001[140]	Dialysis	244	Canada	NR	NR	60	33
Troyanov, 2005[109]	Dialysis	101	Canada	66	NR	57	37
Scott, 2003[130]	Dialysis	71	Europe	69	NR	51	NR
Artunc, 2012[66]	Dialysis	239	Europe	Median: 70	NR	64	74
Beciani, 2003[129]	Dialysis	101	Europe	64	NR	68	NR
Boulier, 2004[119]	Dialysis	191	Europe	Median: 67	NR	51	33
Brunet, 2008[96]	Dialysis	105	Europe	65.5	NR	59	31
Codognotto, 2010[75]	Dialysis	50	Europe	68	NR	72	NR
Conway, 2005[107]	Dialysis	75	Europe	Median: 64	NR	60	33
Deegan, 2001[137]	Dialysis	73	Europe	Median: 64	NR	58	25
Dierkes, 2000[141]	Dialysis	102	Europe	64	NR	49	28
Fernandez-Reyes, 2004[114]	Dialysis	58	Europe	70	NR	50	22

Table 31. Population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome (continued)

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Geerse, 2012[65]	Dialysis	206	Europe	65	NR	52	40
Hallen, 2011[74]	Dialysis	107	Europe	62	NR	75	27
Helleskov Madsen, 2008[92]	Dialysis	109	Europe	62	NR	75	27
Hocher, 2008[89]	Dialysis	230	Europe	66	NR	49	27
Hojs, 2005[111]	Dialysis	90	Europe	56	NR	61	NR
Ie, 2004[116]	Dialysis	49	Europe	57	NR	NR	NR
Iliou, 2003[26]	Dialysis	258	Europe	60	W, 72 AA, 16 Other, 13	58	23
Katerinis, 2008[93]	Dialysis	50	Europe	63	NR	64	40
Lang, 2001[139]	Dialysis	100	Europe	57	NR	62	NR
Le Goff, 2007[155]	Dialysis	86	Europe	60	NR	53	53
Mallamaci, 2002[136]	Dialysis	199	Europe	59	NR	56	NR
Petrovic, 2009[81]	Dialysis	115	Europe	53	NR	62	NR
Sahinarslan, 2008[87]	Dialysis	78	Europe	53	NR	69	NR
Sharma, 2006[106]	Dialysis	126	Europe	52	W, 50 AA, 25 Other, 25	63	38
Stolear, 1999[145]	Dialysis	94	Europe	63	NR	59	NR
Svensson, 2009[153]	Dialysis	206	Europe	67	NR	65	100
Trape, 2008[86]	Dialysis	52	Europe	Median: 74	NR	48	46
Sommerer, 2007[97]	Dialysis	134	Germany	Median: 66	NR	60	21
Wang 2007[98]	Dialysis	238	Hong Kong	56	NR	51	20
Bagheri,2009[83]	Dialysis	138	Iran	65	NR	52	NR
Ishii, 2001[138]	Dialysis	100	Japan	54	NR	61	NR
Havekes, 2006[104]	Dialysis	847	Netherlands	59	NR	60	NR
Hussein, 2004[117]	Dialysis	93	Saudi Arabia	50	NR	49	20
Han, 2009[91]	Dialysis	107	South Korea	52	NR	46	NR
Kang, 2009[88]	Dialysis	121	South Korea	66	NR	44	27
Kalaji, 2012[67]	Dialysis	145	Syria	Median: 45	NR	55	9
Hung, 2004[120]	Dialysis	70	Taiwan	NR	NR	38	NR
Vichairuangthum, 2006[103]	Dialysis	63	Thailand	NR	NR	47	NR
Abaci, 2004[113]	Dialysis	129	Turkey	44	NR	55	NR
Duman, 2005 [112]	Dialysis	65	Turkey	56	NR	55	15
Yakupoglu, 2002[135]	Dialysis	38	Turkey	56	NR	42	NR
Apple, 1997[151]	Dialysis	16	U.S.	46	NR	44	9
Apple, 2002[133]	Dialysis	733	U.S.	62	W, 60 AA, 23 H, 3	56	29
deFilippi, 2003[127]	Dialysis	224	U.S.	Median: 62	W, 38 AA, 38 H, 21	54	36
Farkouh, 2003[131]	Dialysis	137	U.S.	NR	NR	NR	NR
Gaiki, 2012[70]	Dialysis	51	U.S.	62	W, 18 AA, 61 Hi, 14 Other, 8	53	31
Kanwar, 2006[101]	Dialysis	173	U.S.	62	W, 57	53	NR
Khan, 2001[11]	Dialysis	126	U.S.	NR	NR	61	NR

Table 31. Population characteristics of studies evaluating the use of troponin levels in risk stratification among patients with chronic kidney disease without symptoms of acute coronary syndrome (continued)

Author, Year	Dialysis Population	Sample Size	Location	Mean Age in Years	Race, %	% Male	% CAD
Porter, 1998[149]	Dialysis	30	U.S.	66	NR	40	100
Porter, 2000[142]	Dialysis	27	U.S.	48	NR	41	15
Roppolo, 1999[146]	Dialysis	49	U.S.	59	NR	NR	NR
Satyan, 2007[95]	Dialysis	150	U.S.	56	AA, 90	NR	NR
Wolley, 2013 [158]	Dialysis	239	New Zealand	Median; 63	W, 28% Asian 8% Pacific 49% African 0.5%	51	33
Assa, 2013 [157]	Dialysis	90	Europe	Median; 67	NR	52	40
Artunc, 2012 [66]	Dialysis	239	Europe	Median; 70	NR	64	31
Gaiki, 2012 [70]	Dialysis	51	U.S.	62	W, 18 AA, 61 Asian 8 H, 14	53	31
Alam, 2013[162]	Dialysis	133	Canada	65*	NR	72*	28*
Hassan, 2014[163]	Dialysis	431	Australia	64	NR	59	NR
Lamb, 2007[99]	No	227	England	67	W, 100	65	41
Scheven, 2012[69]	No	8121	Europe	49	NR	50	NR
Abbas, 2005[108]	No	Total: 227 CKD: 222	Europe	67	NR	65	NR
Claes, 2010 [78]	No	331	Europe	Median: 53	NR	NR	24
Connolly, 2008[94]	No	372	Europe	47	NR	64	NR
Feringa, 2006[100]	No	Total: 558 CKD: 240	Europe	67	NR	77	43
Goicoechea, 2004[25]	No	176	Europe	Median: 68	NR	62	18
Ilva, 2008[154]	No	Total: 364 CKD: 163	Europe	75	NR	14	30
Kertai, 2004[121]	No	393	Europe	NR	NR	80	NR
Lowbeer, 2002[134]	No	26	Europe	58	NR	50	19
Lowbeer, 2003[132]	No	115	Europe	52	NR	62	29
Sharma, 2006[105]	No	114	Europe	52	W, 45 AA, 29 Other, 1	67	30
Wood, 2003[125]	No	96	Europe	52	NR	67	24
Hasegawa, 2012[68]	No	442	Japan	69	NR	63	NR
Orea-Tejada, 2010[79]	No	152	Mexico	64	NR	54	NR
Bozbas, 2004[115]	No	34	Turkey	31.8	NR	68	12
Hickson, 2008[90]	No	644	U.S.	51	W, 98	56	34
Hickson, 2009[84]	No	603	U.S.	51	W, 98	57	29
Shroff, 2012[71]	No	376	U.S.	NR	W, 86 AA, 5	59	23
McMurray, 2011[73]	No	3857	Worldwide	NR	NR	NR	NR
Quiroga 2013 [156]	No	218	Europe	Median: 69	NR	62	38
Levin, 2014[159]	No	2402	Canada	68	W, 89	63	NR
Bayes-Genis, 2013[161]	No	Total: 879 CKD: 542	Europe	Median: 70	W, 100	72	NR

AA = African American; CAD = coronary artery disease; CKD = chronic kidney disease; H = Hispanic; NR = not reported; U.S. = United States; W = white

*Among patients with troponin I $\geq$ 0.06 mcg/L.

Study Quality

Table 32 describes the quality of studies for KQ4. We rated the overall study quality fair to good as described in methods section. Although the adjustment of confounders was one of the factors considered in study quality assessment, it was not the only factor (i.e., a study could still have fair or good quality even without confounder adjustment if it was otherwise a well-done study with clear cutpoints, clear reporting of outcome ascertainment, and appropriate statistical methods, etc). Industry funding was not factored into the overall quality assessment, but we listed it here for reference.

Table 32. Select quality scores for studies evaluating the risk associated with elevated troponin among patients with chronic kidney disease

Author, Year	Blinding Those Measuring Outcomes	Adjust For Different Followup Length	Adequate Adjustment For Confounding In Analyses	Losses To Followup Taken Into Account	Industry Support	Overall Quality
Abaci, 2004[113]	No	Yes	Yes some	Yes	NR	Fair
Abbas, 2005[108]	UTD	Yes	Yes	Yes	Yes	Fair
Alam, 2013[162]	Yes	Yes	Yes	Yes	No	Good
Apple, 1997[151]	UTD	Yes	No	Yes	Yes	Fair
Apple, 2002[133]	No	Yes	Yes some	Yes	Yes	Fair
Apple, 2004[118]	UTD	Yes	Yes some	Yes	Yes	Good
Artunc, 2012[66]	UTD	Yes	UTD	Yes	NR	Fair
Assa, 2013 [157]	UTD	Yes	Yes	UTD	NR	Fair
Bagheri, 2009[83]	No	Yes	No	Yes	NR	Fair
Bayes-Genis, 2013[161]	UTD	Yes	Yes	Yes	NR	Good
Boulier, 2004[119]	UTD	Yes	Yes	Yes	Yes	Good
Bozbas, 2004[115]	UTD	Yes	No	Yes	NR	Poor
Brunet, 2008[96]	No	Yes	No	Yes	Yes	Good
Choy, 2003[126]	Yes	Yes	Yes	Yes	Yes	Good
Chrysochou, 2009[82]	UTD	Yes	Yes	Yes	NR	Fair
Claes, 2010[78]	UTD	Yes	Yes	Yes	NR	Good
Codognotto, 2010[75]	No	Yes	No	Yes	No	Fair
Connolly, 2008[94]	No	Yes	Yes	Yes	No	Good
Conway, 2005[107]	UTD	Yes	No	Yes	NR	Fair
Deegan, 2001[137]	Yes	Yes	Yes some	Yes	NR	Fair
deFilippi, 2003[127]	UTD	Yes	Yes	Yes	Yes	Fair
Dierkes, 2000[141]	Yes	Yes	Yes some	Yes	NR	Good
Duman, 2005[112]	Yes	Yes	Yes	Yes	No	Fair
Farkouh, 2003[131]	UTD	Yes	Yes	Yes	NR	Fair
Farshid, 2013[160]	No	Yes	Yes	Yes	No	Good
Feringa, 2006[100]	No	Yes	No	Yes	NR	Good
Fernandez-Reyes, 2004[114]	UTD	UTD	No	UTD	NR	Fair
Gaiki, 2012[70]	No	Yes	No	Yes	NR	Fair
Geerse, 2012[65]	UTD	Yes	Yes some	Yes	NR	Fair
Goicoechea, 2004[25]	Yes	Yes	Yes	Yes	NR	Good
Hallen, 2011[74]	No	Yes	Yes	Yes	NR	Fair
Han, 2009[91]	Yes	Yes	Yes some	Yes	NR	Fair
Hasegawa, 2012[68]	Yes	Yes	Yes	Yes	NR	Fair
Hassan, 2014[163]	UTD	Yes	Yes	Yes	No	Good
Havekes, 2006[104]	UTD	Yes	Yes	Yes	No	Fair
Helleskov Madsen, 2008[92]	Yes	Yes	Yes some	Yes	No	Good
Hickman, 2009[77]	No	Yes	Yes	Yes	NR	Good
Hickson, 2008[90]	UTD	Yes	Yes	Yes	No	Good

Table 32. Select quality scores for studies evaluating the risk associated with elevated troponin among patients with chronic kidney disease (continued)

Author, Year	Blinding Those Measuring Outcomes	Adjust For Different Followup Length	Adequate Adjustment For Confounding In Analyses	Losses To Followup Taken Into Account	Industry Support	Overall Quality
Hickson, 2009[84]	UTD	Yes	Yes	Yes	No	Good
Hocher, 2003[124]	UTD	Yes	Yes	Yes	No	Good
Hocher, 2004[122]	UTD	Yes	Yes	Yes	No	Good
Hocher, 2008[89]	UTD	Yes	Yes	Yes	No	Good
Hojs, 2005[111]	UTD	Yes	No	Yes	NR	Poor
Holden, 2012[72]	UTD	Yes	Yes	Yes	NR	Good
Hussein, 2004[117]	No	No	No	No	NR	Fair
Ie, 2004[116]	UTD	Yes	No	Yes	NR	Fair
Iliou, 2003[26]	UTD	Yes	Yes	Yes	Yes	Good
Ilva, 2008[154]	Yes	Yes	Yes some	Yes	Yes	Good
Ishii, 2001[138]	Yes	Yes	Yes	Yes	Yes	Good
Kalaji, 2012[67]	UTD	Yes	Yes	Yes	NR	Fair
Kang, 2009[88]	No	Yes	Yes	Yes	No	Fair
Kanwar, 2006[101]	Yes	Yes	Yes	Yes	Yes	Good
Katerinis, 2008[93]	UTD	Yes	No	Yes	NR	Poor
Kertai, 2004[121]	UTD	Yes	Yes some	Yes	NR	Fair
Khan, 2001[11]	Yes	Yes	Yes	Yes	NR	Good
Lamb, 2007[99]	UTD	Yes	Yes	Yes	Yes	Good
Lang, 2001[139]	UTD	UTD	No	Yes	Yes	Fair
Le Goff, 2007[155]	UTD	UTD	Yes some	UTD	NR	Fair
Levin, 2014[159]	UTD	Yes	Yes	Yes	Yes	Good
Lowbeer, 2002[134]	No	Yes	Yes	Yes	No	Fair
Lowbeer, 2003[132]	UTD	Yes	Yes	Yes	No	Fair
Mallamaci, 2002[136]	UTD	Yes	Yes	Yes	NR	Good
McGill, 2010[76]	UTD	Yes	Yes some	Yes	No	Fair
McMurray, 2011[73]	No	Yes	Yes some	Yes	Yes	Fair
Mockel, 1999[147]	Yes	Yes	Yes	UTD	Yes	Fair
Morton, 1998[150]	No	UTD	Yes some	UTD	No	Good
Musso, 1999[148]	UTD	UTD	No	No	NR	Fair
Ooi, 1999[144]	No	Yes	Yes	Yes	NR	Fair
Ooi, 2001[140]	No	Yes	Yes some	Yes	Yes	Good
Orea-Tejeda, 2010[79]	No	Yes	Yes	Yes	No	Fair
Petrovic, 2009[81]	UTD	Yes	UTD	UTD	NR	Fair
Porter, 1998[149]	No	Yes	No	Yes	NR	Fair
Porter, 2000[142]	UTD	UTD	UTD	Yes	Yes	Fair
Quiroga 2013 [156]	No	No	Yes, some	UTD	No	Fair
Roberts, 2009[85]	UTD	Yes	No	Yes	Yes	Fair
Sahinarslan, 2008[87]	UTD	UTD	Yes	UTD	NR	Fair
Satyan, 2007[95]	Yes	Yes	Yes	Yes	No	Good
Scheven, 2012[69]	UTD	Yes	Yes	Yes	No	Fair
Scott, 2003[130]	UTD	Yes	Yes some	Yes	No	Good
Sharma, 2005[110]	UTD	Yes	Yes some	Yes	NR	Good
Sharma, 2006[105]	UTD	Yes	No	Yes	NR	Fair
Sharma, 2006[106]	No	Yes	Yes some	Yes	No	Fair
Shroff, 2012[71]	UTD	Yes	No	UTD	Yes	Fair
Sommerer, 2007[97]	UTD	Yes	UTD	Yes	NR	Fair
Stolear, 1999[145]	No	Yes	Yes some	Yes	Yes	Good
Svensson, 2009[153]	UTD	Yes	Yes some	Yes	Yes	Fair
Trape, 2008[86]	No	Yes	Yes	Yes	NR	Good
Troyanov, 2005[109]	No	No	Yes some	UTD	Yes	Fair
Vichairuangthum, 2006[103]	No	Yes	Yes	Yes	NR	Fair
Wang, 2006[102]	No	Yes	Yes	Yes	No	Good

Table 32. Select quality scores for studies evaluating the risk associated with elevated troponin among patients with chronic kidney disease (continued)

Author, Year	Blinding Those Measuring Outcomes	Adjust For Different Followup Length	Adequate Adjustment For Confounding In Analyses	Losses To Followup Taken Into Account	Industry Support	Overall Quality
Wang, 2007[98]	UTD	Yes	Yes some	Yes	No	Good
Wang, 2010[152]	UTD	Yes	Yes	Yes	No	Good
Wolley, 2013 [158]	UTD	No	Yes some	UTD	No	Fair
Wood, 2003[125]	UTD	Yes	Yes some	Yes	NR	Fair
Yakupoglu, 2002[135]	UTD	UTD	No	Yes	NR	Fair

NR = not reported; UTD = unable to determine

Results: Inclusion of Studies in Meta-Analysis for KQ 4

Appendix E Tables 1-7 outline the studies used in meta-analysis for KQ4, and whether they were included in meta-analyses for hazard ratios (HR), odds ratios (OR), or excluded from both meta-analyses. We excluded studies from meta-analyses if there was insufficient information to derive any HR or OR, if the study presented troponin as a continuous variable rather than a cutpoint, or if the cutpoint for troponin elevation was unclear. Also, if there are multiple papers of results derived from the same cohort, we presented results from each unique cohort once for each outcome. We also noted the reasons for exclusion in Appendix E Tables 1-7. The meta-anlayses for HRs are stratified by the level of adjustment. The list of covariates for each study is presented in Appendix F.

After performing the literature search, it became clear that the majority of studies reported results in a cohort of patients receiving dialysis. The other studies were a mix of CKD stages 1-5 including or excluding dialysis patients. To avoid further heterogeneity, we presented outcome results for dialysis and nondialysis patients separately in regard to KQs 4.1 and 4.2.

Results for Patients on Dialysis

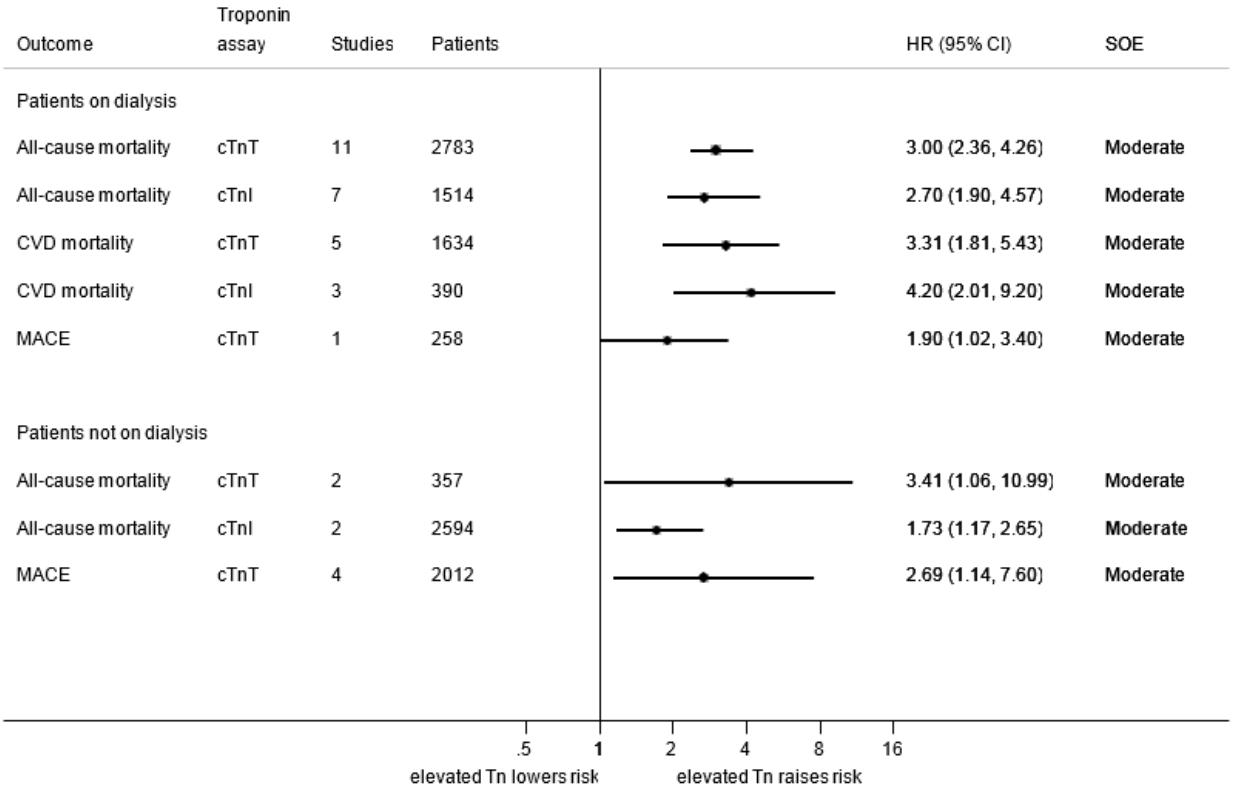
Key Points

- Among dialysis patients without suspected ACS, a baseline elevated value of cardiac troponin was associated with a higher risk (~2-4 fold) for subsequent short- and long-term outcomes including all-cause mortality, cardiovascular-specific mortality, and MACE (i.e., "composite" outcome of MI, cardiovascular death, and/or revascularization) in models adjusted at least for age and CAD or risk equivalent (Figure 6).
- More of the studies we included in the pooled meta-analyses reported outcomes for all-cause mortality than for other outcomes. Thus, the evidence from the pooled meta-analysis is strongest for the association of elevated cardiac troponin with all-cause mortality.
- We found approximately a 3-fold increased risk for the association of cardiac troponin T and I with all-cause mortality, which was highly significant (strength of evidence: moderate). The evidence from meta-analyses for an association of elevated cardiac troponin with cardiovascular-specific mortality and MACE showed similar effect sizes but with wider confidence intervals (CIs) from fewer studies (strength of evidence: moderate for CVD mortality for Troponin T and I; moderate for MACE for Troponin T with insufficient evidence for MACE for Troponin I).
- The association of elevated troponin with adverse outcomes among dialysis patients was generally similar for troponin T versus I. Few studies reported results for high-sensitivity

troponin T and high-sensitivity troponin I assays; thus, less is known about how well these assays predict risk (strength of evidence: low).

- A sensitive assay identifies more patients as being elevated.
- While almost all studies supported a positive association for elevated cardiac troponin with adverse cardiovascular outcomes, particularly mortality, there was substantial heterogeneity among the studies, even though troponin T and I were analyzed separately.
- Much of the heterogeneity across results stemmed from differences across the literature between the various types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing, and newer generations of assays can detect lower concentrations of cardiac troponin. Many of the articles did not report which generation of assay they used.
- The studies varied markedly regarding which cutpoints they selected to define as elevated. Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold was also a changing target depending on what reference population or assay generation was used. The reference populations for the 99th percentiles were largely unclear, and were most likely not taken from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported in each study with the lowest cutpoint for consistency.
- The meta-analyses we performed for the pooled ORs were unadjusted results using number of events in each arm. For the meta-analyses for HRs, we selected the most-adjusted regression model. Many studies only reported an unadjusted HR. While many studies did adjust for age, few studies adjusted for a history of CAD, CAD risk equivalent (such as diabetes mellitus), or for other causes of elevated troponin, such as heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors, such as systolic blood pressure, dyslipidemia, and smoking. However, associations generally did remain robust in adjusted models (when available) and thus we considered them reliable.
- Studies almost exclusively looked at the association of troponin with outcomes in regression models, but did not examine the utility of troponin as a useful marker for prediction by metrics of reclassification or discrimination (i.e. show whether troponin improves re-classification of individuals into lower or higher clinical risk groups).
- Only one study[104] rigorously examined whether troponin testing among dialysis patients added incremental prognosis over routine clinical and laboratory factors, but troponin testing did not change the area under curve in their survival model. Thus, it is unknown whether measuring cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables.
- All of the studies related to this question were observational cohort studies. We did not find any intervention studies that compared management strategies of dialysis patients (without suspected ACS) on the basis of elevated troponin. Thus, while elevated cardiac troponin is clearly a marker of increased risk for subsequent cardiac events, it is unknown whether changing patient management (such as more intensified preventive efforts) on the basis of elevated troponin can reduce cardiovascular morbidity and mortality.

Figure 6. Summary of the meta-analysis results of the pooled hazard ratios from studies that adjusted for at least age and CAD (or risk equivalent) for the association of an elevated troponin with outcomes among dialysis and nondialysis patients*



CI = confidence interval; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CVD = cardiovascular disease; HR = hazard ratio; MACE = major adverse cardiovascular events; SOE = strength of evidence; Tn = troponin

* The strength of evidence for other outcomes not listed here was graded as insufficient because we did not find any studies addressing them or because we were unable to draw a conclusion from the evidence.

KQ 4.1.a: Distribution of Troponin Values Among Patients on Dialysis

The number (percent) of the study populations with elevated troponin values is noted in Table 33. This was only available for studies that listed the number of patients with elevated values out of the total sample. Some studies did not provide this information. As outlined in our methods section, we only abstracted data from studies that also reported outcomes. We did not abstract studies that reported on the prevalence of elevated troponin in their cohort but had no outcome data and thus we did not include them in this list.

Prevalences depend on the clinical characteristics (i.e., pre-test probability) of each study group as well as the heterogeneity between assays and cutpoints. As such, we found prevalences widely varied across studies. For troponin T, the prevalence of dialysis patients with troponin levels above cutpoints ranged from 12 to 82 percent. Some of the heterogeneity was due to different cutpoints the studies used to define "elevated," but heterogeneity across studies remained even when studies used similar cutpoints. In general, lower cutpoints (i.e., 0.03 mcg/L) identified a higher prevalence of patients defined as elevated, as would be anticipated by a more sensitive cutpoint. For example, the prevalence of elevated troponin for cutpoints 0.01 to 0.03 mcg/L ranged from 45 to 82 percent. A more conservative cutpoint (such as 0.1 mcg/L) had a lower prevalence of patients defined as elevated. Still, even for a cutpoint of 0.1 mcg/L, the prevalence ranged from 12 to 50 percent across cohorts, averaging around 25 percent.

For troponin I, the prevalence of patients defined as elevated ranged from 6 to 60 percent. There was no clear pattern of prevalence by cutpoints across studies. For low cutpoints (0.01 to 0.03 mcg/L), the prevalence ranged from 19 to 60 percent. For higher cutpoints (0.3 mcg/L), the prevalence ranged from 6 to 30 percent. Of note, one study used a high cutpoint of 2.3 mcg/L,[135] and the prevalence was still high at 21 percent.

Some studies evaluated prevalences of elevated troponin in the same population as noted in Table 33 below. For example, in a study by Apple et al 2002, the prevalence of elevated troponin T (>0.1 mcg/L) was 20 percent but the prevalence of elevated troponin I (>0.1 mcg/L) was 6 percent when tested in the same cohort of patients.

Table 33. Prevalence of elevated baseline troponin T and I levels at maximum cut-point among patients on dialysis

Author, year	Troponin T Assay	Troponin T Cutpoint (mcg/L)	% with Elevated Troponin T	Troponin I Assay	Troponin I Cutpoint (mcg/L)	% with Elevated Troponin I
Dierkes, 2000[141]	Roche	>0.1	12	NA	NA	NA
Conway, 2005[107]	Roche	>0.1	17	NA	NA	NA
Iliou, 2003[26]	Roche	>0.1	19	NA	NA	NA
Apple, 2002[133]	Roche	>0.1	20	Dade	>0.1	6
Han, 2009[91]	Roche	>0.1	20	NA	NA	NA
Abaci, 2004[113]	Roche	>0.1	21	Abbott	>0.5	24
Kalaji, 2012[67]	Roche	>0.1	21	Siemens	>0.2	35
Lang, 2001[139]	Boehringer Mannheim	>0.1	22	Dade	>0.4	7
Sahinarslan, 2008[87]	NR	>0.1	22	NA	NA	NA
Ishii, 2001[138]	Roche	>0.1	25	Beckman	>0.1	6
Hickman, 2009[77]	Roche	>0.098	25	Abbott	>0.043	25
Trape, 2008[86]	Roche	>0.1	25	NA	NA	NA
Hassan, 2014[163]	Roche	>0.101	25	NA	NA	NA
deFilippi, 2003[127]	Roche	>0.117	25	NA	NA	NA
Brunet, 2008[96]	Roche	>0.1	27	Beckman	>0.06	18
Hojs, 2005[111]	Roche	>0.1	27	NA	NA	NA
Deegan, 2001[137]	Boehringer Mannheim	>0.1	27	NA	NA	NA
Sharma, 2005[110]	Roche	>0.1	30	NA	NA	NA
Ooi, 2001[140]	Roche	>0.1	30	NA	NA	NA
Wang, 2007[98]	Roche	>0.1	35	NA	NA	NA
Porter, 2000[142]	Roche	>0.1	37	Dade	>0.4	11
Choy, 2003[126]	Roche	>0.1	42	Dade	>0.5	15
Duman, 2005[112]	Roche	>0.035	45	DPC	>0.06	6
Stolear, 1999[145]	Boehringer Mannheim	>0.1	50	NA	NA	NA
Farshid, 2013[160]	Roche	>0.01	52	NA	NA	NA
Helleskov Madsen, 2008[92]	Roche	>0.03	52	Beckman	>0.06	11
Lowbeer, 2002[134]	Boehringer	>0.04	54	NA	NA	NA
Hallen, 2011[74]	Roche	>0.01	60	NA	NA	NA
Apple, 1997[151]	Boehringer	>0.2	75	NR	>0.8	19
Ie, 2004[116]	Roche	>0.03	82	NA	NA	NA
Roppolo, 1999[146]	NA	NA	NA	Dade	>0.5	6
Farkouh, 2003[131]	NA	NA	NA	Dade	>1	7
Porter, 1998[149]	NA	NA	NA	Dade	>0.4	7
Katerinis, 2008[93]	NA	NA	NA	Beckman	>0.09	8
Hussein, 2004[117]	NA	NA	NA	Abbott	>0	10
Roberts, 2004[123]	NA	NA	NA	Abbott	>0.3	10
Geerse, 2012[65]	NA	NA	NA	Siemens	>0.1	12
Khan, 2001[11]	NA	NA	NA	Sanofi	>0.03	19
Yakupoglu, 2002[135]	NA	NA	NA	DPC	>2.3	21
Vichairuangthum, 2006[103]	NA	NA	NA	Johnson & Johnson	>0.4	22
Alam, 2013[162]	NA	NA	NA	Beckman	>0.06	27
Beciani, 2003[129]	NA	NA	NA	Dade	>0.15	29
Kang, 2009[88]	NA	NA	NA	Beckman	>0.2	30
Kanwar, 2006[101]	NA	NA	NA	Beckman	>0.01	60
Sommerer, 2007[97]	Roche	>0.026	NA	NA	NA	NA
Gaiki 2012 [70]	NA	NA	NA	Ortho Vitros ES	>0.035	51
Hung, 2004[120]	NA	NA	NA	DPC	>0.2	NA

DPC = Diagnostic Products Corporation; mcg/L = micrograms per liter; NA = not applicable

KQ 4.2a: Troponin Associations With Short- and Long-term Outcomes Among Patients on Dialysis

The Association of Cardiac Troponin T With All-Cause Mortality Among Patients on Dialysis

Overview

Forty-three unique patient cohorts (among 49 publications) presented results regarding the association of baseline troponin T levels with all-cause mortality among dialysis (only) patients without symptoms of ACS.[26, 66, 67, 72, 74, 75, 77, 81, 83, 85-87, 89, 92, 95, 96, 98, 104, 106, 110, 112-114, 116, 118, 122, 124, 126, 127, 130, 133, 134, 136-142, 144, 145, 147-149, 153, 155, 157, 160, 163]

We excluded ten studies from the meta-analyses of both HRs and ORs due to insufficient data, or because the studies did not present results separately for dialysis patients only. We included the remaining studies in HR meta-analysis, OR meta-analysis, or both. We included a summary of the inclusion and exclusion reasons in Appendix E, Table 1.

Followup Time

All studies except one had a followup time for mortality events equal or greater to 1 year with time ranging from 1 to 5 years. Choy[126] reported a followup time of only 6 months.

Assays and Cut-Points

The cardiac troponin T assay was generally measured by one manufacturer (Roche) or by Boehringer Mannheim, which was acquired by Roche Diagnostics in 1997. The most common cut-point studies used to define elevated troponin was a troponin T greater than 0.1 mcg/L, with a cut-point of more than 0.03 mcg/L being the second most common. These do not clearly reflect the 99th percentile (as compared with Appendix G, which outlines the 99th percentile by assay as described by the manufacturer). However, the 99th percentile is a changing target based on the assay generation and reference population. Many of the articles did not clearly state which generation of assay they used, or whether the cut-point was the 99th percentile value or some other threshold. Some studies chose a value selected by a Receiver Operator Curve analysis. Therefore it was difficult to compare studies across the 99th percentile.

Hazard Ratio for All-Cause Mortality Associated With Elevated Cardiac Troponin T

We listed the results from the meta-analysis (n=21 studies) stratified by the level of adjustment that presented HRs for the association of elevated troponin T with all-cause mortality among dialysis patients in Figure 7. All studies we included in this meta-analysis have reported a HR with CIs or we were able to derive the CIs using the spreadsheet provided by Tierney et al.[32]

Of these studies, six were unadjusted, 15 adjusted at least for age, and 11 adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes.

In all studies, there was a positive association between elevated cardiac troponin T and all-cause mortality (HR >1.0), although the HRs varied widely—from as low as 1.07 up to 15.5. Most studies were statistically significant, but in three of the 21 studies the CIs crossed 1.0, although the effect estimate was similar to the other studies which were statistically significant.

The pooled meta-analysis for the HR among studies that adjusted for at least age and CAD or risk equivalent was statistically significant and provided evidence for a 3-fold increased risk of all-cause mortality associated with elevated troponin T (HR, 3.0; 95% CI, 2.4 to 4.3); heterogeneity not significant (I-squared, 42 percent).

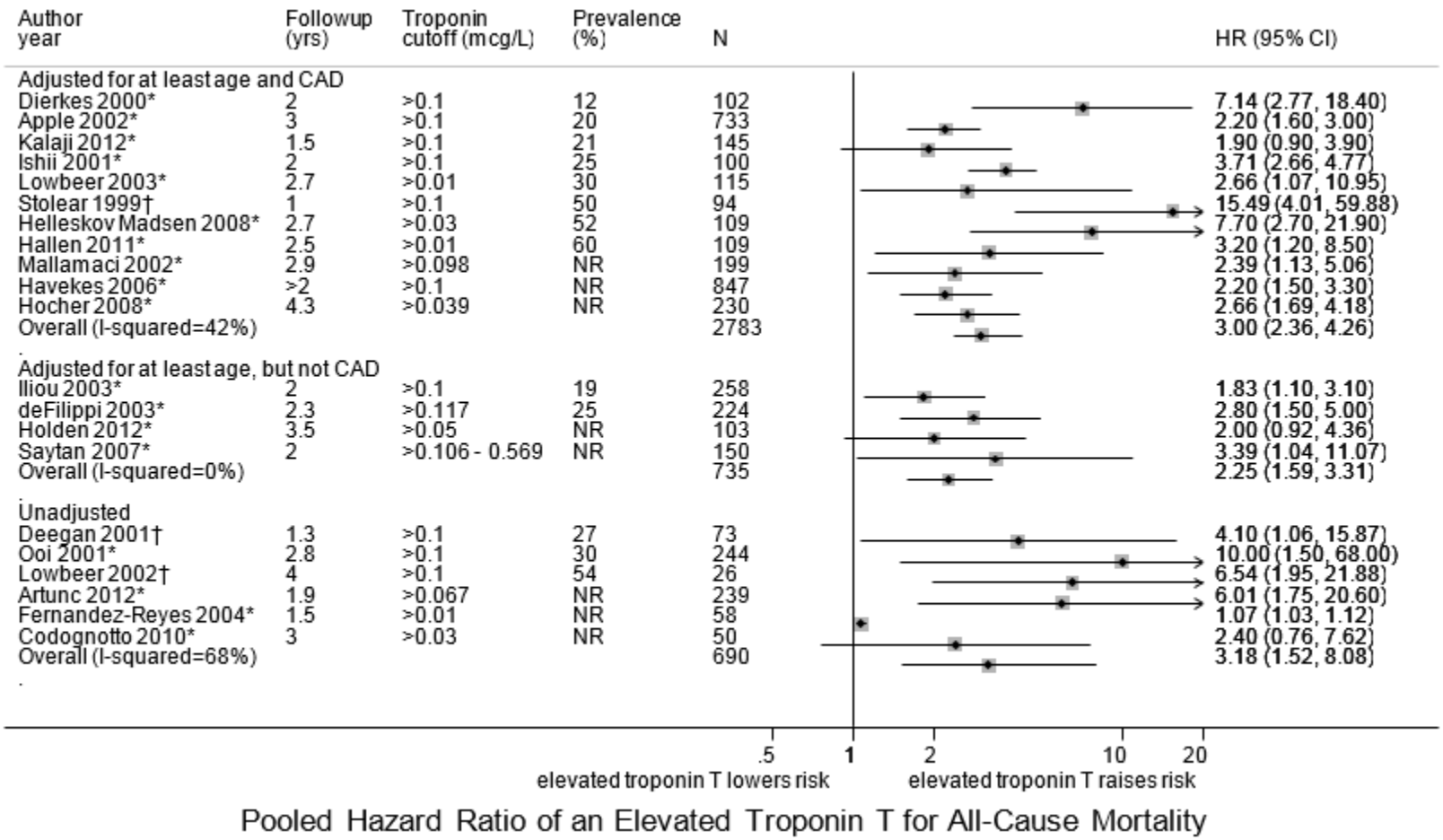
Figure 7 includes studies stratified by level of adjustment, but we also viewed data sorted by year of publication. We found no temporal trends (in terms of strength of association or statistical significance).

Odds Ratio for All-Cause Mortality Associated With Elevated Cardiac Troponin T

Twenty-four studies provided the number of events among elevated and nonelevated troponin T groups making it possible to determine an unadjusted OR. Figure 8 presents the results from the pooled meta-analysis for the unadjusted OR for all-cause mortality by elevated troponin T level among dialysis patients.

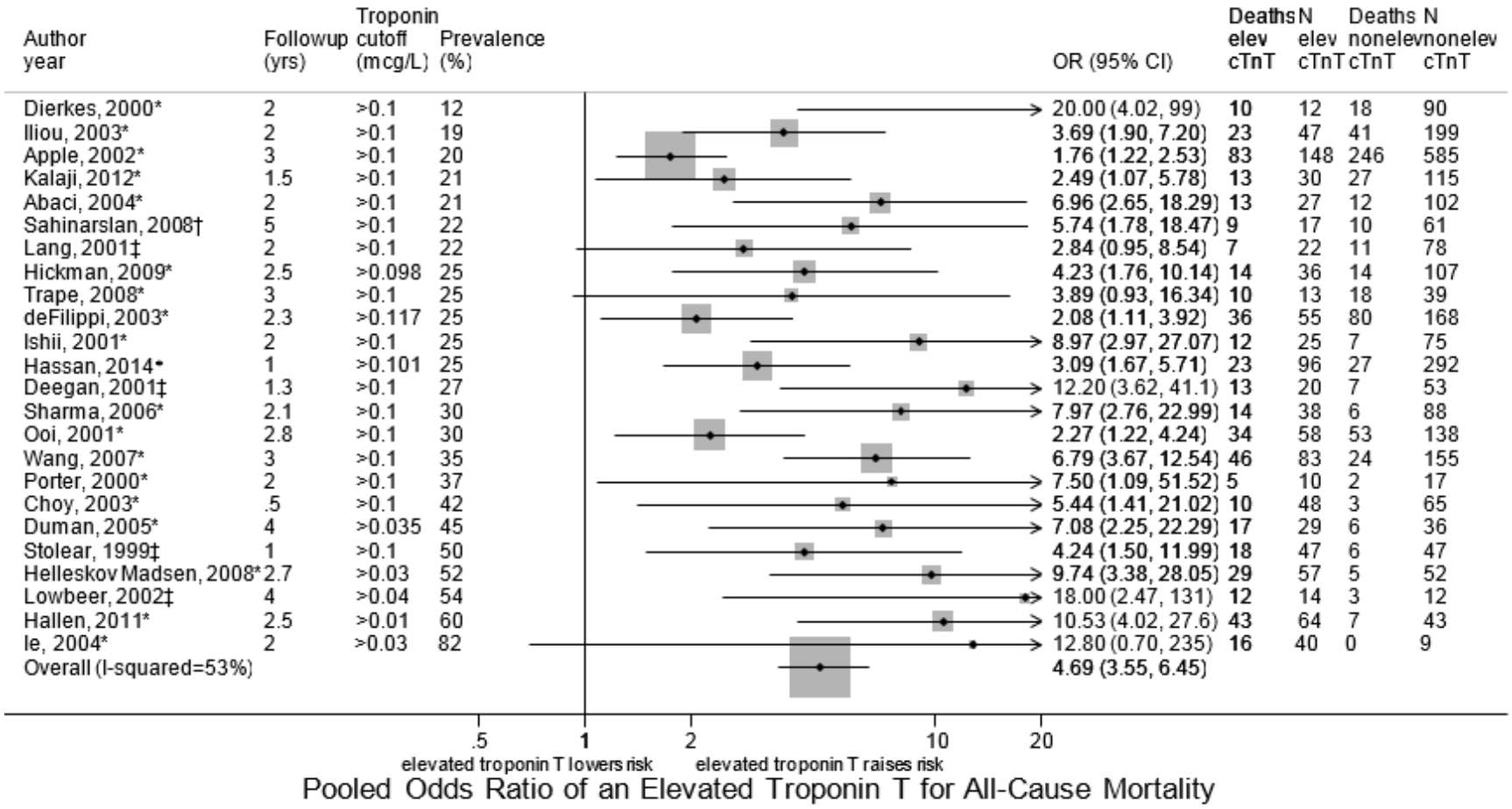
All studies showed a positive association of elevated cardiac troponin T with all-cause mortality (OR >1.0). Most of the studies were statistically significant, but three of the 24 studies reported insignificant associations (CIs crossed 1.0), although the effect estimation was similar to the other studies. The overall pooled OR showed a five-fold increased risk (OR, 4.7; 3.6 to 6.5) with significant heterogeneity (I-squared, 53 percent.)

Figure 7. Pooled hazard ratio of the association of elevated troponin T with all-cause mortality among patients on dialysis (stratified by level of adjustment)



* Study used a troponin assay manufactured by Roche.
† Study used a troponin assay manufactured by Boehringer Mannheim (older assays).
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 8. Pooled odds ratio for the association of elevated troponin T with all-cause mortality among patients on dialysis (sorted by prevalence)



* Study used a troponin assay manufactured by Roche.
† Study did not report the manufacturer of the troponin assay.
‡ Study used a troponin assay manufactured by Boehringer Mannheim (older assays).
CI = confidence interval; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of Cardiac Troponin I With All-Cause Mortality Among Patients on Dialysis

Overview

We identified 31 publications representing 30 unique patient cohorts that presented results regarding the association of baseline cardiac troponin I levels with all-cause mortality among dialysis patients without symptoms of ACS.[11, 65-67, 70, 75, 77, 81, 88, 92, 93, 96, 101, 112, 113, 117-119, 126, 131, 133, 134, 138, 139, 147-150, 157, 162, 168]

We excluded seven studies from the meta-analysis of both HRs and ORs due to insufficient data, troponins presented as continuous variables rather than cut-points, or results that were not presented separately for dialysis patients. We did not include the remaining studies in HR meta-analysis, OR meta-analysis, or both. We presented a summary of these inclusion and exclusion reasons in Appendix E, Table 2.

Followup Time

All studies except one had a followup time for mortality of at least 1 year with time ranging from 1 to 5 years. Choy, 2003[126] reported a followup time of only 6 months.

Assays and Cutpoints

The most common cardiac troponin I assays that studies used were the Beckman, Dade-Behring, and Abbott assays. Multiple studies compared two or more troponin I assays in the same study population.[92, 96, 118, 139, 147-149] For the purpose of meta-analysis, we only used only one cardiac troponin I assay per population. The cut-points for elevation were extremely heterogeneous, ranging from 0.01 to 0.4 mcg/L.

Hazard Ratio for All-Cause Mortality Associated with Elevated Cardiac Troponin I

Ten studies provided HRs and 95 percent CIs suitable for meta-analysis. All of these studies suggested an increased risk of mortality associated with cardiac troponin I elevation (HR >1.0). However two of the studies did not meet statistical significance (CIs crossed 1.0). All except for one of these studies at least adjusted for age, and seven out of 10 additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, diabetes).

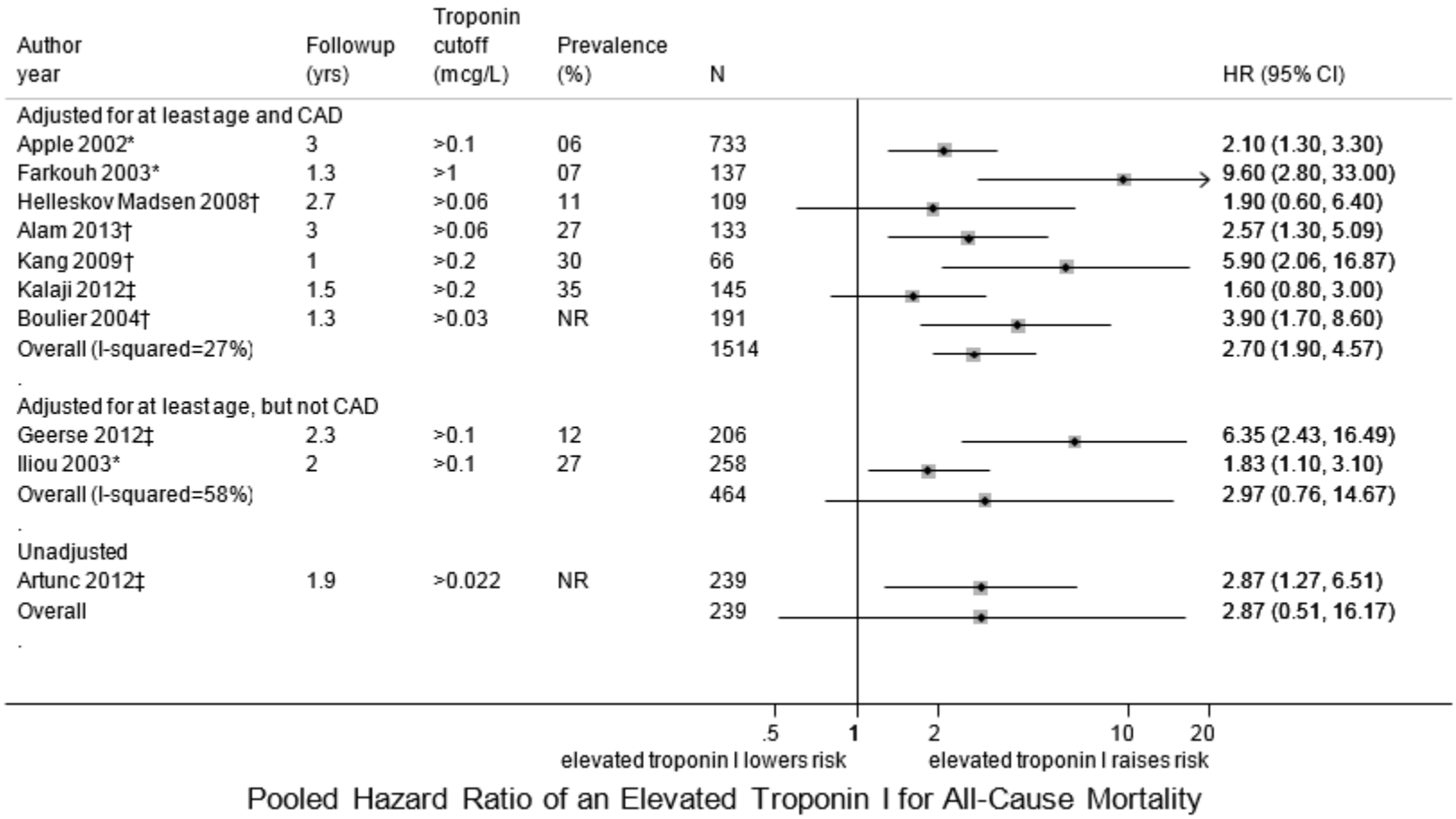
We listed the pooled meta-analysis stratified by level of adjustment in Figure 9. The pooled HR of an elevated cardiac troponin I for all-cause mortality among studies that adjusted for at least age and CAD or risk equivalent was 2.7 (95% CI, 1.9 to 4.6), heterogeneity not-significant (I-squared = 27 percent). Again, we saw no apparent temporal trends when we sorted results by year of publication.

Odds Ratios for All-Cause Mortality Associated with Elevated Cardiac Troponin I

Nineteen studies provided enough data (i.e., number of events in each group) to be included in meta-analysis for ORs. The majority of studies showed a positive association between elevated cardiac troponin I and all-cause mortality. In two studies, the point estimate tended toward an inverse association, although not statistically significant. In fact, eleven of the 19 studies did not reach statistical significance, largely due to small sample size and small number of events in each group, as indicated in Figure 10.

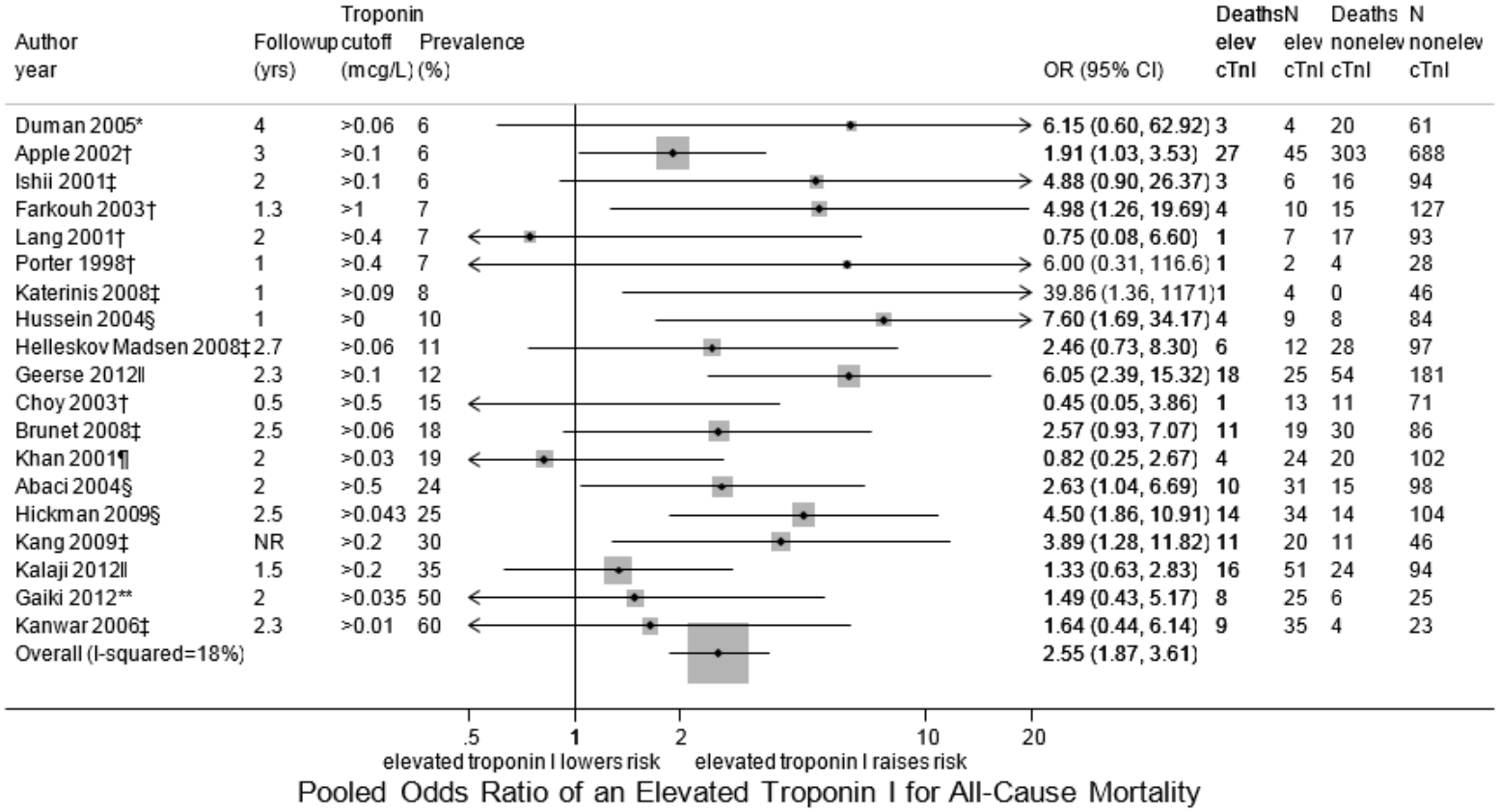
The unadjusted pooled OR for all-cause mortality associated with elevated troponin I was 2.6 (95% CI, 1.9 to 3.6). Heterogeneity was not significant (I-squared=18 percent).

Figure 9. Pooled hazard ratio of the association of an elevated troponin I with all-cause mortality among patients on dialysis (stratified by level of adjustment)



* Study used a troponin assay manufactured by Dade.
† Study used a troponin assay manufactured by Beckman.
‡ Study used a troponin assay manufactured by Siemens.
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 10. Pooled unadjusted odds ratio of the association of an elevated troponin I with all-cause mortality among patients on dialysis (sorted by prevalence)



* Study used a troponin assay manufactured by Diagnostic Products Corporation.
† Study used a troponin assay manufactured by Dade.
‡ Study used a troponin assay manufactured by Beckman.
§ Study used a troponin assay manufactured by Abbott.
‖ Study used a troponin assay manufactured by Siemens.
¶ Study used a troponin assay manufactured by Sanofi.
** Study used a troponin assay manufactured by Ortho.
CI = confidence interval; cTnI = cardiac troponin I; elev = elevated; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of High-Sensitivity Cardiac Troponin T With All-Cause Mortality Among Patients on Dialysis

We found only one study that evaluated the association of a high-sensitivity troponin T assay with mortality. This study[76] tested high-sensitivity troponin T (assayed by Roche E411 analyzer) on a continuous scale, rather than using a cut-point. These authors found that for every 2.72 ng/L increase in high-sensitivity troponin T level, the age-adjusted risk of all-cause mortality increased 1.4-fold (HR, 1.4; 95% CI, 1.0 to 2.0, $P = 0.049$]).

The Association of High-Sensitivity Cardiac Troponin I With All-Cause Mortality Among Patients on Dialysis

We found only one study that evaluated the risk of all-cause mortality for high-sensitivity cardiac troponin I among dialysis patients. Assa et al.[157] evaluated the risk of high-sensitivity troponin I with all-cause mortality per 10 ng/L increase in troponin and did not find a statistically significant association; but the study may have been underpowered for this outcome.

The Association of Cardiac Troponin T With Cardiovascular Mortality Among Patients on Dialysis

Overview

We identified 20 studies representing 16 unique patient cohorts that reported results on the association of cardiac troponin T with cardiovascular-specific mortality.[26, 89, 95, 98, 104, 111-113, 122, 124, 136-140, 144, 151, 152, 155, 158]

We excluded two studies from meta-analysis of both HRs and ORs due to insufficient data. We presented a summary of these inclusion and exclusion reasons in Appendix E, Table 3.

Followup time ranged from 1 to 4.3 years.

Hazard Ratio for Cardiovascular-Specific Mortality Associated With Elevated Cardiac Troponin T

We identified seven studies that reported a HR with CIs. All of these studies suggested an increased risk, although three of seven studies did not meet statistical significance. All except one of the studies adjusted at least for age, and five of the seven studies additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, diabetes, or heart failure). We listed the pooled meta-analysis in Figure 11. Among the five studies that adjusted for at least age and CAD, there was a 3-fold increased risk (HR, 3.3; 95% CI, 1.8 to 5.4), there was substantial heterogeneity (I-squared, 66 percent), and when we sorted results by year, we saw no temporal trend.

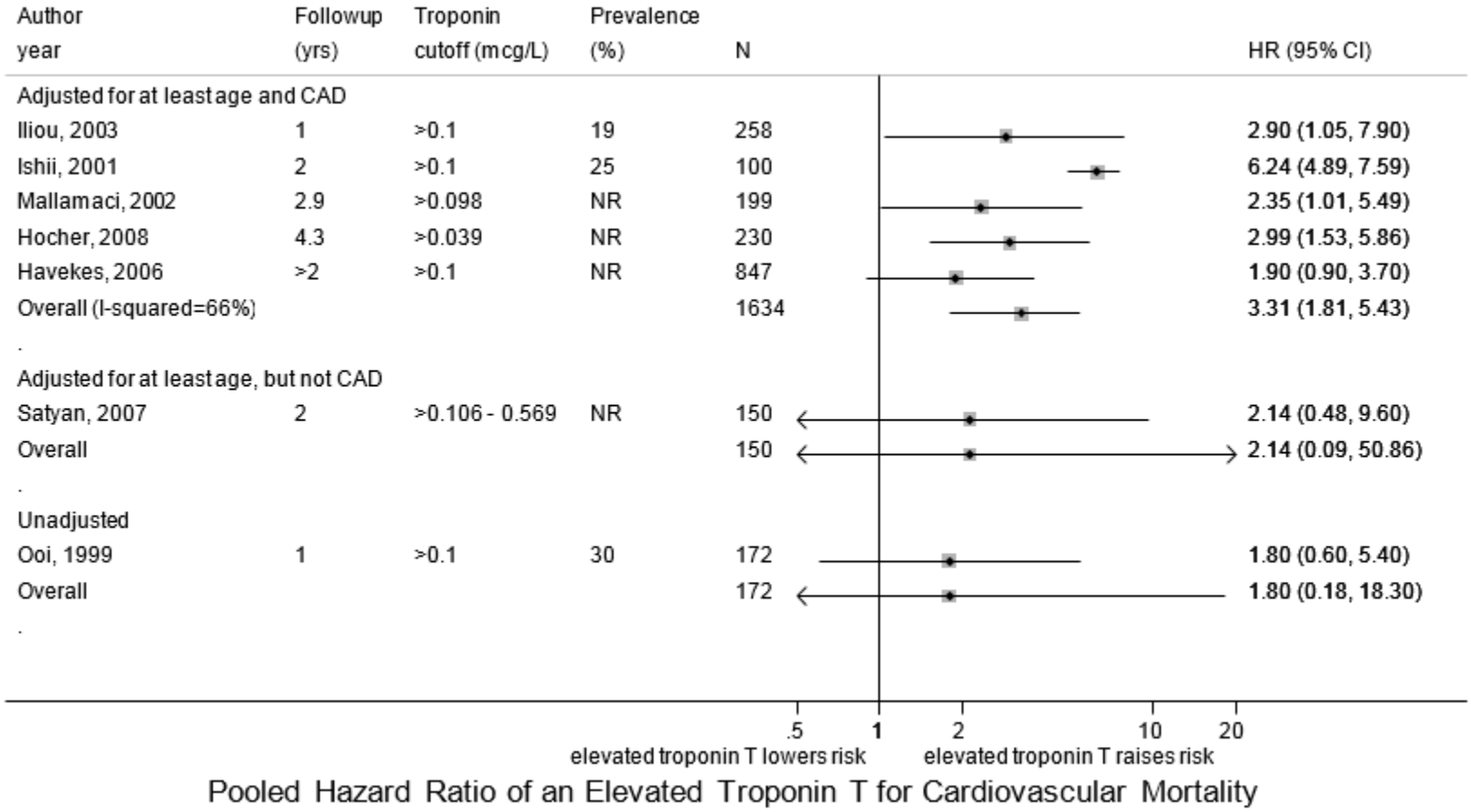
Odds Ratio for Cardiovascular-Specific Mortality Associated With Elevated Cardiac Troponin T

Nine studies provided the number of events in each group, making it possible to determine unadjusted ORs. In one study (Duman 2005[112]), the authors reported an adjusted OR but did not report the number of events and sample sizes in each group. All of the studies suggested a positive association with increased risk, although three of the nine studies did not meet statistical significance.

We reported the pooled meta-analysis for the odds of cardiovascular mortality for elevated cardiac troponin T in Figure 12; it suggests a 4-fold increase in risk (OR, 4.3; 95% CI, 3.0 to 6.4); no heterogeneity found.

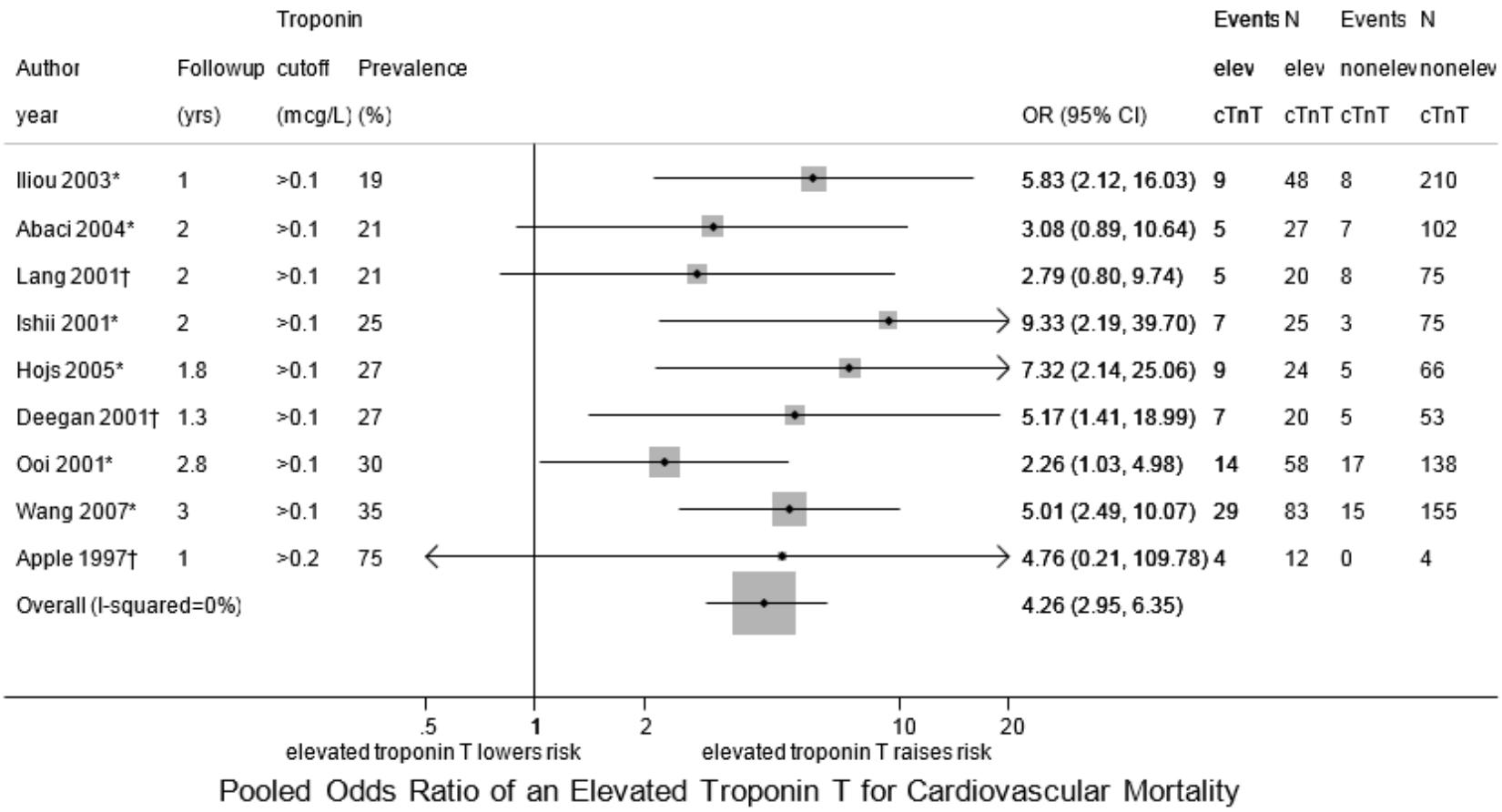
In a sensitivity analysis, including the one study with an adjusted OR, the pooled results were similar (OR, 4.5; 95% CI, 3.2 to 6.3).

Figure 11. Pooled hazard ratio of the association of an elevated troponin T with cardiovascular mortality among patients on dialysis (stratified by level of adjustment)



* All studies used a troponin assay manufactured by Roche.
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 12. Pooled odds ratio of the association of an elevated troponin T with cardiovascular mortality among patients on dialysis (sorted by prevalence)



* Study used a troponin assay manufactured by Roche.
† Study used a troponin assay manufactured by Boehringer Mannheim (older assays).
CI = confidence interval; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of High-Sensitivity Cardiac Troponin T With Cardiovascular Mortality Among Patients on Dialysis

One study[158] presented results using a high-sensitivity cardiac troponin assay (Roche, 99th percentile 0.0135 mcg/L) but presented results as a continuous variable per 100 U increase (OR 1.5, 95 percent CI 1.2-1.9).

The Association of Cardiac Troponin I With Cardiovascular Mortality Among Patients on Dialysis

Overview

We identified 13 studies that reported the association of cardiac troponin I with cardiovascular-specific mortality.[11, 65, 70, 88, 103, 112, 113, 119, 135, 138, 139, 151, 162]

We excluded only one study from meta-analysis of both HRs and ORs due to insufficient data. We presented a summary of these inclusion and exclusion reasons in Appendix E, Table KQ4.

Followup time ranged from 1 to 4 years.

Hazard Ratio for Cardiovascular-Specific Mortality Associated With Elevated Cardiac Troponin I

We included three studies that adjusted for at least age and CAD or risk equivalent in the meta-analysis for HR (Figure 13). The pooled risk of the association of elevated cardiac troponin I with cardiovascular mortality by was 4.2 (95% CI, 2.0-9.2). Confidence intervals were wide, but there was not any significant heterogeneity among the studies (I-squared = 0%).

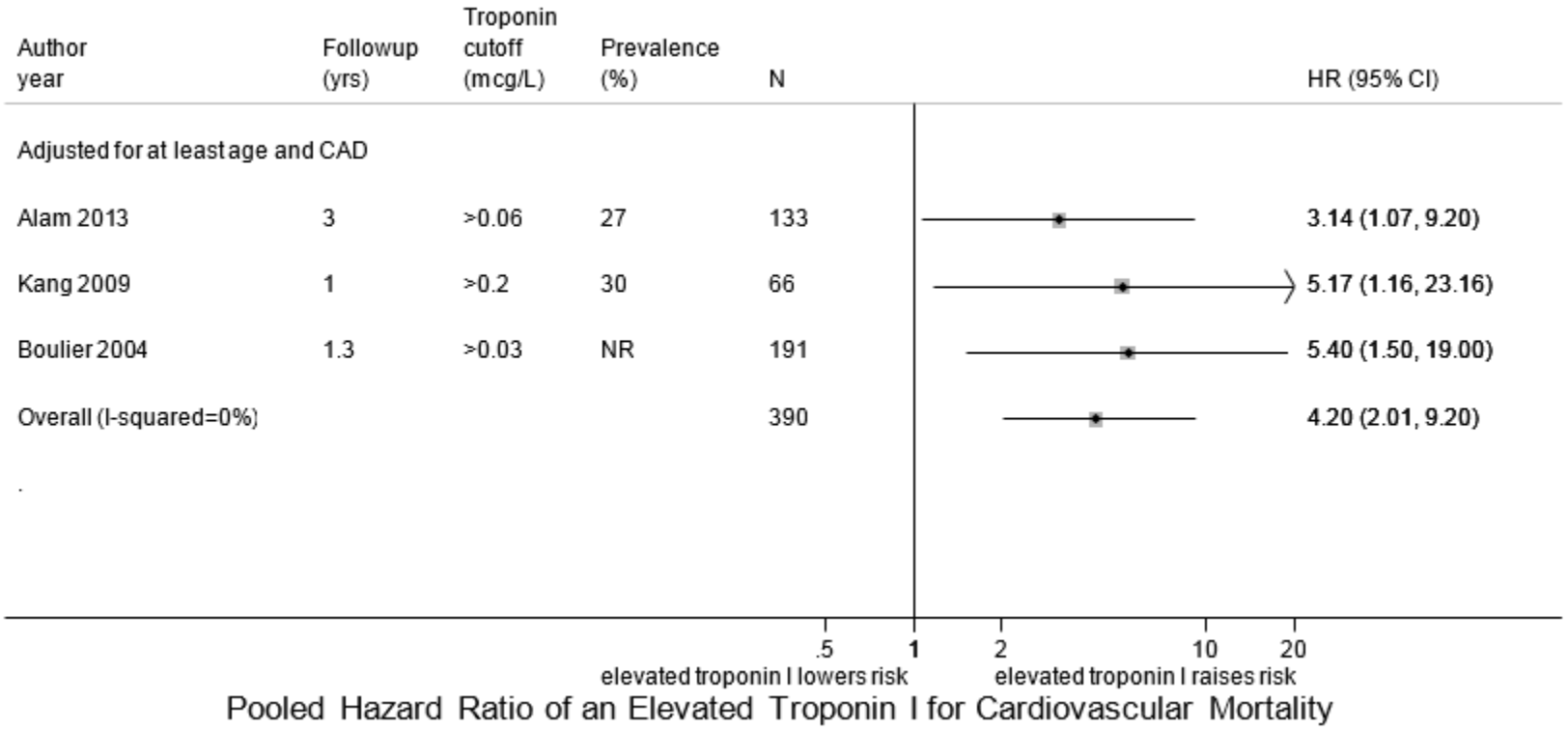
Odds Ratio for Cardiovascular-Specific Mortality Associated With Elevated Cardiac Troponin I

Nine studies reported the number of events in each group and we included them in our meta-analysis. Two studies[103, 151] had very unusual odds ratios (OR 58 and 0.6, respectively). Both studies had zero events in one of the groups, and the Stata statistical program added 0.5 to 0 cells for calculations.

The overall pooled OR showed a 5-fold increased risk (OR, 5.2; 95% CI, 2.8 to 9.0),which was similar to results for elevated cardiac troponin T elevation (Figure 14). Heterogeneity I-squared was 0 percent.

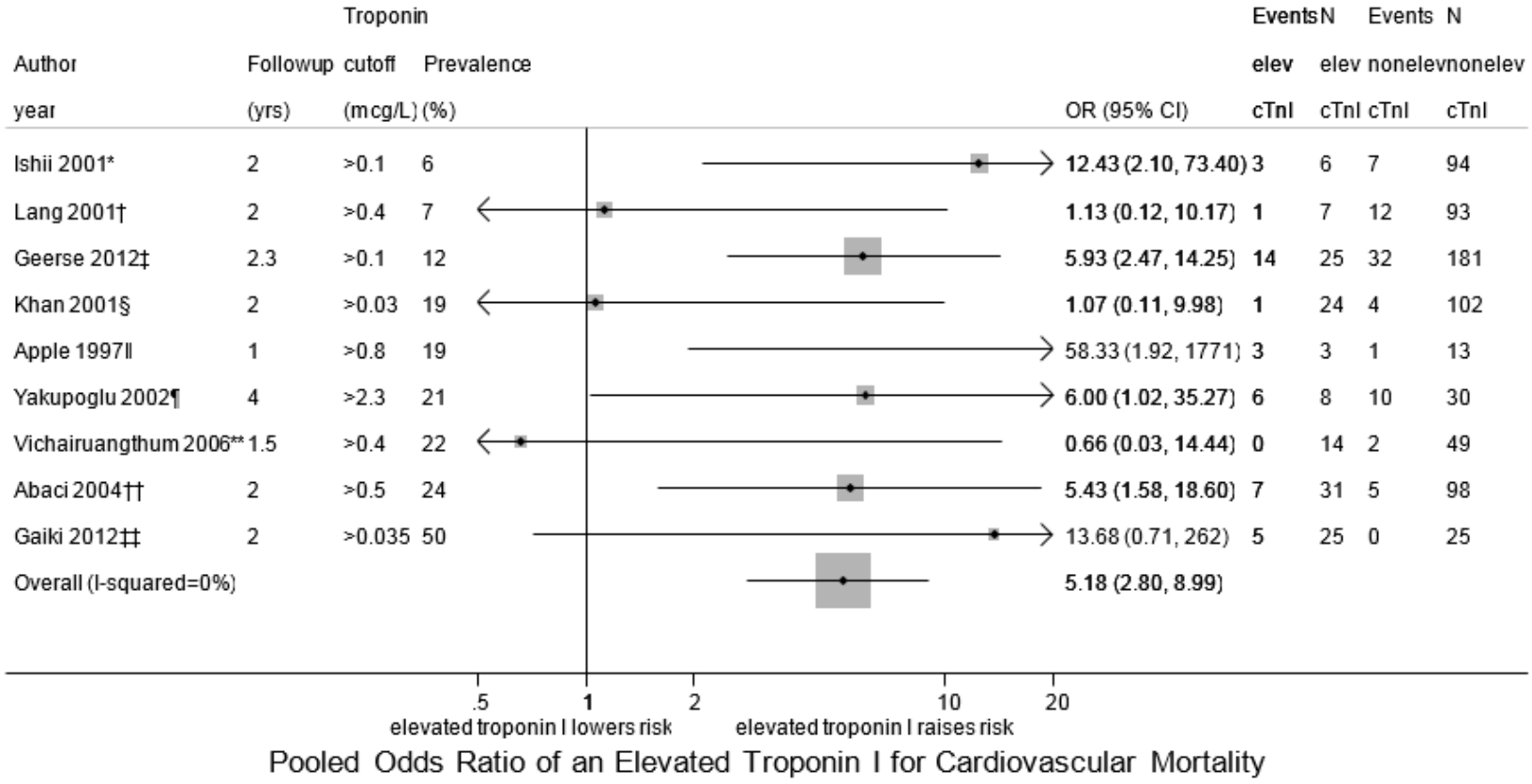
One study[135] used a very high cardiac troponin I cut-point of 2.3 mcg/L. In a sensitivity analysis excluding that study, the estimated risk was similar (OR, 4.5; 2.0 to 9.9).

Figure 13. Pooled hazard ratio of the association of an elevated troponin I with cardiovascular mortality among patients on dialysis



* All studies used a troponin assay manufactured by Beckman.
CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 14. Pooled odds ratio of the association of an elevated troponin I with cardiovascular mortality among patients on dialysis



* Study used a troponin assay manufactured by Beckman.
† Study used a troponin assay manufactured by Dade.
‡ Study used a troponin assay manufactured by Siemens.
§ Study used a troponin assay manufactured by Sanofi.
‖ Study did not report the manufacturer of the troponin assay.
¶ Study used a troponin assay manufactured by Diagnostic Products Corporation.
** Study used a troponin assay manufactured by Johnson & Johnson.
†† Study used a troponin assay manufactured by Abbott.
‡‡ Study used a troponin assay manufactured by Ortho.
CI = confidence interval; cTnI = cardiac troponin I; elev = elevated; mcg/L = micrograms per liter; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of High-Sensitivity Cardiac Troponin I With Cardiovascular Mortality Among Patients on Dialysis

We did not identify any studies that reported an association with a high-sensitivity troponin I assay and cardiovascular mortality among dialysis only patients.

The Association of Cardiac Troponin T With Major Adverse Cardiovascular Events Among Patients on Dialysis

Overview

Twelve studies reported results of the association of cardiac troponin T with MACE.[26, 87, 91, 96-98, 107, 128, 142, 143, 146, 151]

We included all studies in our meta-analysis. We outlined the overview of inclusion/exclusion in Appendix E, Table 5. The followup time ranged from 0.3 to 5 years.

Hazard Ratio for Major Adverse Cardiovascular Events Associated With Elevated Cardiac Troponin T

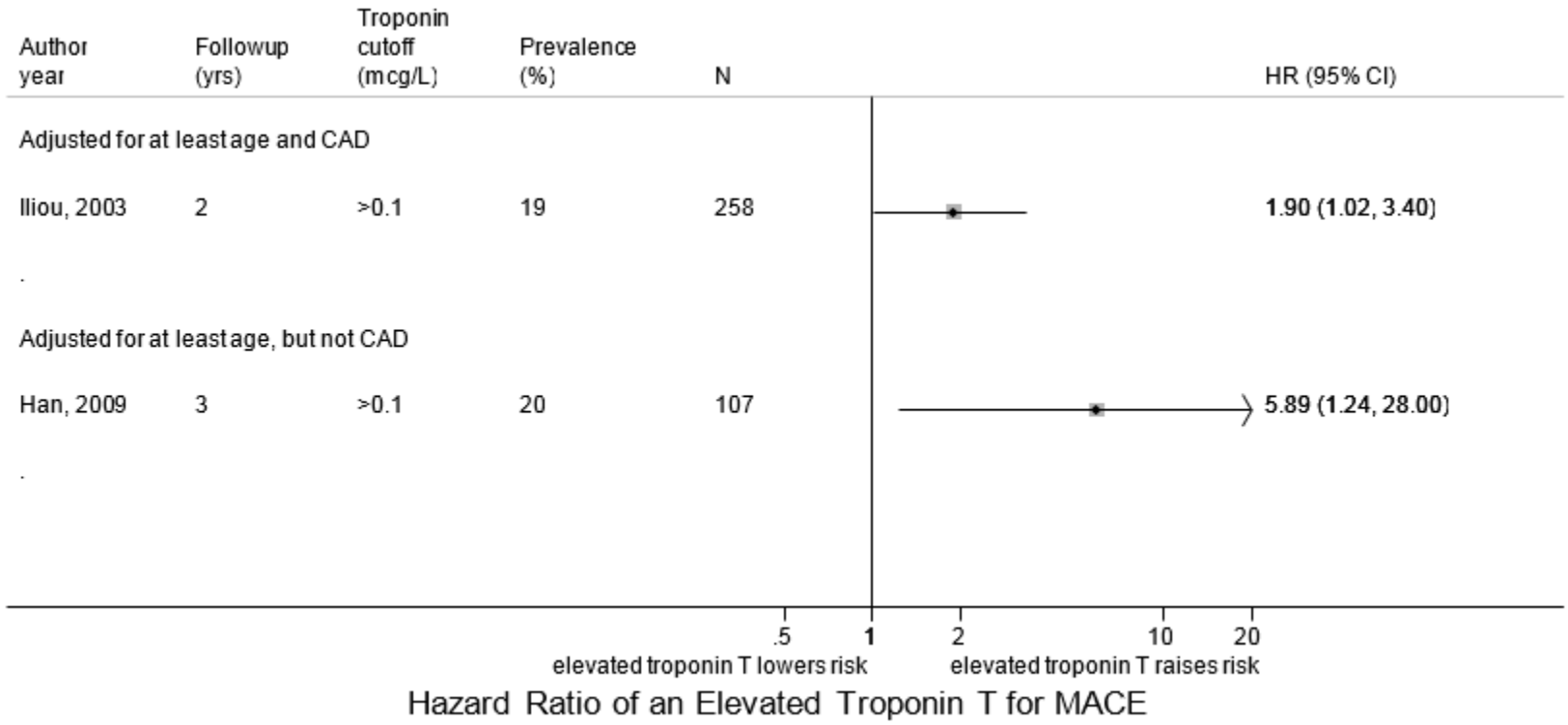
Only one study presented a HR adjusted for at least age and age/CAD risk-equivalent (HR, 1.90; 95% CI 1.02 to 3.4) (Figure 15). One study adjusted for age but not CAD. One study[107] only presented an adjusted HR per 0.01 mcg/L increase in cardiac troponin T as a continuous variable, rather than a cut-point. Therefore a meta-analysis could not be performed.

Odds Ratio for Major Adverse Cardiovascular Events Associated with Elevated Cardiac Troponin T

Nine studies provided results for number of events in each group making it possible to calculate an unadjusted OR. One study[169] only presented an adjusted OR.

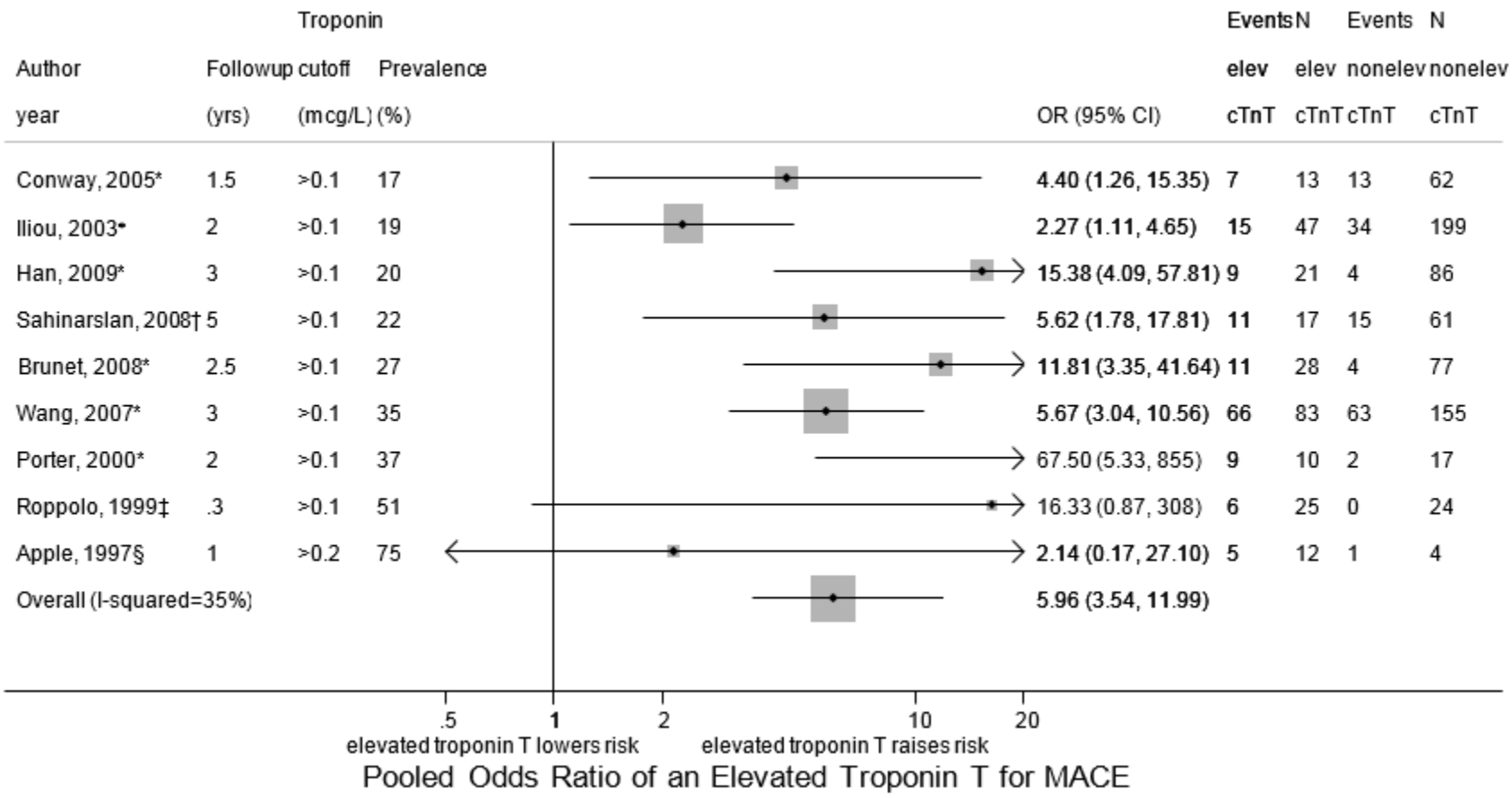
We listed the pooled meta-analysis in Figure 16, with an estimated 6-fold risk of MACE for elevated cardiac troponin T (OR, 6.0; 95% CI, 3.5 to 12.0) without significant heterogeneity (I-squared = 35 percent). In a sensitivity analysis including the study with an adjusted OR, the pooled meta-analysis association was slightly lower but still significant (OR, 5.1, 95% CI, 2.9 to 8.9). When we sorted results by year, it did appear that odds ratios were generally progressively larger in magnitude with more current years.

Figure 15. Hazard ratio of the association of an elevated troponin T with major adverse cardiovascular events among patients on dialysis (stratified by level of adjustment)



* Both studies used a troponin assay that was manufactured by Roche.
CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 16. Pooled odds ratio of the association of an elevated troponin T with major adverse cardiovascular events among patients on dialysis (sorted by prevalence)



* Study used a troponin assay manufactured by Roche.
† Study did not report the manufacturer of the troponin assay.
‡ Study used a troponin assay manufactured by Dade.
§ Study used a troponin assay manufactured by Boehringer Mannheim (older assay).
CI = confidence interval; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; MACE = major adverse cardiovascular events; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of High-Sensitivity Cardiac Troponin T With Major Adverse Cardiovascular Events Among Patients on Dialysis

We did not identify any studies reporting an association of high-sensitivity cardiac troponin T assay with MACE among dialysis patients.

The Association of Cardiac Troponin I With Major Adverse Cardiovascular Events Among Patients on Dialysis

Overview

We identified 12 studies that reported an association of cardiac troponin I with MACE. We outlined these in Appendix E, Table 6.[70, 93, 96, 103, 120, 123, 128, 129, 142, 143, 146, 151]

Hazard Ratio for Major Adverse Cardiovascular Events Associated with Elevated Cardiac Troponin I

No study presented results for the association of cardiac troponin I with MACE using HRs.

Odds Ratio for Major Adverse Cardiovascular Events Associated with Elevated Cardiac Troponin I

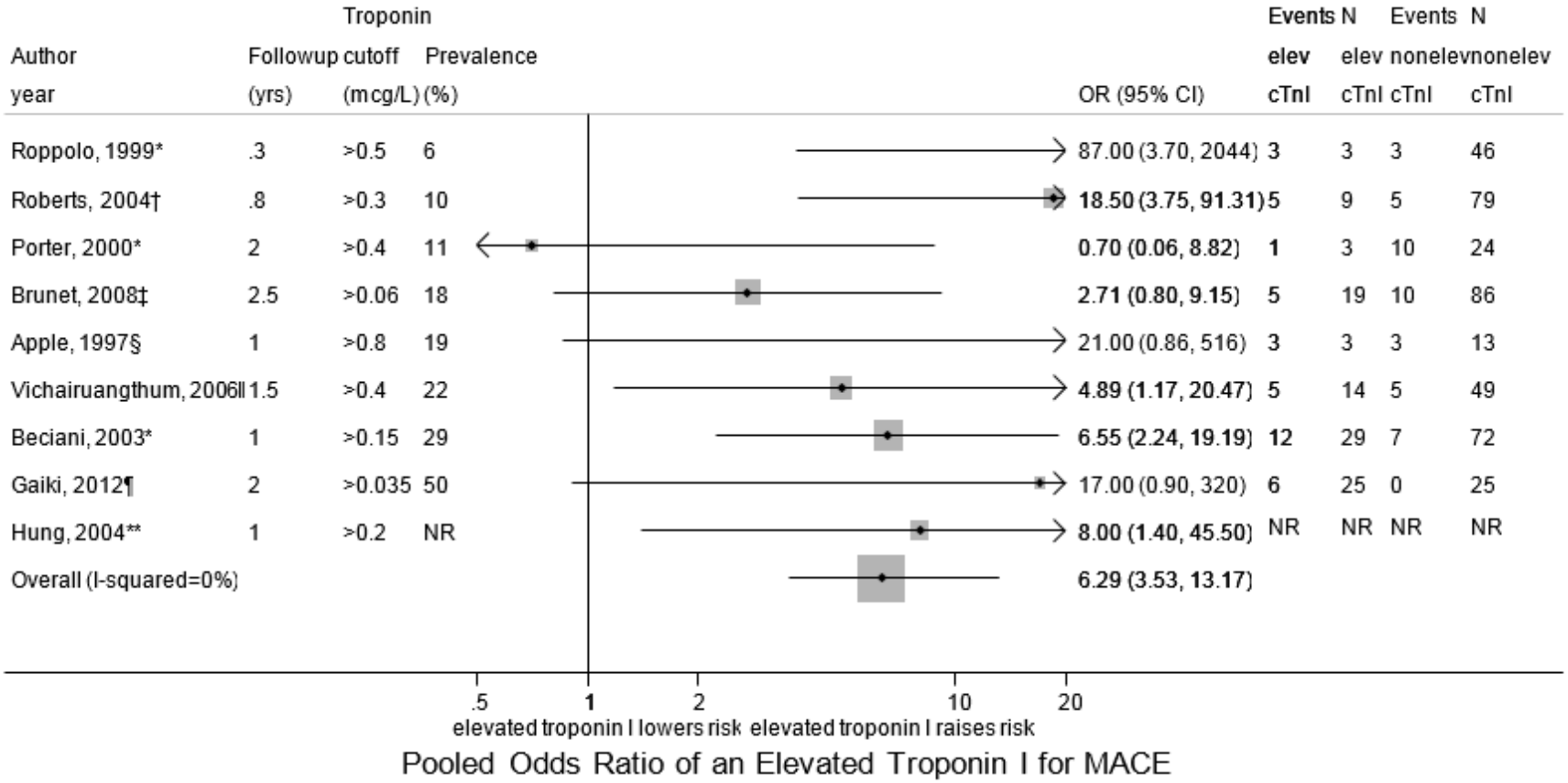
The pooled meta-analysis, including all nine relevant studies (Figure 17), showed a greater than 6-fold association of troponin I with MACE (OR, 6.3; 95% CI, 3.5 to 13.2) without heterogeneity. We could not include Katerinis et al.[93] in the meta-analysis because of zero events, and the inability to generate a log OR. Several studies were small with few events and large CIs; thus, there were widely ranging effect sizes—from OR of 0.7 to 87.0. Heterogeneity I-squared was 0 percent. One study reported an unadjusted OR but not the number of events, and two studies had qualitatively different descriptions of a troponin elevation. We performed sensitivity analyses as described below.

Results were similar in a sensitivity analysis including only the five studies that reported the number of events in each arm (so that unadjusted OR could be determined).[96, 103, 142, 151] The pooled meta-analysis showed a three-fold association of troponin I with MACE with at least 1 year followup (OR, 3.8; 95% CI, 1.6 to 8.9). Heterogeneity I-squared was 6.9 percent.

In another sensitivity meta-analysis of six studies, which additionally included the study by Hung et al.[120] and presented an unadjusted OR but not number of events, the results were similar (OR, 4.3; 95% CI, 2.1 to 8.9). Heterogeneity I-squared was 0 percent.

Finally, we performed an additional sensitivity analysis including two additional studies that had qualitatively different assessments of troponin I rather than a single baseline value. For Katerinis et al.,[93] an elevated troponin included only those with troponin elevated for more than 3 months. For Beciani et al.,[129] an elevated troponin included those with both consistent and variable elevated troponin levels. As mentioned above, Katerinis et al. had zero events and could not generate a log OR. The pooled meta-analysis was again similar (OR, 4.6; 95% CI, 2.4 to 8.7). Heterogeneity I-squared was 0 percent.

Figure 17. Pooled odds ratio of the association of an elevated troponin I with major adverse cardiovascular events among patients on dialysis (sorted by prevalence)



* Study used a troponin assay manufactured by Dade.
† Study used a troponin assay manufactured by Abbott.
‡ Study used a troponin assay manufactured by Beckman.
§ Study did not report the manufacturer of the troponin assay.
‖ Study used a troponin assay manufactured by Johnson and Johnson.
¶ Study used a troponin assay manufactured by Ortho.
** Study used a troponin assay manufactured by Diagnostic Products Corporation.
CI = confidence interval; cTnI = cardiac troponin I; elev = elevated; MACE = major adverse cardiovascular event; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of High-Sensitivity Cardiac Troponin I With Major Adverse Cardiovascular Events Among Patients on Dialysis

Assa et al.[157] found a high-sensitivity troponin I per 10 ng/L increase to be associated with risk of adverse cardiac events [HR 1.21 (95 percent CI 1.06 – 1.38)].

The Association of Cardiac Troponin T or I With Outcomes Among Patients on Dialysis Other Than All-Cause Mortality, Cardiovascular Mortality, or Major Adverse Cardiovascular Events

Heart Failure

One study[102] reported an approximate 3-fold increased risk for cardiovascular congestion (heart failure) for an elevated cardiac troponin T per 1 mcg/L increase in a multivariate model that also adjusted for age, left ventricular mass, and ejection fraction (HR, 3.0; 95% CI, 1.2 to 7.4). This evaluated troponin T on a continuous scale, not a cut-point.

Hospital Admissions

Another study[11] did not find that dialysis patients with elevated troponin I (>0.03 mcg/L) had increased risk of hospital admissions for any cause or cardiac cause over a 2-year time period (*P* not significant).

Subsequent Acute Coronary Syndrome

Troyanov et al.[109] evaluated risk of first ACS event. Both elevated cardiac troponin T and I predicted risk of ACS over a 3-year followup. For elevated cardiac troponin T (> 0.04 mcg/L; Roche Elecsys), the HR was 3.0 (95% CI, 1.0 to 8.6). For elevated cardiac troponin I (>0.3 mcg/L; Abbott AxSym), the HR was 3.4 (95% CI, 1.6 to 7.3). Both had similar areas under the curve for predicting ACS events at 1.5 years (0.73 vs. 0.77 for cardiac Troponin T and I, respectively).

KQ 4.3: Troponin Associations With Short- and Long-Term Outcomes by Subgroups

We presented results for dialysis, nondialysis, and kidney transplant subgroups of CKD patients separately as indicated in previous sections. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Studies were too few to generate meta-analyses for subgroup type. Subgroups described were as follows:

- Persistently elevated troponin levels[93]
- History of CAD[83, 101, 116, 119]
- Gender[89, 122]
- Pro-brain natriuretic peptide levels[155]
- Diabetes[124]
- Hypotension-prone[120]
- Hemodialysis versus peritoneal dialysis.[132]

KQ 4.4: Comparisons Between Troponin Assays To Predict Risk

While many studies evaluated multiple troponin assays in the same population (troponin T vs. troponin I, or multiple troponin I assays by different manufacturers compared with each

other), they presented no formal interaction testing. They never included Troponin T and I levels in the same multivariate model adjusted for the other cardiac biomarker. Some studies hinted at a stronger association with troponin T than with troponin I among dialysis patients. However, in our pooled meta-analyses, the effect sizes of the association of adverse events for elevated cardiac troponin were similar for both T and I overall. Therefore, we are unable to draw any specific conclusion about which biomarker is better in the CKD patient. Both cardiac troponin markers T and I were similarly associated with an increased risk for adverse outcomes.

Strength of Evidence Among Patients on Dialysis

Tables 34 and 35 describe our strength of evidence grading for KQ4 among patients on dialysis.

Table 34. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among patients on dialysis: Strength of evidence domains

Outcome	Troponin Assay	No. Studies	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence
All-cause mortality	Troponin T	43 observational studies overall; 11 in HR meta-analysis adjusting for at least age and CAD; 5 adjusting for at least age; 24 in unadjusted OR meta-analysis	Medium	Direct	Consistent*	Precise	Adjusted HR 3.00; unadjusted OR 4.69	Moderate
All-cause mortality	Troponin I	30 observational studies overall; 7 in HR meta-analysis adjusting for at least age and CAD; 2 adjusting for at least age; 19 in unadjusted OR meta-analysis	Medium	Direct	Consistent*	Precise	Adjusted HR 2.70; unadjusted OR 2.55	Moderate
All-cause mortality	hs troponin T	1 observational study	Medium	Direct	NA	Precise	HR 1.4	Low
All-cause mortality	hs troponin I	1 observational study	High	No	NA	Imprecise	Per 10 ng/L increase, no association found.	Insufficient
Cardiovascular-specific mortality	Troponin T	20 observational studies overall; 5 in HR meta-analysis adjusting for at least age and CAD; 1 adjusting for age 9 in unadjusted OR meta-analysis	Medium	Direct	Consistent*	Precise	Adjusted HR 3.31; unadjusted OR 4.26	Moderate

Table 34. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among patients on dialysis: Strength of evidence domains (continued)

Outcome	Troponin Assay	No. Studies	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence
Cardiovascular-specific mortality	Troponin I	13 observational studies overall; 3 in HR meta-analysis adjusting for at least age and CAD; 9 in unadjusted OR meta-analysis	Medium	Direct	Consistent	Precise	Adjusted HR 4.20; unadjusted OR 5.18	Moderate
MACE	Troponin T	12 observational studies overall; 1 adjusting for at least age and CAD; 1 adjusting for at least age; 9 in unadjusted OR meta-analysis	Medium	Direct	Consistent	Precise	Adjusted HR 1.90; unadjusted OR 5.96	Moderate
MACE	Troponin I	12 observational studies overall; 9 in unadjusted OR meta-analysis	High	Direct	Consistent	Precise	Unadjusted OR 6.29	Low
MACE	hs troponin I	1 study	Medium	Direct	NA	Imprecise	6 cases [24%] vs. 0, P = 0.022	Insufficient

HR = hazard ratio; MACE = major adverse cardiovascular events; OR = odds ratio

* Direction of association was consistent, but high I-squared

Table 35. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among patients on dialysis: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
All-cause mortality	Troponin T	Observational studies	23 fair quality and 20 good quality studies	All studies were observational, but there were substantial number of studies with adjusted analysis and the direction of association was consistent with precise estimates.
All-cause mortality	Troponin I	Observational studies	13 good quality, 16 fair quality, and 1 poor quality studies	All studies were observational design and the heterogeneity was high.
All-cause mortality	hs troponin T	Observational studies	1 fair quality study: 1 with adjusted analyses	Only one study reported adjusted results. We did not conduct meta-analysis because of different troponin categories.
All-cause mortality	hs troponin I	Observational studies	1 fair study: 0 with adjusted analyses	Neither studies reported adjusted results. We did not conduct meta-analysis due to different troponin cut-point.
Cardiovascular-specific mortality	Troponin T	Observational studies	9 fair, 10 good and 1 poor quality studies	All studies were observational, but there were substantial number of studies with adjusted analysis and the direction of association was consistent with precise estimates.
Cardiovascular-specific mortality	Troponin I	Observational studies	8 fair and 5 good quality studies	Only two studies reported adjusted results and both studies were observational design, but the strength of association was high with precise estimates.
MACE	Troponin T	Observational studies	6 fair and 6 good quality studies	All studies were observational.
MACE	Troponin I	Observational studies	6 fair, 2 good, 1 poor quality quality studies	All studies were observational design. No studies reported adjusted results.
MACE	hs troponin I	Observational studies	1 fair quality study with adjusted analysis	Only one study, presented as continuous variable instead of cut-point.

MACE = major adverse cardiovascular events

Results for Nondialysis Chronic Kidney Disease Patients

Of the publications meeting criteria for Key Question (KQ) 4, 26 included nondialysis chronic kidney disease (CKD) patients as part or all of the study population.[25, 68, 69, 71, 73, 78, 79, 82, 84, 90, 94, 99, 100, 105, 108, 115, 121, 125, 132, 147, 148, 154, 156]

We described the results for those that analyzed a pre- or post-kidney transplantation population separately and included them with the results for KQ4.3.

KQ 4.2b: Troponin Associations With Short- and Long-Term Outcomes Among Nondialysis, Nontransplanted Chronic Kidney Disease Patients

Key Points

- Elevated troponin T and troponin I in nondialysis CKD patients predict all-cause mortality (strength of evidence: moderate). Pooled analysis from studies adjusted for at least age and CAD or risk equivalent found the following associations: (Troponin T: pooled HR, 3.1; 95% CI, 1.1 to 11.0. Troponin I: pooled HR 1.7; 95% CI 1.2 to 2.7.) Similar findings were seen for studies with less adjusted HRs and for pooled meta-analyses for the unadjusted ORs.
- Elevated troponin T is associated with an increased risk of composite cardiac outcome (MACE) in nondialysis CKD patients based on pooled analysis (pooled HR, 2.7; 95% CI, 1.1 to 7.6) (strength of evidence: moderate).
- Studies of MACE outcomes with elevated troponin I that included nondialysis patients also included dialysis patients, and ORs were not statistically significant (strength of evidence: insufficient).
- We identified no studies that examined high-sensitivity troponin I in asymptomatic, nondialysis CKD patients (strength of evidence: insufficient).
- The adjusted analyses in nondialysis CKD populations suggest that elevated high-sensitivity troponin T predicts adverse outcomes (strength of evidence: low).

The Association of Cardiac Troponin T With All-Cause Mortality Among Nondialysis Chronic Kidney Disease Patients

Troponin T was the most common troponin assay that studies analyzed in the nondialysis CKD population. Nine reports included an endpoint of all-cause mortality.[79, 82, 99, 100, 108, 121, 125, 132, 154] Four reports were not included in pooled analysis due to inclusion of dialysis patients or troponin presented continuously. Two studies analyzed an identical population; therefore, we presented the results from the study reporting an adjusted analysis. We list results in Table 36.[99, 108]

Two studies presented HR adjusted for at least age and CAD or risk equivalent. Four studies, each reporting a HR and CI, were similar enough to be included in a meta-analysis of HRs.[99, 100] with pooled HR 3.4 (1.1 to 11.0) (Figure 18). Although we used the highest troponin T threshold value for the pooled analysis, one study using multiple cutoffs found a significant difference in mortality rate when it compared troponin T less than 0.03 mcg/L with values ranging from 0.03 to 0.09 mcg/L (HR, 4.3; 95% CI, 1.8 to 10.4, $P < 0.001$) and values greater than 0.1 mcg/L (HR, 5.5; 95% CI, 2.9 to 10.5, $P < 0.001$).[100] One study presented an unadjusted analysis, which was not significant.[121]

A second pooled analysis included the five studies that presented ORs or numbers of events from which we could derive ORs (Figure 19).[79, 99, 121, 125, 154] All results were unadjusted. Threshold values for troponin T ranged from 0.02 mcg/L to 0.1 mcg/L, although all used a troponin T assay from the same manufacturer. The pooled OR was significant and suggested that an elevated troponin T is a predictor of mortality in nondialysis CKD patients (OR, 3.0; 95% CI, 1.4 to 6.7). One study[108] provided adjusted OR but not HR.

We did not include two reports of all-cause mortality in either pooled analysis due to the inclusion of dialysis patients. One of these found an elevated troponin T to be a predictor of all-cause mortality after adjustment (HR, 2.7; 95% CI, 1.1 to 11.0; $P < 0.05$),[132] but the other reported a loss of significance when they adjusted data.[82]

A study by Lamb et al. compared two troponin T cutoff values and found sensitivity and specificity to be 67 and 62 percent, respectively, for a threshold of 0.01 mcg/L, and 51 and 80 percent, respectively, for a threshold of 0.03 mcg/L.[99]

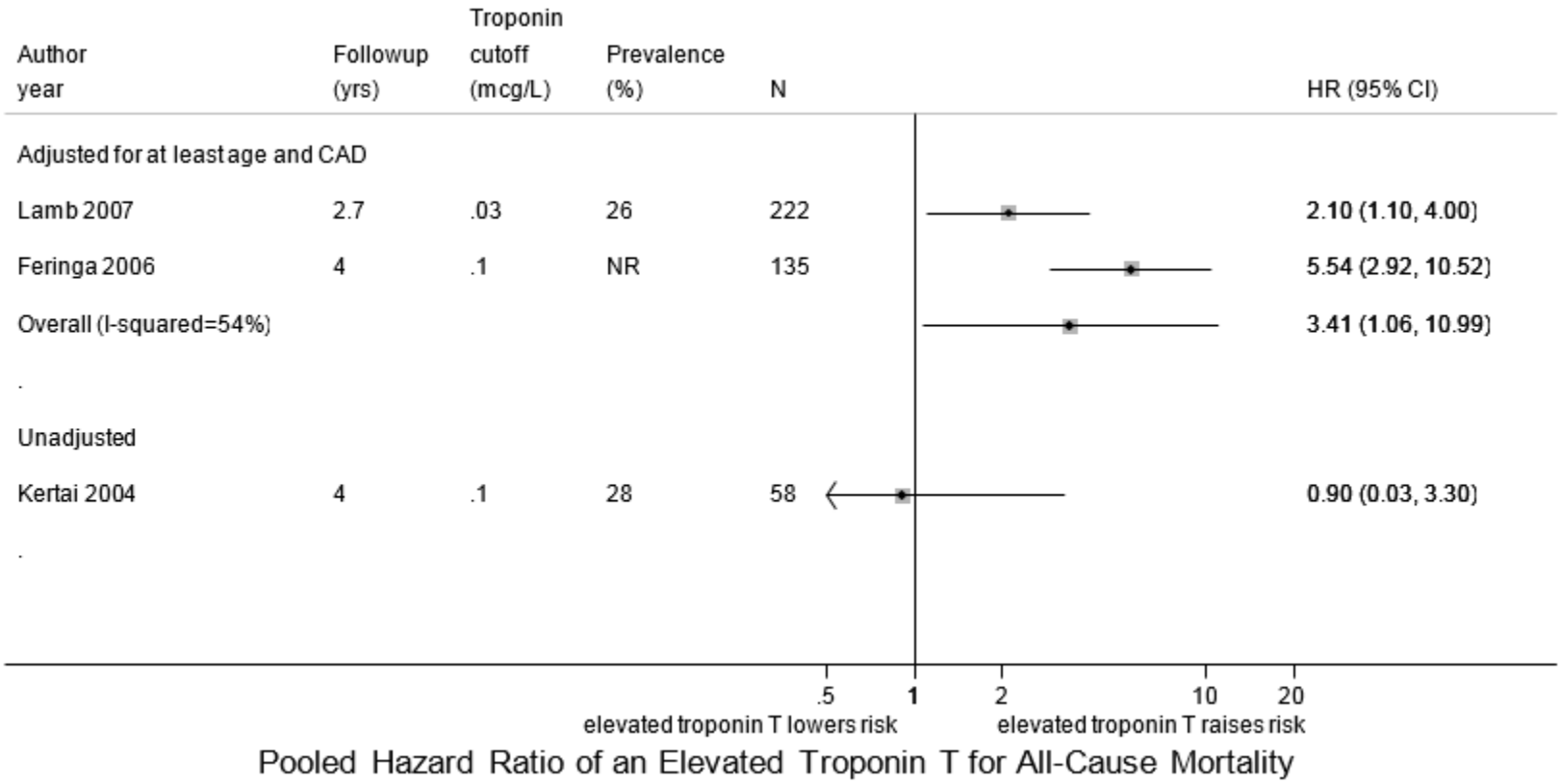
Table 36. Summary of the associations of elevated troponin T with all-cause mortality in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Orea-Tejeda, 2010[79]	Roche; 0.02 mcg/L	Stage 3-5	42 months	21	15 (71.4%)	31	9 (29.0%)	OR 2.46; 95% CI 0.90-6.65, *P* = 0.07
Ilva, 2008[154]	Roche Elecsys; 0.03 mcg/L	CysC >1.2mg/L for age <50, 1.4mg/L age >50	6 months	NR (total n = 29)	NR	NR	NR	OR 1.3; 95% CI 0.7-2.5
Lamb, 2007[99]	Roche Elecsys; 0.01 mcg/L	Stage 3-5	32 months	95	26 (27.4%)	127	13 (10.2%)	HR 2.0; 95% CI 1.0-3.9, *P* = 0.05 adjusted for age, hemoglobin, CAD
Lamb, 2007[99]	Roche Elecsys; 0.03 mcg/L	Stage 3-5	32 months	57	20 (35.1%)	165	19 (11.5%)	HR 2.1; 95% CI 1.1-4.0, *P* = 0.03 adjusted for age, hemoglobin, CAD
Feringa, 2006[100]	Roche Elecsys; 0.03-0.09 mcg/L	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 4.27; 95% CI 1.75-10.4, *P* < 0.001 adjusted for age, sex, CAD
Feringa, 2006[100]	Roche Elecsys; >0.1 mcg/L	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 5.54; 95% CI 2.92-10.52, *P* < 0.001 adjusted for age, sex, CAD
Kertai, 2004[121]	Roche; 0.1 mcg/L	CKD (undefined)	4 years	16	4 (25%)	42	9 (21.4%)	HR 0.9; 95% CI 0.3-3.3, *P* = 0.08
Wood, 2003[125]	Roche Elecsys; 0.1 mcg/L	Cr >500 micromol/L	2 years	25	13 (52%)	71	10 (14.1%)	HR 1.72; 95% CI 1.08-2.74, *P* = 0.02 adjusted for age, sex, diabetes, CAD, creatinine
Lowbeer, 2003[132]	Roche Elecsys; 0.1 mcg/L	Stage 5*	2.7 years	34	NR	81	NR	HR 2.66; 95% CI 1.07-10.95, *P* <0.05 adjusted for age, CVD, malnutrition, DM, sex
Chrysochou, 2009[82]	Roche Elecsys; 0.03 mcg/L	Stages 1-5*	40 months	11	8 (72.7%)	71	23 (32.4%)	HR 3.9; 95% CI 1.8-8.5, *P* = 0.001 (significance was lost when adjusted)

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; Cr = creatinine; CysC = cystatin C; HR = hazard ratio; mcg/L = micrograms per liter; mg/L = milligams per liter; NR = not reported; OR = odds ratio

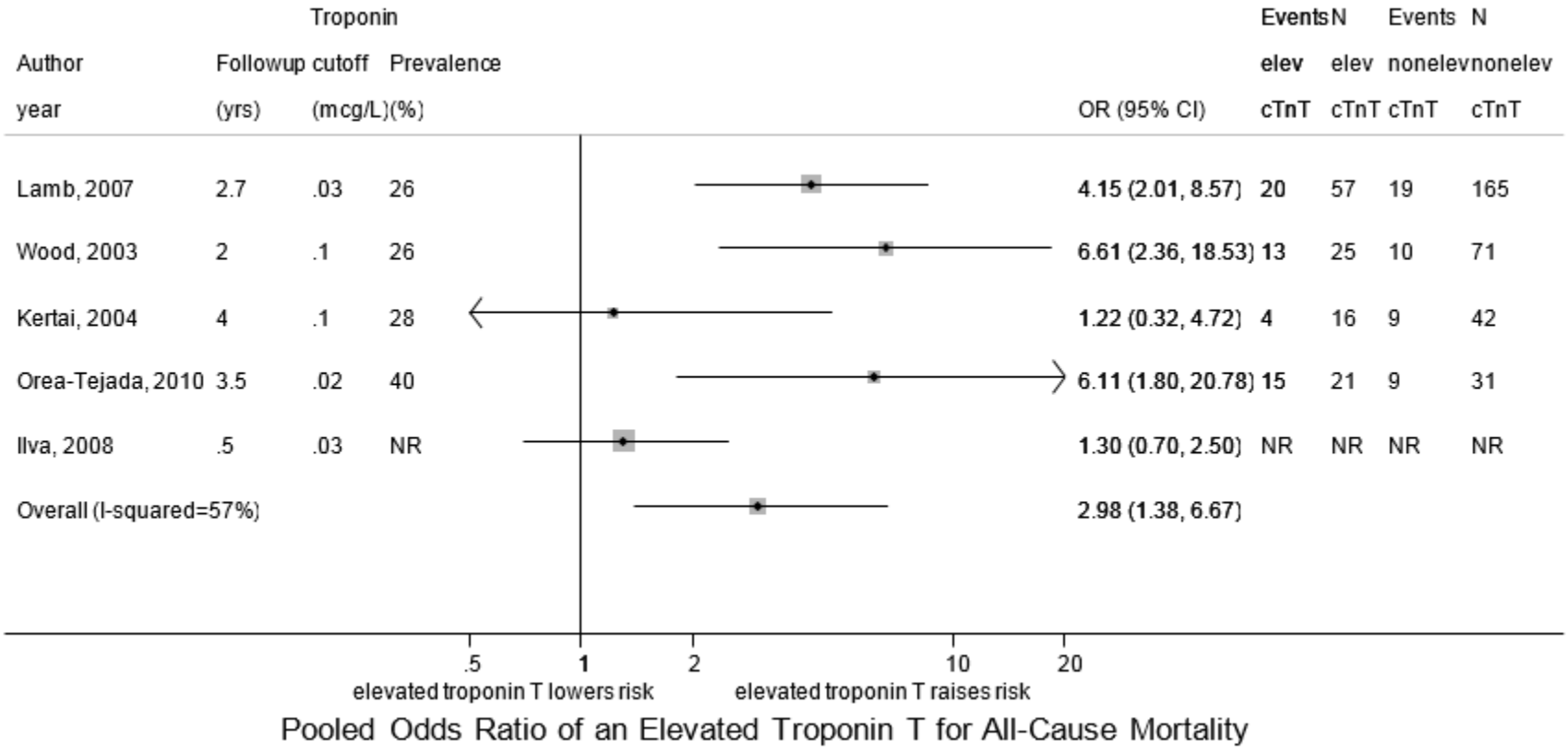
*Included dialysis patients at recruitment or during followup

Figure 18. Pooled hazard ratio of the association of an elevated troponin T with all-cause mortality among nondialysis patients



* All studies used a troponin assay that was manufactured by Roche.
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 19. Pooled odds ratio of the association of an elevated troponin T with all-cause mortality among nondialysis patients



CI = confidence interval; cTnT = cardiac troponin T; elev = elevated; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio; yrs = years
Boxes indicate individual study point estimates. The box size denotes the weight of the study, with larger boxes contributing more to the pooled estimate. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of Cardiac Troponin I With All-Cause Mortality Among Nondialysis Chronic Kidney Disease Patients

We found five studies that assessed troponin I with an outcome of all-cause mortality among nondialysis patients with CKD (Table 37).[99, 108, 148, 154, 159] Two studies were used to perform a meta-analysis of HR adjusted for at least age and CAD or risk equivalent. The pooled HR was 1.73 (95% CI, 1.2 to 2.7) (Figure 20).

One study[108] provided adjusted OR but not HR. A small study of heart failure patients with CKD (n = 29) used a short-term followup period of 6 months and found no significant difference in mortality in an unadjusted analysis (OR, 1.4; 95% CI, 0.7 to 2.8).[154] There was insufficient data to calculate a pooled OR.

One study identified troponin I as having a sensitivity of 60 percent and a specificity of 73 percent for death with an area under the curve of 0.75 (95% CI. 0.66 to 0.84, $P < 0.001$).[99]

Musso et al. studied a small cohort consisting of a combination of dialysis, nondialysis, and post-kidney transplant patients (n = 49), and therefore it was difficult to compare this study with the results from other analyses we presented here.[148]

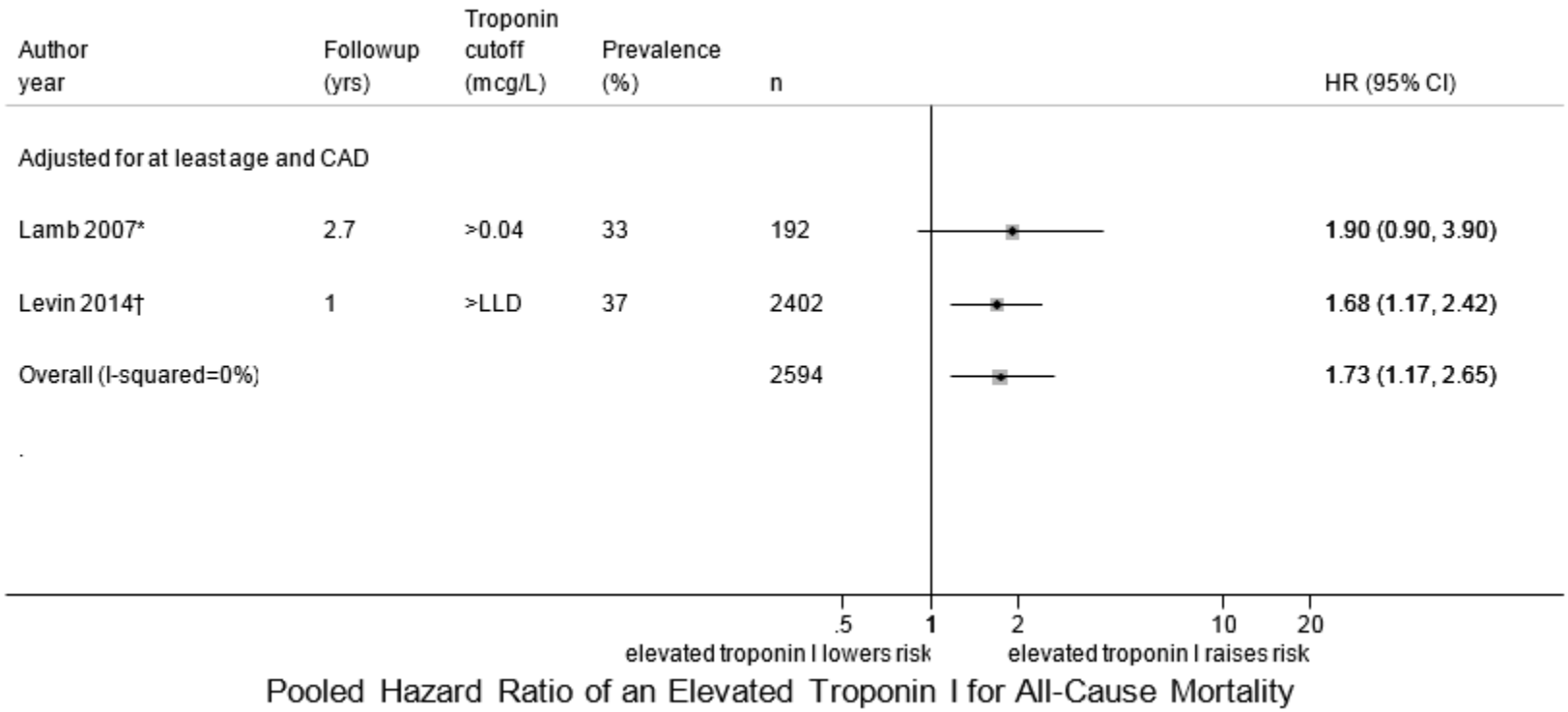
Table 37. Summary of the associations of elevated troponin I with all-cause mortality in patients not on dialysis

Author, Year	Troponin Manufacturer; Cutoff	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Ilva, 2008[154]	Abbott Architect; 0.32 mcg/L	CysC >1.2mg/L for age <50, 1.4mg/L age >50	6 months	NR (total n = 29)	NR	NR	NR	OR 1.4; 95% CI 0.7-2.8
Lamb, 2007[99]	Bayer ADVIA; 0.07 mcg/L (TnI Standard)	Stages 3-5	32 months	38	12 (31.6%)	177	27 (14.3%)	HR 1.4; 95% CI 0.7-3.0, *P* = 0.3, adjusted for age, hemoglobin, CAD
Lamb, 2007[99]	Bayer ADVIA; 0.04 mcg/L (TnI Ultra)	Stage 3-5	32 months	63	12 (19.0%)	129	14 (10.9%)	HR 1.9, 95% CI 0.9-3.9, *P* = 0.08 adjusted for age, hemoglobin, CAD
Musso, 1999[148]	Sanofi Access; 0.04 mcg/L	CKD (undefined)*	18 months	2	0 (0%)	47	2 (4.3%)	OR 3.80; 95% CI 0.14-102.2, *P* = 0.43
Levin, 2014[159]	NR	GFR 15-45 ml/min/1.73m2	1 year	37%	NR	NR	NR	HR 1.68, 95% CI 1.17-2.65; *P* = 0.005
Abbas, 2005[108]	Bayer ADVIA Centaur	CKD (undefined)	19 months	18%	NR	NR	NR	OR 2.4, 95% CI 0.78-7.0 adjusted for age, sex, eGFR, diabetes

CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; CysC = cystatin C; HR = hazard ratio; mcg/L = micrograms per liter; mg/L = milligrams per liter; NR = not reported; OR = odds ratio; TnI = troponin I

*Included dialysis patients at recruitment or during followup

Figure 20. Pooled hazard ratio of the association of an elevated troponin I with all-cause mortality among non-dialysis patients



* Study used a troponin assay that was manufactured by Bayer.
† Study did not specify the manufacturer of the troponin assay.
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; LLD = lower limit of detection; mcg/L = micrograms per liter; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

The Association of Cardiac Troponin T With Major Adverse Cardiovascular Events Among Nondialysis Chronic Kidney Disease Patients

Nine studies evaluated Troponin T in the context of cardiac mortality and MACE outcomes (Table 38).[25, 68, 69, 73, 82, 100, 125, 147, 148]

We pooled four comparable studies that adjusted for at least age and CAD or risk equivalent in an analysis of HRs (Figure 21).[68, 69, 73, 100]. Threshold values for troponin T ranged from 0.01 mcg/L to 0.1 mcg/L. When Hasegawa et al. separated the high-sensitivity troponin T values into four ranges, only the highest cutoff value of 0.033 mcg/L remained significant (HR, 6.2; 95% CI, 1.4 to 27.7).[68]. We used the highest cutpoint in our meta-analysis. The result of this pooled analysis was statistically significant (HR, 2.7; 95% CI, 1.1 to 7.6). One additional study presented an unadjusted HR.[25]

We did not include two studies with a MACE outcome in this meta-analysis because of inclusion of dialysis patients.[147, 148] Neither of these found a significant association between elevated troponin T and MACE.

Two studies analyzed cardiac mortality; however, these results are difficult to compare as one study included both dialysis and nondialysis patients,[82] and the other was comprised of predialysis patients, many of whom began dialysis during the followup period.[125] Neither of these found troponin T to be a predictor of MACE in asymptomatic nondialysis patients.

The Association of Cardiac Troponin I With Major Adverse Cardiovascular Events Among Nondialysis Chronic Kidney Disease Patients

Two studies assessed the association with troponin I and composite MACE (Figure 22). Both studies combined dialysis and nondialysis patients in a small cohort (n = 49 and 40, respectively). One had a followup period of 18 months, and the other 9 months. The latter used two troponin I assays with different cutoff values (0.35 mcg/L for Dade Stratus, and 1.6 mcg/L for Behring OPUS Plus). Results were insignificant for both, despite different rates of elevated and nonelevated troponins within the population. Although results were not statistically significant, the study designs made it impossible to draw the conclusion that troponin I does not predict MACE in this population.[147, 148]

The Association of High-Sensitivity Troponin T With Risk Among Nondialysis Chronic Kidney Disease Patients

Quiroga et al.,[156] using a sensitive cutpoint of troponin T >0.01 ng/L (0.00001 mcg/L), found that elevated troponin T was associated with a 2-fold increase risk of cardiovascular event (unadjusted OR, 2.08; 95 percent CI 1.03-4.16) (Figure 23).

The Association of High-Sensitivity Troponin I With Risk Among Nondialysis Chronic Kidney Disease Patients

No studies meeting criteria for KQ4 addressed high-sensitivity troponin I assays.

Table 38. Summary of the associations of elevated troponin T with major adverse cardiovascular events in patients not on dialysis

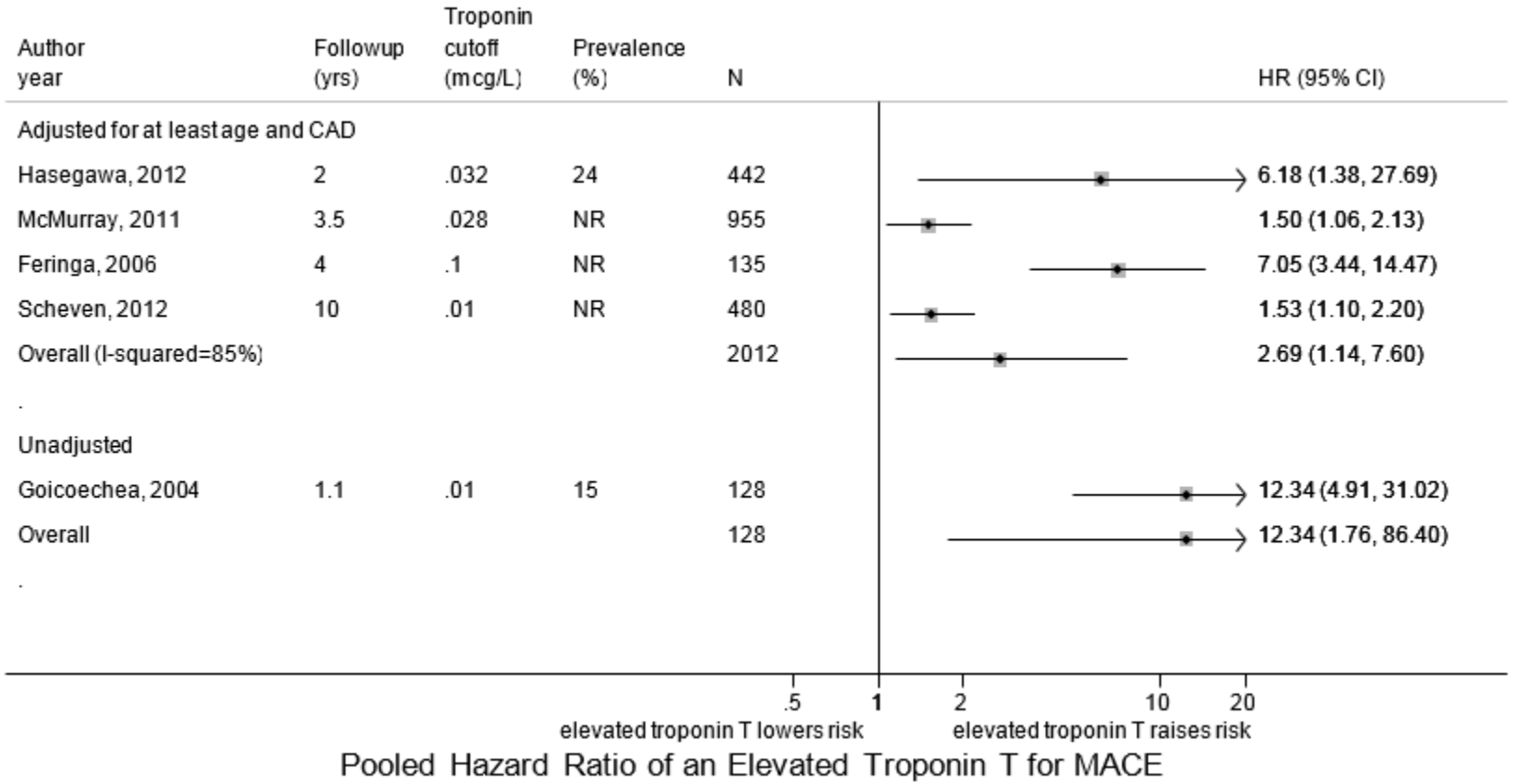
Author, Year	Troponin Manufacturer; Cutoff	Outcome	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Feringa, 2006[100]	Roche Elecsys; 0.03-0.09 mcg/L	Nonfatal MI, death caused by MI, arrhythmia, or CHF, or sudden unexpected death	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 8.09; 95% CI 2.72-24.05, *P* < 0.001 adjusted for age, sex, CAD
Feringa, 2006[100]	Roche Elecsys; >0.1 mcg/L	Nonfatal MI, death caused by MI, arrhythmia, or CHF, or sudden unexpected death	Stage 3-5	4 years	NR (total n = 558)	NR	NR	NR	HR 7.05; 95% CI 3.44-14.47, *P* < 0.001 adjusted for age, sex, CAD
Wood, 2003[125]	Roche Elecsys; 0.1 mcg/L	Cardiac mortality	Cr >500 micromol/L	2 years	25	6 (24%)	71	5 (7.0%)	OR 3.41; 95% CI 0.96-12.15, *P* = 0.06
Musso, 1999[148]	Boerhinger Enzymum; 0.02 mcg/L	Adverse cardiac event	CKD (undefined) *	18 months	23	0 (0%)	26	2 (7.7%)	OR 0.22; 95% CI 0.01-4.94, *P* = 0.34
Chrysochou, 2009[82]	Roche Elecsys; 0.03 mcg/L	Cardiac mortality	Stages 1-5*	40 months	11	4 (36.4%)	71	11 (15.5%)	OR 2.34; 95% CI 0.63-8.69, *P* = 0.20
McMurray, 2011[73]	Roche 0.01-0.028 mcg/L	All-cause death, stroke, HF, or hospitalization for MI	Stage 3-5	10 years	NR (n = 955)	NR	NR	NR	HR 1.42; 95% CI 1.05-1.93, *P* =0.0001
McMurray, 2011[73]	Roche >0.028 mcg/L	All-cause death, stroke, HF, or hospitalization for MI	Stage 3-5	10 years	NR (n = 955)	NR	NR	NR	HR 1.5; 95% CI 1.06-2.13, *P* = 0.0001
Goicoechea, 2004[25]	Roche Elecsys; 0.01 mcg/L	Death, AMI, unstable angina, CHF, arrhythmia, stroke, or stenosis of limb arteries	Stage 3-5	12.9 months	20	NR	156	NR	HR 12.34; 95% CI 4.91-31.02, *P* = 0.0
Mockel, 1999[147]	Roche Elecsys; 0.1 mcg/L	AMI, rehospitalization, or death	Stage 5*	9 months	10	NR	30	NR	OR 1.03; 95% CI 0.18-5.9, *P* =0.969

Table 38. Summary of the associations of elevated troponin T with major adverse cardiovascular events in patients not on dialysis (continued)

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Population	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Hasegawa, 2012[68]	Roche 0.01-0.018 mcg/L	Cardiac death, unstable angina, AMI, or heart failure	Stages 3-5	22 months	111	11.5	113	0.88	HR 2.5; 95% CI 0.5-11.9 adjusted for age, CAD, diabetes, eGFR (reference Troponin T <0.01 mcg/L)
Hasegawa, 2012[68]	Roche 0.019-0.032 mcg/L	Cardiac death, unstable angina, AMI, or heart failure	Stages 3-5	22 months	110	19	113	0.88	HR 3.0; 95% CI 0.7-13.7 adjusted for age, CAD, diabetes, eGFR (reference Troponin T <0.01 mcg/L)
Hasegawa, 2012[68]	Roche >0.033 mcg/L	Cardiac death, unstable angina, AMI, or heart failure	Stages 3-5	22 months	108	41.4	113	0.88	HR 6.2; 95% CI 1.4-27.7 adjusted for age, CAD, diabetes, eGFR (reference Troponin T <0.01 mcg/L)
Scheven, 2012[69]	Roche Modular E170; 0.01 mcg/L	AMI, ischemic cardiovascular disease, or revascularization	Stages 1-5	>10 years	NR total=1505	NR	NR	NR	HR 1.5; *P* = 0.008 adjusted for age, sex, CAD, smoking, BMI, BP, cholesterol, diabetes

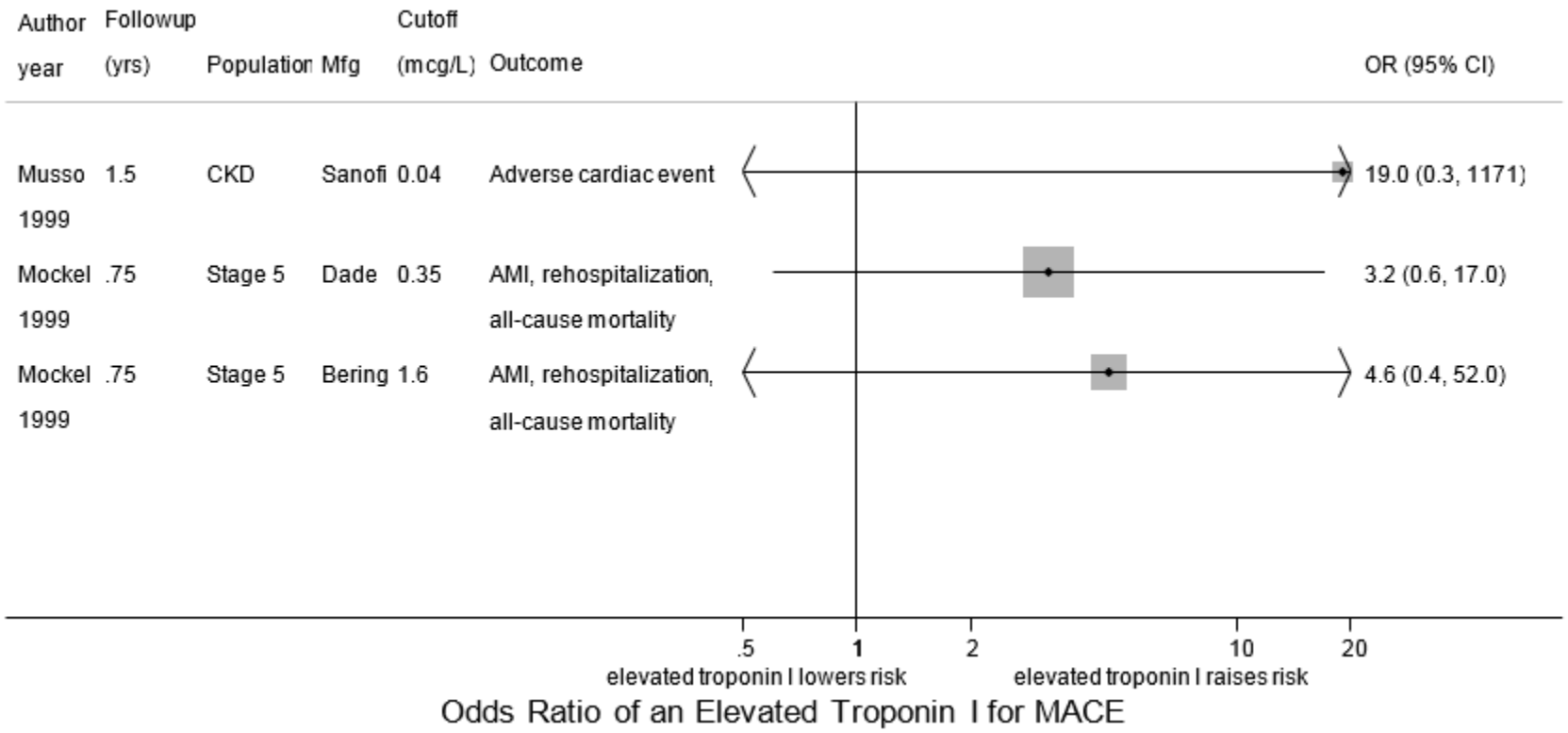
AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CII = confidence interval; CKD = chronic kidney disease; Cr = creatinine; HR = hazard ratio; mcg/L = micrograms per liter; MI = myocardial infarction; NR = not reported; OR = odds ratio
*Included dialysis patients at recruitment or during followup

Figure 21. Pooled hazard ratio of the association of an elevated troponin T with major adverse cardiovascular events among nondialysis patients



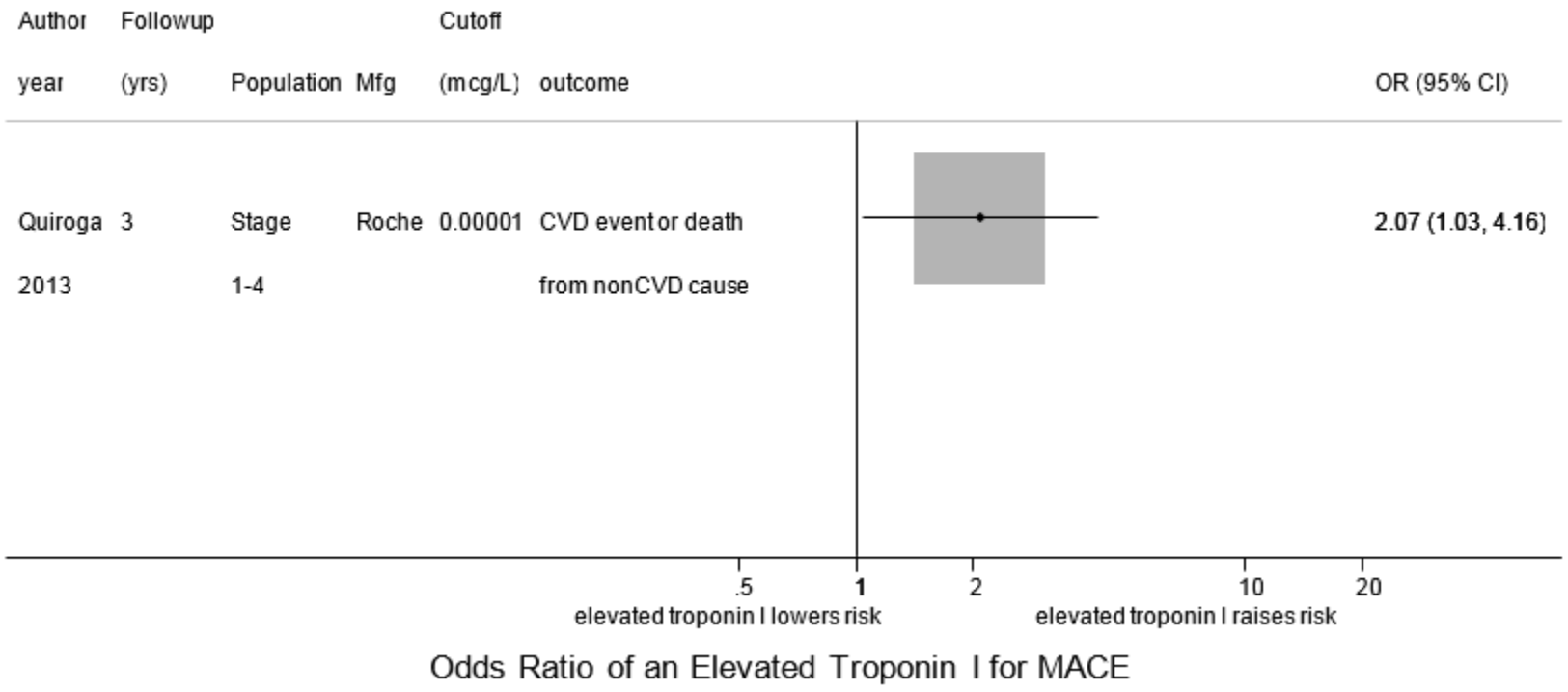
* All studies used a troponin assay manufactured by Roche.
CAD = coronary artery disease or risk equivalent; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event; mcg/L = micrograms per liter; NR = not reported; yrs = years
Boxes indicate individual study point estimates. The width of the horizontal lines represents the 95 percent confidence intervals for each study.

Figure 22. Summary of the associations of elevated troponin I with major adverse cardiac events in patients not on dialysis



AMI = acute myocardial infarction; CI = confidence interval; CKD = chronic kidney disease; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio
*Included dialysis patients at recruitment or during followup

Figure 23. Summary of the associations of high-sensitivity elevated troponin T with major adverse cardiac events in patients not on dialysis



CI = confidence interval; CKD = chronic kidney disease; CVD = cardiovascular disease; mcg/L = micrograms per liter; OR = odds ratio; yrs = years

KQ 4.3b: Troponin Associations With Short- and Long-Term Outcomes by Subgroups of Nondialysis Patients

We presented results for dialysis patients and nondialysis (nontransplanted) CKD patients above in the respective sections.

We found some additional subgroup analyses investigating troponin associations in pre- and post-kidney transplant patients as follows:

Key Points

- We did not identify any studies that analyzed troponin I in pre-kidney transplant patients (strength of evidence: insufficient).
- In pre-kidney transplant populations, data suggested that elevated troponin T values are predictors of adverse outcomes. These studies included both dialysis and nondialysis patients (strength of evidence: moderate).
- Elevations in both troponin I and T are likely predictors of adverse outcomes in the post-kidney transplant period (strength of evidence: low).
- In nondialysis CKD patients with a history of CAD, an elevated troponin I is a predictor of adverse cardiac event (strength of evidence: low).
- Studies did not assess subgroups by age, sex, ethnicity, and comorbidities other than CAD in the asymptomatic, nondialysis CKD population (strength of evidence: insufficient).

Pre-Transplantation

We identified three reports of end-stage renal disease (ESRD) patients referred for kidney transplantation, some of whom had been on dialysis and some of whom had not.[84, 90, 105] All of these evaluated troponin T (Table 39). Two studies by the same author considered a group of 644 ESRD patients with troponin T values that were measured upon referral for kidney transplant. The studies presented results for the entire population, regardless of whether the patient went on to receive transplantation. During a mean followup of 11.5 months, elevated troponin T of greater than 0.01 mcg/L was associated with death in a model adjusting for sex, age, albumin, history of stroke, body mass index, smoking status, cholesterol, hemoglobin, and time on dialysis (HR, 1.6; 95% CI, 1.1 to 2.5, $P = 0.022$).[90]

In a subsequent study of only patients who underwent kidney transplantation, pre-transplant elevated troponin T of at least 0.01 mcg/L was associated with composite MACE (AMI, revascularization, peripheral vascular intervention, or stroke) during a mean followup period of 28.4 months. The study observed this association in a model adjusted for age, time on dialysis, ejection fraction, and delayed graft functioning (HR, 1.6; 95% CI, 1.1 to 2.2, $P = 0.008$).[84]

In a study of 117 patients, Sharma et al. found a troponin T of greater than 0.06 mcg/L to be associated with all-cause mortality in a 3-year followup (OR, 7.1; 95% CI, 5.7 to 10.2, $P = 0.004$), though results were not adjusted. The associated area under the curve was 0.82 (95% CI, 0.64 to 0.99; $P = 0.02$), with a sensitivity of 75 percent and a specificity of 72 percent.[105]

Table 39. Summary of the association with risk of elevated troponin T in pre-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Population	Outcome	Followup	n	Summary of Results
Hickson, 2008[90]	Roche 0.01 mcg/L	Stage 5*	All-cause mortality	11.5 months	603	HR 1.64; 95% CI 1.07-2.51, *P* = 0.022 adjusted for sex, race, albumin, stroke, BMI, smoking, time on dialysis, cholesterol, hemoglobin
Sharma, 2006[105]	Roche Elecsys; 0.06 mcg/L	Stage 5*	All-cause mortality	3 years	117	OR 7.14; 95% CI 5.71-10.22, *P* = 0.004
Hickson, 2009[84]	Roche 0.01 mcg/L	Stage 5*	AMI, revascularization, peripheral vascular intervention, or stroke	54 months	603	HR 1.58; 95% CI 1.12-2.22, *P* = 0.008 adjusted for sex, race, albumin, stroke, BMI, smoking, time on dialysis, cholesterol, hemoglobin

AMI = acute myocardial infarction; BMI = body mass index; CI = confidence interval; HR = hazard ratio; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio

*Included dialysis patients at recruitment or during followup

Post-Transplantation

In the studies of post-kidney transplantation populations, three evaluated troponin I[71, 78, 115] and one evaluated troponin T.[94]

Troponin I

We describe the results for studies of troponin I in Table 40. A cohort of 34 dialysis patients with troponin I measured prior to and following renal transplantation found that 47.1 percent of the patients had an increase in troponin I value after surgery as compared with pre-surgery levels, although none exceeded the cutoff value of 2.3 mcg/L. The study followed patients for 22 months, and none experienced cardiac events or died.[115]

Another study considering postoperative troponin I values following kidney transplant used a threshold value of 0.04 mcg/L. This reported in-hospital acute myocardial infarction (AMI), 1-year all-cause mortality, and 1-year coronary revascularization. Of 376 in-hospital patients, the study observed AMI in 6.3 percent of those with elevated troponin I, but did not observe AMI in patients with a nonelevated value ($P < 0.001$). Rates of in-hospital death and revascularization were not significant. At 1-year followup, the difference in mortality between the two groups was not significant, and the rate of revascularization (percutaneous coronary intervention or coronary artery bypass graft) was marginally significant at 5.3 percent of those in the elevated troponin I group compared with 1.4 percent of those in the nonelevated troponin I group ($P = 0.49$); however, neither percutaneous coronary intervention or coronary artery bypass graft was significant when assessed alone.[71]

A similar study of 331 post-kidney transplantation patients used a higher cutoff value of 0.07 mcg/L. The study defined MACE as AMI, revascularization, or death due to an ischemic event and reported after a 3-month followup. The study noted a significantly lower rate of outcome in those with a nonelevated troponin I when adjusted for a history of CAD (OR, 0.1; 95% CI, 0.03 to 0.4) or age (OR, 0.1; 95% CI 0.03 to 0.3).[78]

Troponin T

We listed the results of troponin T studies in post-kidney transplantation populations in Table 41. A study of 372 patients, who had received kidney transplant in the past 3 months, used troponin T measurements with a cutoff level of 0.03 mcg/L to analyze outcomes during a maximum followup period of 1,626 days. They found a higher rate of all-cause mortality in those with an elevated troponin T (57.1 percent) versus a nonelevated test (14.0 percent) ($P < 0.001$). The study found a similar result for an outcome of cardiac mortality (33.3 vs. 4.8 percent, $P < 0.001$). In a model adjusted for age, sex, smoking history, diabetes, blood pressure, cholesterol, body mass index, and blood biochemical levels, troponin T remained significantly associated with all-cause mortality (Exp(β) 2.7; 95% CI, 1.2 to 6.1, $P < 0.001$).[94]

Other Subgroups

In a subgroup of post-kidney transplantation patients (n = 78) with a history of CAD, Claes et al. found an increased risk of MACE for every 0.01 mcg/L increase in troponin I in an adjusted analysis (OR, 1.2; 95% CI, 1.0 to 1.4, $P = 0.038$).[78]

No other studies performed subgroup analysis in nondialysis populations.

Table 40. Summary of the association of elevated troponin I with risk in post-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Bozbas, 2004[115]	DPC Immulite; 2.3 mcg/L	All-cause mortality	22 months	0	0 (0.0%)	34	0 (0.0%)	OR 69.0; 95% CI 0.56-8490.3801, *P* = 0.08
Shroff, 2012[71]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	All-cause mortality	In-Hospital	95	3 (3.2%)	281	5 (1.8%)	OR 1.77; 95% CI 0.42-7.57, *P* = 0.44
Shroff, 2012[71]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	All-cause mortality	1 year	95	6 (6.3%)	281	0 (0.0%)	OR 38.32; 95% CI 2.14-686.63, *P* = 0.01
Shroff, 2012[71]	Ortho Clinical Diagnostics Vitros; 0.04 mcg/L	Revascularization	1 year	95	5 (5.3%)	281	4 (1.4%)	OR 3.70; 95% CI 0.97-14.05, *P* = 0.05
Claes, 2010[78]	Siemens Heterogeneous; 0.07 mcg/L	AMI, revascularization, or death due to an ischemic event	3 months	NR (total n = 331)	NR	NR	NR	OR 0.104, 95% CI 0.026-0.407 adjusted for CAD; OR 0.096, 95% CI 0.027-0.339 adjusted for age (reference groups reversed compared with other studies)

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = confidence interval; mcg/L = micrograms per liter; NR = not reported; OR = odds ratio

Table 41. Summary of the association of elevated troponin T with risk in post-kidney transplantation populations

Author, Year	Troponin Manufacturer; Cutoff	Outcome	Followup	n with Elevated Troponin	n (%) with Outcome	n with Nonelevated Troponin	n (%) with Outcome	Summary of Results
Connolly, 2008[94]	Roche Elecsys; 0.03 mcg/L	All-cause mortality	4.5 years	21	12 (57.1%)	351	49 (14.0%)	Exp(β) 2.70; 95% CI 1.20-6.06, *P* < 0.001 adjusted for age, sex, smoking, DM, BP, cholesterol, BMI, growth hormone, phosphate, parathormone
Connolly, 2008[94]	Roche Elecsys; 0.03 mcg/L	Cardiac mortality	4.5 years	21	7 (33.3%)	351	17 (4.8%)	OR 6.88; 95% CI 2.57-18.42, *P* = 0.0001

BMI = body mass index; BP = blood pressure; CI = confidence interval; DM = diabetes mellitus; Exp(β) = exponent beta; mcg/L = micrograms per liter; OR = odds ratio

Strength of Evidence (Nondialysis Chronic Kidney Disease Patients)

Tables 42 and 43 describe our strength of evidence grading for KQ4 among nondialysis patients. Tables 44 and 45 describe our strength of evidence grading for KQ4 among subgroups of nondialysis patients.

Table 42. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among nondialysis patients: Strength of evidence domains

Outcome	Troponin Assay	Study design: No. Studies	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of evidence
All-cause mortality	Troponin T	9 observational studies overall; 2 in HR meta-analysis adjusting for at least age and CA; 5 in OR meta-analysis	Medium	Direct	Consistent	Precise	Adjusted HR 3.41; unadjusted OR 2.98	Moderate
All-cause mortality	Troponin I	4 observational studies overall; 2 in HR meta-analysis adjusting for at least age and CAD	Medium	Direct	Consistent	Precise	Adjusted HR 1.73; OR range 1.4 to 3.80	Moderate
MACE	Troponin T	9 observational studies; 4 in HR meta-analysis adjusted for at least age and CAD	High	Direct	Consistent	Precise	Adjusted HR 2.69	Moderate
MACE	Troponin I	2 observational studies overall including both dialysis and non-dialysis patients	High	Indirect	Consistent	Imprecise	N/A (combined dialysis and non-dialysis)	Insufficient
MACE	High-sensitivity troponin T	1 observational study (unadjusted analysis)	Medium	Direct	NA	Precise	OR 2.08	Insufficient

CAD = coronary artery disease; HR = hazard ratio; MACE = major adverse cardiovascular events; OR = odds ratio

Table 43. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among nondialysis patients: Details regarding strength of evidence domains

Outcome	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
All-cause mortality	Troponin T	Observational studies	6 fair quality and 3 good quality studies, none of were blinded, 8 studies with adjusted analyses	Despite the heterogeneity in the study designs, there was a consistent direction of association. Pooled HRs and ORs remained consistent in the sensitivity analyses. Estimates were precise.
All-cause mortality	Troponin I	Observational studies	2 fair quality and 2 good quality studies, none of the studies were blinded, 2 studies adjusted for confounders	Pooled HR analysis suggested a significant association.
MACE	Troponin T	Observational studies	6 fair quality and 3 good quality studies, 1 study blinded the laboratory researchers and clinicians, 5 studies adjusted for confounders	Despite the heterogeneity in the study designs, the studies reporting hazard ratios showed a consistent direction of association and precise estimates.
MACE	Troponin I	Observational studies	2 studies of fair quality, neither blinded outcome assessors and neither adjusted for confounders	Two small studies with imprecise estimates and wide confidence intervals. Both studies included dialysis and nondialysis patients, so neither directly assesses the risk among nondialysis patients.
MACE	High sensitivity troponin T	Prospective	1 fair quality study	This one observational study had precise estimates.

MACE = major adverse cardiovascular events

Table 44. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among subgroups of nondialysis patients: Strength of evidence domains

Subgroup	Troponin Assay	Study design: No. Studies (N)	Risk of Bias Limitations	Directness	Consistency	Precision	Strength of Association	Strength of Evidence
Pre-transplantation	Troponin T	3 (720)	Medium	Direct	Consistent	Precise	HR range 1.58 to 1.64; OR 7.14	Moderate
Post-transplantation	Troponin T	1 (372)	Low	Direct	n/a	Precise	Exp(Beta) 2.70; OR 6.88	Low
Post-transplantation	Troponin I	3 (741)	High	Direct	Consistent	Imprecise	OR range 1.77 to 69.0	Low
History of CAD; Nondialysis	Troponin I	1 (78)	Low	Direct	n/a	Precise	OR 1.17	Low

CAD = coronary artery disease; HR = hazard ratio; N/A = not applicable; OR = odds ratio

Table 45. Association of elevated troponin T or I versus nonelevated troponin T or I in terms of risk stratification among subgroups of nondialysis patients: Details regarding strength of evidence domains

Subgroup	Troponin Assay	Study Design	Risk of Bias Details	Reasons for Downgrading Domains Comments About How Overall Strength of Evidence Derived
Pre-transplantation	Troponin T	Observational studies	2 good quality studies and 1 fair quality study, 2 studies adjusted for confounders, none of the studies were blinded	Effect estimates showed a consistent direction of association and were precise.
Post-transplantation	Troponin T	Observational study	1 study of good quality	There was only one study. Effect estimates were direct and precise, but consistency could not be determined.
Post-transplantation	Troponin I	Observational studies	1 good quality, 1 fair quality, and 1 poor quality observational study, only 1 study provided adjusted results	Despite the heterogeneity in study designs and study quality, the studies showed a consistent direction of association. The effect estimates had wide confidence intervals.
History of CAD; Nondialysis	Troponin I	Observational study	1 good quality study with adjusted analysis	There was only one study. Effect estimates were direct and precise, but consistency could not be determined.

CAD = coronary artery disease

Discussion

Key Findings

KQ 1: Use of Troponin for Diagnosis of Acute Coronary Syndrome Among Patients With Chronic Kidney Disease

We systematically reviewed the available evidence regarding the utility of troponin testing with final (usually adjudicated) ACS diagnosis. However, we only found low-quality or insufficient evidence regarding the use troponin T and I assays to diagnose ACS in CKD patients. Troponin levels were associated with a wide range of sensitivity and specificity compared to final ACS diagnosis.

Studies addressing these operating characteristics were markedly heterogeneous in setting, population, and completeness of reporting regarding adjudication of ACS. In addition, there is also heterogeneity between studies regarding the assay manufacturer and cutpoints used for diagnosing ACS. We found limited evidence directly comparing the use of troponin T and I assays to diagnose ACS in a comparable population of CKD patients, and limited evidence examining the operating characteristics among relevant subgroups. We were unable to perform a meta-analysis of the summary statistics due to insufficient data.

The National Academy of Clinical Biochemistry had recommended that patients with ESRD and suspected ACS should have a dynamic change in troponin levels of greater than 20 percent within 9 hours (with at least one value above the 99th percentile) to warrant a clinical diagnosis of acute MI. We did not find any studies that tested this guideline in terms of operating characteristics (sensitivity, specificity, positive predictive value, and negative predictive value).

Overall, we were struck by the paucity of evidence for this KQ, and thus could not establish a clear cutpoint that maximizes sensitivity and specificity. The lack of direct comparison to patients without CKD in the same population cohort is another major limitation.

The sensitivities and specificities for diagnosing MI, among patients with CKD that we identified in our review may seem problematically low or too variable to draw conclusions (sensitivities ranging from 43 to 100 percent and specificities ranging from 31 to 100 percent).

However, one must keep in mind that using troponin levels to diagnose ACS can be problematic even in a general population of patients (not explicitly CKD). In a study of patients presenting to an emergency room with positive troponin I at a threshold of 0.04 mcg/L, clinicians diagnosed 20.4 percent with type I MI, 9.1 percent with type II MI, but the majority (65.8 percent) did not meet criteria for acute MI.[170] In another study of patients presenting to an emergency room with positive troponin, clinicians ultimately diagnosed only 55 percent with MI.[171] Furthermore, a recent study evaluating four new point-of-care assays for troponin I among patients with suspected ACS found that at the 99th percentile for each assay, sensitivities varied from 26 to 68 percent and specificities varied from 81 to 93 percent for diagnosing MI, versus the gold standard of the Universal Guidelines for MI.[172]

Thus, our findings must be put in context of what we already know about using troponin to diagnose ACS in the general population—that the utility of the diagnostic test is dependent on the pre-test probability for suspected ACS (i.e., Bayes Theorem). Newby et al., in a review on troponins for a consensus document on behalf of the American College of Cardiology Foundation (ACCF),[13] cites this following example: If the pre-test probability for ACS is high, such as 90 percent, based on classic symptoms and ECG changes, the post-test probability for a

positive troponin above the 99th percentile is still 95 percent even if the false positive rate is 40 percent. Conversely, if the pre-test probability is very low, such as 10 percent (due to atypical symptoms or symptoms suggestive of other cause), the post-test probability for ACS is only 50 percent even if false positive rate is only 10 percent. Even with lab evidence suggestive of myocardial necrosis, the post-test probability for ACS for positive troponin is still low if the pre-test probability is low. Conversely, low values do not exclude ACS if the pre-test probability is high. Therefore, it is difficult to interpret the sensitivities and specificities of troponin testing for diagnosing ACS for studies included in our report that do not specifically state the pre-test probability of the population. Furthermore, relying on a single value should be avoided, especially those from a high-sensitivity assay, in favor of serial values.

Newby et al. stress that the problem with troponin testing, like any laboratory test, is inappropriate testing (when not indicated) or inappropriate interpretation of results, not the marker itself, and that clinicians should only test for troponin when appropriate (i.e., clinically indicated). In patients with non-ST elevation ACS, global risk assessment rather than any single marker should be used for diagnosis and to guide therapy.

Therefore, to directly compare the utility of troponin testing in CKD and non-CKD populations, the pre-test probabilities should be similar in order to draw conclusions about comparisons. Although we found no studies that directly compared the use of troponin for diagnosing ACS in CKD versus non-CKD in the same population, our indirect comparison does not suggest that troponin is less effective in diagnosing ACS in CKD.

KQ 2: Do Troponin Levels Help Guide Management Decisions in Acute Coronary Syndrome for Patients With Chronic Kidney Disease?

As described in the background section, frequently, clinicians use troponin levels, along with clinical factors, to further risk-stratify patients presenting with suspected ACS. In regard to ACS management, glycoprotein IIb/IIIA inhibitors, low-molecular-weight heparin, and an early invasive strategy may have a better effect for troponin-positive patients than for troponin-negative patients. Patients with CKD also have a worse prognosis when presenting with ACS compared with non-CKD patients.[173] Furthermore, many RCTs that tested therapeutic agents for ACS management excluded patients with advanced CKD.

Unfortunately, since elevated cardiac biomarkers are such an integral component of the diagnosis and risk-assessment in ACS, it is difficult to study this question in an evidence-based way. It may not be ethical to randomize or withhold therapy based on troponin values alone, as ACS treatment algorithms depend on a whole host of clinical factors and timing of presentation.

As was anticipated, we did not find any study that directly addressed the question of whether troponin levels can affect management strategies in CKD patients with ACS symptoms (i.e., no studies randomized patients to any management strategy by troponin levels). Therefore we cannot draw conclusions to directly answer this question. We recommend further study in this area, such as a carefully-designed post hoc analyses of clinical trials testing ACS management strategies, comparing gradations of troponin elevation across treatment groups with a highlighted focus on CKD patients.

KQ 3: Do Troponin Levels Facilitate Short- and Long-Term Prognosis in Patients With Chronic Kidney Disease Presenting With Suspected Acute Coronary Syndrome?

As described in the background section, studies have examined elevated troponin as an independent predictor of morbidity and mortality in populations following an acute ischemic event but data is limited in CKD.

Overall, evidence is limited for the prognostic significance of elevated cardiac troponin with regard to short-term and long-term MACE, as well as for the mortality of patients with both CKD and ACS. Our review lends support toward higher rates of MACE within 1 year in CKD patients with ACS who have elevated (vs. nonelevated) troponins for both troponin T and I, with more available evidence linking an association of troponin I with MACE within 1 year than for troponin T. Regarding the outcome of all-cause mortality following a suspected ACS event, we also found limited data for troponin T (two insignificant studies), but did find a generally positive association of troponin I with all-cause mortality. However, few studies met our inclusion criteria for KQ3, and many studies were small and/or at risk of bias.

Overall, our findings suggest that elevated cardiac troponin (particularly troponin I) compared with nonelevated cardiac troponin, does appear to identify CKD patients who are at higher risk for subsequent MACE (following a presentation for ACS). However, all studies were observational in design. And no studies evaluated changes in management decision. Clinicians treat all patients with suspected ACS based on the guideline-recommended treatment for acute ACS interventions, and then prescribe subsequent secondary prevention management (antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, etc.). Thus, although elevated troponin can identify a CKD patient as being a higher prognostic risk, the available evidence does not indicate how to lower a patient's risk (based on elevated troponin), beyond usual guideline-directed therapy.

KQ 4: Risk Stratification Among Patients With Chronic Kidney Disease Without Acute Coronary Syndrome

Risk Prediction

The results from our systematic review found that in observational data, elevated troponin (defined by varying cutpoints across studies) strongly and fairly consistently identifies CKD patients at higher risk for subsequent adverse events, compared with patients with nonelevated troponin. Among dialysis patients without suspected ACS, a baseline elevated cardiac troponin is associated with a higher risk (~2-4 fold) for all-cause mortality, cardiovascular-specific mortality, and MACE (e.g., "composite" outcome of MI, cardiovascular death, and/or revascularization) in pooled analyses of studies adjusted for at least age and CAD or risk equivalent.

A substantial number of observational studies confirmed this association among patients on dialysis, and results were largely consistent (in terms of direction of a positive association). More of the studies included in the pooled meta-analyses reported outcomes for all-cause mortality than for other outcomes. Thus, the evidence from the pooled meta-analysis is strongest for the association of elevated cardiac troponin with all-cause mortality; an approximately 3-fold increased risk was found, which was highly significant. The evidence from meta-analyses for the

association of elevated cardiac troponin with cardiovascular-specific mortality and MACE, showed similar effect sizes but with wider confidence intervals from fewer studies.

The association of elevated troponin with adverse outcomes among dialysis patients was generally similar for troponin T versus I. Few studies reported results for high-sensitivity troponin T and I assays, so less is known about how well these assays predict risk. Studies that used a sensitive assay identified more patients as having elevated troponin.

While almost all studies of dialysis patients supported a positive association for elevated cardiac troponin with adverse cardiovascular outcomes (particularly mortality), we noted heterogeneity in some of the pooled meta-analyses results (as defined by the I-squared statistic) among the studies, even though we analyzed troponin T and I separately. We performed sensitivity analyses, such as only including studies that adjusted for age or age and CAD, but we were unable to eliminate all of the heterogeneity in the meta-analyses. Generally, the direction of association was similar (indicating increased risk for elevated troponin levels), but the magnitude of risk varied substantially across studies.

Previous to our report, Khan et al. published the largest meta-analysis of the use of cardiac troponin for risk prediction among dialysis patients in 2005.[23] The authors reviewed studies through December 2004, and found 17 studies evaluating troponin T for all-cause mortality (pooled relative risk 2.6; 95% confidence interval, 2.2 to 3.2, also with high heterogeneity). Of note, this pooled meta-analysis used a relatively high troponin T cutpoint of >0.1 mcg/L, almost 10-fold higher than the lower limit of detection. They found 12 studies for troponin I for all-cause mortality (pooled relative risk, 1.7; 95% confidence interval, 1.3 to 2.4). Many of the individual studies identified for troponin I were not statistically significant, but their pooled relative risk was significant.

We have now updated the literature by performing a comprehensive review through May 2014. We found 43 studies for troponin T and 30 studies for troponin I for all-cause mortality. We were able to perform meta-analyses for both HRs (time to event) and ORs (relative risk) as available, whereas Khan et al. only performed relative risk analyses. We used all cut-points available in literature (and did not limit studies to troponin T >0.1 mcg/L as per Khan's study). In our meta-analyses, we found similar (if not stronger) effect sizes for both troponin T and I with all-cause mortality compared with the previous results by Khan et al. We similarly noted heterogeneity across studies. We also performed meta-analyses for the other outcomes of cardiovascular-specific mortality and MACE.

Researchers has previously questioned troponin I as not being an important prognostic marker for risk prediction among dialysis patients given null results from several of the individual studies. However, the results from our meta-analyses do not clearly support this conclusion, as our pooled results showed a strong association (albeit slightly less than for troponin T). Differences may be due to more heterogeneity of the troponin I assays (multiple manufacturers) compared with troponin T (largely handled by one manufacturer).

We can conclude that elevated troponin T levels, and to a slightly lesser extent elevated troponin I levels, are both strongly associated with increased risk of mortality among dialysis patients (strength of evidence: moderate). Therefore, elevated baseline troponin among CKD and dialysis patients is not "spurious" but portends a worse prognosis. Of note, in May 2004 the U.S. Food and Drug Administration approved the measurement of troponin T in dialysis patients for the express purpose of risk stratification (i.e., prediction of mortality). The findings of our updated review lend continuing support for this recommendation for risk prediction. However, how to manage patients based on the results from risk prediction (i.e., whether dialysis patients

with elevated troponin should be treated differently than dialysis patients with nonelevated level beyond usual clinical risk-factor guided care), remains an important clinical question that this review did not answer.

Troponin Testing Versus Clinical Risk Markers

Almost all of the studies found by our review determined the "prognostic" value of troponin by its associations with outcomes in regression models. However, while one must critically examine the utility of a biomarker for "prediction", the more clinically relevant question is how the marker stacks up in metrics of discrimination and re-classification. Discrimination [which is most often measured by the area under the curve (AUC) of a receiver operating characteristics (ROC)] is a measure of how well a model can distinguish those who and who do not have the disease of interest. Net reclassification index (NRI) is a newer statistical measure that quantifies the number of people correctly reclassified to higher and lower risk categories. Can troponin re-classify CKD patients into higher and lower risk groups (i.e., net reclassification index)? And, is this better than existing clinical models (i.e., comparing the area under the curve with clinical models)? We found very few studies that used AUC results and no studies that used NRI.

The meta-analyses performed for the pooled ORs were unadjusted results using number of events in each arm. For the meta-analyses for HRs, we selected the most-adjusted regression model. However, many studies only reported an unadjusted HR. While many studies adjusted for age, fewer studies adjusted for a history of CAD or CAD risk equivalent, such as diabetes mellitus, or adjusted for other cause of elevated troponin, such as heart failure. Even fewer studies adjusted more comprehensively for other cardiovascular risk factors, such as systolic blood pressure, dyslipidemia, and smoking. Elevated troponin levels may simply be a surrogate marker of someone with underlying CAD (i.e., a person already known to be at predicted higher risk). However, for the studies presenting adjusted HRs, results generally showed a positive association of elevated troponin levels with adverse outcomes even in progressively adjusted models, but again this was not well assessed.

The most robust evidence after adjustment for clinical factors was for the association of elevated troponin T and all-cause mortality among dialysis patients (strength of evidence: moderate). Of 21 studies available for HR analyses, 6 were unadjusted, 15 adjusted at least for age, and eleven adjusted at least for age and history of CAD (or CAD risk equivalents such as cardiovascular disease, congestive heart failure, ejection fraction, or diabetes mellitus) in their models. In two studies, the authors performed a more thorough regression model by additionally adjusting for numerous cardiovascular risk factors including blood pressure, lipids, and diabetes. For the HR analyses for troponin I, all of these studies at least adjusted for age, and six out of nine additionally adjusted for CAD or CAD risk equivalent (CAD, cardiovascular disease, heart failure, and diabetes). These studies predominantly used traditional regression models to show that the associations persisted after adjustment for clinical factors, but most did not use a more rigorous method of comparing C-statistics (area under the curve) against clinical models.

Havekes et al.[104] was one of the largest studies (847 dialysis patients) to rigorously examine whether troponin testing adds incremental prognosis over routine clinical factors. While a troponin T level greater than 0.1 mcg/L was a potent predictor of mortality in their study (adjusted HR, 2.2; 95 percent confidence interval, 1.5 to 3.3), it did not improve prediction over clinical factors. A survival model with clinical factors and routine laboratory markers predicted mortality with an area under the curve of 0.81, but adding troponin T to this model did not change this estimate. The area under the curve for predicting mortality for troponin T alone was

0.67. This data suggests that the troponin T biomarker is a potent predictor of mortality on its own, however, it may have little prognostic utility over clinical factors when more rigorously assessed (i.e., change in the C-statistic).

Thus, whether measuring this biomarker of cardiac troponin facilitates risk prediction in dialysis patients better than a traditional risk prediction model using only clinical variables is still somewhat uncertain.

Management of Nonacute Coronary Syndrome Patients Based on Troponin Testing

The National Kidney Foundation already endorses that all patients with CKD should be considered in the "highest risk" group for cardiovascular disease risk prediction, irrespective of levels of traditional cardiovascular risk factors (i.e., that CKD should be considered a CAD risk equivalent).[174] Therefore, if patients with CKD are already candidates for intensive management of their cardiovascular risk factors for prevention, what, if any, is the additive role of measuring troponin?

All of the studies we found that related to KQ4 were observational cohort studies. We did not find any intervention studies that compared management strategies of dialysis patients (without suspected ACS) on the basis of elevated troponin. Thus, while elevated cardiac troponin is clearly a marker of a patient at increased risk for subsequent cardiac events, it is unknown whether changing or altering patient management (such as implementing more intensified preventive efforts) on the basis of elevated troponin can reduce/prevent cardiovascular events and mortality. This is even a greater concern with the introduction of high-sensitivity assays, as more patients are labeled as having elevated troponin.

In the absence of MI, there are no specific interventions recommended to reduce cardiovascular disease risk in patients with CKD based solely on elevated troponin. Therefore the role of screening asymptomatic individuals, or how to use the prognostic information from the results in a way that affects patient management and outcomes is not clear.

KQs 1–4: Heterogeneity With Assays Platforms, Cutpoints, and 99th Percentile Considerations

Much heterogeneity across results for KQs 1–4 stemmed from differences between studies in the types of troponin assays used (different manufacturers, different assay platforms). Troponin assays have been changing over time, and newer generations of assays can detect lower and lower concentrations of cardiac troponin. Many of the papers did not report which generation of assay they used; and this was a significant limitation of our analyses. For troponin T, there was generally only one manufacturer (Roche, or Boehringer Mannheim which was acquired by Roche Diagnostics in 1997). However, there were multiple manufacturers of the troponin I assay. The studies were also heterogeneous regarding what cutpoints they considered elevated. Many studies did not report what the manufacturer-reported 99th percentile threshold was for that assay. The 99th percentile threshold also changed depending on the reference population and assay generation that the study used. The reference populations for the 99th percentiles were largely unclear, and were most likely not from a dialysis cohort. Therefore, we were not able to perform meta-analyses using the 99th percentile cutpoint, but instead compared the highest cutpoint reported with the lowest for consistency. All of our findings in this systematic review must be interpreted with this important caveat in mind.

The European Society of Cardiology/American College of Cardiology guidelines support a 99th percentile cutpoint, and studies that have used the 99th percentile cutpoint did confirm its utility in predicting risk. However, most studies presented results using higher cutpoints. For example, the Roche Elecsys assay lists a 99th percentile of 0.014 mcg/L, but most studies presented the 0.1 mcg/L cutpoint, which is 10-fold higher. A current list (as of 2013) of the 99th percentile for commercial and research assays is on the Web site for the International Federation of Clinical Chemistry and Laboratory Medicine (see http://www.ifcc.org/ifcc-scientific-division/documents-of-the-sd/troponinassayanalyticalcharacteristics2013/).

Applicability

Chronic Kidney Disease Stages

We found the largest body of evidence relating to dialysis patients without suspected ACS. Whereas these findings are most likely generalizable to the typical cohort of dialysis patients treated in clinical practice, these findings cannot necessarily be extrapolated to other stages of CKD I-IV. We did find limited data for nondialysis patients with CKD with strength of evidence ranging from low to moderate, suggesting a positive association for all-cause mortality, but results were not stratified by CKD stages.

Other Subgroups

We found limited data regarding subgroups classified by gender, history of CAD, and pre-or post-renal transplantation, but data were insufficient to generate pooled meta-analyses results by these subgroups or to make conclusive statements about generalizability to apply findings across these select groups. Regarding dialysis-only cohorts, few studies stratified by other subgroups. Subgroups described were as follows: persistently elevated troponin levels (one study), history of CAD (four studies), gender (two studies), pro-brain natriuretic peptide levels (one study), diabetes (one study), hypotension-prone (one study), and hemodialysis versus peritoneal dialysis (one study). We did not find any data in regard to subgroups of ECG changes or 10-year CAD risk status.

Limitations

We identified over 6,000 titles on this topic, narrowing it down to 130 publications that met our inclusion criteria. All of these studies were observational in design and have at least a moderate risk of bias due to known confounding associations. Patients with elevated troponin levels are more likely to have underlying CAD, heart failure, or co-morbidities that place them at higher risk of mortality. As described further in the above sections, we were limited by the fact that most studies were either unadjusted or minimally adjusted for other risk factors. Studies determined the use of troponin for "prognosis" by its association with outcomes in regression models, which is not the most clinically useful way to evaluate a biomarker. None of the studies evaluated the utility of troponin as a predictor by metrics of net reclassification index (i.e., its ability to re-classify patients into higher or lower risk groups). Only one study compared discrimination against a model of clinical factors.

As described above, studies were very heterogeneous in the assays (particularly for troponin I), troponin cutpoints, and definitions of ACS they used. This limited our ability to pool data and perform meta-analyses. Many studies failed to report any rigorous adjudication for ACS

diagnosis. Therefore, without a "gold standard" outcome to gauge troponin testing, we were limited in our ability to draw conclusions about the operating characteristics of the troponin biomarker for diagnosing ACS in CKD patients.

Our inclusion criteria deliberately selected only studies that reported clinical outcomes. This is because evidence-based guidelines are largely directed by studies with clinical outcomes, as there are many examples where findings in surrogate outcome studies do not translate into clinical benefits. Thus we did not evaluate elevated troponin with any surrogate markers (echocardiography, stress testing, left ventricular hypertrophy, etc.), only hard clinical outcomes. Therefore, our review is unable to explore potential mediating mechanisms for the associations presented, for which therapeutic strategies could be devised.

We did not explore the prevalence of elevated baseline troponin across all potential studies, but only for studies that also reported hard outcomes (i.e., we did not include cross-sectional studies). Thus, our assessment of the prevalence of elevated baseline troponin may be incomplete (KQ4.1).

We only reviewed studies that included results for patients with CKD by troponin levels. To keep the scope of our review specific to the topic at hand, we did not review all studies relevant to troponin testing and did not report results for general populations that did not specifically stratify by CKD subgroups. As further described above, 99th percentiles for troponin vary across study populations as well as pre-test probabilities for ACS; this makes indirect comparisons across studies very problematic. Therefore, we were unable to make any indirect comparisons of our results to non-CKD patients. There were no studies that directly compared troponin testing for non-CKD and CKD in the same population.

Research Gaps

Issues Related to Troponin Assays (KQ 1–4)

Need for Harmonization

Standardization of the troponin assays (particularly troponin I, where assays vary between numerous manufacturers), would facilitate interpretation across future studies. This is currently one of the goals of the International Federation of Clinical Chemistry Working Group on Standardization of Cardiac Troponin I. This goal is challenging given the complexity of troponin I (multiple isoforms), and that the antibodies used in the various immunoassays recognize different epitopes with variable reactivity.[175] In spite of these challenges, the need for harmonization, so that results can be compared across studies, is paramount. This need is only further emphasized by our review.

Need To Rigorously Standardize and Test the 99th Percentile

As further described above, we need to standardize the 99th percentile threshold in a unifying reference population. While universal guidelines have endorsed the 99th percentile threshold, studies are still being published using higher cutpoints, sometimes 10-fold higher. Thus, we need more studies that actually test the 99th percentile cutpoint for diagnosis and prognosis. Future studies should focus on using guideline-established cutpoints for consistency in the literature and relevance to clinical practice.

Timing of Measurement

Some studies involving only dialysis patients imply that the timing of troponin measurement (before vs. after a dialysis session) may be important. If clinicians are going to use troponin for risk stratification, studies recommend that troponin be measured prior to dialysis as dialysis can affect cardiac troponin levels. This review did not consider this, and it may be a research gap.

Diagnosis of Acute Coronary Syndrome (KQ 1)

Future work should seek to compare the operating characteristics of troponin T and I as an a priori objective of a well-designed series of studies using standardized assays and cutoffs. These studies should consider, in their design, testing the use of troponin among different subgroups of patients with CKD (such as stages 1 to 5) among which the operating characteristics of a troponin assay for ACS diagnosis might vary. Therapeutic options and likelihood of impact on outcomes may vary across stages of CKD. Studies also need to include a direct comparison to non-CKD patients to assess the assay head-to-head among the same reference population with the same pre-test probability. Furthermore, future studies should emphasize the pre-test probability of their population for suspected ACS using global risk assessment criteria in their reports, as the interpretation of troponin post-testing is largely driven by the pre-test probabilities.

The 20 percent rise/fall guideline (with at least one value above the 99th percentile) for acute MI diagnosis should be vetted against other potential diagnostic criteria such as single absolute thresholds or other delta of change in CKD patients.

Since RCTs are unlikely to be done, well-designed retrospective and post hoc analyses could potentially address this question. Such studies would provide highly useful information to clinicians as to the use of troponin assays in the real-world care of CKD patients.

Management of Acute Coronary Syndrome (KQ 2)

Whether the results from troponin testing for patients with CKD and suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies remains uncertain. This is an area for potential further investigation. Since RCTs likely will never be done, future research should focus on post hoc analyses of pre-existing clinical trials of ACS management.

Prognosis After Acute Coronary Syndromes (KQ 3)

The articles included for this study focused mainly on troponin values measured at the time of ACS presentation. Baseline, or previous values, of troponin are largely unknown. Thus, there is limited data supporting that a change in troponin from baseline is associated or not associated with different prognosis for adverse cardiac events in CKD patients with ACS.

It is unclear from this review if major increases in troponin levels in CKD patients with ACS should carry more weight than minor increases, as the studies we identified generally evaluated above and below a diagnostic cutpoint (of modest elevation) and not gradations of more significant increases in troponin. However prior literature among general populations supports that a large increase of troponin (evidence of more myocardial damage) portends a worse prognosis.[3]

There are current guidelines already in existence for management of ACS.[20] Area of future research should focus on management to reduce the risk of both short and long term events in

CKD patients with suspected ACS who have elevated troponins. Future studies should address whether management in CKD patients is different than non-CKD patients with similar degrees of elevated troponins. And if more elevated troponin levels in ACS are associated with worse outcomes, should these patients be managed differently (i.e., subjected to different medications and interventions) than CKD patients with ACS who have absent or lower degrees of troponin elevation? A prognostic biomarker by itself is insufficient without guidance of how to use this biomarker to guide or alter therapy.

Risk Prediction in Nonacute Coronary Syndrome Chronic Kidney Disease Patients (KQ 4)

What is the Pathophysiological Mechanism for the Association?

Elevated cardiac troponin levels indicate that a patient is at higher risk for adverse outcomes, particularly all-cause mortality among patients without suspected ACS. Cardiovascular mortality and MACE were also higher in patients with elevated troponin. But what is the precise cause of death? Is elevated cardiac troponin simply a marker of underlying CAD or a marker of silent ischemia? Are patients dying from MIs, heart failure, arrhythmias, or other causes? Once we clearly define the cause of death associated with elevated troponin, we can test and implement potential interventional strategies.

Need To Compare Troponin Testing Against Conventional Risk Prediction/Clinical Factors

As described above, a CKD patient with elevated troponin is at higher risk of adverse outcomes (the evidence being strongest for dialysis patients). It is less clear whether troponin testing offers incremental prognostic value over assessing risk based on clinical factors alone. Any future studies published on this topic should vigorously test troponin against other clinical models (i.e., whether troponin testing changes the area under the curve compared with other traditional clinical and laboratory risk markers). Studies should focus on metrics of net reclassification to determine whether this biomarker can appropriately re-classify CKD patients into higher and lower risk groups.

Need for Guidance for Management—Next Step Beyond Risk Prediction

Once a patient is identified at higher risk on the basis of an elevated serum troponin level, what is the next step? Should cardiac troponin testing include other diagnostic tests, such as stress testing or echocardiography? Should clinicians prescribe additional preventive medications such as aspirin, statins, or beta-blockers to CKD patients with elevated troponin levels? Many patients may already have indications for these therapies; what additional treatment should clinicians prescribe in these cases?

The next area of investigation should be large-scale clinical trials or carefully designed post hoc analyses to determine the next steps in therapeutic intervention and clinical management.

Conclusion

In summary, we conclude that even relatively minor elevations of cardiac troponin are associated with a worse prognosis for patients with and without suspected ACS. In particular, for

dialysis patients without suspected ACS, increased troponin T or I is a potent predictor of subsequent mortality. Whether elevated troponin provides strong incremental prognostic value over and above carefully assessed clinical risk factors for CAD and mortality, is not conclusive.

Regarding troponin testing, until there is harmonization and standardization of the troponin assay (similar to other laboratory markers), comparison of results from study to study and from population to population remains problematic.

Regarding patients with suspected ACS, troponin is already the gold standard for diagnosing MI and it is measured routinely in patients with suspected ACS. Established guidelines for ACS diagnosis and management are already in existence for the general population of patients. Successfully interpreting troponin levels in diagnosing ACS (vs. non-ACS) conditions largely depends on pre-test probability based on symptoms, ECG changes, and clinical factors.

Our findings do not dispute the utility of troponin for diagnosis or prognosis among CKD patients, with findings generally similar to studies reported for general populations of patients (indirect comparison), but we found very limited evidence for guiding disease management based on troponin levels alone.

Regarding CKD patients without suspected ACS, our findings support the current Food and Drug Administration and National Kidney Foundation recommendations that measuring troponin levels may be reasonable for additional risk stratification. Further work in this area should focus on improving our knowledge of the utility of this biomarker in regard to discrimination and the ability to appropriately reclassify CKD patients into higher and lower risk groups. However, unless we can identify the next steps regarding how best to manage these patients with elevated troponin levels (how and if treatments would vary from those treatments indicated by clinical factors alone), the applicability of this screening recommendation is incomplete. Thus it is difficult to endorse the routine measurement of cardiac troponin in clinical practice because of the uncertainty regarding appropriate clinical strategies that may use this information. New research should focus on testing patient management strategies that incorporate measuring this biomarker in their algorithms.

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Appendix A. Detailed Electronic Database Search Strategies

PubMed Strategy

Search	String
#1	"kidney failure, chronic"[mh]
#2	Renal[tiab]
#3	Kidney[tiab]
#4	Dialysis[tiab]
#5	Hemodialysis[tiab]
#6	Haemodialysis[tiab]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	"acute coronary syndrome"[mh]
#9	“acute coronary syndrome”[tiab] OR “acute coronary syndromes”[tiab]
#10	"angina, unstable"[mh]
#11	“unstable angina”[tiab]
#12	“myocardial infarction”[tiab]
#13	“Non-ST-segment elevation”[tiab] OR “non-ST-elevation”[tiab] OR “non-ST elevation”[tiab] OR “ST-segment elevation”[tiab] OR “ST-elevation”[tiab] OR “ST elevation”[tiab] OR (elevation[tiab] AND (ST[tiab] OR “S-T”[tiab] OR “ST-segment”[tiab]))
#14	Acute[tiab]
#15	#12 AND (#13 OR #14)
#16	#8 OR #9 OR #10 OR #11 OR #15
#17	“Troponin I”[mh] OR “Troponin T”[mh]
#18	Troponin*[tiab]
#19	#17 OR #18
#20	(#7 AND #16) OR (#7 AND #19)
#21	(animal[mh] NOT human [mh])
#22	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR “Case Reports”[pt] OR “Classical Article”[pt] OR “Clinical Conference”[pt] OR “Collected Works”[pt] OR Comment[pt] OR Congresses[pt] OR “Consensus Development Conference”[pt] OR “Consensus Development Conference, NIH”[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR “Legal Cases”[pt] OR Legislation[pt] OR News[pt] OR “Newspaper Article”[pt] OR Portraits[pt]
#23	#20 NOT #21 NOT #22
	Publication date from 1990/01/01

EMBASE Strategy

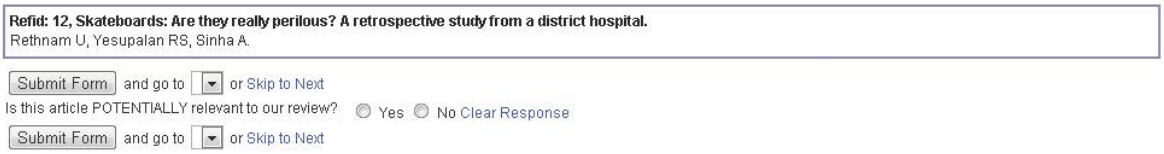
Search	String
#1	'chronic kidney failure'/exp
#2	"Renal”:ti,ab
#3	"Kidney":ti,ab
#4	"Dialysis":ti,ab
#5	"Hemodialysis":ti,ab
#6	"Haemodialysis":ti,ab
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	'acute coronary syndrome'/exp
#9	"acute coronary syndrome":ti,ab OR "acute coronary syndromes":ti,ab
#10	'unstable angina pectoris'/exp
#11	"unstable angina”:ti,ab
#12	"myocardial infarction”:ti,ab
#13	“Non-ST-segment elevation”:ti,ab OR “non-ST-elevation”:ti,ab OR “non-ST elevation”:ti,ab OR “ST-segment elevation":ti,ab OR “ST-elevation”:ti,ab OR “ST elevation”:ti,ab OR ("elevation":ti,ab AND ("ST":ti,ab OR “S-T”:ti,ab OR “ST-segment”:ti,ab))
#14	"acute":ti,ab
#15	#12 AND (#13 OR #14)
#16	#8 OR #9 OR #10 OR #11 OR #15
#17	'Troponin i'/exp OR 'Troponin T'/exp
#18	Troponin*:ti,ab
#19	#17 OR #18
#20	(#7 AND #16) OR (#7 AND #19)
#21	([animals]/lim NOT [humans]/lim)
#22	'conference abstracts':it OR 'conference paper':it OR 'conference reviews':it OR editorial:it OR erratum:it OR letter:it OR note:it
#23	#20 NOT #21 NOT #22
#24	Publication date from 1990

Cochrane Strategy

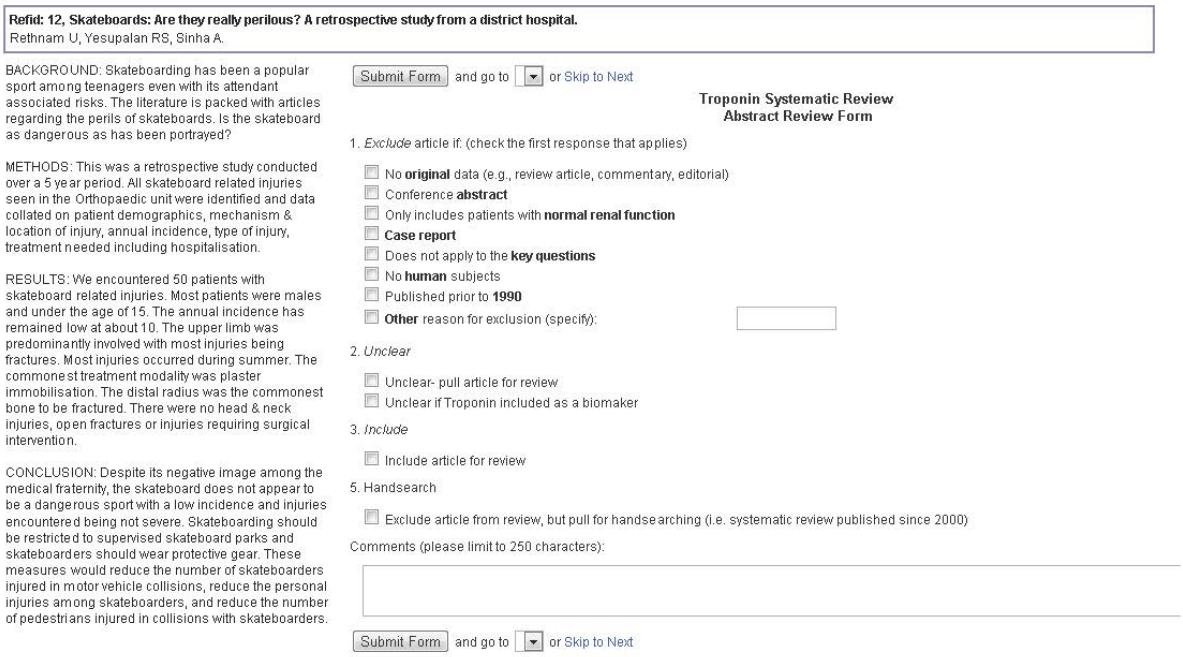
Search	String
#1	"kidney failure, chronic":ti,ab,kw
#2	Renal:ti,ab,kw
#3	Kidney:ti,ab,kw
#4	Dialysis:ti,ab,kw
#5	Hemodialysis:ti,ab,kw
#6	Haemodialysis:ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	"acute coronary syndrome":ti,ab,kw
#9	“acute coronary syndrome”:ti,ab,kw OR “acute coronary syndromes”:ti,ab,kw
#10	"angina, unstable":ti,ab,kw
#11	“unstable angina”:ti,ab,kw
#12	“myocardial infarction”:ti,ab,kw
#13	“Non-ST-segment elevation”:ti,ab,kw OR “non-ST-elevation”:ti,ab,kw OR “non-ST elevation”:ti,ab,kw OR “ST-segment elevation”:ti,ab,kw OR “ST-elevation”:ti,ab,kw OR “ST elevation”:ti,ab,kw OR (elevation:ti,ab,kw AND (ST:ti,ab,kw OR “S-T”:ti,ab,kw OR “ST-segment”:ti,ab,kw))
#14	Acute:ti,ab,kw
#15	#12 AND (#13 OR #14)
#16	#8 OR #9 OR #10 OR #11 OR #15
#17	“Troponin I”:ti,ab,kw OR “Troponin T”:ti,ab,kw
#18	Troponin*:ti,ab,kw
#19	#17 OR #18
#20	(#7 AND #16) OR (#7 AND #19)
	Publication date from 1990/01/01 and only trials

Appendix B. Forms

Title Review



Abstract Review



Article Review

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

Troponin Systematic Review
Article Review Form

1. Exclude article if: (check the first response that applies)

- ☐ No **original data** (e.g., review article, commentary, editorial)
- ☐ Meeting abstract
- ☐ Published prior to **1990**
- ☐ Does not include patients with **chronic kidney disease or end-stage renal disease**
- ☐ Does not evaluate **troponin I or T levels**
- ☐ Troponin & CKD results not presented separately
- ☐ No **human** subjects
- ☐ Does not evaluate a **comparison of interest**
- ☐ Does not evaluate an **outcome of interest**
- ☐ Does not apply to a **key question**
- ☐ Other reason for exclusion (specify):

2. Include article for review (indicate the main intervention of interest):

- ☐ KQ1 (diagnostic performance of troponin testing for detection of ACS in patients with CKD)
- ☐ KQ2 (do troponin levels improve management in patients with ACS and CKD)
- ☐ KQ3 (troponin and prognostication of patients with ACS and CKD)
- ☐ KQ4 (troponin help risk stratification in adults with CKD and no ACS symptoms)

3. Reference

- ☐ Exclude article from review, but pull for handsearching (i.e. systematic review published since 2000)
- ☐ Flag for background (i.e. discusses troponin prevalence for clearance in CKD population)

Comments (limit 250 characters)

Submit Form and go to or Skip to Next

Study Design

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Troponin EPC
Study Design Form

1. Where did the study occur?

- ☐ United States
- ☐ Canada
- ☐ Europe
- ☐ Worldwide
- ☐ Other (specify):

2. When was the study enrollment? (Enter the 4-digit year for the start and end dates)

- ☐ Start date:
- ☐ End date:
- ☐ Not reported

3. What was the length of followup?

- ☐ Days (mean):
- ☐ Days (median):
- ☐ Weeks (mean):
- ☐ Weeks (median):
- ☐ Months (mean):
- ☐ Months (median):
- ☐ Years (mean):
- ☐ Years (median):
- ☐ Maximum followup time
- ☐ Not reported

4. What was the total number at enrollment or cohort inception?

- ☐ Total:
- ☐ CKD Patients:
- ☐ Not reported

5. What study design was used?

- ○ Post-hoc analysis of an RCT
- ○ Prospective cohort
- ○ Retrospective cohort
- ○ Case control
- ○ Other study design (specify):

Clear Response

6. What was the setting?

- ☐ Outpatient
- ☐ Emergency department
- ☐ Hospital
- ☐ Other (specify):

7. Did the study include patients presenting with symptoms of acute coronary syndrome?

- ○ Yes
- ○ No
- ○ Not reported

Clear Response

8. How was acute coronary syndrome defined?

- [ ] ICD-9 codes
- [ ] Adjudicated (e.g. panel of physicians adjudicated cases)
- [ ] Other method (specify):

9. Was a cardiologist involved in the adjudication?

- ( ) Yes
- ( ) No
- ( ) Not reported

Clear Response

10. How was it adjudicated?

- ( ) Single adjudicator
- ( ) Panel adjudicator (specify number):
- ( ) Not specified

Clear Response

11. What definition was used to adjudicate?

- [ ] Global consensus on MI
- [ ] ACC/AHA
- [ ] Other (specified):
- [ ] Not reported

12. What stages of chronic kidney disease were included?

- [ ] CKD (combined stages 1-4)
- [ ] Stage 1 (eGFR: 90+)
- [ ] Stage 2 (eGFR: 60-89)
- [ ] Stage 3 (eGFR: 30-59)
- [ ] Stage 4 (eGFR: 15-29)
- [ ] Stage 5 (eGFR: <15)
- [ ] Dialysis
- [ ] Kidney transplant patients
- [ ] Creatinine level <
- [ ] Creatinine level >
- [ ] Other (specify):
- [ ] Not reported

13. What equation was used to define GFR?

- [ ] MDRD
- [ ] CKD Epi formula
- [ ] Creatinine available, but GFR not provided
- [ ] Cockcroft-Gault
- [ ] Other (specify):
- [ ] Not reported

14. Other exclusion criteria

- [ ] Age <
- [ ] Age >
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Other (specify):
- [ ] Not reported

15. Did the study present a subgroup analysis on:

- [ ] Gender
- [ ] Age
- [ ] Ethnicity
- [ ] Stage of kidney disease
- [ ] Dialysis status
- [ ] Status post renal transplant
- [ ] Presence of baseline or prior elevated troponins
- [ ] Presence of ischemic EKG changes
- [ ] 10-year CHD risk
- [ ] History of CAD
- [ ] No subgroups

16. Comments

Submit Form and go to or Skip to Next

Population characteristics

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Troponin EPC
Population Characteristics Form

Please record baseline characteristics for each group below.

Assign groups in the following order:

- TBD

	Group 1	Group 2	Group 3	G
Group Name	Total Sample Other (specify):	Other: Clear Response	Other: Clear Response	
Number enrolled				
Age Age not reported Clear Response	Mean: Median:	Mean: Median:	Mean: Median:	
Gender Gender not reported Clear Response	Male, n: Male, %:	Male, n: Male, %:	Male, n: Male, %:	
Dialysis status Dialysis status not reported Clear Response	On dialysis, n: On dialysis, %:	On dialysis, n: On dialysis, %:	On dialysis, n: On dialysis, %:	
Known CAD Known CAD not reported Clear Response	Known CAD, n: Known CAD, %:	Known CAD, n: Known CAD, %:	Known CAD, n: Known CAD, %:	
Stage of Kidney Disease Stage kidney disease not reported Clear Response	1, n: 1, %: 2, n: 2, %: 3, n: 3, %: 4, n: 4, %: 5, n: 5, %:	1, n: 1, %: 2, n: 2, %: 3, n: 3, %: 4, n: 4, %: 5, n: 5, %:	1, n: 1, %: 2, n: 2, %: 3, n: 3, %: 4, n: 4, %: 5, n: 5, %:	
GFR levels GFR not reported Clear Response	Mean: Median:	Mean: Median:	Mean: Median:	
Race/Ethnicity Not reported Clear Response	White, n: White, %: African American, n: African American, %: Hispanic, n: Hispanic, %: Other, n: Other, %:	White, n: White, %: African American, n: African American, %: Hispanic, n: Hispanic, %: Other, n: Other, %:	White, n: White, %: African American, n: African American, %: Hispanic, n: Hispanic, %: Other, n: Other, %:	

Comments:

Comments:

Submit Form and go to or Skip to Next

Key Question 1 Outcomes

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Troponin EPC
Outcomes Form-KQ1

Please describe only one outcome and one reference group per form

This is data for:

- Total sample
- Subgroup (specify):

Clear Response

Describe the characteristics of the index test(s)

	Assay	Manufacturer	Assay used	Cut-off value for normal	Timing	99th upper reference
Index test #1	Select an Answer	Select an Answer	Select an Answer	Select an Answer	Select an Answer	Select an Answe
Index test #2	Select an Answer	Select an Answer	Select an Answer	Select an Answer	Select an Answer	Select an Answe

1. How was acute coronary syndrome defined?

- ICD-9 codes
- Adjudicated (e.g. panel of physicians adjudicated cases)
- Other method (specify):

2. How was it adjudicated?

- Single adjudicator
- Panel adjudicator (specify number):
- Not specified

Clear Response

3. Was a cardiologist involved in the adjudication?

- Yes
- No
- Not reported

Clear Response

4. What definition was used to adjudicate?

- Global Consensus on MI
- ACC/AHA
- Other (specified):
- Not reported

Clear Response

	Reference standard (+)	Reference standard (-)	Total
Index test (+ elevated troponin)	True positives (A)	False positives (B)	A + B
Index test (- normal troponin)	False negative (C)	True negative (D)	C + D
Total	A + C	B + D	N

PLEASE NOTE: FORMULAS ARE PROVIDED FOR YOUR REFERENCE. PLEASE DO NOT MANUALLY CALCULATE ANY VALUES

	Value	Measure of variability	95% Confidence Interval
		Select an Answer	

Sensitivity A / (A+C)			☐ UL ☐ LL
Specificity D / (B+D)			☐ UL ☐ LL
% positive agreement A / (A+ C)			☐ UL ☐ LL
% negative agreement D / (B+D)			☐ UL ☐ LL
Positive likelihood ratio			☐ UL ☐ LL
Negative likelihood ratio			☐ UL ☐ LL
Positive predictive value			☐ UL ☐ LL
Negative predictive value			☐ UL ☐ LL
AUC			☐ UL ☐ LL
% false-positive tests B / (B+D)			☐ UL ☐ LL
% false-negative tests C / (A+C)			☐ UL ☐ LL
Test accuracy			☐ UL ☐ LL

Comments

Submit Form and go to or Skip to Next

Key Question 2-4 Outcomes

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Troponin EPC
Outcomes Form-KQ2-4

Please describe only one outcome per form

This is data for:

- Total sample
- Subgroup (specify):

Clear Response

Please indicate the outcome being reported

Outcome	Adjudicated	Definition	Followup
All-cause mortality select Clear Response	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Cardiovascular mortality select Clear Response	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Subsequent myocardial infarction select Clear Response	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Stroke select Clear Response	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Hospital readmission rate select Clear Response	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Composite outcome (check all that apply) ≥ 1 year MACE rates; < 1 year MACE rate; Revascularization	Select an Answer	Define: Not specified Clear Response	days weeks months years Not reported
Other major adverse event (select one) Select an Answer	Select an Answer	Define: Not specified Clear Response	days weeks months

			☐ years ☐ Not reported

Please record how the troponin was categorized

Group	Assay	Manufacturer	Assay used	Troponin Level
Group 1	Select an Answer	Select an Answer	Select an Answer	☐ >___ng/L ☐ <___ng/L ☐ >___µg/L ☐ <___µg/L ☐ Other: ☐ Other:
Group 2	Select an Answer	Select an Answer	Select an Answer	☐ >___ng/L ☐ <___ng/L ☐ >___µg/L ☐ <___µg/L ☐ Other: ☐ Other:
Group 3	Select an Answer	Select an Answer	Select an Answer	☐ >___ng/L ☐ <___ng/L ☐ >___µg/L ☐ <___µg/L ☐ Other: ☐ Other:
Group 4	Select an Answer	Select an Answer	Select an Answer	☐ >___ng/L ☐ <___ng/L ☐ >___µg/L ☐ <___µg/L ☐ Other: ☐ Other:
Group 5	Select an Answer	Select an Answer	Select an Answer	☐ >___ng/L ☐ <___ng/L ☐ >___µg/L ☐ <___µg/L ☐ Other: ☐ Other:

Table 1. Incidence of Outcome

Group	N for analysis	Outcome measure	Denominator	p-value	Reference gro
Group 1		☐ # of patients with one or more events: ☐ % of patients with one or more events: ☐ # of events:	Select an Answer		Select an
Group 2		☐ # of patients with one or more events: ☐ % of patients with one or more events: ☐ # of events:	Select an Answer		Select an
Group 3		☐ # of patients with one or more events: ☐ % of patients with one or more events: ☐ # of events:	Select an Answer		Select an

Group 4		☐ # of patients with one or more events: ☐ % of patients with one or more events: ☐ # of events:	Select an Answer	
Group 5		☐ # of patients with one or more events: ☐ % of patients with one or more events: ☐ # of events:	Select an Answer	

Table 2. Measure of Association

Group	N for analysis	Point estimate Select an Answer	Measure of variability Select an Answer	95% CI	P-value
Group 1				☐ UL ☐ LL	
Group 2				☐ UL ☐ LL	
Group 3				☐ UL ☐ LL	
Group 4				☐ UL ☐ LL	
Group 5				☐ UL ☐ LL	

Is the above data adjusted?

- ◯ Yes, adjusted
- ◯ No, not adjusted

Clear Response

If a multivariable analysis, what other variables were adjusted for in the model?

- ☐ Age
- ☐ Sex
- ☐ Race/ethnicity
- ☐ History of coronary artery disease
- ☐ Other
- ☐ Other
- ☐ Other
- ☐ Other
- ☐ Other
- ☐ Other

Table 3. AUC values

	Value	P-value	95% Confidence Interval
AUC Value			☐ UL ☐ LL
Sensitivity			☐ UL ☐ LL
Specificity			☐ UL ☐ LL

Comments

Submit Form and go to or Skip to Next

Study Quality

Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

Troponin EPC
Downs and Black Checklist for Measuring Study Quality

REPORTING

1. Is the hypothesis/aim/objective of the study clearly described?

   Yes
   No
   Clear Response

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

   If the main outcomes are first mentioned in the Results section, the question should be answered 'no.'

   Yes
   No
   Clear Response

3. Are the characteristics of the subjects included in the study clearly described?

   In trials, inclusion and/or exclusion criteria should be given.

   Yes
   No
   Clear Response

4. Are the tests of interest clearly described?

   Tests results (where relevant) that are to be compared should be clearly described.

   Yes
   No
   Clear Response

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

   A list of principal confounders is provided.

   Yes
   No
   Clear Response

6. Are the main findings of the study clearly described?

   Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).

   Yes
   No
   Clear Response

7. Does the study provide estimates of the random variability in the data for the main outcomes?

   In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

   Yes
   No
   Clear Response

8. Have the characteristics of subjects lost to follow-up been described?

   This should be answered 'yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'no' where a study does not report the number of patients lost to follow-up.

   Yes
   No
   Clear Response

9. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main

outcomes except where the probability value is less than 0.001?

- Yes
- No

Clear Response

EXTERNAL VALIDITY

10. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

The study must identify the source population for patients and describe how the patients were selected. Subjects would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the subjects are derived, the question should be answered 'unable to determine.'

- Yes
- No
- Unable to determine

Clear Response

11. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.

- Yes
- No
- Unable to determine

Clear Response

12. Were the staff, places, and facilities where the subjects were treated/tested representative of the testing the majority of subjects receive?

For the question to be answered 'yes' the study should demonstrate that the testing was representative of that in use in the source population. The question should be answered 'no' if, for example, the testing was undertaken in a specialist center unrepresentative of the hospitals most of the source population would attend.

- Yes
- No
- Unable to determine

Clear Response

INTERNAL VALIDITY-BIAS

13. Was an attempt made to blind those measuring the main outcomes of the testing strategy?

- Yes
- No
- Unable to determine
- Not feasible

Clear Response

14. If any of the results of the study were based on "data dredging", was this made clear?

Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'yes.'

- Yes
- No
- Unable to determine

Clear Response

15. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?

Where follow-up was the same for all study participants the answer should be 'yes.' If different lengths of follow-up were adjusted, for example, by survival analysis, the answer should be 'yes.' Studies where differences in follow-up are ignored should be answered 'no.'

- Yes
- No
- Unable to determine
- Not applicable (i.e. no followup for this type of study)

Clear Response

16. Were the statistical tests used to assess the main outcomes appropriate?

The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'yes.' If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'yes.'

- Yes
- No
- Unable to determine

Clear Response

17. Were the main outcome measures used accurate (valid and reliable)?

For studies where the outcome measures are clearly described, the question should be answered 'yes.' For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'yes.'

- Yes
- No
- Unable to determine

Clear Response

INTERNAL VALIDITY- CONFOUNDING AND SELECTION BIAS

18. Were the subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

For example, subjects for all comparison groups should be selected from the same school. The question should be answered unable to determine for cohort where there is no information concerning the source of subjects included in the study.

- Yes
- No
- Unable to determine

Clear Response

19. Were study subjects in different testing groups groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.

- Yes
- No
- Unable to determine

Clear Response

20. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

This question should be answered 'no' for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies, if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'no.' "Yes" for adjusted for all major confounders (demographic and common comorbidities) and "Yes, some" if some, not all major confounders were adjusted for.

- Yes (adjusted for all confounders)
- Yes, some (adjusted for some confounders)
- No (did not adjust for confounders)
- Unable to determine
- Not applicable (i.e. diagnostic test paper)

Clear Response

21. Were losses of subjects to follow-up taken into account?

If the numbers of subjects lost to follow-up are not reported, the question should be answered 'unable to determine.' If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'yes.'

- Yes
- No
- Unable to determine
- Not applicable (i.e. no followup period such as KQ1)

Clear Response

POWER

22. Did they report a power calculation?

- Yes
- No

Clear Response

23. Was the study supported by industry?

- Yes (e.g. supported financially by industry, treatment provided by industry, co-author involved with industry)
- No (sources of funding provided by non-industry sponsors such as government, etc.)
- Not reported

Clear Response

24. What was the overall quality of the study?

*• **Good** (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.*
*• **Fair**. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.*
*• **Poor** (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.*

- Good
- Fair
- Poor

Clear Response

25. For Questions 1-9, how many were answered "no"?

26. Is the number in question 25 greater than or equal to 5?

- Yes (sum is 5 or more)
- No (sum is 4 or less)

Clear Response

27. For questions 10-12, how many questions were answered "no"

28. Is the number in question 27 greater than or equal to 2?

- Yes (sum is 2 or more)
- No (sum is 1 or 0)

Clear Response

29. For questions 13-22, how many were answered "no"?

30. Is the number in question 29 greater than or equal to 5?

- Yes (sum is 5 or more)
- No (sum is 4 or less)

Clear Response

Comments:

Submit Form and go to or Skip to Next

Appendix C. Exclusion Report

No Original Data

1. Babinska M, Chudek J, Owczarek AJ, et al. [Acute coronary syndrome in patients with chronic kidney disease--risk stratification]. Pol Arch Med Wewn. 2005 Dec;114(6):1226-35. PMID: 16789494.
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3. Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. Circulation. 2012;125(21):2649-61.
4. Carney EF. Acute coronary syndromes: Management of acute coronary syndrome-renal outcomes. Nat Rev Nephrol. 2013 Sep;9(9):492. PMID: 23877589.
5. Celik T, Iyisoy A, Yilmaz MI, et al. Another battlefield for drug-eluting coronary stents: Chronic kidney disease. Int J Cardiol. 2009;133(2):245-6.
6. Chen BH. Cardiac troponin T levels in patients with renal failure. CMAJ. 2002 Sep 17;167(6):671. PMID: 12358205.
7. Chen P, Tanasijevic M. Use of serum cardiac troponin-I levels in dialysis patients. Semin Dial. 2000 Jan-Feb;13(1):58-9. PMID: 10740676.
8. Cichocka E, Gumprecht J. [Diabetes, renal dysfunction and acute coronary syndrome]. Kardiol Pol. 2012;70(3):287-90. PMID: 22430415.
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15. Johnston N, Dargie H, Jardine A. Diagnosis and treatment of coronary artery disease in patients with chronic kidney disease. Heart. 2008;94(8):1080-8.
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17. Kavsak PA. Serial cardiac troponin T measurements in haemodialysis patients: absolute versus changing concentrations? Ann Clin Biochem. 2010 Jan;47(Pt 1):97. PMID: 19900984.
18. Kavsak PA, Jaffe AS. High-sensitivity cardiac troponin assays--change is important. Clin Chem. 2012 Jan;58(1):311-3; author reply 3-4. PMID: 21976552.
19. Kes P, Basic-Jukic N, Juric I, et al. [Diagnostic significance of cardiac troponins in chronic renal failure]. Lijec Vjesn. 2007 Jan-Feb;129(1-2):44-5. PMID: 17489518.
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Appendix D. Evidence Tables

Table 1. Study design characteristics of included articles

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Abaci, 2004[1]	Prospective	Turkey Hospital	Study date NR Mean followup: 2 years	129	No ACS	Dialysis, ESRD GFR equation NR	Angiographically proven stenosis, ACS, history of MI, ECG changes suggestive of ischemia, Chronic stable angina pectoris, previous coronary revascularization, regional wall motion abnormalities in ECG
Abbas, 2005[2]	Prospective	Europe outpatient	Start: 2003 End: 2004 Mean followup: 19 months	Total: 227 CKD: 222	No ACS	Stage 3, stage 4, stage 5, dialysis MDRD	Age < 18, acute renal failure, functioning renal transplant, patients on dialysis, recent cardiac event
Acharji, 2012[3]	Post hoc	United States Hospital	Study date NR Mean followup: 1 year	2179	Patients with ACS included Cardiologist adjudication NR panel Definition: Adjudication definition NR	Stage 3, stage 4, dialysis Cockcroft-Gault formula	Other exclusions NR
Alcalai, 2007[4]	Prospective	Israel Hospital	Start: 2003 End: 2003 Maximum followup: 2.5 years	615	Patients with ACS included Adjudicated Cardiologist adjudicated panel adjudicator panel: 2 people Definition: ESC/ACC	Dialysis, creatinine > 2.26 mg/dL GFR equation NR	Age < 16, out-of hospital cardiac arrest who died within 48 hours of admission
Apple,1997[5]	Retrospective	United States outpatient	Start: 1994 End: 1994 Mean followup: 12 months	16	No ACS	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Apple,1999[6]	Retrospective	United States hospital	Study date NR Followup NR	1601	Patients with ACS included Adjudicated Cardiologist adjudication NR panel adjudicator Definition: 2 of 3: chest pain, ECG changes, biomarkers	Dialysis, stage NR GFR equation NR	Other exclusions NR
Apple, 2002[7]	Prospective	United States outpatient; dialysis centers	Start: 1998 End: 1999 Median followup: 1.6 years	733	ACS NR	Stage 5, dialysis, ESRD GFR equation NR	Other exclusions NR
Apple, 2004[8]	Prospective	United States outpatient	Start: 1998 End: 1999 Median followup: 1.7 years	399	ACS NR	Dialysis, ESRD GFR equation NR	Other exclusions NR
Apple, 2007[9]	Prospective	United States emergency dept	Study date NR Mean followup: 6 months	Total: 510 CKD: NS	Patients with ACS included Definition: clinical features considered indicative of ACS Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, dialysis MDRD	Other exclusions NR
Artunc, 2012[10]	Prospective	Europe outpatient; 4 hemodialysis centers	Start: 2009 End: 2011 Mean followup: 2 years	239	No ACS Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Dialysis GFR equation NR	Patients with cardiac diseases that elevated serum troponin, evidence of an acute illness
Assa, 2013[11]	Prospective	Europe outpatient;	Start:2006 Maximum followup: 52 months	90	No ACS	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Aviles, 2002[12]	Post hoc	Worldwide hospital	Start: 1998 End: 2000 Maximum followup: 30 days	Total: 7033 CKD: 1733	Patients with ACS included other dx: one or more episodes of angina while at rest that lasted at least five minutes and new ST-segment depression of at least 0.5 mm; or an abnormal result on a cardiac troponin Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, stage 5, dialysis, Cockcroft-Gault formula	Underwent early revascularization
Bagheri, 2009[13]	Prospective	Iran hospital; dialysis center	Start: 2005 End: 2007 Mean followup: 30 months	138	ACS NR	Dialysis, GFR equation NR	Systemic inflammation, ongoing ischemia or any revascularization procedure within past 8 weeks
Barthelemy, 2012[14]	Post hoc	Europe hospital	Start: 2006 End: 2008 Mean followup: 1 month	Total: 345 CKD: 75	Patients with ACS included other dx: 2 out 3: symptoms of myocardial ischemia, ST segment abnormalities, elevated cTnI Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 3, stage 4, dialysis, Cockcroft-Gault formula	Age < 18, refractory ischemia, major arrhythmias, or hemodynamic instability requiring immediate catheterization, ongoing treatment with warfarin, fibrinoloysis or GPIIb/IIIa inhibitors, contraindications to abciximab
Beciani, 2003[15]	Prospective	Europe hospital	Study date NR Mean followup: 1 year	101	No ACS	Dialysis GFR equation NR	Recent (3 month) acute CAD, recent chest pain, recent major cardiovascular surgery
Bhagavan, 1998[16]	Retrospective	United States hospital	Study date NR Followup NR	Total: 155 CKD: 31	ACS NR	Dialysis GFR equation NR	Other exclusions NR
Boulier, 2004[17]	Prospective	Europe outpatient; hospital	Start: 2001 End: 2001 Median followup: 418 days	191	No ACS	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Bozbas, 2004[18]	Prospective	Turkey hospital	Start: 2001 End: 2002 Mean followup: 30 days	34	ACS NR	Dialysis, kidney transplant GFR equation NR	Other exclusions NR
Brunet, 2008[19]	Prospective	Europe outpatient dialysis unit	Start: 2003 End: 2003 Mean followup: 2.5 years	105	No ACS	dialysis, GFR equation NR	No ACS within 3 months, treated with different HD parameters
Bueti, 2006[20]	Prospective	Canada emergency dept	Start: 2001 End: 2002 Mean followup: 30 days	149	Patients with ACS included other dx: not defined No cardiologist adjudication Adjudicator NS Definition: Adjudication definition NR	Dialysis GFR equation NR	Other exclusions NR
Chenevier-Gobeaux, 2013[127]	Prospective	Europe emergency dept	Study date NR Followup NR	375	Patients with ACS included Adjudicated Yes cardiologist panel adjudicator panel: 2 Definition: Global MI definition	Stage 3, stage 4, stage 5, MDRD	Other exclusion NR
Chew, 2008[21]	Retrospective	Singapore hospital	Start: 2002 End: 2005 Followup NR	227	Patients with ACS included Adjudicated Cardiologist adjudicated panel adjudicator panel: 2 Definition: based on the clinical picture, serial ECG, cardiac enzymes, and cardiac catheter or noninvasive cardiac imaging	Stage 4, dialysis GFR equation NR	Other exclusions NR
Choy, 2003[22]	Prospective	Canada outpatient	Study date NR Mean followup: 6 months	113	ACS NR	Stage 5, dialysis GFR equation NR	Patients refusing to give consent

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Chrysochou, 2009[23]	Prospective	Europe dialysis center	Study date NR Mean followup: 40.2 months	82	No ACS	Combined CKD, stage 1, stage 2, stage 3, stage 4, dialysis, kidney transplant Cockcroft-Gault formula	Atrial Fibrillation, poor ECG Images
Claes, 2010[24]	Prospective	Europe hospital	Start: 2005 End: 2008 Mean followup: 2 weeks	331	ACS NR	Dialysis, kidney transplant GFR equation NR	Combined transplant other than renal/pancreatic
Codognotto, 2010[25]	Prospective	Europe hospital	Study date NR Maximum followup: 3 years	50	ACS NR	Dialysis GFR equation NR	Atrial fibrillation, pacemakers, previous surgical heart procedures, valvular and congenital heart disorders
Connolly, 2008[26]	Prospective	Europe hospital	Start: 2000 End: 2002 Mean followup: 1626 days Median followup: 1739 days	372	No ACS	Dialysis, kidney transplant MDRD	Chest pain - deferred until re-assessment, signs of sepsis - deferred until re-assessment
Conway, 2005[27]	Prospective	Europe outpatient; hospital	Start: 2003 End: 2003 Mean followup: 18 months	75	No ACS Definition: hospital admission with diagnostic code of ACS	Dialysis GFR equation NR	Other exclusions NR
Deegan, 2001[28]	Prospective	Europe hospital; hemodialysis	Study date NR Mean followup: 15 months	73	ACS NR	Dialysis GFR equation NR	Other exclusions NR
deFilippi, 2003[29]	Prospective	United States outpatient; dialysis	Start: 1998 End: 1998 Mean followup: 827 days	224	No ACS	Dialysis GFR equation NR	Age < 18, on hemodialysis less than 30days, Acute coronary event less than 4 weeks

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
deFilippi, 2012[30]	Prospective	United States outpatient	Start: 2006 End: 2007 Median followup: 4.8 years	148	No ACS	Combined CKD, dialysis MDRD	Age < 30, stage V CKD, renal replacement therapy, history of MI or CABG within 90 days of enrollment, patients with symptoms greater than NY heart association class I HF, patients with symptoms greater than Canadian CV society class I angina
Dierkes, 2000[31]	Prospective	Europe dialysis center	Study date NR Mean followup: 2 years	102	No ACS	Dialysis, ESRD GFR equation NR	Age > 85, unstable clinical status, no ACS within 4 weeks
Duman, 2005[32]	Prospective	Turkey outpatient	Study date NR Mean followup: 48 months	65	no ACS	Dialysis GFR equation NR	Patients with CV disease within 4 weeks of study onset.
Farkouh, 2003[33]	Prospective	United States outpatient; dialysis centers	Study date NR Mean followup: 15 months	137	no ACS	Stage 5, dialysis GFR equation NR	Refusal to participate, ACS within preceding 30 days
Fehr, 2003[34]	Retrospective	Europe NR	Study date NR Mean followup: 12 months	31	Patients with ACS included other dx: NR Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Dialysis GFR equation NR	Other exclusions NR
Feringa, 2006[35]	Prospective	Europe hospital	Start: 2000 End: 2006 Mean followup: 3.5 years	Total: 558 CKD: 240	No ACS	Combined CKD, stage 1, stage 2, stage 3, stage 4, dialysis MDRD	Patients who died during surgery, patients who died before hospital discharge

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Fernandez-Reyes, 2004[36]	Prospective	Europe hospital	Start: 2000 End: 2002 Mean followup: 2.5 years	58	ACS NR	Dialysis GFR equation NR	Clinical signs of HF or ischemic heart disease during previous month
Flores, 2006[37]	Retrospective	Europe, Spain ED (64%) ICU(10%) and IM-cardiology and nephrology services	Start: 2004 End: 2004 Followup NR	467	Patients with ACS included Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Combined CKD, dialysis MDRD	
Flores-Solis, 2012[38]	Prospective	Europe hospital	Start: 2009 End: 2010 Mean followup: 6 months	484	Patients with ACS included other dx: ESC AMI definition Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 3, stage 4, dialysis, MDRD	Patients transferred to another hospital, psychiatric patients, patients who refused to sign an informed consent, patients diagnosed with multiple conditions who could not be assigned to a group.
Gaiki, 2012[39]	Prospective	United States hospital	Study date NR Mean followup: 2 years	51	No ACS	Dialysis GFR equation NR	Other exclusions NR
Geerse, 2012[40]	Prospective	Europe hospital	Start: 2007 End: 2009 Median followup: 28 months	206	ACS NR	Dialysis GFR equation NR	Age < 18
Goicoechea, 2004[41]	Prospective	Europe outpatient	Start: 2002 End: 2002 Mean followup: 12.9 months	176	No ACS Definition: Joint ESC/ACC	Combined CKD, dialysis Cockcroft-Gault formula	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Gruberg, 2002[42]	Prospective	United States hospital	Start: 1994 End: 1999 Mean followup: 12 months	116	Patients with ACS included Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Dialysis, creatinine > , chronic renal insufficiency, Cockcroft-Gault formula	Patients on dialysis, patients with baseline increased cTnI >0.15 ng/mL, patients with AMI within previous 72 hrs
Haaf, 2013[43]	Prospective	Europe hospital	Start: 2006 End: 2009 Mean followup: 2 years	1117	Patients with ACS included Adjudicated Yes cardiologist panel adjudicator panel:3 Definition: Global MI definition	Stage NR MDRD	Other exclusion NR
Hallen, 2011[44]	Retrospective	Europe hospital, dialysis	Start: 2002 End: 2003 Mean followup: 926 days	107	ACS NR	Dialysis, ESRD GFR equation NR	Age < 18, failure to cooperate, hepatic disease, malignant disease, rhabdomyolysis, dermatomyositis, polymyositis, history of epilepsy or convulsions
Han, 2005[45]	Retrospective	United States emergency dept	Start: 1999 End: 2003 Mean followup: 6 months	90	Patients with ACS included other dx: medical record and social security death index Cardiologist adjudication NR	Combined CKD, dialysis, CrCl <30 ml/min GFR equation NR	Kidney transplant, died secondary to trauma, terminal cancer, trauma, terminal cancer
Han, 2009[46]	Prospective	South Korea hospital	Study date NR Mean followup: 3 years	107	ACS NR	Dialysis GFR equation NR	CVD - AMI, PVD, cerebrovascular, angina, Infection within past 3 months, history of malignancy, chronic inflammatory disease
Hasegawa, 2012[47]	Prospective	Japan outpatient	Start: 2009 End: 2010 Median followup: 22 months	442	ACS NR	Stage 3, stage 4, dialysis, stage 5 MDRD	CKD patients on dialysis.

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Havekes, 2006[48]	Prospective	Netherlands outpatient	Start: 1997 End: 2001 Followup NR	847	No ACS	Dialysis, mean creatinine and urea clearances adjusted for body surface area	Age < 18
Heeschen, 2000[49]	Prospective	Europe outpatient	Start: 1994 End: 1998 Maximum followup: 30 days	26	No ACS	Dialysis GFR equation NR	Other exclusion NR
Helleskov Madsen, 2008[50]	Prospective	Europe hospital hemodialysis	Start: 2002 End: 2003 Mean followup: 712 days	109	No ACS	Dialysis GFR equation NR	Age < 18, conditions giving falsely elevated troponins (liver disease, malignancy, rhabdomyolysis, dermatomyositis/polymyositis, epilepsy), patients unable to cooperate
Hickman, 2009[51]	Prospective	Australia outpatient	Study date NR Median followup: 30 months	143	No ACS	Dialysis GFR equation NR	Other exclusions NR
Hickson, 2008[52]	Prospective	United States outpatient	Start: 2004 End: 2006 Mean followup: 11.5 months Median followup: 6.2 months	644	No ACS	Dialysis, kidney transplant candidates GFR equation NR	Patients on kidney transplant waiting list
Hickson, 2009[53]	Prospective	United States outpatient	Start: 2004 End: 2007 Mean followup: 28.4 months	603	No ACS	Dialysis, kidney transplant GFR equation NR	Kidney transplant recipients

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Hocher, 2003[54]	Prospective	Europe hospital; dialysis center	Start: 2000 Mean followup: 775 days	245	No ACS	Dialysis GFR equation NR	Malignancies, chronic infections, conditions that affect serum parameters
Hocher, 2004[55]	Prospective	Europe outpatient; dialysis Center	Start: 2000 Mean followup: 1140 days	245	No ACS	Dialysis, ESRD GFR equation NR	Other exclusions NR
Hocher, 2008[56]	Prospective	Europe outpatient	Start: 2000 End: 2000 Mean followup: 52 months	230	No ACS	Dialysis GFR equation NR	Acute disease including unstable angina, acute MI, arterial embolism, acute neurological disorder, malignancy, chronic infection, other conditions that might affect the serum parameters
Hojs, 2005[57]	Prospective	Europe outpatient	Study date NR Mean followup: 21 months	90	No ACS	Dialysis GFR equation NR	Other exclusions NR
Holden, 2012[58]	Prospective	Canada dialysis Center	Start: 2002 Mean followup: 3.5 years	103	ACS NR	Dialysis GFR equation NR	Other exclusions NR
Hung, 2004[59]	Prospective	Taiwan outpatient	Study date NR Mean followup: 12 months	70	No ACS	Dialysis GFR equation NR	Age < 20, receiving HD for <6months, MI within 3 months, major vascular surgery within 3 months, acute chest pain, intramuscular injection/trauma, history of autoimmune disease
Hussein, 2004[60]	Prospective	Saudi Arabia outpatient	Study date NR Mean followup: 1 year	93	No ACS	Dialysis GFR equation NR	Other exclusions NR
Ie, 2004[61]	Prospective	Europe dialysis center	Study date NR Mean followup: 2 years	49	No ACS	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Ikeda, 2002[62]	Retrospective	Japan hospital	Study date NR Followup NR	Total: 173 CKD: 28	Patients with ACS included NR cardiologist adjudicator ns Definition: Adjudication definition NR	Dialysis GFR equation NR	Other exclusion NR
Iliou, 2003[63]	Prospective	Europe outpatient; hospital; hemodialysis centers	Start: 1999 End: 1999 Mean followup: 2 years	258	No ACS	Dialysis GFR equation NR	MI, revascularization, angina within 3 weeks of study, sever infection 8 days before study, hemoglobin <8 g/dl
Ilva, 2008[64]	Prospective	Europe hospital	Start: 2004 End: 2004 Mean followup: 6 months	Total: 364 CKD: 163	No ACS	Dialysis, renal failure defined as CysC above 1.2 for age <50 and 1.4 for age >50	ACS, patients with missing troponin values
Ishii, 2001[65]	Prospective	Japan outpatient; dialysis center	Start: 1997 End: 1997 Mean followup: 2 years	100	No ACS	Dialysis GFR equation NR	Dialysis for <12months, acute coronary syndrome <3months
Jensen,2012[66]	Prospective	Europe hospital	Start: 2003 End: 2004 Median followup: 4.4 years	193	No ACS	Dialysis GFR equation NR	Unwillingness to participate, prior MI, symptoms of acute MI, unstable angina, pathological Q Waves upon admission, previous coronary angioplasty, atrial fibrillation, stroke-like symptoms >7 days prior to admission
Kalaji, 2012[67]	Prospective	Syria hospital	Start: 2008 End: 2008 Median followup: 551 days	145	No ACS	Dialysis, Stage V CKD GFR equation NR	Age < 18, Acute coronary event within 1 month, undergoing dialysis for less than 1 month, refusal to participate in the study.
Kang, 2009[68]	Prospective	South Korea hospital	Start: 2003 End: 2005 Mean followup: 90 days	121	No ACS	Dialysis GFR equation NR	Age < 18, dialysis <3 months

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Kanwar, 2006[69]	Prospective	United States dialysis center	Start: 2001 End: 2002 Mean followup: 27 months	173	No ACS	Dialysis GFR equation NR	Any evidence of ongoing ischemia, PCI or revascularization 6 weeks before evaluation, systemic inflammatory disorders
Katerinis, 2008[70]	Prospective	Switzerland dialysis center	Study date NR Mean followup: 12 months	50	No ACS	Dialysis GFR equation NR	ACS within four weeks
Kertai, 2004[71]	Prospective	Europe outpatient; hospital	Start: 1996 End: 2000 Median followup: 4 years	Total: 393 CKD: 58	No ACS	Dialysis GFR equation NR	Mortality or MI within 30 days of their vascular surgery
Khan, 2001[72]	Prospective	United States hospital	Study date NR Mean followup: 2 years	128	No ACS	Dialysis, CRF GFR equation NR	ACS within 3 months, chronic stable angina pectoris, chest pain in peridialysis period, recent major CV surgery, ECG changes suggesting MI / EKG changes-ishcemia
Kontos, 2005[73]	Prospective	United States hospital	Start: 1996 End: 2000 Mean followup: 1 year	3774	Patients with ACS included other dx: NR Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 2, stage 3, stage 4, dialysis Cockcroft-Gault formula	ST-segment elevation that met criteria for fibrinolytic therapy, did not have 8-hour cTnI determined
Kontos, 2005[74]	Prospective	United States emergency dept	Start: 1996 End: 2000 Followup NR	3074	Patients with ACS included other dx: ECG changes, known coronary disease w/ typical symtpoms, or MPI with positive results Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, dialysis Cockcroft-Gault formula	ST-segment elevation, no 8-hour cardiac isoform of cTnI obtained, no EF obtained

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Kontos, 2008[75]	Retrospective	United States hospital	Start: 1996 End: 2000 Mean followup: 1 year	Total: 4343 CKD: NS	Patients with ACS included other dx: NS Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, dialysis, no kidney disease MDRD; Cockcroft-Gault formula	STEMI, did not have 8-hour troponin measured, did not have weight measurement available
Kostrubiec, 2010[76]	Prospective	Europe hospital	Start: 2006 End: 2009 Mean followup: 30 days	220	ACS NR	Combined CKD, dialysis, acute pulmonary embolism, MDRD	Other exclusions NR
Lamb, 2007[77]	Prospective	England outpatient	Start: 2003 End: 2004 Maximum followup: 32 months	227	No ACS	Stage 3, stage 4, stage 5, dialysis MDRD	Age < 18, functioning renal transplant, receiving dialysis; recent (< 1 month) cardiac event, acute renal failure, cardiac event <1 month
Lang, 2001[78]	Prospective	Europe hospital	Study date NR Mean followup: 2 years	100	No ACS	Dialysis, ESRD, GFR equation NR	History of angina pectoris within 3 mos., MI within 2 years, malignancies, systemic autoimmune disease, inflammatory or hereditary muscle disease, trauma in previous 6 mos., known myocarditis, idiopathic dilated cardiomyopathy, hypertrophic or restrictive cardiomyopathy
Le Goff, 2007[79]	Prospective	Europe outpatient;	Study date NR Mean followup: 3 years	86	ACS NR	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Lowbeer, 2002[80]	Prospective	Europe outpatient; dialysis center	Study date NR Mean followup: 48 months	26	No ACS	Dialysis, chronic ambulator peritoneal dialysis GFR equation NR	AMI 3 weeks prior to study enrollment, clinical symptoms of inflammation
Lowbeer, 2003[81]	Prospective	Europe outpatient	Study date NR Mean followup: 2.7 months	115	ACS NR	Dialysis, ESRD GFR equation NR	Age > 70, unwillingness to participate
Mallamaci, 2002[82]	Prospective	Europe outpatient	Study date NR Mean followup: 35 months	199	No ACS	Dialysis, ESRD GFR equation NR	Other exclusions NR
Martin, 1998[83]	Prospective case-series	United States hospital	Study date NR Mean followup: 6 months	56	ACS NR	Dialysis, ESRD, chronic renal failure, or acute renal failure, GFR equation NR	Other exclusions NR
McCullough, 2002[84]	Prospective	United States hospital	Start: 1999 End: 1999 Mean followup: 30 days	1024	Patients with ACS included Adjudicated Cardiologist adjudicated panel adjudicator panel: 2 people Definition: Thrombolysis in Myocardial Infarction Study Group	Dialysis, corrected CrCl, GFR equation NR	Patients with ST-elevation AMI receiving thrombolytic therapy or immediate angioplasty
McGill, 2010[85]	Retrospective	Australia hospital	Study date NR Mean followup: 3.9 years	143	ACS NR	Dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
McMurray, 2011[86]	Post hoc	Worldwide hospital	Start: 2004 End: 2007 Median followup: 2.4 years	955	No ACS	Dialysis, eGFR 20 - 60 mL/min MDRD	Uncontrolled hypertension, previous kidney transplant or scheduled transplant, use of antibiotics, use of chemotherapy or radiation therapy, cancer (excluding basal- or squamous-cell carcinoma of skin), active bleeding, hematologic disease or pregnancy
Melloni, 2008[87]	Post hoc	United States hospital	Start: 2003 End: 2005 Followup NR	31586	Patients with ACS included Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, stage 5, dialysis MDRD	Patients transferring in or out of the hospital, inadequate troponin data, missing data for age, sex, creatinine, etc needed for MDRD to calculate eGFR
Mockel, 1999[88]	Prospective	Europe dialysis center	Study date NR Median followup: 9 months	40	No ACS	Stage 4, stage 5, dialysis GFR equation NR	Age > 80, neoplasia, ARF, ACS in the last 4 weeks
Morton, 1998[89]	Prospective	Canada hospital dialysis center	Study date NR Mean followup: 1 year	112	No ACS	Dialysis GFR equation NR	Other exclusions NR
Musso, 1999[90]	Prospective	Europe outpatient	Study date NR Maximum followup: 18 months	Total: 166 CKD: 49	ACS NR	Stage 5, dialysis GFR equation NR	History of CAD or angina symptoms, ischemic changes or segmental wall abnormality on ECG, cardiomegaly on CXR, diabetes, muscular disease

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Noeller, 2003[91]	Prospective	United States hospital	Study date NR Mean followup: 14 months	695	Patients with ACS included other dx: STEMI: ECG changes plus chest pain or CK-MB increase; NSTEMI: EKG changes and either CP or EkG changes; UA: angina change/at rest/EKG changes Cardiologist adjudication NR Adjudicator NS Definition: definition as above	Dialysis GFR equation NR	cardiopulmonary resuscitation within 7 days of presentation, PCI or thrombolytic therapy within 3 weeks before presentation, vasopressors before enrollment, major abdominal/thoracic/orthopedic surgery within 7 days of presentation
Ooi, 1999[92]	Prospective	Canada hospital	Start: 1997 End: 1997 Maximum followup: 1 year	172	No ACS	Dialysis GFR equation NR	Other exclusions NR
Ooi, 2001[93]	Prospective	Canada dialysis center	Start: 1997 End: 1999 Mean followup: 34 months	244	No ACS	Dialysis GFR equation NR	Increased cTnT values that were collected during an acute coronary event were excluded
Orea-Tejeda, 2010[94]	Prospective	Mexico hospital	Study date NR Mean followup: 42 months	152	ACS NR	Dialysis, Patients with eGFR <60 mL/min were included, but it did not specify ranges Cockcroft-Gault formula	Age < 18, myopericarditis, cardiac trauma, neoplastic and infiltrative processes, chemotherapy, pulmnoary embolism, end stage kidney failure, terminal liver failure
Peetz, 2003[95]	Prospective	Europe outpatient; hospital	Study date NR Mean followup: 6 months	104	ACS NR	Dialysis GFR equation NR	Patients with acute myocardial infarction within 3 months, patients with acute symptoms of angina pectoris within 3 months, on dialysis less than one year, on dialysis less than three times a week

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Petrovic, 2009[96]	Prospective	Europe hospital	Study date NR Mean followup: 2 years	115	No ACS	Dialysis GFR equation NR	Other exclusions NR
Porter, 1998[97]	Prospective	United States Hospital; dialysis center	Study date NR Mean followup: 12 months	30	ACS NR	Dialysis GFR equation NR	Other exclusions NR
Porter, 2000[98]	Prospective	United States outpatient; dialysis center	Start: 1996 End: 1996 Maximum followup: 24 months	30	No ACS	Dialysis GFR equation NR	Other exclusions NR
Quiroga, 2013[99]	Prospective	Europe outpatient;	Study date NR Mean followup: 38 months	218	No ACS Cardiologist NR Adjudicator NS Definition: Adjudication definition NR	Stage 1, stage 2, stage 3, stage 4, CKD-EPI formula	Other exclusions NR
Roberts, 2004[100]	Prospective	Australia outpatient; hospital	Study date NR Mean followup: 9 months Maximum followup: 9 months	88	ACS NR	Dialysis GFR equation NR	Poor life expectancy (<6 months)
Roberts, 2009[101]	Prospective	Australia hospital	Start: 2003 End: 2004 Mean followup: 1.8 years	81	ACS NR	Combined CKD, dialysis GFR equation NR	Began dialysis in past 6 months, had CV event in past 3 months, expected to survive less than 3 months
Roppolo, 1999[102]	Prospective	United States hospital	Study date NR Maximum followup: 6 months	134	ACS NR	Dialysis, chronic renal failure, but not on dialysis GFR equation NR	Other exclusions NR

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Sahinarslan, 2008[103]	Prospective	Europe hospital	Study date NR Mean followup: 5 years	78	No ACS	Dialysis GFR equation NR	CVD - CAD, revascularization, HF, stroke, malignancy, any systemic disease other than RF
Satyan, 2007[104]	Prospective	United States hospital	Start: 2003 End: 2005 Median followup: 24 months	150	ACS NR	Dialysis GFR equation NR	Age < 18, Active drug abuse, Chronic atrial fibrillation, BMI ≥ 40 kg/m^2, expected survival <6 mos, active cancer or known HIV, recent change in antihypertensive drugs, inability to learn/perform BP monitoring
Scheven, 2012[105]	Prospective	Europe hospital	Start: 1997 Followup NR	Total: 8121 CKD: 1805	ACS NR	Combined CKD, stage 1, stage 2, stage 3, stage 4, dialysis CKD-EPI formula	Type I Diabetics, pregnancy, failure to sign consent form, no baseline troponin information.
Scott, 2003[106]	Prospective	Europe dialysis centers	Study date NR Mean followup: 1 year	71	ACS NR	Dialysis GFR equation NR	Other exclusions NR
Sharma, 2005[107]	Prospective	Europe outpatient; hospital	Study date NR Mean followup: 1.32 years	118	No ACS	Dialysis, stage 5, pre-dialysis GFR equation NR	Age < 18, severe aortic stenosis, unstable angina, inability to consent
Sharma, 2006[108]	Prospective	Europe hospital	Start: 2002 End: 2003 Mean followup: 2.25 years	114	No ACS	Dialysis, renal transplant candidates Cockcroft-Gault formula	Age < 18, severe aortic stenosis, unstable angina, inability to consent, unstable angina
Sharma, 2006[109]	Prospective	Europe outpatient; hospital	Study date NR Followup NR	126	No ACS	Dialysis, stage 5, pre-dialysis, Cockcroft-Gault formula	Age < 18, severe aortic stenosis, unstable angina

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Shroff, 2012[110]	Retrospective	United States hospital	Start: 2005 End: 2007 Mean followup: 1 year	376	ACS NR	Dialysis, kidney transplant GFR equation NR	Other exclusions NR
Sommerer, 2007[111]	Prospective	Germany outpatient; chronic dialysis center	Start: 2001 End: 2003 Maximum followup: 36 months	134	No ACS	Dialysis GFR equation NR	Age < 18, on hemodialysis < 6 months, < 3 hemodialysis sessions for four hours per week, acute infections, malignancy, acute myocardial ischemia, cardiomyopathy, and amyloidosis
Stolear, 1999[112]	Prospective	Europe in-hospital dialysis unit	Study date NR Mean followup: 12 months	94	No ACS	Dialysis GFR equation NR	Other exclusions NR
Sukonthasarn, 2007[113]	Cross-sectional	Thailand hospital	Start: 2005 End: 2006 Mean followup: NR	53	Patients with ACS included other dx: European Society of Cardiology AMI definition Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Dialysis GFR equation NR	Patients with suspected ACS do not match symptoms of AMI, pulmonary embolism, muscle diseases, acute stroke, renal dysfunction less than 3 months, recent ACS other than at admission
Svensson, 2009[114]	Post hoc	Europe dialysis	Study date NR Mean followup: 2 years	206	ACS NR	Dialysis GFR equation NR	Other exclusions NR
Trape, 2008[115]	Prospective	Europe hospital	Start: 2002 End: 2004 Mean followup: 3 years	52	ACS NR	Dialysis, ESRD GFR equation NR	Dialysis less than three months.

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Troyanov, 2005[116]	Prospective	Canada hospital	Start: 2001 End: 2001 Mean followup: 3 years	101	No ACS	Dialysis GFR equation NR	Patients with angina within previous 14 days of admission or dx of ACS within previous 4 weeks, pericarditis, documented left ventricular ejection fraction <25%, pulmonary embolism 14 days prior
Van Lente, 1999[117]	Prospective	United States emergency dept	Start: 1995 End: 1997 Maximum followup: 6 months	Total: 153 CKD: 51	Patients with ACS included other dx: not specified Cardiologist adjudication NR single adjudicator Definition: WHO criteria of at least 2 of the following: chest pain c/w cardiac origin, ECG changes or changes in CK and CK-MB	Dialysis	Cardiopulmonary resuscitation within 7 days of presentation, angiography or thrombolytic therapy within 3 weeks of presentation, those given vasopressors
Vichairuangthum, 2006[118]	Prospective	Thailand hospital; dialysis center	Study date NR Mean followup: 18 months	63	No ACS	Dialysis GFR equation NR	ACS within 3 mos., chronic stable angina pectoris, chest pain in peridialysis period or 4 weeks before enrollment, recent major CV surgery, significant EEG changes suggestive of myocardial ischemia, refusal to participate
Wang, 2006[119]	Prospective	Hong Kong outpatient;	Study date NR Mean followup: 3 years	222	No ACS	Dialysis GFR equation NR	Acute heart failure, underlying malignancy, chronic liver disease, SLE, rheumatic HD, congenital HD, those on automated PD, those with incomplete data
Wang, 2007[120]	Prospective	China hospital; dialysis center	Start: 1999 End: 2000 Mean followup: 3 years	238	No ACS	Dialysis, ESRD GFR equation NR	ACS, malignancy, chronic liver disease, systemic lupus erhthematosus, chronic rheumatic heart disease, congenital heart disease, refusal to give consent

Author, Year	Design	Location Setting	Enrollment Followup	Sample Size	ACS information (if applicable)	CKD Stages GFR Definition	Exclusion Criteria
Wang, 2010[121]	Prospective	Hong Kong outpatient; outpatient dialysis center	Start: 1999 End: 2005 Maximum followup: 5 years	230	No ACS	Dialysis Residual GFR calculated as average of 24 hour urine area and creatinine clearances	Underlying malignancy, COPD, chronic rheumatic heart disease, congenital heart disease
Wang, 2010[122]	Prospective	China dialysis center	Start: 1999 End: 2005 Mean followup: 5 years	230	ACS NR	Dialysis, ESRD GFR equation NR	Underlying malignancy, COPD, chronic rheumatic heart disease, congenital heart disease, refusal to provide consent
Wayand, 2000[123]	Prospective	Europe dialysis center	Study date NR Mean followup: 2 years	59	Patients with ACS included Cardiologist adjudication NR Adjudicator NS Definition: Adjudication definition NR	Dialysis, ESRD GFR equation NR	Other exclusions NR
Wolley, 2013[124]	Prospective	New Zealand dialysis center	Start: 2011 End: 2011 Mean followup: 6 months	238	No ACS Cardiologist NR Adjudicator NS Definition: Adjudication definition NR	Dialysis GFR equation NR	Other exclusions NR
Wood, 2003[125]	Prospective	Europe outpatient	Study date NR Mean followup: 2 years	96	ACS NR	Stage 5, dialysis, advanced Renal Impairment, planning to receive dialysis GFR equation NR	Acute Renal Failure, acute on CRF
Yakupoglu, 2002[126]	Prospective	Turkey outpatient; dialysis center	Study date NR Mean followup: 48 months	38	ACS NR	Dialysis GFR equation NR	Other exclusions NR

ACS=acute coronary syndrome; AMI=acute myocardial infarction; ARF=acute renal failure; BMI=body mass index; CABG=coronary artery bypass graft; CAD=coronary artery disease; CK=creatine kinase; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; CRF=chronic renal failure; cTnI=cardiac troponin I; cTnT=cardian troponin T; CV=cardiovascular; CXR=chest xray; CysC=cystatin C ECG=electrocardiography; dx=disease; ED=emergency department; EEG=electroencephalography; EF=ejection fraction; ESC/ACC= European Society of Cardiology/American College of Cardiology; ESRD=end stage renal disease; eGFR=estimated glomerular filteration rate; GP=glycoprotein; HD=hemodialysis; HF=heart failure; HIV=human immunodeficiency syndrome; ICU=intensive care unit; IM=internal medicine; MDRD=modification of diet in renal disease; mg/dL=milligrams per deciliter; MI=myocardial infarction; ml/min=milliliters per minute; mos=months; NR=not reported; NS=not specified; PCI=percutaneous coronary intervention; PD=peritoneal dialysis; PVD=peripheral vascular disease; RF=renal failure; SLE=systemic lupus erythematosus; STEMI=ST elevation myocardial infarction; WHO=world health organization

Table 2. Study population characteristics of studies included in Troponin report

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
Abaci, 2004[1]	Total sample, 129	44	55	On dialysis: 76	NR	NR	NR
Abaci, 2004[1]	cTnT >0.1 ng/mL, 27	50	70	NR	NR	NR	NR
Abaci, 2004[1]	cTnT 0.03-0.1 ng/mL, 27	46	59	NR	NR	NR	NR
Abaci, 2004[1]	cTnT <0.03 ng/mL, 75	42	48	NR	NR	NR	NR
Abbas, 2005[2]	Total sample, 222	67	65	NR	NR	Stage 3 kidney disease, percent: 25, Stage 4 kidney disease, percent: 31, Stage 5 kidney disease, percent: 43	NR
Abbas, 2005[2]	Stage 3, 56	68	77	NR	NR	NR	NR
Abbas, 2005[2]	Stage 4, 70	71	70	NR	NR	NR	NR
Abbas, 2005[2]	Stage 5, 96	64	55	NR	NR	NR	NR
Acharji, 2012[3]	Troponin positive, 1291	Median: 76	53.3	NR	NR	NR	NR
Acharji, 2012[3]	Troponin negative, 888	Median: 75	53.7	NR	NR	NR	NR
Alcalai, 2007[4]	Nonthrombotic troponin elevation, 254	71.4	61	NR	NR	NR	NR
Alcalai, 2007[4]	ACS, 326	65	69	NR	NR	NR	NR
Alcalai, 2007[4]	Unknown, 35	72.2	51	NR	NR	NR	NR
Alcalai, 2007[4]	Total sample, 615	68	65	NR	NR	NR	NR
Apple, 1997[5]	Total sample, 16	46	44	On dialysis: 100	Known CAD: 56	Stage 5 kidney disease, percent: 100	NR
Apple, 1999[6]	Total sample, 1601	NR	NR	NR	NR	NR	NR
Apple, 2002[7]	Total sample, 733	62	56	On dialysis: 100	Known CAD: 29	Stage 5 kidney disease, percent: 100	White: 60, African American: 23, Hispanic: 3
Apple, 2004[8]	Total sample, 399	61	58	On dialysis: 100	Known CAD: 30	Stage 5 kidney disease, percent: 100	White: 59, African American: 26, Hispanic: 2, Other

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
							race/ethnicity: 12
Apple, 2007[9]	Tosoh cTnI	57	NR	NR	NR	NR	NR
Apple, 2007[9]	Roche cTnT, 420	58	13	NR	NR	NR	White: 11, African American: 8, Other race/ethnicity: 4
Apple, 2007[9]	Beckman cTnI, 421	58	14	NR	NR	NR	White: 11, African American: 9, Other race/ethnicity: 4
Apple, 2007[9]	Dade cTnI, 490	58	12	NR	NR	NR	White: 10, African American: 7, Other race/ethnicity: 4
Artunc, 2012[10]	Total sample, 239	Median: 70	64	On dialysis: 100	Known CAD: 74	Stage 5 kidney disease, percent: 100	NR
Assa, 2013[11]	Total sample, 90	Median: 67	57	On dialysis: 100	Known CAD: 40	Stage 5 kidney disease, percent: 100	NR
Aviles, 2002[12]	CrCl and Trop T both normal, 2605	NR	59	NR	NR	NR	NR
Aviles, 2002[12]	Trop T abnormal and CrCl normal, 2695	NR	75	NR	NR	NR	NR
Aviles, 2002[12]	Total sample, 7033	NR	NR	NR	NR	NR	NR
Aviles, 2002[12]	CrCl abnormal and Trop T normal, 783	NR	41	NR	NR	NR	NR
Aviles, 2002[12]	CrCl and Trop T both abnormal, 950	NR	51	NR	NR	NR	NR
Bagheri, 2009[13]	CAD-, cTnT >0.05 mg/L, 10	NR	NR	NR	NR	NR	NR
Bagheri, 2009[13]	Total sample, 138	65	52	On dialysis: 100	NR	NR	NR
Bagheri, 2009[13]	CAD+, cTnT <0.05 mg/L,	NR	NR	NR	NR	NR	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	20						
Bagheri, 2009 [13]	CAD+, cTnT >0.05 mg/L, 46	NR	NR	NR	NR	NR	NR
Bagheri, 2009[13]	CAD-, cTnT <0.05 mg/L, 62	NR	NR	NR	NR	NR	NR
Barthelemy, 2012[14]	CrCl ≥ to 60mL/min, 270	62	NR	NR	NR	NR	NR
Barthelemy, 2012[14]	Renal failure - CrCl < 60 mL/min, 75	76	NR	NR	NR	NR	NR
Beciani, 2003[15]	Group 3: >0.15ng/ml cTNI, 14	67	NR	On dialysis: 100	NR	NR	NR
Beciani, 2003[15]	Group 2: </>0.15ng/ml cTNI, 15	64	NR	On dialysis: 100	NR	NR	NR
Beciani, 2003[15]	Group 1: <0.15ng/ml cTNI, 72	60	NR	On dialysis: 100	NR	NR	NR
Bhagavan, 1998[16]	Total sample, 155	NR	NR	NR	NR	NR	NR
Boulier, 2004[17]	Total sample, 191	Median: 66.7	50.8	On dialysis: 100	Known CAD: 32.5	Stage 5 kidney disease, percent: 100	NR
Bozbas, 2004[18]	Total sample, 34	31.8	68	On dialysis: 100	Known CAD: 12	Stage 5 kidney disease, percent: 294	NR
Brunet, 2008[19]	Total sample, 105	65.5	59	On dialysis: 100	Known CAD: 31	Stage 5 kidney disease, percent: 100	NR
Bueti, 2006[20]	Total sample, 149	Median: 63	49	On dialysis: 100	Known CAD: 43	Stage 5 kidney disease, percent: 100	NR
Chenevier-Gobeaux, 2013[127]	Total sample, 367	Mean: 57	65	NR	Known CAD: 28	Stage NR	NR
Chew, 2008[21]	Total sample,	66.26	54	On dialysis: 48	Known CAD: 63	NR	Other race/ethnicity:

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	227						100
Choy, 2003[22]	Total sample, 113	Median: 63	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Choy, 2003[22]	cTnI>0.5, 17	NR	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Choy, 2003[22]	cTnT >0.1 ug/L, 48	NR	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Choy, 2003[22]	cTnT <0.1 ug/L, 65	NR	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Choy, 2003[22]	cTnI<0.5, 96	NR	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Chrysochou, 2009[23]	cTnT >0.03 ng/mL, 11	74	55	NR	Known CAD: 55	NR	NR
Chrysochou, 2009[23]	cTnT <0.03 ng/mL, 71	72	63	NR	Known CAD: 62	NR	NR
Claes, 2010[24]	Total sample	Median: 53	NR	NR	Known CAD: 23.6NR	NR	
Codognotto, 2010[25]	Total sample, 50	68	72	On dialysis: 100	NR	NR	NR
Connolly, 2008[26]	cTnT >0.03 ug/L, 21	56.5	76	NR	NR	NR	NR
Connolly, 2008[26]	cTnT <0.03 ug/L, 351	46.7	64	NR	NR	NR	NR
Conway, 2005[27]	Total sample, 75	Median: 64	60	On dialysis: 100	Known CAD: 33	Stage 5 kidney disease, percent: 100	NR
Deegan,2001[28]	Total sample, 73	Median: 64	58	On dialysis: 100	Known CAD: 25	Stage 5 kidney disease, percent: 100	NR
deFilippi,2003[29]	Total sample, 224	Median: 62	54	On dialysis: 100	Known CAD: 36	Stage 5 kidney disease, percent: 100	White: 38, African American: 38, Hispanic: 21
deFilippi,2012[30]	Total sample, 148	63.2	68.9	NR	Known CAD: 16.9	NR	White: 59.5
Dierkes, 2000[31]	Total sample, 102	64	49	On dialysis: 100	Known CAD: 28	Stage 5 kidney disease, percent: 100	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
Dierkes, 2000[31]	cTnT >0.04 ng/mL, 40	NR	NR	NR	NR	NR	NR
Dierkes, 2000[31]	cTnT <0.04 ng/mL, 62	NR	NR	NR	NR	NR	NR
Duman, 2005[32]	cTnT >0.035 ng/mL, 29	NR	NR	NR	Known CAD: 24	NR	NR
Duman, 2005[32]	cTnT <0.035 ng/mL, 36	NR	NR	NR	Known CAD: 8	NR	NR
Duman, 2005[32]	Total sample, 65	56	55	On dialysis: 100	Known CAD: 15	NR	NR
Facila, 2006[128]	creatinine >1.3, 217	73.8	71.4	NR	Known CAD: 53	NR	NR
Facila, 2006[128]	Creatinine <=1.3, 812	67.1	64	NR	Known CAD: 46	NR	NR
Farkouh, 2003[33]	Total sample, 137	58	NR	On dialysis: 100	NR	NR	NR
Farkouh, 2003[33]	cTnI >1.0 ng/mL, 10	66	50	On dialysis: 100	Known CAD: 60	NR	NR
Farkouh, 2003[33]	cTnI <1.0 ng/ml, 127	58	58	On dialysis: 100	Known CAD: 36	NR	NR
Fehr, 2003[34]	Total sample, 31	55	65	On dialysis: 100	NR	NR	NR
Feringa, 2006[35]	Trop T >=0.10,	70.7	78.3	NR	Known CAD: 58.7	NR	NR
Feringa, 2006[35]	Trop T 0.03-0.09, 25	68.6	76	NR	Known CAD: 60	NR	NR
Feringa, 2006[35]	Trop T <0.03, 487	66.6	76.6	NR	Known CAD: 40.5	NR	NR
Feringa, 2006[35]	Total sample, 558	66.6	76.7	NR	Known CAD: 42.8	NR	NR
Fernandez-Reyes, 2004[36]	Moderate risk: cTnT 0.04-0.1 ng/mL, 11	NR	NR	NR	NR	NR	NR
Fernandez-Reyes, 2004[36]	High risk: cTnT >0.1 ng/mL, 12	NR	NR	NR	NR	NR	NR
Fernandez-Reyes, 2004[36]	Changing group: cTnT values change during follow-	NR	NR	NR	NR	NR	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	up, 16						
Fernandez-Reyes, 2004[36]	Low risk: cTnT <0.04 ng/mL, 23	NR	NR	NR	NR	NR	NR
Fernandez-Reyes, 2004[36]	Total sample, 58	69.9	50	On dialysis: 100	Known CAD: 22	NR	NR
Flores, 2006[37]	Total sample, 467	Median: 80	67	NR	Known CAD: 19	Stage 4 kidney disease, percent: 50	NR
Flores-Solis, 2012[38]	Patients with other non-cardiac pathologies	76	67	NR	NR	NR	NR
Flores-Solis, 2012[38]	Patients with other cardiac pathologies, 140	78	67	NR	NR	NR	NR
Flores-Solis, 2012[38]	Total sample, 484	77	68	NR	NR	Stage 3 kidney disease, percent: 58, Stage 4 kidney disease, percent: 31, Stage 5 kidney disease, percent: 11	NR
Flores-Solis, 2012[38]	Patients with ACS, 54	77	76	NR	NR	NR	NR
Gaiki, 2012[39]	cTnI (-), 25	NR	NR	NR	NR	NR	
Gaiki, 2012[39]	cTnI (+), 26	NR	NR	NR	NR	NR	
Gaiki, 2012[39]	Total sample, 51	61.94	53	On dialysis: 100	Known CAD: 31	NR	White: 18, African American: 61, Hispanic: 14, Other race/ethnicity: 8
Geerse, 2012[40]	Total sample, 206	65.3	52	On dialysis: 100	Known CAD: 40	NR	NR
Geerse, 2012[40]	>0.10 ug/L troponin, 25	NR	NR	On dialysis: 100	NR	NR	NR
Geerse, 2012[40]	0.05-0.10 ug/L troponin, 28	NR	NR	On dialysis: 100	NR	NR	NR
Geerse, 2012[40]	<0.01 ug/L troponin, 59	NR	NR	On dialysis: 100	NR	NR	NR
Geerse, 2012[40]	0.01-0.05	NR	NR	On dialysis: 100	NR	NR	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	ug/L troponin, 94						
Goicoechea, 2004[41]	cTnT<0.01 ng/ml w/ CKD, 108	Median: 68	64	NR	Known CAD: 19	NR	NR
Goicoechea, 2004[41]	cTnT>0.01 w/ CKD, 20	Median: 77	45	NR	Known CAD: 35	NR	NR
Goicoechea, 2004[41]	Control (no CKD), 48	Median: 55.5	65	On dialysis: 0	Known CAD: 8	NR	NR
Gruberg, 2002[42]	cTnI >0.15 ng/mL, 50	73	76	On dialysis: 0	Known CAD: 100	NR	NR
Gruberg, 2002[42]	cTnI <0.15 ng/mL, 66	69	68.2	On dialysis: 0	Known CAD: 100	NR	NR
Haaf, 2013[43]	Total sample, 1117	Median: 64	67	On dialysis: 0	Known CAD: 36	NR	NR
Hallen, 2011[44]	Total sample, 109	62	75	On dialysis: 100	Known CAD: 27	NR	NR
Hallen, 2011[44]	cTnT <0.01 ug/L, 43	NR	NR	NR	NR	NR	NR
Hallen, 2011[44]	cTnT >0.01 ug/L, 64	NR	NR	NR	NR	NR	NR
Han, 2005[45]	Pts with no ACS, 27	48.1	63	On dialysis: 51.9	Known CAD: 25.9	NR	White: 18.5, African American: 77.8, Other race/ethnicity: 3.7
Han, 2005[45]	Pts with ACS, 34	61	50	On dialysis: 33.3	Known CAD: 26.5	NR	White: 20.6, African American: 79.4, Other race/ethnicity: 0
Han, 2005[45]	Total sample, 64	54.9	57.8	On dialysis: 43.7	Known CAD: 40.6	NR	White: 18.8, African American: 79.7, Other race/ethnicity: 1.6
Han, 2009[46]	cTnT >0.1 ug/L, 21	54.6	52	On dialysis: 100	NR	NR	NR
Han, 2009[46]	cTnT <0.1 ug/L, 86	47.8	44	On dialysis: 100	NR	NR	NR
Hasegawa, 2012[47]	Quartile 4: >33 pg/mL,	Median: 73	NR	NR	NR	Stage 3 kidney disease, percent: 8.3, Stage 4 kidney disease, percent: 33.3, Stage 5 kidney disease, percent: 58.3	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
Hasegawa, 2012[47]	Quartile 3: 19-32 pg/mL, 110	Median: 73	61	On dialysis: 0	NR	Stage 3 kidney disease, percent: 23.6, Stage 4 kidney disease, percent: 52.7, Stage 5 kidney disease, percent: 23.6	Other race/ethnicity: 100
Hasegawa, 2012[47]	Quartile 2: 10-18 pg/mL, 111	Median: 68	67	On dialysis: 0	NR	Stage 3 kidney disease, percent: 35.1, Stage 4 kidney disease, percent: 49.5, Stage 5 kidney disease, percent: 15.3	Other race/ethnicity: 100
Hasegawa, 2012[47]	Quartile 1: <9 pg/mL, 113	Median: 63	58	On dialysis: 0	NR	Stage 3 kidney disease, percent: 78.8, Stage 4 kidney disease, percent: 17.7, Stage 5 kidney disease, percent: 3.5	Other race/ethnicity: 100
Havekes, 2006 [48]	Total sample, 847	59	60	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Heeschen, 2000[49]	ESRD patients, 26	Median: 45.8	62	On dialysis: 100	Known CAD: 0	Stage 5 kidney disease, percent: 100	NR
Helleskov Madsen, 2008[50]	Total sample, 109	61.8	75	On dialysis: 100	Known CAD: 26.6	Stage 5 kidney disease, percent: 100	NR
Hickman, 2009[51]	Total sample, 143	59.67	63	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	White: 89.3, African American: 3.6, Other race/ethnicity: 7.1
Hickson, 2008[52]	Total sample, 644	51	56	On dialysis: 62	Known CAD: 34	NR	White: 98
Hickson, 2009[53]	Total sample, 603	51	57	On dialysis: 67.6	Known CAD: 29	NR	White: 98
Hocher, 2003[54]	Survivors, 172	63.5	49	On dialysis: 100	Known CAD: 33	Stage 5 kidney disease, percent:	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
						100	
Hocher, 2003[54]	Total sample, 245	NR	50	On dialysis: 100	Known CAD: 41	Stage 5 kidney disease, percent: 100	NR
Hocher, 2003[54]	Nonsurvivors, 73	70.4	53	On dialysis: 100	Known CAD: 45	Stage 5 kidney disease, percent: 100	NR
Hocher, 2004[55]	Women, 122	NR	NR	NR	NR	Stage 5 kidney disease, percent: 100	NR
Hocher, 2004[55]	Men, 123	NR	NR	NR	NR	Stage 5 kidney disease, percent: 100	NR
Hocher, 2004[55]	Total sample, 245	63.5	50	On dialysis: 100	Known CAD: 64	Stage 5 kidney disease, percent: 100	NR
Hocher, 2008[56]	Men, 112	63	100	On dialysis: 100	Known CAD: 32	Stage 5 kidney disease, percent: 100	NR
Hocher, 2008[56]	Women, 118	68	0	On dialysis: 100	Known CAD: 23	Stage 5 kidney disease, percent: 100	NR
Hocher, 2008[56]	Total sample, 230	65.6	49	On dialysis: 100	Known CAD: 27	Stage 5 kidney disease, percent: 100	NR
Hojs, 2005[57]	Total sample, 90	56.2	61	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Holden, 2012[58]	Total sample, 103	62.9	69	On dialysis: 100	Known CAD: 47.1	NR	NR
Hung, 2004[59]	Hypotension Prone, 29	61.4	34	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Hung, 2004[59]	Hypotension resistant, 41	58.3	41	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Hussein, 2004[60]	Total sample, 93	50	49	On dialysis: 100	Known CAD: 20	Stage 5 kidney disease, percent: 100	NR
Ie, 2004[61]	Total sample, 49	57	NR	On dialysis: 100	NR	NR	NR
Ikeda, 2002[62]	Total sample,	NR	NR	NR	Known CAD: 100	Stage 5 kidney	Other race/ethnicity:

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	173					disease, percent: 16	100
Iliou, 2003[63]	cTnT>0.15, 18	63.1	63	On dialysis: 100	Known CAD: 21.7	Stage 5 kidney disease, percent: 100	NR
Iliou, 2003[63]	cTnT<=0.1 ng/ml, 210	58.5	58.2	On dialysis: 100	Known CAD: 20	Stage 5 kidney disease, percent: 100	NR
Iliou, 2003[63]	cTnT<=0.15, 240	59.6	57.1	On dialysis: 100	Known CAD: 23.1	Stage 5 kidney disease, percent: 100	NR
Iliou, 2003[63]	Total sample, 258	60.2	58.1	On dialysis: 100	Known CAD: 22.9	Stage 5 kidney disease, percent: 100	White: 72, African American: 15.5, Other race/ethnicity: 12.5
Iliou, 2003[63]	cTNT>0.1 ng/ml, 48	67.5	56.2	On dialysis: 100	Known CAD: 35.4	Stage 5 kidney disease, percent: 100	NR
Ilva, 2008[64]	Total sample, 364	74.8	14	NR	Known CAD: 13	NR	NR
Ishii, 2001[65]	Total sample, 100	54	61	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Jensen, 2012[66]	hsTnT < or = 14 ng/L, 128	67	54	NR	NR	NR	NR
Jensen, 2012[66]	hsTnT > 14 ng/L, 65	74	62	NR	NR	NR	NR
Kalaji, 2012[67]	Total sample, 145	Median: 45	55.2	On dialysis: 100	Known CAD: 9	Stage 5 kidney disease, percent: 100	NR
Kang, 2009[68]	Elevated cTnI levels, 50	67	44	On dialysis: 100	Known CAD: 22	Stage 5 kidney disease, percent: 100	NR
Kang, 2009[68]	Lower cTnI levels, 71	66	44	On dialysis: 100	Known CAD: 15	Stage 5 kidney disease, percent: 100	NR
Kanwar, 2006[69]	Total sample, 173	62	53	On dialysis: 100	NR	NR	White: 57
Katerinis, 2008[70]	Elevated cTnI, 4	70.2	100	On dialysis: 100	Known CAD: 100	Stage 5 kidney disease, percent: 100	NR
Katerinis,	Normal cTnI,	62.2	61	On dialysis: 100	Known CAD: 35	Stage 5 kidney	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
2008[70]	46					disease, percent: 100	
Kertai, 2004[71]	cTNT >=0.1ng/ml, 339	NR	79	NR	Known CAD: 19	NR	NR
Kertai, 2004[71]	cTNT <0.1ng/ml, 54	NR	83	NR	Known CAD: 43	NR	NR
Khan, 2001[72]	cTnI <0.03 ng/mL, 102	59	62	On dialysis: 100	Known CAD: 13	Stage 5 kidney disease, percent: 100	NR
Khan, 2001[72]	cTnI >0.03 ng/mL, 24	62.2	58	On dialysis: 100	Known CAD: 3	Stage 5 kidney disease, percent: 100	NR
Kontos, 2005[73]	Normal renal function, >60 mL/min,	54	NR	NR	NR	NR	NR
Kontos, 2005[73]	Severe renal failure, <30 mL/min, 329	65	47	NR	NR	NR	NR
Kontos, 2005[73]	Total sample, 3774	58	50	NR	NR	NR	NR
Kontos, 2005[73]	Moderate renal failure, 30-59 mL/min, 755	72	45	NR	NR	NR	NR
Kontos, 2005[74]	CrCl >60, 2259	53	52	NR	NR	NR	NR
Kontos, 2005[74]	CrCl <30, 233	64	45	NR	NR	NR	NR
Kontos, 2005[74]	CrCl=30-59, 582	70	42	NR	NR	NR	NR
Kontos, 2008[75]	Total sample, 4343	58	51	NR	NR	NR	White: 36, African American: 64
Kostrubiec, 2010[76]	Normal cTnI or cTnT, 122	NR	NR	NR	NR	NR	NR
Kostrubiec, 2010[76]	Total sample, 212	64	38	NR	Known CAD: 22	NR	NR
Kostrubiec, 2010[76]	Elevated cTnI or cTnT, 90	NR	NR	NR	NR	NR	NR
Lamb, 2007[77]	Total sample, 222	67	65	On dialysis: 0	Known CAD: 42	Stage 3 kidney disease, percent: 25, Stage 4 kidney disease, percent:	White: 100

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
						32, Stage 5 kidney disease, percent: 43	
Lang, 2001[78]	Total sample, 100	56.6	62	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Le Goff, 2007[79]	cTnT >0.1 ug/L, 22	NR	NR	NR	NR	NR	NR
Le Goff, 2007[79]	cTnT 0.031-0.1 ug/L, 32	NR	NR	NR	NR	NR	NR
Le Goff, 2007[79]	cTnT <0.03 ug/L, 7	NR	NR	NR	NR	NR	NR
Le Goff, 2007[79]	Total sample, 86	60	53	On dialysis: 100	Known CAD: 53	Stage 5 kidney disease, percent: 100	NR
Lowbeer, 2002[80]	Survivors, 11	52	36	On dialysis: 100	Known CAD: 0	Stage 5 kidney disease, percent: 100	NR
Lowbeer, 2002[80]	Non-survivors, 15	64	60	On dialysis: 100	Known CAD: 33	Stage 5 kidney disease, percent: 100	NR
Lowbeer, 2002[80]	Total sample, 26	58	50	On dialysis: 100	Known CAD: 19	Stage 5 kidney disease, percent: 100	NR
Lowbeer, 2003[81]	Total sample, 115	52	62	On dialysis: 100	Known CAD: 29	Stage 5 kidney disease, percent: 100	NR
Lowbeer, 2003[81]	HD, 49	NR	NR	NR	NR	NR	NR
Lowbeer, 2003[81]	PD, 64	NR	NR	NR	NR	NR	NR
Mallamaci, 2002[82]	cTnT <0.048 ug/L,	NR	NR	NR	NR	NR	NR
Mallamaci, 2002[82]	cTnT >0.098 ug/L,	NR	NR	NR	NR	NR	NR
Mallamaci, 2002[82]	cTnT 0.049-0.098 ug/L,	NR	NR	NR	NR	NR	NR
Mallamaci, 2002[82]	Total sample, 199	58.8	56	On dialysis: 100	NR	NR	NR
Martin, 1998[83]	Total sample, 56	62	50	NR	NR	NR	White: 55, African American: 43, Other race/ethnicity: 2
McCullough, 2002[84]	Quartile 1: >99.4	47.9	37.6	On dialysis: 0	Known CAD: 22.2	NR	White: 16.4, African American: 78.3, Other

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	mL/min/72kg, 189						race/ethnicity: 5.3
McCullough, 2002[84]	Quartile 2: 99.3-72.7 mL/min/72kg, 189	60.9	48.7	On dialysis: 0	Known CAD: 27	NR	White: 20.1, African American: 76.2, Other race/ethnicity: 3.7
McCullough, 2002[84]	Quartile 4: <47.0 mL/min/72kg, 189	75	45	On dialysis: 0	Known CAD: 36	NR	White: 12.7, African American: 85.7, Other race/ethnicity: 1.6
McCullough, 2002[84]	Quartile 3: 72.8-47.0 mL/min/72kg, 190	70.9	48.9	On dialysis: 0	Known CAD: 35.3	NR	White: 14.7, African American: 83.7, Other race/ethnicity: 1.6
McCullough, 2002[84]	End stage renal disease on dialysis, 51	65.2	54.9	On dialysis: 100	Known CAD: 49	NR	White: 11.8, African American: 86.3, Other race/ethnicity: 2
McGill, 2010[85]	Total sample, 143	NR	NR	On dialysis: 100	NR	NR	NR
McMurray, 2011[86]	>0.028 ng/mL, 217	65	67	NR	NR	NR	White: 64, African American: 28, Other race/ethnicity: 8
McMurray, 2011[86]	<.028 ng/mL, 230	69	55	NR	NR	NR	White: 62, African American: 23, Other race/ethnicity: 15
McMurray, 2011[86]	Undetectable TnT, 548	68	30	NR	NR	NR	White: 70, African American: 20, Other race/ethnicity: 10
Melloni, 2008[87]	>3 x ULN cTn ratio, 20843	Median: 70	59.2	NR	NR	NR	White: 81.9
Melloni, 2008[87]	Total sample, 31586	Median: 70	58.6	NR	NR	NR	White: 80.4
Melloni, 2008[87]	1-3 x ULN cTn ratio, 5214	Median: 71	55.3	NR	NR	NR	White: 77.4
Melloni, 2008[87]	<1 x ULN cTn ratio, 5529	Median: 66	59.8	NR	NR	NR	White: 77.2
Mockel, 1999[88]	ESRD, 20	51.5	50	On dialysis: 100	NR	NR	NR
Mockel, 1999[88]	Pre-ESRD, 20	63.5	60	On dialysis: 0	NR	NR	NR
Morton, 1998[89]	Total sample,	61.1	62	On dialysis: 100	Known CAD: 47	Stage 5 kidney	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	112					disease, percent: 100	
Musso, 1999[90]	Controls, 117	50	50	On dialysis: 0	NR	NR	NR
Musso, 1999[90]	CRF: medical, 12	65	58	On dialysis: 0	NR	NR	NR
Musso, 1999[90]	CRF: transplant, 17	44	100	On dialysis: 0	NR	NR	NR
Musso, 1999[90]	CRF: dialysis, 20	51	50	On dialysis: 100	NR	NR	NR
Noeller, 2003[91]	Age >=65, 301	NR	57	NR	Known CAD: 24	NR	White: 65
Noeller, 2003[91]	Age <65, 321	NR	61	NR	Known CAD: 7	NR	White: 51
Ooi, 1999[92]	cTnT <0.1, 111	Median: 61	53	On dialysis: 100	Known CAD: 28	Stage 5 kidney disease, percent: 100	NR
Ooi, 1999[92]	cTnT >0.2, 24	Median: 62.8	79	On dialysis: 100	Known CAD: 50	Stage 5 kidney disease, percent: 100	NR
Ooi, 1999[92]	cTnT 0.1-0.2, 37	Median: 64.5	70	On dialysis: 100	Known CAD: 30	Stage 5 kidney disease, percent: 100	NR
Ooi, 2001[93]	cTnT >0.200, 26	NR	77	On dialysis: 100	Known CAD: 31	Stage 5 kidney disease, percent: 100	NR
Ooi, 2001[93]	cTnT<0.010 ug/L, 26	NR	50	On dialysis: 100	Known CAD: 8	Stage 5 kidney disease, percent: 100	NR
Ooi, 2001[93]	cTnT 0.100-0.199, 36	NR	67	On dialysis: 100	Known CAD: 39	Stage 5 kidney disease, percent: 100	NR
Ooi, 2001[93]	cTnT 0.05-0.099, 62	NR	65	On dialysis: 100	Known CAD: 37	Stage 5 kidney disease, percent: 100	NR
Ooi, 2001[93]	cTnT 0.010-0.049, 94	NR	52	On dialysis: 100	Known CAD: 35	Stage 5 kidney disease, percent: 100	NR
Orea-Tejeda, 2010[94]	cTnT >0.02 ng/mL and eGFR<60, 21	63.19	47.6	NR	NR	NR	NR
Peetz, 2003[95]	Women, 41	65	0	On dialysis: 100	Known CAD: 31.7	Stage 5 kidney disease, percent: 100	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
Peetz,2003[95]	Men, 63	63	100	On dialysis: 100	Known CAD: 39.1	Stage 5 kidney disease, percent: 100	NR
Petrovic, 2009[96]	Total sample, 115	53.3	62	On dialysis: 100	NR	NR	NR
Porter, 1998[97]	Total sample, 30	66.1	40	NR	Known CAD: 100	NR	NR
Porter, 2000[98]	Those available for analysis and the end of the f/u period, 27	48.1	41	On dialysis: 100	Known CAD: 15	Stage 5 kidney disease, percent: 100	NR
Quiroga, 2013[99]	Total sample, 218	69	62	NR	NR	Stage 1 kidney disease, percent: 10, Stage 2 kidney disease, percent: 17, Stage 3 kidney disease, percent: 48, Stage 4 kidney disease, percent: 23	NR
Roberts, 2004[100]	Negative cTnI, 79	59.2	64.6	On dialysis: 100	Known CAD: 25.3	NR	NR
Roberts, 2004[100]	Detectable cTnI, 9	58.6	55.6	On dialysis: 100	Known CAD: 33.3	NR	NR
Roberts, 2009[101]	1-4/5 measurements cTnT >0.04 ug/L, 20	66.6	50	NR	NR	NR	NR
Roberts, 2009[101]	0/5 measurements cTnT >0.04 ug/L, 28	56.2	50	NR	NR	NR	NR
Roberts, 2009[101]	5/5 measurements cTnT >0.04 ug/L, 33	64.6	64	NR	NR	NR	NR
Roppolo, 1999[102]	Total sample, 49	58.5	NR	NR	NR	NR	NR
Sahinarslan, 2008[103]	cTnT >0.1 ug/L, 17	NR	NR	NR	NR	NR	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
Sahinarslan, 2008[103]	cTnT <0.1 ug/L, 61	NR	NR	NR	NR	NR	NR
Sahinarslan, 2008[103]	Total sample, 78	53.2	69	On dialysis: 100	NR	NR	NR
Satyan, 2007[104]	cTnT 0.056-0.106 ng/mL, 37	62.4	59	On dialysis: 100	Known CAD: 54	NR	White: 8, African American: 89, Other race/ethnicity: 3
Satyan, 2007[104]	cTnT 0.106-0.569 ng/mL, 37	53.6	62	On dialysis: 100	Known CAD: 54	NR	White: 8, African American: 92, Other race/ethnicity: 0
Satyan, 2007[104]	cTnT 0.01-0.022 ng/mL, 38	47.9	58	On dialysis: 100	Known CAD: 29	NR	White: 5, African American: 95, Other race/ethnicity: 0
Satyan, 2007[104]	cTnT 0.022-0.056 ng/mL, 38	59.5	71	On dialysis: 100	Known CAD: 53	NR	White: 13, African American: 84, Other race/ethnicity: 3
Scheven, 2012[105]	hs cTnT >0.01 ug/L, 544	64.2	78.9	NR	NR	NR	NR
Scheven, 2012[105]	hs cTnT <0.01 ug/L, 7577	49.3	47.7	NR	NR	NR	NR
Scott, 2003[106]	Total sample, 71	68.7	NR	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Sharma, 2005[107]	Total sample, 118	52	64	On dialysis: 54	Known CAD: 30	Stage 5 kidney disease, percent: 100	NR
Sharma, 2006[108]	Total sample, 114	52	67	On dialysis: 58	Known CAD: 30	NR	White: 45, African American: 29, Other race/ethnicity: 1
Sharma, 2006[108]	cTnT >0.06 ng/mL, 51	NR	NR	NR	NR	NR	NR
Sharma, 2006[108]	cTnT <0.06 ng/mL, 62	NR	NR	NR	NR	NR	NR
Sharma, 2006[109]	Total sample, 126	52	63	On dialysis: 55	Known CAD: 38	Stage 5 kidney disease, percent: 100	White: 50, African American: 25, Other race/ethnicity: 25
Sharma, 2006[109]	cTNT>0.1, 38	54	NR	NR	Known CAD: 32	Stage 5 kidney disease, percent: 100	NR
Sharma, 2006[109]	cTnT>0.04	54	NR	NR	Known CAD: 22	Stage 5 kidney	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	ug/L, 52					disease, percent: 100	
Sharma, 2006[109]	<0.04 ug/L, 74	51	NR	NR	Known CAD: 22	Stage 5 kidney disease, percent: 100	NR
Sharma, 2006[109]	cTNT<0.1, 88	51	NR	NR	Known CAD: 27	Stage 5 kidney disease, percent: 100	NR
Shroff, 2012[110]	cTnI<0.04 ng/mL, 281	48.3	60	On dialysis: 58	Known CAD: 20	NR	White: 85, African American: 6
Shroff, 2012[110]	cTnI>0.04 ng/mL, 95	52.2	55	On dialysis: 65	Known CAD: 32	NR	White: 88, African American: 4
Sommerer, 2007[111]	Total sample, 134	Median: 66	59.7	On dialysis: 100	Known CAD: 20.9	Stage 5 kidney disease, percent: 100	NR
Stolear, 1999[112]	Total sample, 94	62.9	59	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Sukonthasarn, 2007[113]	AMI group, 23	71.7	34.8	NR	Known CAD: 0	Stage 3 kidney disease, percent: 21.7, Stage 4 kidney disease, percent: 47.8, Stage 5 kidney disease, percent: 30.4	African American: 100
Sukonthasarn, 2007[113]	Control group, 23	65.7	34.8	NR	Known CAD: 8.7	Stage 3 kidney disease, percent: 34.8, Stage 4 kidney disease, percent: 34.8, Stage 5 kidney disease, percent: 30.4	African American: 100
Svensson, 2009[114]	Total sample, 206	67	65	On dialysis: 100	Known CAD: 100	Stage 5 kidney disease, percent: 100	NR
Trape, 2008[115]	Total sample, 52	Median: 74	48	On dialysis: 100	Known CAD: 46	NR	NR
Troyanov, 2005[116]	Total sample, 101	66	57	On dialysis: 100	Known CAD: 37	NR	NR
Van Lente,	Creatinine	70.1	59	On dialysis: 9	NR	NR	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
1999[117]	>20mg/L, 51						
Vichairuangthum, 2006[118]	cTnT >0.4 ng/mL, 14	63.21	36	On dialysis: 100	NR	NR	NR
Vichairuangthum, 2006[118]	cTnT <0.08 ng/mL, 16	59.6	50	On dialysis: 100	NR	NR	NR
Vichairuangthum, 2006[118]	cTnT >0.08 ng/mL, 47	54.6	47	On dialysis: 100	NR	NR	NR
Vichairuangthum, 2006[118]	cTnT <0.4 ng/mL, 49	53.84	51	On dialysis: 100	NR	NR	NR
Wang, 2006[119]	Total sample, 222	56	50	On dialysis: 100	Known CAD: 23.4	Stage 5 kidney disease, percent: 100	NR
Wang, 2007[120]	cTnT <0.01 ug/L, 77	52.1	40.3	On dialysis: 100	Known CAD: 6.5	NR	NR
Wang, 2007[120]	cTnT 0.01-0.099 ug/L, 78	57	50	On dialysis: 100	Known CAD: 23.1	NR	NR
Wang, 2007[120]	cTnT >0.099 ug/L, 83	57.9	62.7	On dialysis: 100	Known CAD: 30.1	NR	NR
Wang, 2010[121]	Total sample, 230	56	50.9	On dialysis: 100	Known CAD: 22.6	Stage 5 kidney disease, percent: 100	NR
Wang, 2010[122]	Total sample, 230	56	51	On dialysis: 100	Known CAD: 23	NR	NR
Wang, 2010[122]	cTnT 0.01-0.099 ug/L, 70	NR	NR	NR	NR	NR	NR
Wang, 2010[122]	cTnT >=0.1 ug/L, 79	NR	NR	NR	NR	NR	NR
Wang, 2010[122]	cTnT <0.01 ug/L, 81	NR	NR	NR	NR	NR	NR
Wayand, 2000[123]	Cardiac symptoms, 28	67.3	NR	On dialysis: 100	NR	NR	NR
Wayand, 2000[123]	No cardiac symptoms, 31	51	NR	On dialysis: 100	NR	NR	NR
Wolley, 2013[124]	Total sample, 238	Median: 63	51	On dialysis: 100	Known CAD: 33	Stage 5 kidney disease, percent: 100	White, percent: 28, African American, percent: 0.5
Wood, 2003[125]	cTnT	59	68	On dialysis: 0	Known CAD: 36	Stage 5 kidney	NR

Author, Year	Group, N	Mean Age	Males, Percent	Dialysis status, Percent	Known CAD, Percent	CKD stage, Percent	Race/Ethnicity, Percent
	>0.1ng/mL, 25					disease, percent: 100	
Wood, 2003[125]	cTnT <0.1ng/mL, 71	50.1	66.2	On dialysis: 0	Known CAD: 19.7	Stage 5 kidney disease, percent: 100	NR
Wood, 2003[125]	Total sample, 96	52.4	66.7	On dialysis: 0	Known CAD: 24	Stage 5 kidney disease, percent: 100	NR
Yakupoglu, 2002[126]	cTnI <2.3 ng/mL, 30	NR	NR	NR	NR	Stage 5 kidney disease, percent: 100	NR
Yakupoglu, 2002[126]	Total sample, 38	55.9	42	On dialysis: 100	NR	Stage 5 kidney disease, percent: 100	NR
Yakupoglu, 2002[126]	cTnI >2.3 ng/mL, 8	NR	NR	NR	NR	Stage 5 kidney disease, percent: 100	NR

CAD=coronary artery disease; CrCl=creatinine clearance; CRF=chronic renal failure; cTnI=cardiac troponin I; cTnT=cardian troponin T; ECG=electrocardiography; dx=disease; ESRD=end stage renal disease; eGFR=estimated glomerular filteration rate; f/u=followup; HD=hemodialysis; hs=high sensitivity; ml/min=milliliters per minute; ng/mL=nanograms per liter; NR=not reported; NS=not specified; PD=peritoneal dialysis; pg/mL=picograms per liter; Trop=troponin; ug/L=micrograms per liter; ULN=upper limit of normal; w/=without

Table 3. Key Question 1: Outcomes

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
Alcalai, 2007[4]	Age <70 and creatinine <1.13 mg/dL, cTnT >1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 89; 95% CI: 79 to 95
Alcalai, 2007[4]	Age <70 and creatinine <1.13 mg/dL, cTnT 0.1-1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR Type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 73; 95% CI: 65 to 80
Alcalai, 2007[4]	Age <70 and creatinine <1.13 mg/dL, cTnT any positive result subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 78; 95% CI: 72 to 84
Alcalai, 2007[4]	Age <70 and creatinine >=1.13 mg/dL, cTnT >1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists adjudicated: yes Definition: ESC/ACC			PPV: 59; 95% CI: 36 to 79
Alcalai, 2007[4]	Age <70 and creatinine >=1.13 mg/dL, cTnT 0.1-1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 73; 95% CI: 65 to 80
Alcalai, 2007[4]	Age <70 and creatinine >=1.13 mg/dL, cTnT Any positive result subgroup data	Assay: cTnT Mfg: NR type: NR	ICD-9 code: ICD-9 Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 44; 95% CI: 35 to 55
Alcalai, 2007[4]	Age >70 and creatinine <1.13 mg/dL, cTnT >=1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC			PPV: 90; 95% CI: 68 to 99

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR				
Alcalai, 2007[4]	Age >70 and creatinine <1.13 mg/dL, cTnT 0.1-1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC	NR	NR	PPV: 42; 95% CI: 31 to 54
Alcalai, 2007[4]	Age >70 and creatinine <1.13 mg/dL, cTnT any positive result subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC	NR	NR	PPV: 52; 95% CI: 42 to 63
Alcalai, 2007[4]	Age >70 and creatinine >=1.13 mg/dL, cTnT >1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC	NR	NR	PPV: 59; 95% CI: 43 to 73
Alcalai, 2007[4]	Age >70 and creatinine >=1.13 mg/dL, cTnT 0.1-1.0 ng/mL subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC	NR	NR	PPV: 27; 95% CI: 20 to 37
Alcalai, 2007[4]	Age >70 and creatinine >=1.13 mg/dL, cTnT any positive result subgroup data	Assay: cTnT Mfg: NR type: NR cut off normal: 0.1 mcg/L timing: NR 99th upper ref: NR	Adjudicated by: panel of 2 cardiologists Definition: ESC/ACC	NR	NR	PPV: 37; 95% CI: 29 to 45
Apple, 1999[6]	Total sample	Assay: cTnI Mfg: other Mfg: BioSite Diagnostics	NR	NR	AUC: 0.961; 95% CI: 0.931 to	AUC: 0.961; 95% CI: 0.931 to 0.979

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		type: other type: Triage Cardiac Panel cut off normal: 0.4 mcg/L timing: samples taken every 8 hours for 24 hours 99th upper ref: 0.4 mcg/L			0.979	
Bhagavan, 1998[16]	subgroup data	Assay: cTnI Mfg: other Mfg: Baxter type: Stratus cut off normal: 0.6 mcg/L timing: every 8 hours at and after admission 99th upper ref: NR	NR	NR	NR	Sens: 90 Spec: 81 NPV: 98
Chenevier-Gobeaux, 2013[127]	Total sample	Assay: hs cTnT Mfg: Roche type: Elecsys cut off normal: 14.0 ng/L timing: NR 99th upper ref: 14 ng/L	Adjudicated by: panel of 2 cardiologist Definition: global mi	75	NR	NR
Chenevier-Gobeaux, 2013[127]	Total sample	Assay: hs cTnT Mfg: Roche type: Elecsys cut off normal: 35.8 ng/L timing: NR 99th upper ref: 14 mg/L	Adjudicated by: panel of 2 cardiologist Definition: global mi	75	NR	NR
Chenevier-Gobeaux, 2013[127]	Total sample	Assay: hs cTnT Mfg: Roche type: Elecsys cut off normal: 14.0 ng/L timing: NR 99th upper ref: 14 ng/L	Adjudicated by: panel of 2 cardiologist Definition: global mi	72	NR	NR

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
Chenevier-Gobeaux, 2013[127]	Total sample	Assay: hs cTnT Mfg: Roche type: Elecsys cut off normal: 43.2 ng/L timing: NR 99th upper ref: 14 ng/L	Adjudicated by: panel of 2cardiologist Definition: global mi	72	NR	NR
Fehr, 2003[34]	ACS, cTnI subgroup data	Assay: cTnI Mfg: DPC type: Immulite cut off normal: 1 mcg/L timing: beginning of hemodialysis session 99th upper ref: NR	NR	NR	NR	Sens: 45 Spec: 100
Fehr, 2003[34]	ACS, cTnTsubgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L timing: Beginning of hemodialysis session 99th upper ref: NR	NR	NR	NR	Sens: 100 Spec: 42
Flores, 2006[37]	Total sample	Assay: cTnI Mfg: Beckman type: Access cut off normal: 0.5 ng/mL timing: NR	NR	NR	NR	FP: 20 Sens: 70; 95% CI: 57 to 83 Spec: 92; 95% CI: 90 to 95 PPV: 51; 95% CI: 39 to 63 NPV: 97; 95% CI: 95 to 98
Flores-Solis, 2012[38]	NR	Assay: cTnI Mfg: other Mfg: type: other type: Vidas cut off normal: 0.11	Definition: European Society for Cardiology 2007	NR	AUC: 0.83; 95% CI: 0.76 to 0.9	TP: 36 FP: 53 FN: 20 TN: 367 Sens: 0.64 Spec: 0.87

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		ng/mL other timing: other timing: Upon hospitalization and 6 months follow-up 99th upper ref: 0.01 ng/mL				PPV: 0.4 NPV: 0.95 AUC: 0.83; 95% CI: 0.76 to 0.9
Flores-Solis, 2012[38]	NR	Assay: cTnI Mfg: Beckman type: Access cut off normal: 0.50 ng/mL timing: Upon hospitalization and 6 months followup 99th upper ref:: 0.04 ng/mL	Definition: European Society for Cardiology 2007	484	AUC: 0.85; 95% CI: 0.91 to 0.78	TP: 24 FP: 24 FN: 32 TN: 403 Sens: 0.43 Spec: 0.94 PPV: 0.5 NPV: 0.93 AUC: 0.85; 95% CI: 0.91 to 0.78
Haaf, 2013[43]	Total sample	Assay: hs cTnT Mfg: Roche type: elecsys cut off normal: 19.4 ng/L timing: NR 99th upper ref: 14 ng/L	Adjudicated by: panel of 3 cardiologist Definition: J. Am. Coll. Cardiol	NR	NR	NR
Haaf, 2013[43]	Total sample	Assay: hs cTnI Mfg: Beckman type: Access cut off normal: 9.9 ng/L timing: NR 99th upper ref: 9 ng/L	Adjudicated by: panel of 3 cardiologist Definition: J. Am. Coll. Cardiol	NR	NR	NR
Haaf, 2013[43]	Total sample	Assay: hs cTnI Mfg: Siemens type: NR cut off normal: 6.3 ng/L timing: NR 99th upper ref: 9 ng/L	Adjudicated by: panel of 3 cardiologist Definition: J. Am. Coll. Cardiol	NR	NR	NR
Haaf, 2013[43]	Total sample	Assay: cTnT Mfg: Roche type: Elecsys	Adjudicated by: panel of 3 cardiologist Definition: J. Am. Coll. Cardiol	NR	NR	NR

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		cut off normal: 9 ng/L timing: NR 99th upper ref: 0.01 mcg/ L				
Ikeda, 2002[62]	Total sample	Assay: cTnI Mfg: other cut off normal: 0.8ng/ml 99th upper ref: NR	Adjudicated by: NS cardiologist adjudicated: NR Definition: NR	NR	NR	NR
Ikeda, 2002[62]	Total sample	Assay: cTnT cut off normal: 0.16ng/ml 99th upper ref: NR	Adjudicated by: NS cardiologist adjudicated: NR Definition: NR	NR	NR	NR
Martin, 1998[83]	Total sample	Assay: cTnI Mfg: Dade-Behring type: Stratus cut off normal: 0.8 mcg/L timing: 48 hours after admission 99th upper ref: NR	NR	NR	NR	Sens: 94; 95% CI: 82 to 106 Spec: 100 PPV: 100 NPV: 94
McCullough, 2002[84]	End-stage renal disease on dialysis subgroup data	Assay: cTnI Mfg: other Mfg: Biosite Incorporated type: other type: Triage Cardiac System Package Insert cut off normal: 0.4 mcg/L timing: 9 hrs after onset 99th upper ref: NR	Adjudicated by: Panel of 2 cardiologists Definition: Thrombolysis in Myocardial Infarction Study Group	NR	AUC: 0.99 SD: 0.01	AUC: 0.99 SD: 0.01
McCullough, 2002[84]	Quartile 1 >99.4 mL/min/72kgsubgroup data	Assay: cTnI Mfg: other Mfg: Biosite Incorporated Type: other Type: Triage Cardiac System Package	Adjudicated by: Panel of 2 cardiologists Definition: Thrombolysis in Myocardial Infarction Study Group	NR	AUC: 0.93 SD: 0.04	AUC: 0.93 SD: 0.04

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		Insert cut off normal: 0.4 mcg/L timing:9 hrs after onset 99th upper ref: NR				
McCullough, 2002[84]	Quartile 1 >99.4 mL/min/72kg subgroup data	Assay: cTnI Mfg: other Mfg: Biosite Incorporated type: other type: Triage Cardiac System Package Insert cut off normal: 0.4 mcg/L timing:9 hrs after onset 99th upper ref: NR	Adjudicated by: Panel of 2 cardiologists Definition: Thrombolysis in Myocardial Infarction Study Group	NR	AUC: 1 SD: 0	AUC: 1 SD: 0
McCullough, 2002[84]	Quartile 2: 99.3-72.7 mL/min/72kg subgroup data	Assay: cTnI Mfg: other Mfg: Biosite Incorporated type: other type: Triage Cardiac System Package Insert cut off normal: 0.4 mcg/L timing: 9 hrs after onset 99th upper ref: NR	Adjudicated by: Panel of 2 cardiologists Definition: Thrombolysis in Myocardial Infarction Study Group	NR	AUC: 0.94 SD: 0.02	AUC: 0.94 SD: 0.02
McCullough, 2002[84]	Quartile 3: 72.8-47.0mL/min/72kg subgroup data	Assay: cTnI Mfg: other Mfg: Biosite Incorporated type: other type: Triage Cardiac System Package Insert cut off normal: 0.4 mcg/L timing: 9 hrs after	Adjudicated by: Panel of 2 cardiologists Definition: Thrombolysis in Myocardial Infarction Study Group Study Group	NR	AUC: 0.97 SD: 0.01	AUC: 0.97 SD: 0.01

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		onset 99th upper ref: NR				
Noeller, 2003[91]	Age <65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1 mcg/L timing: 16 hrs after onset 99th upper ref: NR	NR	NR	NR	Sens: 45 Spec: 94 PPV: 77 NPV: 78
Noeller, 2003[91]	Age >=65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1 mcg/L timing: 16 hrs after onset 99th upper ref: NR	Definition: ICD-9 code	NR	NR	Sens: 44 Spec: 83 PPV: 62 NPV: 71
Noeller, 2003[91]	Creatinine <1.5 mg/dL, age <65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1 mcg/L timing: 16 hrs after onset 99th upper ref: NR	Definition: ICD-9 code	NR	NR	Sens: 45 Spec: 96 Negative LR: 83 PPV: 78
Noeller, 2003[91]	Creatinine <1.5 mg/dL, age >=65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1 mcg/L timing: 16 hrs after onset 99th upper ref: NR	Definition: ICD-9 code	NR	NR	Sens: 41 Spec: 89 PPV: 69 NPV: 71
Noeller, 2003[91]	Creatinine >=1.5 mg/dL, age <65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1	Definition: ICD-9 code	NR	NR	Sens: 43 Spec: 69 PPV: 38 NPV: 73

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		mcg/L timing: 16 hrs after onset 99th upper ref: NR				
Noeller, 2003[91]	Creatinine >=1.5 mg/dL, age >=65 subgroup data	Assay: cTnT Mfg: Roche type: CARDIAC-ELISA ES300 cut off normal: 0.1 mcg/L timing: 16 hrs after onset 99th upper ref: NR	Definition: ICD-9 code	NR	NR	Sens: 52 Spec: 66 PPV: 48 NPV: 69
Roppolo, 1999[102]	cTnI >0.5 ng/mL subgroup data	Assay: cTnI Mfg: Dade-Behring type: Opus cut off normal: 0.5 mcg/L timing: 1 week before admission 99th upper ref: NR	Definition: ECG changes, wall motion abnormality by multigated angiogram; echocardiography, angiography or autopsy	NR	NR	Sens: 50; 95% CI: 10 to 90 Spec: 100 PPV: 100 NPV: 93.5; 95% CI: 86.4 to 100
Roppolo, 1999[102]	cTnT >0.1 ng/mL subgroup data	Assay: cTnT Mfg: Dade-Behring type: Opus cut off normal: 0.1 mcg/L timing: 1 week before admission 99th upper ref: NR	Definition: ECG changes, wall motion abnormality by multigated angiogram; echocardiography, angiography or autopsy	NR	NR	Sens: 100 Spec: 55.8; 95% CI: 5.3 to 100 PPV: 24; 95% CI: 7.6 to 40.4 NPV: 100
Roppolo, 1999[102]	cTnT >0.2 ng/mL subgroup data	Assay: cTnT Mfg: Dade-Behring type: Opus cut off normal: 0.2 mcg/L timing: 1 week before admission 99th upper ref: NR	Definition: ECG changes, wall motion abnormality by multigated angiogram; echocardiography, angiography or autopsy	NR	NR	Sens: 83.3; 95% CI: 53.5 to 100 Spec: 90; 95% CI: 82 to 99.4 PPV: 55.6; 95% CI: 23.1 to 88.1 NPV: 97.5; 95% CI: 92.7 to 100
Sukonthasarn, 2007[113]	CrCl <15ml/min/1.73m^2 subgroup data	Assay: cTnT Mfg: Roche	Definition: European Society of Cardiology	NR	AUC: 0.645	Sens: 85.71 Spec: 48

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		type: Elecsys cut off normal: 0.1 mcg/L timing: 24 hours after admission 99th upper ref: NR				AUC: 0.645
Sukonthasarn, 2007[113]	CrCl <60ml/min/1.73m^2, except hemodialysis subgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L timing: 24 hours after admission 99th upper ref: NR	Definition: European Society of Cardiology	NR	AUC: 0.976	Sens: 91.3 Spec: 100 AUC: 0.976
Sukonthasarn, 2007[113]	CrCl <60ml/min/1.73m^2 subgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L timing: 24 horus after admission 99th upper ref: NR	Definition: European Society of Cardiology	NR	AUC: 0.94	Sens: 90.9 Spec: 84.5 AUC: 0.94
Sukonthasarn, 2007[113]	CrCl 15-29 ml/min/1.73m^2 subgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L timing: 24 hours after admission 99th upper ref: NR	Definition: European Society of Cardiology	NR	AUC: 0.987	Sens: 97.5 Spec: 92.9 AUC: 0.987
Sukonthasarn, 2007[113]	CrCl 15-59 ml/min/1.73m^2 subgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L timing: 24 hours after admission 99th upper ref: NR	Definition: European Society of Cardiology	NR	AUC: 0.983	Sens: 100 Spec: 96.6 AUC: 0.983
Sukonthasarn, 2007[113]	CrCl 30-59 ml/min/1.73m^2 subgroup data	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.1 mcg/L	Definition: European Society of Cardiology	NR	AUC: 0.987	Sens: 90 Spec: 96.8 AUC: 0.987

Author, Year	Data Group	Test	ACS Definition	Total Sample	AUC	Values
		timing: 24 hours after admission 99th upper ref: NR				
Sukonthasarn, 2007[113]	Group 2: Renal insufficiency on dialysis subgroup data	Assay: cTnI Mfg: other Mfg: Accu type: Access cut off normal: 0.1 ng/mLtiming: 8 hour intervals after admission 99th upper ref: NR	Definition: ICD-9 code	32	NR	TP: 19 FP: 1 FN: 5 TN: 7 Sens: 73%; 95% CI: 98 to 55 Spec: 83%; 95% CI: 120 to 70
Troyanov, 2005[116]	Total sample	Assay: cTnI Mfg: other Mfg: AxSYM type: other type: MEIA cut off normal: 0.3 mcg/L timing: NR 99th upper ref: 1 mcg/L	NR	101	NR	Spec: 99%
Troyanov, 2005[116]	Total sample	Assay: cTnT Mfg: Roche type: Elecsys cut off normal: 0.4 mcg/L timing: NR 99th upper ref: 0.1 mcg/L	Definition: ICD-9 code	101	NR	Sens: 84%

ACS=acute coronary syndrome; AUC=area under the curve; CI=confidence interval; CrCl=creatinine clearance; cTnI=cardiac troponin I; cTnT=cardian troponin T; ECG=electrocardiography; hrs=hours; ESC/ACC= European Society of Cardiology/American College of Cardiology; FN=false negative; FP=false positive; hs=high sensitivity; J.Am.Coll.Cardio=journal of american college of cardiology; ICD=international classification of diseases; kg=kilograms; LR=likelihood ratio; mcg/L=micrograms per liter; mg/dL=milligrams per liter; MI=myocardial infarction; ml/min=milliliters per minute; N=number; ng/mL=nanograms per liter; ng/L=nanograms per liter; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; ref=reference; SD=standard deviation; sens=sensitivity; spec=specificity; TN=true negative; TP=true positive

Table 4. Outcomes reported for Key Question 2, 3, and 4

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Abaci, 2004[1]	All-cause mortality	Years: 2	NR	NR	Pts with event: 25 / 25 persons Results: unadjusted	NR	NR
Abaci, 2004[1]	All-cause mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Abbott; other; Axsym	> 0.5 mcg/L	Pts with event: 10 / 25 persons Results: unadjusted	N: 31 log rank: 5.15 p value: 0.0232; ref group: other; ref group: All TnI	NR
Abaci, 2004[1]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 6 / 25 persons Results: unadjusted	N: 75	NR
Abaci, 2004[1]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 13 / 25 persons Results: unadjusted	N: 27 log rank: 23.85 p value: <0.0001; ref group: Other; ref group: All TnT	NR
Abaci, 2004[1]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	0.03-0.1 mcg/mL	Pts with event: 6 / 25 persons Results: unadjusted	NR	NR
Abaci, 2004[1]	Cardio mortality	Years: 2	NR	NR	Pts with event: 12 / 12 persons Results: unadjusted	NR	NR
Abaci, 2004[1]	Cardio mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Abbott; other; Axsym	> 0.5 mcg/L	Pts with event: 7 / 12 persons Results: unadjusted	NR	NR
Abaci, 2004[1]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 3 / 12 persons Results: unadjusted	NR	NR
Abaci, 2004[1]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 5 / 12 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Abaci, 2004[1]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	0.03-0.1 ug/mL	Pts with event: 4 / 12 persons Results: unadjusted	NR	NR
Abbas, 2005[2]	All-cause mortality	NR	Assay: cTnI Mfg: Bayer; other; ADVIA Centaur	< 0.07 mcg/L	Pts with event: 1 / 177 persons Results: adjusted	N: 177 OR: 1	NR
Abbas, 2005[2]	All-cause mortality	NR	Assay: cTnI Mfg: Bayer; other; ADVIA Centaur	> 0.07 mcg/L	Pts with event: 7 / 38 persons Results: adjusted	N: 38 OR: 2.439 95% CI: 0.771 to 6.977 p value: 0.0786; ref group: Grp3	NR
Abbas, 2005[2]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 0 / 127 persons Results: adjusted	N: 127 OR: 1	NR
Abbas, 2005[2]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Pts with event: 16 / 95 persons Results: adjusted	N: 95 OR: 3.471 95% CI: 1.274 to 10.394 p value: 0.0075; ref group: Grp1	NR
Acharji, 2012[3]	All-cause mortality	Days: 30	NR	Greater than upper limit of lab normal	% Pts with event: 11.9% / 1291 persons	N: 1291 RH: 2.05 95% CI: 1.48 to 2.83 p value: <0.0001; ref group: Grp2	NR
Acharji, 2012[3]	All-cause mortality	Days: 30	NR	Lower than upper limit of lab normal	% Pts with event: 5.6% / 888 persons	N: 888	NR
Acharji, 2012[3]	All-cause mortality	Years: 1	NR	Greater than upper limit of lab normal	% Pts with event: 20.9% / 1291 persons	N: 1291 RH: 1.72 95% CI: 1.36 to 2.17 p value: <0.0001; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Acharji, 2012[3]	All-cause mortality	Years: 1	NR	Lower than upper limit of lab normal	% Pts with event: 13.1% / 888 persons	N: 888 RH: 1	NR
Apple, 1997[5]	Cardio mortality	Years: 1	Assay: cTnI Mfg: NR; NR	< 0.8 mcg/L	Pts with event: 1 / 13 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Cardio mortality	Years: 1	Assay: cTnI Mfg: NR; NR	> 0.8 mcg/L	Pts with event: 3 / 3 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Cardio mortality	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	< 0.2 mcg/L	Pts with event: 0 / 4 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Cardio mortality	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	> 0.2 mcg/L	Pts with event: 4 / 12 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Other composite (unstable angina)	Years: 1	Assay: cTnI Mfg: NR	< 0.8 mcg/L	Pts with event: 2 / 13 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Other composite (unstable angina)	Years: 1	Assay: cTnI Mfg: NR	> 0.8 mcg/L	Pts with event: 0 / 3 persons Results: unadjusted	NR	NR
Apple, 1997[5]	Other composite (unstable angina)	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	< 0.2 mcg/L	Pts with event: 1 / 4 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Apple, 1997[5]	Other composite (unstable angina)	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	> 0.2 mcg/L	Pts with event: 1 / 12 persons Results: unadjusted	NR	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnI Mfg: Dade Behring; dimension	< 0.1 mcg/L	% Pts with event: 44% / 688 persons Results: adjusted	N: 688 RR: 1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnI Mfg: Dade Behring; dimension	> 0.1 mcg/L	% Pts with event: 60% / 45 persons Results: adjusted	N: 45 RR: 2.1 95% CI: 1.3 to 3.3 p value: 0.005; ref group: Grp1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	% Pts with event: 8.4% / 132 persons Results: adjusted	N: 132 RR: 1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.04 mcg/L	% Pts with event: 28% / 346 persons Results: adjusted	N: 346 RR: 1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 42% / 585 persons Results: adjusted	N: 585 RR: 1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	% Pts with event: 51% / 601 persons Results: adjusted	N: 601 RR: 4.3 95% CI: 2.1 to 8.7 p value: <0.001; ref group: Grp1	NR
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	% Pts with event: 57% / 387 persons Results: adjusted	N: 387 RR: 2.1 95% CI: 1.6 to 3 p value: <0.001; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Apple, 2002[7]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 56% / 148 persons Results: adjusted	N: 148 RR: 2.2 95% CI: 1.6 to 3 p value: <0.001; ref group: Grp1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Beckman; other; AccuTnI	< 0.04 mcg/L	% Pts with event: 26% / 323 persons Results: adjusted	N: 323 RR: 1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Beckman; other; AccuTnI	> 0.04 mcg/L	% Pts with event: 47% / 76 persons Results: adjusted	N: 76 RR: 1.8 95% CI: 1.1 to 2.7 p value: 0.01; ref group: Grp1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; dimension	< 0.1 mcg/L	% Pts with event: 28% / 379 persons Results: adjusted	N: 379 RR: 1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; dimension	> 0.1 mcg/L	% Pts with event: 61% / 20 persons Results: adjusted	N: 20 RR: 2.7 95% CI: 1.5 to 5 p value: 0.004; ref group: Grp1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	% Pts with event: 11% / 60 persons Results: adjusted	N: 60 RR: 1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	% Pts with event: 14% / 139 persons	N: 139 RR: 1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	% Pts with event: 33% / 339 persons Results: adjusted	N: 339 RR: 2.8 95% CI: 1.5 to 5 p value: 0.01; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L< 0.074 mcg/L	% Pts with event: 36% / 129 persons	N: 129 RR: 2.4 95% CI: 1.4 to 4.3 p value: <0.0001; ref group: Grp1	NR
Apple, 2004[8]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.074 mcg/L	% Pts with event: 41% / 131 persons	N: 131 RR: 3.2 95% CI: 1.9 to 5.6 p value: <0.0001; ref group: Grp1	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman	< 0.1 males/0.04 females mcg/L	No. of events: 9 / 46 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman	> 0.1males/ 0.04females mcg/L	No. of events: 8 / 18 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	< 0.06 mcg/L	No. of events: 8 / 46 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	> 0.06 mcg/L	No. of events: 10 / 25 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA	< .07 males/0.06 females mcg/L	No. of events: 3 / 22 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA	>.07males /0.06 females mcg/L	No. of events: 5 / 19 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	No. of events: 2 / 17 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	No. of events: 14 / 45 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman; access	<0.1males /0.04females mcg/L	No. of events: 5 / 61 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman; access	>0.1males /0.04females mcg/L	No. of events: 4 / 13 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	< 0.06 mcg/L	No. of events: 5 / 67 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	> 0.06 mcg/L	No. of events: 4 / 16 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA	<.07males /0.06 females mcg/L	No. of events: 2 / 41 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA	>.07males /0.06 females mcg/L	No. of events: 5 / 16 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; access	< 0.1 mcg/L	No. of events: 5 / 49 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; access	> 0.1 mcg/L	No. of events: 4 / 24 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman; access	< 0.1males/ 0.04females mcg/L	Pts with event: 11 / 252 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Beckman; access	> 0.1males/ 0.04females mcg/L	Pts with event: 0 / 26 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	< 0.06 mcg/L	Pts with event: 11 / 299 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; dimension	> 0.06 mcg/L	Pts with event: 0 / 31 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA200	< .07males/ 0.06females mcg/L	Pts with event: 9 / 181 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnI Mfg: other Mfg: Tosoh; other; AIA200	> 0.07males /0.06females mcg/L	Pts with event: 1 / 22 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 9 / 243 persons Results: unadjusted	NR	NR
Apple, 2007[9]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 2 / 37 persons Results: unadjusted	NR	NR
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	NR	NR	Results: unadjusted	NR	AUC: 0.665 Sens: 0.61 Spec: 0.7

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	NR	NR	Results: unadjusted	NR	AUC: 0.684 Sens: 0.91 Spec: 0.41
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnI Mfg: other Mfg: Siemens; other; ADIVA Centaur	<10 pg/mL	% Pts with event: 14.8% Results: unadjusted	RH: 1	AUC: 0.665 Sens: 0.61 Spec: 0.7
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnI Mfg: other Mfg: Siemens; other; ADIVA Centaur	>22 pg/mL	% Pts with event: 29.9% Results: unadjusted	RH: 2.87 to 6.51	AUC: 0.665 Sens: 0.61 Spec: 0.7
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnI Mfg: other Mfg: Siemens; other; ADIVA Centaur	10-22 pg/mL	% Pts with event: 15.5% Results: unadjusted	RH: 1.23 95% CI: 0.472 to 3	AUC: 0.665 Sens: 0.61 Spec: 0.7
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnT Mfg: Roche; Elecsys	<37 pg/mL	% Pts with event: 7% Results: unadjusted	RH: 1	AUC: 0.684 Sens: 0.91 Spec: 0.41
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnT Mfg: Roche; Elecsys	>68 pg/mL	% Pts with event: 29.1% Results: unadjusted	RH: 6.01 to 20.6 p value: <.001; ref group: Grp1	AUC: 0.684 Sens: 0.91 Spec: 0.41

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Artunc, 2012[10]	All-cause mortality	Days: 710 Followup NR	Assay: hs cTnT Mfg: Roche; Elecsys	38-67 pg/mL	% Pts with event: 23% Results: unadjusted	RH: 5.14 95% CI: 1.91 to 17.6 p value: <.01; ref group: Grp1	AUC: 0.684 Sens: 0.91 Spec: 0.41
Assa, 2013[11]	All cause mortality subgroup data : intra-HD change in cTnI levels		Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 0.9 95% CI: 0.75 to 1.08 p value: 0.25; ref group: cont. variable	NR
Assa, 2013[11]	All cause mortality subgroup data: postdialysis cTnI		Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 0.9 95% CI: 0.75 to 1.08 p value: 0.25; ref group: cont. variable	NR
Assa, 2013[11]	All cause mortality subgroup data: predialysis cTnI		Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 1 95% CI: 0.94 to 1.07 p value: 0.979; ref group: cont. variable	NR
Assa, 2013[11]	One plus MACE subgroup data: intra-HD change in cTnI levels		Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 1.21 95% CI: 1.06 to 1.38 p value: 0.005; ref group: cont. variable	NR
Assa, 2013[11]	One plus MACE subgroup data: post-dialysis cTnI	NR	Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 1.21 95% CI: 1.06 to 1.38 p value: 0.005; ref group: cont. variable	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Assa, 2013[11]	One plus MACE subgroup data: predialysis cTnI	NR	Assay: hs cTnI Mfg: ARCHITECT STAT; NR	per 10 ng/L	Results: adjusted	N: 90 RH: 1.05 95% CI: 0.97 to 1.14 p value: 0.192; ref group: cont. variable	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< ng/L< 0.03 mcg/L	Pts with event: 42 / 553 persons Results: adjusted	OR: 2.7 95% CI: 1.9 to 3.8 p value: <0.001; ref group: Grp3	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 70 / 783 persons Results: adjusted	OR: 2.5 95% CI: 1.8 to 3.3 p value: <0.001; ref group: Grp1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 214 / 1180 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 186 / 950 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 20 / 805 persons Results: adjusted	OR: 2.3 95% CI: 1.3 to 4.1 p value: 0.003; ref group: Grp1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 58 / 1117 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 8 / 618 persons Results: adjusted	OR: 4.8 95% CI: 2.3 to 10.4 p value: <0.001; ref group: Grp3	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 46 / 930 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 36 / 690 persons Results: adjusted	OR: 2.4 95% CI: 1.6 to 3.6 p value: <0.001; ref group: Grp3	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 60 / 917 persons Results: adjusted	OR: 1.8 95% CI: 1.3 to 2.6 p value: <0.001; ref group: Grp1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 115 / 1113 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 91 / 886 persons Results: adjusted	OR: 1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 22 / 660 persons Results: adjusted	OR: 2.6 95% CI: 1.6 to 4.4 p value: <0.001; ref group: Grp3	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 47% / 883 persons Results: adjusted	OR: 1.4 95% CI: 0.9 to 2.1 p value: 0.16; ref group: Grp1	NR
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 86 / 1102 persons Results: adjusted	OR: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Aviles, 2002[12]	MACE < 1 year	Days: 30	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 61 / 879 persons Results: adjusted	OR: 1	NR
Bagheri, 2009[13]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	<0.05 mg/L	% Pts with event: 24.2% / 46 persons Results: unadjusted	NR	NR
Bagheri, 2009[13]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	>0.05 mg/L	24% / 66 persons Results: unadjusted	NR	NR
Bagheri, 2009[13]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	>0.05 mg/L	% Pts with event: 6.9% / 20 persons Results: unadjusted	NR	NR
Beciani, 2003[15]	Cardio mortality/ Subs. MI/ revasc	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	>0.15 ng/ml	Pts with event: 9 % Pts with event: 64% / 14 persons	NR	NR
Beciani, 2003[15]	Cardio mortality/ Subs. MI/ revasc	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	<0.15 ng/ml	Pts with event: 7 % Pts with event: 9.7% / 72 persons	NR	NR
Beciani, 2003[15]	Cardio mortality/ Subs. MI/ revasc	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	</>0.15 ng/ml	Pts with event: 3 % Pts with event: 20% / 15 persons	NR	NR
Boulier, 2004[17]	All-cause mortality	Days: 418	Assay: cTnI Mfg: Beckman; access	< 0.03 mcg/L	Results: adjusted	RR: 1	NR
Boulier, 2004[17]	All-cause mortality	Days: 418	Assay: cTnI Mfg: Beckman; access	> 0.03 mcg/L	Results: adjusted	RR: 1.3 95% CI: 0.2 to 11.1; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Boulier, 2004[17]	All-cause mortality	Days: 418	Assay: cTnI Mfg: Beckman; access	< 0.03 mcg/L	Results: adjusted	N: without CHD RR: 1	NR
Boulier, 2004[17]	All-cause mortality	Days: 418	Assay: cTnI Mfg: Beckman; access	> 0.03 mcg/L	Results: adjusted	N: without CHD RR: 9.3 95% CI: 2.5 to 35; ref group: Grp1	NR
Boulier, 2004[17]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; access	< 0.03 mcg/L	Results: adjusted	N: 143 RR: 1 p value: 0.0009	NR
Boulier, 2004[17]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; access	> 0.03 mcg/L	Results: adjusted	N: 48 RR: 3.9 95% CI: 1.7 to 8.6 p value: 0.0009; ref group: Grp1	NR
Boulier, 2004[17]	Cardio mortality	NR	Assay: cTnI Mfg: Beckman; access	< 0.03 mcg/L	Results: adjusted	N: 143 RR: 1 p value: 0.009	NR
Boulier, 2004[17]	Cardio mortality	NR	Assay: cTnI Mfg: Beckman; access	> 0.03 mcg/L	Results: adjusted	N: 48 RR: 5.4 95% CI: 1.5 to 19 p value: 0.009; ref group: Grp1	NR
Bozbas, 2004[18]	All-cause mortality	Days: 30	Assay: cTnI Mfg: DPC; immulite	> 2.3 mcg/L	Pts with event: 0 / 34 persons	NR	NR
Bozbas, 2004[18]	Subs. MI	Days: 30	Assay: cTnI Mfg: DPC; immulite	> 2.3 mcg/L	Pts with event: 0 / 34 persons	NR NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Beckman; access	< 0.5 mcg/L	Pts with event: 41 % Pts with event: 40% / 103 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Beckman; access	> 0.5 mcg/L	Pts with event: 0 % Pts with event: 0% / 2 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	> 0.6 mcg/L	Pts with event: 1 % Pts with event: 33% / 3 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Dade Behring; Troponin I Stat	< 0.6 mcg/L	Pts with event: 40 % Pts with event: 39% / 102 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 24 % Pts with event: 31% / 77 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 17 % Pts with event: 61% / 28 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Beckman; access	< 0.06 mcg/L	Pts with event: 30 % Pts with event: 35% / 86 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Beckman; access	> 0.06 mcg/L	Pts with event: 11 % Pts with event: 58% / 19 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	< 0.14 mcg/L	Pts with event: 38 % Pts with event: 39% / 98 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	> 0.14 mcg/L	Pts with event: 3 % Pts with event: 43% / 7 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 11 % Pts with event: 27% / 41 persons	NR	NR
Brunet, 2008[19]	All-cause mortality	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 30 % Pts with event: 47% / 64 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Beckman; access	< 0.5 mcg/L	Pts with event: 14 % Pts with event: 14% / 103 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Beckman; access	> 0.5 mcg/L	Pts with event: 1 % Pts with event: 50% / 2 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 4 % Pts with event: 5% / 77 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 11 % Pts with event: 39% / 28 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	< 0.14 mcg/L	Pts with event: 13 % Pts with event: 13% / 98 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	< 0.6 mcg/L	Pts with event: 13 % Pts with event: 13% / 102 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	> 0.14 mcg/L	Pts with event: 2 % Pts with event: 29% / 7 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Dade Behring; dimension	> 0.6 mcg/L	Pts with event: 2 % Pts with event: 67% / 3 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 2 % Pts with event: 5% / 41 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 13 % Pts with event: 20% / 64 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Beckman; access	< 0.06 mcg/L	Pts with event: 10 % Pts with event: 12% / 86 persons	NR	NR
Brunet, 2008[19]	MACE ≥ 1 year	Years: 2.5	Assay: cTnI Mfg: Beckman; access	> 0.06 mcg/L	Pts with event: 5 % Pts with event: 26% / 19 persons	NR	NR
Bueti, 2006[20]	MACE < 1 year-revasc	NR	Assay: cTnI	< 0.1 ng/L	NR	NR	NR
Bueti, 2006[20]	MACE < 1 year-revasc	NR	Assay: cTnI	> 0.1 ng/L	NR	OR: 10.7 95% CI: 3.6 to 31; ref group: < 0.1 ng/L	NR
Bueti, 2006[20]	MACE < 1 year-revasc	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	< 0.1 ng/L	Results: unadjusted	LR: 0.32 95% CI: 0.16 to 0.63	NR
Bueti, 2006[20]	MACE < 1 year-revasc	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	> 0.1 ng/L < 0.3 ng/L	Results: unadjusted	LR: 0.7 95% CI: 0.09 to 5.5	NR
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	> 0.3 ng/L < 1 ng/L	Results: unadjusted	Likelihood ratio: 4.33 95% CI: 1.04 to 18	NR
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	> 1 ng/L < 2 ng/L	Results: unadjusted	Likelihood ratio: 5.77 95% CI: 0.85 to 39	NR
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	> 2 ng/L	Results: unadjusted	Likelihood ratio: 11.7 95% CI: 4.4 to 31	NR
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	NR	NR	Results: unadjusted	NR	NR
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	< 0.1 ng/L	Results: unadjusted	OR: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Bueti, 2006[20]	MACE < 1 year-Revascularization	Days: 30	Assay: cTnI Mfg: Bayer; other; Immuno 1	> 0.1 ng/L	Results: unadjusted	OR: 15.2 95% CI: 5.26 to 43.6 p value: 4e-007; ref group: Grp1	NR
Chew, 2008[21]	All-cause mortality	NR	Assay: cTnT Mfg: NR; NR	< 0.1 mcg/L	NR/ 106 persons Results: unadjusted	NR	NR
Chew, 2008[21]	All-cause mortality	NR	Assay: cTnT Mfg: NR; NR	> 0.1 mcg/L	NR/ 121 persons Results: unadjusted	NR	NR
Choy, 2003[22]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring	< 0.5 mcg/L	Pts with event: 11 / 96 persons	NR	NR
Choy, 2003[22]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring	> 0.5 mcg/L	Pts with event: 1 / 17 persons	NR	NR
Choy, 2003[22]	All-cause mortality	NR	Assay: cTnT Mfg: Roche	> 0.1 mcg/L	Pts with event: 10 / 48 persons	NR	NR
Choy, 2003[22]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	< 0.1 mcg/L	Pts with event: 3 / 65 persons	N: 48 OR: 13.6 95% CI: 2.5 to 73.2 p value: 0.002; ref group: Grp1	NR
Choy, 2003[22]	All-cause mortality	NR	Assay: NR Mfg: Roche; NR	NR	Pts with event: 13 / 113 persons	N: 65 OR: 1	NR
Choy, 2003[22]	Subs. MI	NR	Assay: cTnI Mfg: Dade Behring; NR	< 0.5 mcg/L	Pts with event: 0 / 96 persons	NR	NR
Choy, 2003[22]	Subs. MI	NR	Assay: cTnI Mfg: Dade Behring; NR	> 0.5 mcg/L	Pts with event: 1 / 17 persons	NR	NR
Choy, 2003[22]	Subs. MI	NR	Assay: cTnT Mfg: Roche; NR	> 0.1 mcg/L	Pts with event: 0 / 48 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Choy, 2003[22]	Subs. MI	NR	Assay: cTnT Mfg: Roche; NR	> 0.1 mcg/L	Pts with event: 0 / 65 persons	NR	NR
Chrysochou, 2009[23]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	<0.03 ng/mL	Results: unadjusted	N: 71 RH: 1	NR
Chrysochou, 2009[23]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	>0.03 ng/mL	Results: unadjusted	N: 11 RH: 3.9 95% CI: 1.8 to 8.5 p value: 0.001; ref group: Grp1	NR
Chrysochou, 2009[23]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	<0.03 ng/mL	Pts with event: 11 / 71 persons Results: unadjusted	NR	NR
Chrysochou, 2009[23]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	>0.03 ng/mL	No. of events: 4 / 11 persons Results: unadjusted	NR	NR
Claes, 2010[24]	MACE < 1 year	Weeks: 2	NR	NR	NR	NR	AUC: 0.85 Sens: 0.55 Spec: 0.98
Claes, 2010[24]	MACE < 1 year	Weeks: 2	Assay: cTnI Mfg: other Mfg: Siemens; Heterogenous Immunoassay	< 0.02 mcg/L	NR	NR	AUC: 0.85 Sens: 0.55 Spec: 0.98

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Claes, 2010[24]	MACE < 1 year	Weeks: 2	Assay: cTnI Mfg: other Mfg: Siemens; Heterogenous Immunoassay	> 0.02 mcg/L< 0.06 mcg/L	NR	NR	AUC: 0.85 Sens: 0.55 Spec: 0.98
Claes, 2010[24]	MACE < 1 year	Weeks: 2	Assay: cTnI Mfg: other Mfg: Siemens; Heterogenous Immunoassay	> 0.06 mcg/L< 0.13 mcg/L	NR	NR	AUC: 0.85 Sens: 0.55 Spec: 0.98
Claes, 2010[24]	MACE < 1 year	Weeks: 2	Assay: cTnI Mfg: other Mfg: Siemens; Heterogenous Immunoassay	> 0.13 mcg/L	NR	NR	AUC: 0.85 Sens: 0.55 Spec: 0.98
Codognotto, 2010[25]	All-cause mortality	Years: 3	Assay: cTnI Mfg: other Mfg: Siemans; lithium-heparin plasma	< 0.15 mcg/L	% Pts with event: 20.6% Results: adjusted	NR	NR
Codognotto, 2010[25]	All-cause mortality	Years: 3	Assay: cTnI Mfg: other Mfg: Siemans; lithium-heparin plasma	> 0.15 mcg/L	% Pts with event: 43.3% Results: adjusted	NR	NR
Codognotto, 2010[25]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	% Pts with event: 13.2% Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Codognotto, 2010[25]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; NR	> 0.01 mcg/L	% Pts with event: 40.2% Results: adjusted	NR	NR
Connolly, 2008[26]	All-cause mortality	Days: 1626	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 49 / 351 persons Results: adjusted	N: 351 Exponent Beta: 1	NR
Connolly, 2008[26]	All-cause mortality	Days: 1626	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 12 / 21 persons Results: adjusted	N: 21 Exponent Beta: 2.669 95% CI: 1.201 to 6.056 p value: <0.016; ref group: Grp1	NR
Connolly, 2008[26]	Cardio mortality	Days: 1626	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 17 / 351 persons Results: unadjusted	NR	NR
Connolly, 2008[26]	Cardio mortality	Days: 1626	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 7 / 21 persons Results: unadjusted	NR	NR
Conway, 2005[27]	MACE ≥ 1 year-MACE < 1 year-Other composite (unstable angina)		Assay: cTnT Mfg: Roche; other; ECLIA	> 0.03 mcg/L< 0.1 mcg/L	Pts with event: 9 / 22 persons Results: unadjusted	NR	NR
Conway, 2005[27]	MACE ≥ 1 year-MACE < 1 year-Other composite (unstable angina)		Assay: cTnT Mfg: Roche; other; ECLIA	< 0.03 mcg/L	Pts with event: 4 / 40 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Conway, 2005[27]	MACE ≥ 1 year-MACE < 1 year-Other composite (unstable angina)		Assay: cTnT Mfg: Roche; other; ECLIA	> 0.1 mcg/L	Pts with event: 7 / 13 persons Results: unadjusted	NR	NR
Deegan, 2001[28]	All-cause mortality		NR	NR	Results: unadjusted	NR	AUC: 0.857 95% CI: 0.755 to 0.928 Sens: 0.6 Spec: 0.85
Deegan, 2001[28]	All-cause mortality		Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	< 0.1 mcg/L	Pts with event: 7 % Pts with event: 15% / 53 persons Results: unadjusted	N: 53 Ref	AUC: 0.857 95% CI: 0.755 to 0.928 Sens: 0.6 Spec: 0.85
Deegan, 2001[28]	All-cause mortality		Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	> 0.1 mcg/L	Pts with event: 13 % Pts with event: 65% / 20 persons Results: unadjusted	N: 20 RH: 4.1; ref group: Grp1	AUC: 0.857 95% CI: 0.755 to 0.928 Sens: 0.6 Spec: 0.85
Deegan, 2001[28]	Cardio mortality		Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	< 0.1 mcg/L	Pts with event: 5 / 53 persons Results: unadjusted	NR	NR
Deegan, 2001[28]	Cardio mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	> 0.1 mcg/L	Pts with event: 7 / 20 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
deFilippi, 2003[29]	All-cause mortality	Days: 827	Assay: cTnT Mfg: Roche; Elecsys	< 0.029 mcg/L	Pts with event: 16 % Pts with event: 28% / 57 persons Results: adjusted	N: 57 HR: NR	NR
deFilippi, 2003[29]	All-cause mortality	Days: 827	Assay: cTnT Mfg: Roche; Elecsys	> 0.117 mcg/L	Pts with event: 36 % Pts with event: 65% / 55 persons Results: adjusted	N: 55 HR: 2.8 95% CI: 5 to 1.5 p value: 0.001; ref group: Grp1	NR
deFilippi, 2003[29]	All-cause mortality	Days: 827	Assay: cTnT Mfg: Roche; Elecsys	0.029-0.064 ng/mL	Pts with event: 30 % Pts with event: 54% / 56 persons Results: adjusted	N: 56 HR: 1.6 95% CI: 3 to 0.9 p value: 0.14; ref group: Grp1	NR
deFilippi, 2003[29]	All-cause mortality	Days: 827	Assay: cTnT Mfg: Roche; Elecsys	0.065-0.116 ng/mL	Pts with event: 34 % Pts with event: 62% / 55 persons Results: adjusted	N: 55 HR: 2.3 95% CI: 4.2 to 1.3 p value: 0.006; ref group: Grp1	NR
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnI Mfg: other Mfg: Siemens; other; Dimension Vista 1500	< 11.6 ng/L	NR	RH: 6.34 95% CI: 2.18 to 18.5; ref group: Grp1	NR
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnI Mfg: other Mfg: Siemens; other; Dimension Vista 1500	< 4 ng/L	NR	RH: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnI Mfg: other Mfg: Siemens; other; Dimension Vista 1500	> 4 ng/L < 11.6 ng/L	NR	RH: 2.07 95% CI: 0.62 to 6.88; ref group: Grp1	NR
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnI Mfg: Roche; Elecsys	> 13.2 ng/L< 24.3 mcg/L	NR	RH: 1.19 95% CI: 0.36 to 3.9; ref group: Grp1	NR
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnT Mfg: Roche; Elecsys	< 13.2 ng/L	NR	RH: 1	NR
deFilippi, 2012[30]	All-cause mortality	Years: 4.8	Assay: hscTnT Mfg: Roche; Elecsys	> 24.4 ng/L	NR	RH: 5.2 95% CI: 13.73 to 1.97; ref group: Grp1	NR
Dierkes, 2000[31]	All-cause mortality	Years: 2		< 0.04 mcg/L	Pts with event: 0 / 17 persons Results: adjusted	NR	NR
Dierkes, 2000[31]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; NR	> 0.04 mcg/L	Pts with event: 18 / 40 persons Results: adjusted	NR	NR
Dierkes, 2000[31]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; NR	> 0.1 mcg/L	Pts with event: 10 / 12 persons Results: adjusted	RH: 7.31 95% CI: 1.85 to 28.83	NR
Duman, 2005[32]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Diagnostic Product corp; immulite	> 0.06 mcg/L	No. of events: 3 / 4 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Duman, 2005[32]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	No. of events: 10 / 15 persons Results: adjusted	N: 36 OR: 1 SE: NR	NR
Duman, 2005[32]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.035 mcg/L	Pts with event: No. of events: 17 / 29 persons Results: adjusted	N: 29 OR: 4.31 SE: 0.67 95% CI: 1.16 to 16.04 p value: 0.02; ref group: Grp1	NR
Duman, 2005[32]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	No. of events: 16 / 23 persons Results: unadjusted	N: 36 OR: 1 SE: NR	NR
Duman, 2005[32]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.035 mcg/L	No. of events: 16 / 23 persons Results: unadjusted	N: 29 OR: 8.94 SE: 0.71 95% CI: 2.23 to 35.88 p value: 0.002; ref group: Grp1	NR
Farkouh, 2003[33]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; other; Stratus-II enzyme immunoassay	< 1 mcg/L	Pts with event: 15 / 127 persons Results: adjusted	N: 127 RH: 1	NR
Farkouh, 2003[33]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; other; Stratus-II enzyme immunoassay	> 1 mcg/L	Pts with event: 4 / 10 persons Results: adjusted	N: 10 RH: 9.6 95% CI: 2.8 to 33 p value: <0.01; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Feringa, 2006[35]	All-cause mortality	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 ng/L	Results: adjusted	RH: 1	NR
Feringa, 2006[35]	All-cause mortality	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 ng/L < 0.09 ng/L	Results: adjusted	RH: 4.27 95% CI: 1.75 to 10.4 p value: <0.001; ref group: Grp1	NR
Feringa, 2006[35]	All-cause mortality	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 ng/L	Results: adjusted	RH: 5.54 95% CI: 2.92 to 10.52 p value: <0.001; ref group: Grp1	NR
Feringa, 2006[35]	MACE ≥ 1 year-MACE < 1 year	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 ng/L	Results: adjusted	RH: 1	NR
Feringa, 2006[35]	MACE ≥ 1 year-MACE < 1 year	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 ng/L < 0.09 ng/L	Results: adjusted	RH: 8.09 95% CI: 2.72 to 24.05 p value: <0.001; ref group: Grp1	NR
Feringa, 2006[35]	MACE ≥ 1 year-MACE < 1 year	Years: 4	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 ng/L	Results: adjusted	RH: 7.05 95% CI: 3.44 to 14.47 p value: <0.001; ref group: Grp1	NR
Fernandez-Reyes, 2004[36]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Results: unadjusted	N: 53 RR: 1.07 Cox hazard model: 95% CI: 1.03 to 1.12 p value: 0.01	NR
Fernandez-Reyes, 2004[36]	Other composite (heart failure)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	<0.04 ng/mL	Pts with event: 2 / 23 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Fernandez-Reyes, 2004[36]	Other composite (heart failure)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	>0.04 ng/mL	Pts with event: 1 / 12 persons	NR	NR
Fernandez-Reyes, 2004[36]	Other composite (heart failure)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	0.04-0.1 ng/mL	Pts with event: 1 / 11 persons	NR	NR
Fernandez-Reyes, 2004[36]	Other composite (ischemic heart disease)	Years: 2.5	NR	NR	Pts with event: 5 / 16 persons	NR	NR
Fernandez-Reyes, 2004[36]	Other composite (ischemic heart disease)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	<0.04 ng/mL	Pts with event: 0 / 23 persons	NR	NR
Fernandez-Reyes, 2004[36]	Other composite (ischemic heart disease)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	>0.04 ng/mL	Pts with event: 3 / 12 persons	NR	NR
Fernandez-Reyes, 2004[36]	Other composite (ischemic heart disease)	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	0.04-0.1 ng/mL	Pts with event: 1 / 11 persons	NR	NR
Flores, 2006[37]	Subs. MI	Followup NR	Assay: cTnI Mfg: Beckman; access	<0.05 ng/mL	Pts with event: 0 / 47 persons Results: unadjusted	NR	NR
Flores, 2006[37]	Subs. MI	Followup NR	Assay: cTnI Mfg: Beckman; access	> 0.05 ng/mL	Pts with event: 14 / 47 persons Results: unadjusted	NR	NR
Flores, 2006[37]	Subs. MI	Followup NR	Assay: cTnI Mfg: Beckman; access	>0.5 ng/mL	Pts with event: 33 / 47 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Gaiki, 2012[39]	All-cause mortality	Years: 2	Assay: hscTnI Mfg: other Mfg: Ortho clinical diagnostics; Vitro ES	<0.035 ng/mL	No. of events: 6 / 25 persons Results: unadjusted	NR	NR
Gaiki, 2012[39]	All-cause mortality	Years: 2	Assay: hscTnI Mfg: other Mfg: Ortho clinical diagnostics; Vitro ES	>0.035 ng/mL	No. of events: 8 / 25 persons Results: unadjusted	NR	NR
Gaiki, 2012[39]	Other composite (composite of ACS, revasc, cardiac arrest, sudden death)	Years: 2	Assay: hscTnI Mfg: other Mfg: Ortho clinical diagnostics; Vitro ES	<0.035	No. of events: 0 / 25 persons Results: unadjusted	NR	NR
Gaiki, 2012[39]	Other composite (Composite of ACS, revasc, cardiac arrest, sudden death)	Years: 2	Assay: hscTnI Mfg: other Mfg: Ortho clinical diagnostics; Vitro ES	>0.035 ng/mL	No. of events: 6 / 25 persons Results: unadjusted	NR	NR
Geerse, 2012[40]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Siemens medical solutions diagnostics; other; Advia Centaur	< 0.01 mcg/L	% Pts with event: 10.1% / 59 persons Results: adjusted	N: 59 RH: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Geerse, 2012[40]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Siemens medicals solutions diagnostics; other; Advia Centaur	> 0.01 mcg/L< 0.05 mcg/L	% Pts with event: 36.6% / 94 persons Results: adjusted	N: 94 RH: 2.55 95% CI: 1.05 to 6.21 p value: 0.039; ref group: Grp1	NR
Geerse, 2012[40]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Siemens medical solutions diagnostics; other; Advia Centaur	> 0.05 mcg/L< 0.1 mcg/L	% Pts with event: 50.4% / 28 persons Results: adjusted	N: 28 RH: 3.57 95% CI: 1.31 to 9.71 p value: 0.013; ref group: Grp1	NR
Geerse, 2012[40]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Siemens medical solutions diagnostics; other; Advia Centaur	> 0.1 mcg/L	% Pts with event: 72.3% / 25 persons Results: adjusted	N: 25 RH: 6.35 95% CI: 2.43 to 16.49 p value: <0.001; ref group: Grp1	NR
Geerse, 2012[40]	Cardio mortality	NR	NR	< 0.01 mcg/L	% Pts with event: 5.05% / 59 persons	NR	NR
Geerse, 2012[40]	Cardio mortality	NR	NR	> 0.01 mcg/L< 0.05 mcg/L	% Pts with event: 21.2% / 94 persons	NR	NR
Geerse, 2012[40]	Cardio mortality	NR	NR	> 0.05 mcg/L< 0.1 mcg/L	% Pts with event: 32.3% / 28 persons	NR	NR
Geerse, 2012[40]	Cardio mortality	NR	NR	> 0.1 mcg/L	% Pts with event: 56.2% / 25 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Goicoechea, 2004[41]	MACE ≥ 1 year-MACE < 1 year-Revascularization	NR	NR		Results: unadjusted	NR	NR
Goicoechea, 2004[41]	MACE ≥ 1 year-MACE < 1 year-revasc	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 ng/L	Results: unadjusted	N: 156 RH: 1 p value: 0	NR
Goicoechea, 2004[41]	MACE ≥ 1 year-MACE < 1 year-revasc	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 ng/L	Results: unadjusted	N: 20 RH: 12.34 95% CI: 4.91 to 31.02 p value: 0; ref group: Grp1	NR
Gruberg, 2002[42]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent immunoenzymatic assay	< 0.15 mcg/L	% Pts with event: 9.9% / 66 persons Results: adjusted	OR: NR	NR
Gruberg, 2002[42]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent immunoenzymatic assay	> 0.15 mcg/L	% Pts with event: 28% / 50 persons Results: adjusted	OR: 2.26 95% CI: 1.07 to 4.77 p value: 0.03; ref group: Grp1	NR
Gruberg, 2002[42]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent Immunoenzymatic Assay	< 0.15 mcg/L	% Pts with event: 30.1% / 66 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Gruberg, 2002[42]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent immunoenzymatic assay	> 0.15 mcg/L	% Pts with event: 40.3% / 50 persons	NR	NR
Gruberg, 2002[42]	Revascularization	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent Immunoenzymatic Assay	< 0.15 mcg/L	% Pts with event: 20% / 66 persons	NR	NR
Gruberg, 2002[42]	Revascularization	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent Immunoenzymatic Assay	> 0.15 mcg/L	% Pts with event: 19% / 50 persons	NR	NR
Gruberg, 2002[42]	Subs. MI	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent Immunoenzymatic Assay	< 0.15 mcg/L	% Pts with event: 13.8% / 66 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Gruberg, 2002[42]	Subs. MI	NR	Assay: cTnI Mfg: Beckman; other; Chemiluscent Immunoenzymatic Assay	> 0.15 mcg/L	% Pts with event: 25% / 50 persons	NR	NR
Hallen, 2011[44]	All-cause mortality	Days: 926	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Pts with event: 43 / 64 persons Results: adjusted	N: 64 RH: 3.2 95% CI: 1.2 to 8.5 p value: <0.017; ref group: Grp1	NR
Hallen, 2011[44]	All-cause mortality	Days: 926	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Pts with event: 7 / 43 persons Results: adjusted	N: 43 RH: 1	NR
Han, 2005[45]	Other composite (ACE)	NR	NR	NR	Results: unadjusted	NR	AUC: 0.6 95% CI: 0.45 to 0.74 Sens: 27 Spec: 96
Han, 2005[45]	Other composite (ACE)	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Results: unadjusted	NR	AUC: 0.6 95% CI: 0.45 to 0.74 Sens: 27 Spec: 96
Han, 2009[46]	Other composite (cardiac events)	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 4 / 86 persons Results: adjusted	N: 86 RH: 1	NR
Han, 2009[46]	Other composite (cardiac events)	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 9 / 21 persons Results: adjusted	N: 21 RH: 5.89 95% CI: 1.24 to 28 p value: <0.05; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hasegawa, 2012[47]	Other composite (cardiac events)	NR	Assay: hscTnT Mfg: Roche; NR	<9 pg/mL	% Pts with event: 0.88% / 113 persons Results: adjusted	N: 113 RH: 1	NR
Hasegawa, 2012[47]	Other composite (cardiac events)	NR	Assay: hscTnT Mfg: Roche; NR	>33 pg/mL	% Pts with event: 41.4% / 108 persons Results: adjusted	N: 108 RH: 6.18 95% CI: 1.38 to 27.69; ref group: Grp1	NR
Hasegawa, 2012[47]	Other composite (cardiac events)	NR	Assay: hscTnT Mfg: Roche; NR	10-18 pg/mL	% Pts with event: 11.5% / 111 persons Results: adjusted	N: 111 RH: 2.54 95% CI: 0.54 to 11.93; ref group: Grp1	NR
Hasegawa, 2012[47]	Other composite (cardiac events)	NR	Assay: hscTnT Mfg: Roche; NR	19-32 pg/mL	% Pts with event: 19% / 110 persons Results: adjusted	N: 110 RH: 3 95% CI: 0.66 to 13.7; ref group: Grp1	NR
Havekes, 2006[48]	All-cause mortality	Followup NR	Assay: cTnT Mfg: Roche; NR	> 0.05 mcg/L< 0.1 mcg/L	Results: adjusted	N: 188 RH: 1.2 95% CI: 0.9 to 1.7; ref group: Grp1	NR
Havekes, 2006[48]	All-cause mortality	Followup NR	Assay: cTnT Mfg: Roche; NR	> 0.1 mcg/L	Results: adjusted	N: 93 RH: 2.2 95% CI: 1.5 to 3.3; ref group: Grp1	NR
Havekes, 2006[48]	All-cause mortality	Followup NR	Assay: cTnT Mfg: Roche; other; 3rd generation immunochemical test	< 0.04 mcg/L	Results: adjusted	N: 566 RH: 1	NR
Havekes, 2006[48]	Cardio mortality	Followup NR	Assay: cTnT Mfg: Roche; NR	< 0.04 mcg/L	Results: adjusted	N: 566 RH: 1	NR
Havekes, 2006[48]	Cardio mortality	Followup NR	Assay: cTnT Mfg: Roche; NR	> 0.04 mcg/L< 0.1 mcg/L	Results: adjusted	N: 188 RH: 1 95% CI: 0.6 to 1.7; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Havekes, 2006[48]	Cardio mortality	Followup NR	Assay: cTnT Mfg: Roche; NR	> 0.1 mcg/L	Results: adjusted	N: 93 RH: 1.9 95% CI: 0.9 to 3.7; ref group: Grp1	NR
Heeschen, 2000[49]	MACE < 1 year-revasc	Days: 30	Assay: cTnI Mfg: other Mfg: Abbott; other; AxSYM	< 1 mcg/L	Pts with event: 0 / 24 persons Results: unadjusted	NR	NR
Heeschen, 2000[49]	MACE < 1 year-revasc	Days: 30	Assay: cTnI Mfg: other Mfg: Abbott; other; AxSYM	> 1 mcg/L	Pts with event: 0 / 2 persons Results: unadjusted	NR	NR
Heeschen, 2000[49]	MACE < 1 year-revasc	Days: 30	Assay: cTnT Mfg: other Mfg: Boehringer; Elecsys	< 0.06 mcg/L	Pts with event: 0 / 12 persons Results: unadjusted	NR	NR
Heeschen, 2000[49]	MACE < 1 year-revasc	Days: 30	Assay: NR Mfg: other Mfg: Boehringer; Elecsys	> 0.06 mcg/L	Pts with event: 0 / 14 persons Results: unadjusted	NR	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: Beckman; access	< 0.06 mcg/L	Pts with event: 28 / 97 persons Results: adjusted	RR: 1	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: Beckman; access	> 0.06 mcg/L	Pts with event: 6 / 12 persons Results: adjusted	RR: 1.9 95% CI: 0.6 to 6.4; ref group: Grp3	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: Dade Behring; dimension	< 0.14 mcg/L	Pts with event: 30 / 101 persons Results: adjusted	RR: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: Dade Behring; dimension	> 0.14 mcg/L	Pts with event: 4 / 8 persons Results: adjusted	RR: 2 95% CI: 0.7 to 5.8 p value: ns; ref group: Grp3	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: other Mfg: TOSOH; AIA-600II	< 0.1 mcg/L	Pts with event: 32 / 107 persons Results: adjusted	RR: 1	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnI Mfg: other Mfg: TOSOH; AIA-600II	> 0.1 mcg/L	Pts with event: 2 / 2 persons Results: adjusted	RR: 2.8 95% CI: 0.6 to 13.4 p value: ns; ref group: Grp1	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 5 / 52 persons Results: adjusted	RR: 1	NR
Helleskov Madsen, 2008[50]	All-cause mortality	Days: 970	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 29 / 57 persons Results: adjusted	RR: 7.7 95% CI: 2.7 to 21.9; ref group: Grp1	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200		Results: unadjusted	OR: ref	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	< 0.01 mcg/L	Pts with event: 1 / 34 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	< 0.043 mcg/L	Results: unadjusted	N: 104 OR: ref	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	> 0.011 mcg/L< 0.02 mcg/L	Pts with event: 3 / 35 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	> 0.021 mcg/L< 0.043 mcg/L	Pts with event: 10 / 35 persons Results: unadjusted	NR	NR NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	> 0.043 mcg/L	Results: unadjusted	N: 34 OR: 4.5 95% CI: 1.86 to 10.91 p value: <0.001; ref group: Grp2	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	> 0.043 mcg/L	Pts with event: 14 / 34 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; Architect ci8200	detectable	Results: unadjusted	OR: 6.37 95% CI: 0.82 to 49.58 p value: 0.087; ref group: Grp2	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 1 / 35 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.098 mcg/L	Results: unadjusted	N: 107 OR: ref	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.011 mcg/L< 0.042 mcg/L	Pts with event: 6 / 36 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.043 mcg/L< 0.097 mcg/L	Pts with event: 7 / 36 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.098 mcg/L	Results: unadjusted	N: 36 OR: 4.23 95% CI: 1.76 to 10.14 p value: 0.001; ref group: Grp2	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.098 mcg/L	Pts with event: 14 / 36 persons Results: unadjusted	NR	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	detectable	Results: unadjusted	OR: 11.33 95% CI: 1.48 to 86.79 p value: 0.004; ref group: Grp2	NR
Hickman, 2009[51]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	not detectable	Results: unadjusted	OR: ref	NR
Hickson, 2008[52]	All-cause mortality	NR	NR		Results: unadjusted	NR	Sens: 70% Spec: 69%
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	< 0.03 mcg/L	% Pts with event: 2% / 437 persons Results: unadjusted	NR	Sens: 70% Spec: 69%
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	> 0.03 mcg/L	% Pts with event: 12% / 207 persons Results: unadjusted	NR	Sens: 70% Spec: 69%

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	Results: adjusted	RH: ref	NR
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	% Pts with event: 2% / 253 persons Results: unadjusted	N: 253 RH: ref	NR
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	>=0.01 mcg/L	% Pts with event: 15% / 81 persons Results: unadjusted	N: 81 RH: 4.085 95% CI: 11.74 to 1.42 p value: 0.009; ref group: Grp1	NR
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	> 0.01 mcg/L< 0.03 mcg/L	% Pts with event: 3% / 184 persons Results: unadjusted	N: 184 p value: NS; ref group: Grp1	NR
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	> 0.04 mcg/L< 0.09 mcg/L	% Pts with event: 10% / 126 persons Results: unadjusted	N: 126 RH: 3.011 95% CI: 8.61 to 1.05 p value: 0.04; ref group: Grp1	NR
Hickson, 2008[52]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; NR	cTnT were analyzed as after grouping values at four levels: <0.01, 0.01-0.03, 0.04-0.09, >=0.01 ng/mL	Results: adjusted	RH: 1.642 95% CI: 1.07 to 2.51 p value: 0.022; ref group: Grp1	NR
Hickson, 2009[53]	MACE ≥ 1 year		Assay: cTnT Mfg: Roche; NR	analyzed as groups: 0.01-0.03, 0.04-0.09, >=0.1 ng/mL	Results: adjusted	RH: 1.584 95% CI: 1.125 to 2.225 p value: 0.008; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hickson, 2009[53]	MACE ≥ 1 year		Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	Results: adjusted	RH: ref	NR
Hickson, 2009[53]	MACE ≥ 1 year		Assay: cTnT Mfg: Roche; NR	analyzed as groups: 0.01-0.03, 0.04-0.09; >=0.1 ng/mL	Results: unadjusted	RH: 1.693 95% CI: 1.693 to 2.473 p value: 0.006; ref group: Grp1	NR
Hickson, 2009[53]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	Results: unadjusted	RH: ref	NR
Hickson, 2009[53]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; NR	>=0.1 mcg/L	Results: unadjusted	N: 64 RH: 6.126 95% CI: 2.124 to 17.665 p value: 0.001; ref group: Grp1	NR
Hickson, 2009[53]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; NR	> 0.04 mcg/L< 0.1 mcg/L	Results: unadjusted	N: 115 RH: 4.478 95% CI: 1.656 to 12.109 p value: 0.003; ref group: Grp1	NR
Hickson, 2009[53]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; NR	> 0.01 mcg/L< 0.03 mcg/L	Results: unadjusted	N: 160 RH: 2.52 95% CI: 0.897 to 7.079 p value: 0.08; ref group: Grp1	NR
Hickson, 2009[53]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; NR	< 0.01 mcg/L	Results: unadjusted	N: 264 RH: ref	NR
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 84 RR: 1 ; ref group: other; ref group: all diabetic Pts	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 43 RR: 1.464 95% CI: 0.667 to 3.216 p value: 0.342; ref group: Grp1	NR
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 161 RR: 1; ref group: other; ref group: all non-diabetic Pts	NR
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 30 RR: 3.998 95% CI: 1.583 to 10.098 p value: 0.003; ref group: Grp1	NR
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 245 RR: 1; ref group: other; ref group: total sample	NR
Hocher, 2003[54]	All-cause mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 73 RR: 2.75 95% CI: 1.538 to 4.916 p value: 0.001; ref group: Grp1	NR
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 84 RR: 1	NR
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 28 RR: 1.195 95% CI: 0.45 to 3.173 p value: 0.72; ref group: Grp1	NR
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 161 RR: 1; ref group: other; ref group: all non-diabetic Pts	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 13 RR: 5.378 95% CI: 1.108 to 26.1 p value: 0.037; ref group: Grp1	NR
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	< 0.054 mcg/L	NR	N: 245 RR: 1; ref group: other; ref group: total sample	NR
Hocher, 2003[54]	Cardio mortality	Days: 775	Assay: cTnT Mfg: Roche; Elecsys	> 0.054 mcg/L	NR	N: 41 RR: 2.478 95% CI: 1.129 to 5.436 p value: 0.024; ref group: Grp1	NR
Hocher, 2004[55]	All-cause mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	Results: unadjusted	RR: 1	NR
Hocher, 2004[55]	All-cause mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	Results: unadjusted	RR: 9.06 95% CI: 2.62 to 31.35 p value: 0.001; ref group: Grp1	NR
Hocher, 2004[55]	All-cause mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	Results: unadjusted	RR: 1	NR
Hocher, 2004[55]	All-cause mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	Results: unadjusted	RR: 3.22 95% CI: 1.6 to 6.49 p value: 0.001; ref group: Grp1	NR
Hocher, 2004[55]	Cardio mortality	Days: 1140	NR	NR	Results: unadjusted	RR: 17.17 95% CI: 2.13 to 138.29 p value: 0.008; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hocher, 2004[55]	Cardio mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	Results: unadjusted	N: 123 RR: 1; ref group: other; ref group: total sample	NR
Hocher, 2004[55]	Cardio mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	Results: unadjusted	RR: 1; ref group: Grp1	NR
Hocher, 2004[55]	Cardio mortality	Days: 1140	NR	NR	NR	RR: 4.2 95% CI: 1.6 to 11.07 p value: 0.004; ref group: Grp1	NR
Hocher, 2004[55]	Cardio mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	NR	N: 122 ref group: other; ref group: total sample	NR
Hocher, 2004[55]	Cardio mortality	Days: 1140	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	NR	RR: 1 ref group: Grp1	NR
Hocher, 2008[56]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.053 mcg/L	Results: adjusted	RR: 1 p value: 0.048	NR
Hocher, 2008[56]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.053 mcg/L	Results: adjusted	RR: 2.01 95% CI: 1.01 to 4.01 p value: 0.048; ref group: Grp1	NR
Hocher, 2008[56]	All-cause mortality	Weeks: 52	Assay: cTnT Mfg: Roche; Elecsys	< 0.034 mcg/L	Results: adjusted	RR: 1 p value: <0.001	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hocher, 2008[56]	All-cause mortality	Weeks: 52	Assay: cTnT Mfg: Roche; Elecsys	> 0.034 mcg/L	Results: adjusted	RR: 3.54 95% CI: 1.92 to 6.54 p value: <0.001; ref group: Grp1	NR
Hocher, 2008[56]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	Results: adjusted	RR: 1 p value: <0.001	NR
Hocher, 2008[56]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	Results: adjusted	RR: 2.66 95% CI: 1.69 to 4.18 p value: <0.001; ref group: Grp1	NR
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.053 mcg/L	Results: adjusted	RR: 1 p value: 0.23	NR
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.053 mcg/L	Results: adjusted	RR: 1.69 95% CI: 0.72 to 3.96 p value: 0.23; ref group: Grp1	NR
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.034 mcg/L	Results: adjusted	RR: 1 p value: 0.004	NR
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.034 mcg/L	Results: adjusted	RR: 5.16 95% CI: 1.67 to 15.88 p value: 0.004; ref group: Grp1	NR
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.039 mcg/L	Results: adjusted	RR: 1 p value: 0.001	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hocher, 2008[56]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.039 mcg/L	Results: adjusted	RR: 2.99 95% CI: 1.53 to 5.86 p value: 0.001; ref group: Grp1	NR
Hojs, 2005[57]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.05 mcg/L	Pts with event: 3 / 51 persons Results: unadjusted	NR	NR
Hojs, 2005[57]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 5 / 66 persons Results: unadjusted	NR	NR
Hojs, 2005[57]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.05 mcg/L	Pts with event: 11 / 39 persons Results: unadjusted	NR	NR
Hojs, 2005[57]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 9 / 24 persons Results: unadjusted	NR	NR
Holden, 2012[58]	All-cause mortality	Years: 3.5	Assay: cTnT Mfg: Roche; E170 Analyzer - immunoassay		Results: adjusted	RH: 0.76 95% CI: 0.24 to 2.4 p value: 0.2; ref group: Grp1	NR
Holden, 2012[58]	All-cause mortality	Years: 3.5	Assay: cTnT Mfg: Roche; E170 Analyzer - immunoassay		Results: adjusted	RH: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Hung, 2004[59]	MACE < 1 year	NR	Assay: cTnI Mfg: DPC; immulite	< 0.2 ng/L	Results: adjusted	OR: 1 p value: 0.012	NR
Hung, 2004[59]	MACE < 1 year	NR	Assay: cTnI Mfg: DPC; immulite	> 0.2 ng/L	Results: adjusted	OR: 15 95% CI: 1.8 to 125.5 p value: 0.012; ref group: Grp1	NR
Hung, 2004[59]	MACE < 1 year	NR	Assay: cTnI Mfg: DPC; immulite	< 0.2 ng/L	Results: unadjusted	OR: 1 p value: 0.019	NR
Hung, 2004[59]	MACE < 1 year	NR	Assay: cTnI Mfg: DPC; immulite	> 0.2 ng/L	Results: unadjusted	OR: 8 95% CI: 1.4 to 45.5 p value: 0.019; ref group: Grp1	NR
Hussein, 2004[60]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; NR	< 0 ng/L	Pts with event: 8 / 84 persons Results: unadjusted	NR	NR
Hussein, 2004[60]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; NR	> 0 ng/L	Pts with event: 4 / 9 persons Results: unadjusted	NR	NR
Ie, 2004[61]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 ng/L	Pts with event: 0 % Pts with event: 0% / 9 persons	NR	NR
Ie, 2004[61]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 16 / 40 persons	NR	NR
Ie, 2004[61]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 5 No. of events: 7 / 30 persons	NR	NR
Ie, 2004[61]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 ng/L	Pts with event: 0 No. of events: 0 / 19 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Iliou, 2003[63]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 41 % Pts with event: 20.6% / 199 persons Results: adjusted	N: 199 RR: 1	NR
Iliou, 2003[63]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.15 mcg/L	Pts with event: 49 % Pts with event: 24.5% / 200 persons Results: adjusted	NR	NR
Iliou, 2003[63]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 23 % Pts with event: 23.4% / 47 persons Results: adjusted	N: 47 RR: 1.83 95% CI: 1.1 to 3.1 p value: 0.03; ref group: Grp1	NR
Iliou, 2003[63]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.15 mcg/L	Pts with event: 15 % Pts with event: 32.6% / 46 persons Results: adjusted	NR	NR
Iliou, 2003[63]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 8 % Pts with event: 3.8% / 210 persons Results: adjusted	N: 199 RR: 1	NR
Iliou, 2003[63]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.15 mcg/L	Pts with event: 15 % Pts with event: 7.1% / 212 persons Results: adjusted	NR	NR
Iliou, 2003[63]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 9 % Pts with event: 18.7% / 48 persons Results: adjusted	N: 47 RR: 2.9 95% CI: 1.05 to 7.9 p value: 0.04; ref group: Grp1	NR
Iliou, 2003[63]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.15 mcg/L	Pts with event: 2 % Pts with event: 4.3% / 46 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Iliou, 2003[63]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 34 % Pts with event: 17.1% / 199 persons Results: adjusted	N: 199 RR: 1	NR
Iliou, 2003[63]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.15 mcg/L	Pts with event: 42 % Pts with event: 21% / 200 persons Results: adjusted	NR	NR
Iliou, 2003[63]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 15 % Pts with event: 31.9% / 47 persons Results: adjusted	N: 47 RR: 1.9 95% CI: 1.02 to 3.4 p value: 0.04; ref group: Grp1	NR
Iliou, 2003[63]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.15 mcg/L	Pts with event: 7 % Pts with event: 15.2% / 46 persons Results: adjusted	NR	NR
Ilva, 2008[64]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; other; Architect STAT	< 0.032 mcg/L	/ 67 persons Results: unadjusted	N: 67 RR:	NR
Ilva, 2008[64]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; other; Architect STAT	> 0.032 mcg/L	/ 96 persons Results: unadjusted	N: 96 (59% - cTnI) RR: 1.4 95% CI: 0.7 to 2.8 p value: NS; ref group: Grp3	NR
Ilva, 2008[64]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	/ 90 persons Results: unadjusted	N: 90 RR: NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Ilva, 2008[64]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	/ 73 persons Results: unadjusted	N: 73 (45% - cTnT) RR: 1.3 95% CI: 0.7 to 2.5 p value: NS; ref group: Grp1	NR
Ishii, 2001[65]	All-cause mortality	Years: 2	NR	NR	NR	NR	AUC: 0.517 95% CI: 0.36 to 0.674 Sens: 17.60% Spec: 96.30%
Ishii, 2001[65]	All-cause mortality	Years: 2	NR	NR	NR	NR	AUC: 0.517 95% CI: 0.36 to 0.674 Sens: 17.60% Spec: 96.30%
Ishii, 2001[65]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Beckman; access	< 0.1 mcg/L	Pts with event: 16 % Pts with event: 17% / 94 persons	NR	AUC: 0.517 95% CI: 0.36 to 0.674 Sens: 17.60% Spec: 96.30%
Ishii, 2001[65]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Beckman; access	> 0.1 mcg/L	Pts with event: 3 % Pts with event: 50% / 6 persons	NR	AUC: 0.517 95% CI: 0.36 to 0.674 Sens: 17.60% Spec: 96.30%
Ishii, 2001[65]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 7 % Pts with event: 9% / 75 persons Results: adjusted	N: 75 RH: ref	AUC: 0.857 95% CI: 0.773 to 0.941 Sens: 62.30% Spec: 86.70%
Ishii, 2001[65]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 12 % Pts with event: 48% / 25 persons Results: adjusted	N: 25 RH: 3.71 95% CI: 2.66 to 4.77 p value: <0.05; ref group: Grp1	AUC: 0.857 95% CI: 0.773 to 0.941 Sens: 62.30% Spec: 86.70%

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Ishii, 2001[65]	Cardio mortality	Years: 2	NR	NR	Results: adjusted	NR	AUC: 0.861 95% CI: 0.749 to 0.972 Sens: 69.50% Spec: 82.50%
Ishii, 2001[65]	Cardio mortality	Years: 2	Assay: Access	NR	Results: adjusted	NR	AUC: 0.861 95% CI: 0.749 to 0.972 Sens: 69.50% Spec: 82.50%
Ishii, 2001[65]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; other; ECLusys	< 0.1 mcg/L	Pts with event: 3 % Pts with event: 4% / 75 persons Results: adjusted	N: 75 RH: ref	AUC: 0.861 95% CI: 0.749 to 0.972 Sens: 69.50% Spec: 82.50%
Ishii, 2001[65]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; other; ECLusys	> 0.1 mcg/L	Pts with event: 7 % Pts with event: 28% / 25 persons Results: adjusted	N: 25 RH: 6.24 95% CI: 4.89 to 7.59 p value: <0.001; ref group: Grp1	AUC: 0.861 95% CI: 0.749 to 0.972 Sens: 69.50% Spec: 82.50%
Ishii, 2001[65]	Cardio mortality	Years: 2	NR	NR	NR	NR	AUC: 0.609 95% CI: 0.394 to 0.824 Sens: 30.30% Spec: 94.40%
Ishii, 2001[65]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Beckman	> 0.1 mcg/L	Pts with event: 3 % Pts with event: 50% / 6 persons	NR	AUC: 0.609 95% CI: 0.394 to 0.824 Sens: 30.30% Spec: 94.40%
Ishii, 2001[65]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Beckman; access	< 0.1 mcg/L	Pts with event: 7 % Pts with event: 7% / 94 persons	NR	AUC: 0.609 95% CI: 0.394 to 0.824 Sens: 30.30% Spec: 94.40%

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Jensen, 2012[66]	All-cause mortality	Years: 4.4	Assay: cTnT Mfg: Roche; Elecsys	< or = to 14 ng/L	NR	N: 128 RH: 1	NR
Jensen, 2012[66]	All-cause mortality	Years: 4.4	Assay: cTnT Mfg: Roche; Elecsys	> 14 ng/L	NR	N: 65 RH: 1.32 95% CI: 0.62 to 2.81 p value: 0.48; ref group: Grp1	NR
Jensen, 2012[66]	Cardio mortality	Years: 4.4	Assay: cTnT Mfg: Roche; Elecsys	> 14 ng/L	NR	N: 65 RH: 1.34 95% CI: 0.44 to 4.1 p value: 0.61; ref group: Grp1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	NR	NR	Results: adjusted	NR	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	NR	Results: adjusted	NR	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 ng/L	No. of events: 27 / 115 persons Results: adjusted	N: 115	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 ng/L	No. of events: 13 / 30 persons Results: adjusted	N: 30 RH: 1.9 95% CI: 0.9 to 3.9 p value: 0.07; ref group: Grp1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	% Pts with event: 7.1% No. of events: 1 / 14 persons Results: adjusted	N: 14 RH: 1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	% Pts with event: 15.4% No. of events: 6 / 39 persons Results: adjusted	N: 39 RH: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	% Pts with event: 29.8% No. of events: 39 / 131 persons Results: adjusted	N: 131 RH: 3.9 95% CI: 0.5 to 28.6 p value: NS; ref group: Grp1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	% Pts with event: 32.1% No. of events: 34 / 106 persons Results: adjusted	N: 106 RH: 1.9 95% CI: 0.8 to 4.7 p value: NS; ref group: Grp1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnI Mfg: other Mfg: Siemens; other; Immulite Troponin I kit	<0.2 ng/mL	% Pts with event: 25.5% No. of events: 24 / 94 persons Results: adjusted	N: 94 RH: 1	NR
Kalaji, 2012[67]	All-cause mortality	Days: 551	Assay: cTnI Mfg: other Mfg: Siemens; other; Immulite Troponin I kit	>0.2 ng/mL	% Pts with event: 31.4% No. of events: 16 / 51 persons Results: adjusted	N: 51 RH: 1.6 95% CI: 0.8 to 3 p value: NS; ref group: Grp1	NR
Kang, 2009[68]	All-cause mortality	Followup NR	Assay: cTnI Mfg: Beckman; AccuTnI	< 0.2 mcg/L	% Pts with event: 23.9% / 46 persons Results: adjusted	N: 46 HR: 1 p value: 0.001	NR
Kang, 2009[68]	All-cause mortality	Followup NR	Assay: cTnI Mfg: Beckman; AccuTnI	> 0.2 mcg/L	% Pts with event: 55% / 20 persons Results: adjusted	N: 20 HR: 5.9 95% CI: 2.06 to 16.87 p value: 0.001; ref group: Grp1	NR
Kang, 2009[68]	All-cause mortality	Days: 90	Assay: cTnI Mfg: Beckman; AccuTnI	< 0.2 mcg/L	% Pts with event: 35.2% / 71 persons Results: adjusted	N: 71 OR: 1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kang, 2009[68]	All-cause mortality	Days: 90	Assay: cTnI Mfg: Beckman; AccuTnI	> 0.2 mcg/L	% Pts with event: 60% / 50 persons Results: adjusted	N: 50 OR: 5.13 95% CI: 1.73 to 15.18 p value: 0.003; ref group: Grp1	NR
Kang, 2009[68]	Cardio mortality	Followup NR	Assay: cTnI Mfg: Beckman; AccuTnI	< 0.2 mcg/L	Results: adjusted	N: 46 HR: 1	NR
Kang, 2009[68]	Cardio mortality	Followup NR	Assay: cTnI Mfg: Beckman; AccuTnI	> 0.2 mcg/L	Results: adjusted	N: 20 hazard ratio: 5.17 95% CI: 1.16 to 23.16 p value: 0.032; ref group: Grp1	NR
Kanwar, 2006[69]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; NR	< 0.01 mcg/L	Pts with event: 4 / 23 persons	NR	NR
Kanwar, 2006[69]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; NR	> 0.01 mcg/L	Pts with event: 9 / 35 persons	NR	NR
Kanwar, 2006[69]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; NR	< 0.01 mcg/L	Pts with event: 7 / 34 persons	NR	NR
Kanwar, 2006[69]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; NR	> 0.01 mcg/L	Pts with event: 46 / 81 persons	NR	NR
Katerinis, 2008[70]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; AccuTnI	< 0.09 mcg/L	Pts with event: 0 / 46 persons Results: unadjusted	NR	NR
Katerinis, 2008[70]	All-cause mortality	NR	Assay: cTnI Mfg: Beckman; AccuTnI	> 0.09 mcg/L	Pts with event: 1 / 4 persons Results: unadjusted	NR	NR
Katerinis, 2008[70]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Beckman; AccuTnI	< 0.09 mcg/L	Pts with event: 0 / 46 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Katerinis, 2008[70]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Beckman; AccuTnI	> 0.09 mcg/L	Pts with event: 0 / 4 persons	NR	NR
Kertai, 2004[71]	All-cause mortality	Years: 4	Assay: cTnT Mfg: Roche; other; Trop T	< 0.1 ng/L	Pts with event: 9 / 42 persons Results: unadjusted	RH: 1	NR
Kertai, 2004[71]	All-cause mortality	Years: 4	Assay: cTnT Mfg: Roche; other; Trop T	> 0.1 ng/L	Pts with event: 4 / 16 persons Results: unadjusted	RH: 0.9 95% CI: 0.3 to 3.3; ref group: Grp1	NR
Khan, 2001[72]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Sanofi; access	< 0.03 mcg/L	Pts with event: 20 / 102 persons Results: unadjusted	NR	NR
Khan, 2001[72]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Sanofi; access	> 0.03 mcg/L	Pts with event: 4 / 24 persons Results: unadjusted	NR	NR
Khan, 2001[72]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Sanofi; access	< 0.03 mcg/L	Pts with event: 4 / 102 persons	NR	NR
Khan, 2001[72]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Sanofi; access	> 0.03 mcg/L	Pts with event: 1 / 24 persons	NR	NR
Khan, 2001[72]	Hospital readmission	Years: 2	Assay: cTnI Mfg: Sanofi; access	< 0.03 mcg/L	No. of events: 177 / 102 persons	NR	NR
Khan, 2001[72]	Hospital readmission	Years: 2	Assay: cTnI Mfg: Sanofi; access	> 0.03 mcg/L	No. of events: 30 / 24 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Khan, 2001[72]	Hospital readmission	Years: 2	Assay: cTnI Mfg: Sanofi; access	< 0.03 mcg/L	No. of events: 53 / 102 persons	NR	NR
Khan, 2001[72]	Hospital readmission	Years: 2	Assay: cTnI Mfg: Sanofi; access	> 0.03 mcg/L	No. of events: 8 / 24 persons	NR	NR
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: from 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; from 1996-1998, used Behring Opus Magnum Analyzer. from 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 14%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 18%	RR: 1.4 95% CI: 2.4 to 0.8; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 29%	RR: 2.6 95% CI: 5.2 to 1.2; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 4.9%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 9.7%	RR: 2.1 95% CI: 3.3 to 1.3; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 7.1%	RR: 1.5 95% CI: 3.1 to 0.7; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 26%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 57%	RR: 3.8 95% CI: 6.8 to 2; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 43%	RR: 2.1 95% CI: 4.8 to 0.9; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 7.7%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 17%	RR: 2.5 95% CI: 5.9 to 1; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 15%	RR: 2.1 95% CI: 4 to 1.1; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 5.4%	RR: 2.7 95% CI: 6.5 to 1.1; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 7.2%	RR: 3.7 95% CI: 6.6 to 2; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 2%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: <=1.0 ng/mL	% Pts with event: 12%	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: >=2.5 ng/mL. For Bayer assay: >=0.9 ng/mL	% Pts with event: 40%	RR: 4.8 95% CI: 9.3 to 2.3; ref group: Grp2	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[73]	Cardio mortality	Years: 1	Assay: cTnI Mfg: other Mfg: From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One; other; From 1996-1998, used Behring Opus Magnum Analyzer. From 1998-2000, used Bayer Immuno One	For Opus assay: 1.0 ng/mL - 2.5 ng/mL. For Bayer assay: 0.3 ng/mL - 0.9 ng/mL	% Pts with event: 18%	RR: 1.6 95% CI: 4.5 to 0.5; ref group: Grp2	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 3.6% / 1635 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 5.9% / 270 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 17% / 52 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 47% / 34 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	Pts with event: 19 / 95 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	Pts with event: 28 / 39 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 17% / 120 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 24% / 45 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 6.6% / 228 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 15% / 55 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 5.4% / 297 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 19% / 57 persons Results: unadjusted	NR	NR
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Negative: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 25% / 101 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2005[74]	All-cause mortality	Years: 1	Assay: cTnI	Positive: optimal diagnostic values, similar to those recommended by a consensus panel	% Pts with event: 53% / 45 persons Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 3.8% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Positive	% Pts with event: 10% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Negative	% Pts with event: 15% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Positive	% Pts with event: 26% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 8.6% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Positive	% Pts with event: 26% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Negative	% Pts with event: 32% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Positive	% Pts with event: 53% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 0.8% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Positive	% Pts with event: 3.9% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Negative	% Pts with event: 5.1% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Positive	% Pts with event: 9.9% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 3.3% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Positive	% Pts with event: 10% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 9.6% Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Negative	% Pts with event: 30% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Years: 1	Assay: cTnI	Positive	% Pts with event: 54% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Negative	% Pts with event: 1% Results: unadjusted	NR	NR
Kontos, 2008[75]	All-cause mortality	Days: 30	Assay: cTnI	Positive	% Pts with event: 4.7% Results: unadjusted	NR	NR
Kostrubiec, 2010[76]	All-cause mortality	Days: 30	NR	GFR < 35 and Troponin positive	Pts with event: 10 / 21 persons	NR	NR
Lamb, 2007[77]	All-cause mortality	NR	NR	NR	Results: adjusted	NR	Sens: 31 95% CI: 17 to 48 Spec: 85 95% CI: 79 to 90
Lamb, 2007[77]	All-cause mortality	NR	NR	NR	Results: adjusted	NR	Sens: 51 95% CI: 35 to 68 Spec: 80 95% CI: 73 to 85
Lamb, 2007[77]	All-cause mortality	NR	NR	NR	Results: adjusted	NR	Sens: 67 95% CI: 50 to 81 Spec: 62 95% CI: 55 to 69
Lamb, 2007[77]	All-cause mortality	NR	NR	NR	Results: adjusted	NR	AUC: 0.75 p value: <0.001 95% CI: 0.663 to 0.838 Sens: 60 95% CI: 42 to 76 Spec: 73 95% CI: 66 to 80
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnI Mfg: Bayer; Advair Centaur (standard)	< 0.07 mcg/L	Pts with event: 27 / 177 persons Results: adjusted	N: 177 RH: REF	Sens: 31 95% CI: 17 to 48 Spec: 85 95% CI: 79 to 90
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnI Mfg: Bayer; Advair Centaur (standard)	> 0.07 mcg/L	Pts with event: 12 / 38 persons Results: adjusted	N: 38 RH: 1.4 95% CI: 0.7 to 3 p value: 0.3; ref group: Grp1	Sens: 31 95% CI: 17 to 48 Spec: 85 95% CI: 79 to 90

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 13 / 127 persons Results: adjusted	N: 127 RH: REF	Sens: 67 95% CI: 50 to 81 Spec: 62 95% CI: 55 to 69
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 19 / 165 persons Results: adjusted	N: 165 RH: REF	Sens: 51 95% CI: 35 to 68 Spec: 80 95% CI: 73 to 85
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L	Pts with event: 26 / 95 persons Results: adjusted	N: 95 RH: 2 95% CI: 1 to 3.9 p value: 0.05; ref group: Grp1	Sens: 67 95% CI: 50 to 81 Spec: 62 95% CI: 55 to 69
Lamb, 2007[77]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.03 mcg/L	Pts with event: 20 / 57 persons Results: adjusted	N: 57 RH: 2.1 95% CI: 1.1 to 4 p value: 0.03; ref group: Grp1	Sens: 51 95% CI: 35 to 68 Spec: 80 95% CI: 73 to 85
Lamb, 2007[77]	All-cause mortality	NR	Assay: hscTnI Mfg: Bayer; other; Advia Centaur (Ultra)	< 0.04 mcg/L	Pts with event: 14 / 129 persons Results: adjusted	N: 129 RH: REF	AUC: 0.75 p value: <0.001 95% CI: 0.663 to 0.838 Sens: 60 95% CI: 42 to 76 Spec: 73 95% CI: 66 to 80
Lamb, 2007[77]	All-cause mortality	NR	Assay: hscTnI Mfg: Bayer; other; Advia Centaur (Ultra)	> 0.04 mcg/L	Pts with event: 21 / 63 persons Results: adjusted	N: 63 RH: 1.9 95% CI: 0.9 to 3.9 p value: 0.08; ref group: Grp1	AUC: 0.75 p value: <0.001 95% CI: 0.663 to 0.838 Sens: 60 95% CI: 42 to 76 Spec: 73 95% CI: 66 to 80
Lang, 2001[78]	All-cause mortality	Years: 2		NR	NR	NR	Sens: 5 Spec: 93

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	< 0.4 mcg/L	Pts with event: 17 / 93 persons	NR	Sens: 5 Spec: 93
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	> 0.4 mcg/L	Pts with event: 1 / 7 persons	NR	Sens: 5 Spec: 93
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	< 0.1 mcg/L	Pts with event: 10 / 73 persons	NR	NR
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	> 0.1 mcg/L	Pts with event: 8 / 27 persons	NR	NR
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	< 0.1 mcg/L	Pts with event: 11 / 78 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	> 0.1 mcg/L	Pts with event: 7 / 22 persons	NR	NR
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	< 0.1 mcg/L	Pts with event: 6 / 59 persons	NR	NR
Lang, 2001[78]	All-cause mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	> 0.1 mcg/L	Pts with event: 12 / 41 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	< 0.1 mcg/L	Pts with event: 8 / 78 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	> 0.1 mcg/L	Pts with event: 5 / 22 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	< 0.4 mcg/L	Pts with event: 12 / 93 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	> 0.4 mcg/L	Pts with event: 1 / 7 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	< 0.1 mcg/L	Pts with event: 5 / 73 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	> 0.1 mcg/L	Pts with event: 8 / 27 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	< 0.1 mcg/L	Pts with event: 3 / 59 persons	NR	NR
Lang, 2001[78]	Cardio mortality	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	> 0.1 mcg/L	Pts with event: 10 / 41 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	< 0.1 mcg/L	Pts with event: 4 / 59 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; TropT-sensitive rapid test	> 0.1 mcg/L	Pts with event: 10 / 41 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	< 0.4 mcg/L	Pts with event: 13 / 93 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnI Mfg: Dade Behring; other; Stratus Cardiac Troponin I	> 0.4 mcg/L	Pts with event: 1 / 7 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	< 0.1 mcg/L	Pts with event: 5 / 73 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnI Mfg: other Mfg: Astra; other; Cardiac STATus Troponin I rapid test	> 0.1 mcg/L	Pts with event: 9 / 27 persons	NR	NR
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	< 0.1 mcg/L	Pts with event: 9 / 78 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lang, 2001[78]	Subs. MI	Years: 2	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; ELISA	> 0.1 mcg/L	Pts with event: 5 / 22 persons	NR	NR
Le Goff, 2007[79]	All-cause mortality	Years: 3			% Pts with event: 73.2% / 22 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	Pts with event: 61 / 86 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.031 mcg/L< 0.1 mcg/L	% Pts with event: 43% / 7 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 53% / 32 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	Cardio mortality	Years: 3	NR	NR	% Pts with event: 32% / 22 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	Cardio mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.03 mcg/L	% Pts with event: 61% / 86 persons Results: adjusted	NR	NR
Le Goff, 2007[79]	Cardio mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.031 mcg/L< 0.1 mcg/L	% Pts with event: 14% / 7 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Le Goff, 2007[79]	Cardio mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 9% / 32 persons Results: adjusted	NR	NR
Lowbeer, 2002[80]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	< 0.04 mcg/L	Pts with event: 3 / 12 persons	N: 16	NR
Lowbeer, 2002[80]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	> 0.04 mcg/L	Pts with event: 12 / 14 persons	N: 10 Exponent Beta: 6.54 SE: 0.54 p value: 0.00056; ref group: Grp1	NR
Lowbeer, 2002[80]	Cardio mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	< 0.04 mcg/L	Pts with event: 3 / 12 persons	NR	NR
Lowbeer, 2002[80]	Cardio mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; ELISA	> 0.04 mcg/L	Pts with event: 8 / 14 persons	NR	NR
Lowbeer, 2003[81]	Other composite (survival)	Years: 2.7	Assay: cTnT Mfg: Roche; Elecsys	NR	Pts with event: NR/ 49 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Lowbeer, 2003[81]	Other composite (survival)	Years: 2.7	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 72% / 35 persons	NR	NR
Lowbeer, 2003[81]	Other composite (survival)	Years: 2.7	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 65% / 14 persons	NR	NR
Lowbeer, 2003[81]	Other composite (survival)	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 75% / 44 persons	NR	NR
Lowbeer, 2003[81]	Other composite (survival)	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 45% / 20 persons	NR	NR
Lowbeer, 2003[81]	Other composite (survival)	Years: 2.7	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 74.4% / 81 persons Results: adjusted	N: 81 RH: 1	NR
Lowbeer, 2003[81]	Other composite (survival)	Years: 2.7	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 45.5% / 34 persons Results: adjusted	N: 34 RH: 2.66 95% CI: 1.07 to 10.95 p value: <0.05; ref group: Grp1	NR
Mallamaci, 2002[82]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 0 / 12 persons Results: adjusted	NR	NR
Mallamaci, 2002[82]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.048 mcg/L	Results: adjusted	RH: 1 95% CI: to	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Mallamaci, 2002[82]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.049 mcg/L< 0.098 mcg/L	Results: adjusted	RH: 1.15 95% CI: 0.53 to 2.51 p value: 0.73; ref group: Grp2	NR
Mallamaci, 2002[82]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.098 mcg/L	Results: adjusted	RH: 2.39 95% CI: 1.13 to 5.06 p value: 0.02; ref group: Grp2	NR
Mallamaci, 2002[82]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.048 mcg/L	Results: adjusted	RH: 1	NR
Mallamaci, 2002[82]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.049 mcg/L< 0.098 mcg/L	Results: adjusted	RH: 1.19 95% CI: 0.5 to 2.82 p value: 0.69; ref group: Grp1	NR
Mallamaci, 2002[82]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.098 mcg/L	Results: adjusted	RH: 2.35 95% CI: 1.01 to 5.49 p value: 0.048; ref group: Grp1	NR
Martin, 1998[83]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; stratus	< 0.8 mcg/L	Pts with event: 5 % Pts with event: 15% / 33 persons Results: unadjusted	NR	NR
Martin, 1998[83]	All-cause mortality		Assay: cTnI Mfg: Dade Behring; stratus	> 0.8 mcg/L	Pts with event: 4 % Pts with event: 29% / 14 persons Results: unadjusted	NR	NR
McGill, 2010[85]	All-cause mortality	Years: 3.9	Assay: hscTnT Mfg: Roche; E411 analyzer	Ln hs-cTnT, cut off 3 ng/L	Results: adjusted	N: 143 RH: 1.404 95% CI: 1.001 to 1.968 p value: 0.049	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
McMurray, 2011[86]	Cardio mortality	Years: 2.4	Assay: cTnT Mfg: Roche; 4th generation TnT assay	<0.028 ng/mL	NR	N: 230 RH: 1.42 95% CI: 1.05 to 1.93 p value: 0.0001; ref group: Grp1	NR
McMurray, 2011[86]	Cardio mortality	Years: 2.4	Assay: cTnT Mfg: Roche; 4th generation TnT assay	>0.028 ng/mL	NR	N: 217 RH: 1.5 95% CI: 2.13 to 10.6 p value: 0.0001; ref group: Grp1	NR
McMurray, 2011[86]	Cardio mortality	Years: 2.4	Assay: cTnT Mfg: Roche; 4th generation TnT assay	Undetectable	NR	N: 548 RH: 1	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	<1 x ULN	% Pts with event: 3.3% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	>3 x ULN	% Pts with event: 7.4% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	1-3 x ULN	% Pts with event: 5.4% / 5214 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	<1 x ULN	% Pts with event: 3.7% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	>3 x ULN	% Pts with event: 7.3% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	1-3 x ULN	% Pts with event: 3.5% / 5214 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	<1 x ULN	% Pts with event: 1.7% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	>3 x ULN	% Pts with event: 2.1% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	1-3 x ULN	% Pts with event: 2.1% / 5214 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	<1 x ULN	% Pts with event: 1% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	> 3 x ULN	% Pts with event: 2.6% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	1-3 x ULN	% Pts with event: 2.2% / 5214 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	<1 x ULN	% Pts with event: 10.1% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	>3 x ULN	% Pts with event: 14.6% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnI	1-3 x ULN	% Pts with event: 9.6% / 5214 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	<1 x ULN	% Pts with event: 7% / 5529 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	>3 x ULN	% Pts with event: 14% / 20843 persons	NR	NR
Melloni, 2008[87]	All-cause mortality	Followup NR	Assay: cTnT	1-3 x ULN	% Pts with event: 5.7% / 5214 persons	NR	NR
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	< 0.5 mcg/L	Pts with event: 2 / 16 persons	NR	NR
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	> 0.5 mcg/L	Pts with event: 1 / 4 persons	NR	NR
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Pts with event: 4 / 28 persons	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Pts with event: 1 / 2 persons	NR	NR
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 1 / 20 persons	NR	NR
Mockel, 1999[88]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 4 / 10 persons	NR	NR
Mockel, 1999[88]	MACE < 1 year	Years: 1	Assay: cTnI Mfg: Dade Behring; opusplus	> 0.5 mcg/L	NR	N: 7 OR: 4.57 95% CI: 0.4 to 5.2 p value: 0.22	NR
Mockel, 1999[88]	MACE < 1 year	Years: 1	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	NR	N: 7 OR: 3.22 95% CI: 0.6 to 17 p value: 0.168	NR
Mockel, 1999[88]	MACE < 1 year	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	NR	N: 7 OR: 1.63 95% CI: 0.18 to 5.9 p value: 0.969	NR
Morton, 1998[89]	All-cause mortality	NR	NR	NR	Results: unadjusted	NR	Spec: 100% (for >1.5)
Morton, 1998[89]	All-cause mortality	NR	Assay: cTnI Mfg: Sanofi; access	< 0.15 mcg/L	/ 108 persons Results: unadjusted	NR	Spec: 100% (for >1.5)
Morton, 1998[89]	All-cause mortality	NR	Assay: cTnI Mfg: Sanofi; access	> 0.15 mcg/L< 1.5 mcg/L	/ 4 persons Results: unadjusted	NR	Spec: 100% (for >1.5)
Morton, 1998[89]	All-cause mortality	NR	Assay: cTnI Mfg: Sanofi; access	> 1,5 mcg/L	Pts with event: 0 % Pts with event: 0% / 0 persons Results: unadjusted	NR	Spec: 100% (for >1.5)

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Pts with event: 2 / 47 persons Results: unadjusted	NR	NR
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Pts with event: 0 / 2 persons Results: unadjusted	NR	NR
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnI Mfg: Sanofi; access	< 0.04 mcg/L	Pts with event: 2 / 49 persons Results: unadjusted	NR	NR
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnI Mfg: Sanofi; access	> 0.4 mcg/L	Pts with event: 0 / 0 persons Results: unadjusted	NR	NR
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boerhinger; other; Enzymum	< 0.1 mcg/L	Pts with event: 2 / 26 persons Results: unadjusted	NR	NR
Musso, 1999[90]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boerhinger; other; Enzymum	> 0.1 mcg/L	Pts with event: 0 / 23 persons Results: unadjusted	NR	NR
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Pts with event: 0 / 47 persons Results: unadjusted	NR	NR
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Pts with event: 0 / 2 persons Results: unadjusted	NR	NR
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Sanofi; access	< 0.4 mcg/L	Pts with event: 0 / 49 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Sanofi; access	> 0.4 mcg/L	Pts with event: 0 / 0 persons Results: unadjusted	NR	NR
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: other Mfg: Boerhinger; other; Enzymum	< 0.1 mcg/L	Pts with event: 0 / 26 persons Results: unadjusted	NR	NR
Musso, 1999[90]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: other Mfg: Boerhinger; other; Enzymum	> 0.1 mcg/L	Pts with event: 0 / 23 persons Results: unadjusted	NR	NR
Ooi, 1999[92]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 10% / 111 persons Results: unadjusted	RR: 1	NR
Ooi, 1999[92]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 33% / 61 persons Results: unadjusted	RR: 3.3 95% CI: 1.7 to 6.4 p value: <0.001; ref group: Grp1	NR
Ooi, 1999[92]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 5% / 111 persons Results: unadjusted	RR: 1	NR
Ooi, 1999[92]	Cardio mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 10% / 61 persons Results: unadjusted	RR: 1.8 95% CI: 0.6 to 5.4 p value: ns; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Ooi, 2001[93]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 1 % Pts with event: 6% / 17 persons Results: unadjusted	N: 17 RR: 1	NR
Ooi, 2001[93]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Pts with event: 52 % Pts with event: 43% / 121 persons Results: unadjusted	N: 121 RR: 7.3 95% CI: 1.1 to 49 p value: <0.005; ref group: Grp1	NR
Ooi, 2001[93]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 34 % Pts with event: 59% / 58 persons Results: unadjusted	N: 58 RR: 10 95% CI: 1.5 to 68 p value: <0.001; ref group: Grp1	NR
Ooi, 2001[93]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 0 / 17 persons Results: unadjusted	NR	NR
Ooi, 2001[93]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Pts with event: 17 % Pts with event: 14% / 121 persons Results: unadjusted	NR	NR
Ooi, 2001[93]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 14 % Pts with event: 24% / 58 persons Results: unadjusted	NR	NR
Orea-Tejeda, 2010[94]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	NR	Results: adjusted	NR	NR
Orea-Tejeda, 2010[94]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	>=0.02 ng/mL	% Pts with event: 83.5% / 21 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Peetz, 2003[95]	MACE < 1 year	NR	NR	NR	Results: unadjusted	NR	AUC: 0.574 Sens: 16% Spec: 93.70%
Peetz, 200[95]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Results: unadjusted	N: 101 (97.1%)	AUC: 0.574 Sens: 16% Spec: 93.70%
Peetz, 2003[95]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Results: unadjusted	N: 3 (2.9%)	AUC: 0.574 Sens: 16% Spec: 93.70%
Peetz, 2003[95]	MACE < 1 year	NR	NR	NR	Results: unadjusted	NR	AUC: 0.708 Sens: 53.50% Spec: 72.50%
Peetz, 2003[95]	MACE < 1 year	NR	Assay: cTnI Mfg: Bayer; acs180	< 0.15 mcg/L	Results: unadjusted	N: 70 (69.6%) OR: REF	AUC: 0.708 Sens: 53.50% Spec: 72.50%
Peetz, 2003[95]	MACE < 1 year	NR	Assay: cTnI Mfg: Bayer; acs180	> 0.15 mcg/L	Results: unadjusted	N: 34 (32.4%) OR: 4 p value: 0.22; ref group: Grp1	AUC: 0.708 Sens: 53.50% Spec: 72.50%
Peetz, 2003[95]	MACE < 1 year	NR	NR	NR	Results: unadjusted	NR	AUC: 0.726 Sens: 58.4 Spec: 77.9
Peetz, 2003[95]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Results: unadjusted	N: 36 (34.6%) OR: REF	AUC: 0.726 Sens: 58.4 Spec: 77.9
Peetz, 2003[95]	MACE < 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Results: unadjusted	N: 68 (65.7%) OR: 16 p value: <0.01; ref group: Grp1	AUC: 0.726 Sens: 58.4 Spec: 77.9

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	<0.15 ng/mL	% Pts with event: 2.41% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	>0.15 ng/mL	% Pts with event: 15.62% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	NR	NR	Results: unadjusted	NR	AUC: 0.637 95% CI: 0.542 to 0.725 Sens: 0.5172 95% CI: 32.5 to 70.5 Spec: 0.814 95% CI: 71.6 to 89
Petrovic, 2009[96]	All-cause mortality	NR	NR	NR	Results: unadjusted	NR	AUC: 0.744 95% CI: 0.654 to 0.821 Sens: 0.7586 95% CI: 56.5 to 89.7 Spec: 0.7209 95% CI: 61.4 to 81.2
Petrovic, 2009[96]	All-cause mortality	NR	NR	<0.15 ng/mL	% Pts with event: 0% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	NR	>0.15 ng/mL	% Pts with event: 31.11% Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	<0.15 ng/mL	% Pts with event: 14.46% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	<0.15 ng/mL	% Pts with event: 16.87% Results: unadjusted	NR	AUC: 0.637 95% CI: 0.542 to 0.725 Sens: 0.5172 95% CI: 32.5 to 70.5 Spec: 0.814 95% CI: 71.6 to 89
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	<0.15 ng/mL	% Pts with event: 7.23% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	>0.15 ng/mL	% Pts with event: 25% Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	>0.15 ng/mL	% Pts with event: 34.37% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnI Mfg: other Mfg: Abbott; ADV AxSYM cTnI Immunoassay	>0.15 ng/mL	% Pts with event: 46.87% Results: unadjusted	NR	AUC: 0.637 95% CI: 0.542 to 0.725 Sens: 0.5172 95% CI: 32.5 to 70.5 Spec: 0.814 95% CI: 71.6 to 89
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 0% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality		Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 2.86% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 2.86% Results: unadjusted	NR	AUC: 0.744 95% CI: 0.654 to 0.821 Sens: 0.7586 95% CI: 56.5 to 89.7 Spec: 0.7209 95% CI: 61.4 to 81.2
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 15.56% Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 46.67% Results: unadjusted	NR	NR
Petrovic, 2009[96]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 60% Results: unadjusted	NR	AUC: 0.744 95% CI: 0.654 to 0.821 Sens: 0.7586 95% CI: 56.5 to 89.7 Spec: 0.7209 95% CI: 61.4 to 81.2
Porter, 1998[97]	All-cause mortality	NR	NR	NR	NR	NR	Sens: 0.25 Spec: 0.909
Porter, 1998[97]	All-cause mortality	NR	NR	NR	NR	NR	Sens: 0.875 Spec: 0.864
Porter, 1998[97]	All-cause mortality	NR	NR	NR	Results: unadjusted	NR	Sens: 0.125 Spec: 0.955
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; NR	< 0.4 mcg/L	Pts with event: 4 / 28 persons Results: unadjusted	NR	Sens: 0.125 Spec: 0.955
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; NR	< 0.5 mcg/L	Pts with event: 2 / 16 persons	NR	Sens: 0.25 Spec: 0.909
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; NR	> 0.4 mcg/L	Pts with event: 1 / 2 persons Results: unadjusted	NR	Sens: 0.125 Spec: 0.955
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnI Mfg: Dade Behring; NR	> 0.5 mcg/L	Pts with event: 1 / 4 persons	NR	Sens: 0.25 Spec: 0.909

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; other; Enzymum	< 0.1 mcg/L	Pts with event: 1 / 20 persons	NR	Sens: 0.875 Spec: 0.864
Porter, 1998[97]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; other; Enzymum	> 0.1 mcg/L	Pts with event: 4 / 10 persons	NR	Sens: 0.875 Spec: 0.864
Porter, 2000[98]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 2 / 17 persons Results: unadjusted	NR	NR
Porter, 2000[98]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 5 / 10 persons Results: unadjusted	NR	NR
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	NR	NR	Results: unadjusted	NR	Sens: 18.2 Spec: 87.5
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	NR	NR	Results: unadjusted	NR	Sens: 9.1 Spec: 87.5
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Pts with event: 10 / 24 persons Results: unadjusted		Sens: 9.1 Spec: 87.5
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Pts with event: 1 / 3 persons Results: unadjusted	NR	Sens: 9.1 Spec: 87.5
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnI Mfg: other Mfg: Abbott; other; AxSym	< 0.5 mcg/L	Pts with event: 9 / 23 persons Results: unadjusted	NR	Sens: 18.2 Spec: 87.5

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnI Mfg: other Mfg: Abbott; other; AxSym	> 0.5 mcg/L	Pts with event: 2 / 4 persons Results: unadjusted	NR	Sens: 18.2 Spec: 87.5
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	NR	NR	Results: unadjusted	NR	Sens: 81.8 Spec: 88.2
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 2 / 17 persons Results: unadjusted	NR	Sens: 81.8 Spec: 88.2
Porter, 2000[98]	MACE ≥ 1 year	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 9 / 10 persons Results: unadjusted	NR	Sens: 81.8 Spec: 88.2
Quiroga, 2013[99]	Other composite (CV events + non-CV mortality)		Assay: cTnT Mfg: Roche; other; ECLIA	> 0.01 ng/L	N: 218 % pts with event: 50% pts with event: 23 Results: unadjusted	N: 218 OR: 2.07 95% CI: 1.03 to 4.16 p value: 0.042; ref group: whole group	NR
Roberts, 2004[100]	MACE < 1 year-Revascularization-Other composite		Assay: cTnI Mfg: other Mfg: Abott; other; Abott AXSYM	< 0.3 mcg/L	Pts with event: 5 / 79 persons Results: unadjusted	N: 79 RR: 1	NR
Roberts, 2004[100]	MACE < 1 year-Revascularization-Other composite		Assay: cTnI Mfg: other Mfg: Abott; other; Abott AXSYM	> 0.3 mcg/L	Pts with event: 5 / 9 persons Results: unadjusted	N: 9 RR: 8.8 95% CI: 1.8 to 31.8; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Roberts, 2009[101]	All-cause mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	< 0.04 mcg/L	Pts with event: 0 / 28 persons	NR	NR
Roberts, 2009[101]	All-cause mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	Pts with event: 2 / 20 persons	NR	NR
Roberts, 2009[101]	All-cause mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	Pts with event: 7 / 33 persons	NR	NR
Roberts, 2009[101]	Cardio mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	< 0.04 mcg/L	Pts with event: 0 / 26 persons	NR	NR
Roberts, 2009[101]	Cardio mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	Pts with event: 1 / 17 persons	NR	NR
Roberts, 2009[101]	Cardio mortality	Years: 1.8	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	Pts with event: 6 / 29 persons	NR	NR
Roppolo, 1999[102]	MACE < 1 year	NR	Assay: cTnI Mfg: Dade Behring; opus	> 0.5 mcg/L	Pts with event: 3 / 3 persons Results: unadjusted	NR	NR
Roppolo, 1999[102]	MACE < 1 year	NR	Assay: cTnT Mfg: Dade Behring; opus	> 0.1 mcg/L	Pts with event: 6 / 24 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Roppolo, 1999[102]	MACE < 1 year	NR	Assay: cTnT Mfg: Dade Behring; opus	> 0.2 mcg/L	Pts with event: 5 / 9 persons Results: unadjusted	NR	NR
Sahinarslan, 2008[103]	All-cause mortality	Years: 5	Assay: cTnT Mfg: NR; NR	< 0.1 mcg/L	% Pts with event: 16.4% / 61 persons Results: unadjusted	NR	NR
Sahinarslan, 2008[103]	All-cause mortality	Years: 5	Assay: cTnT Mfg: NR; NR	> 0.1 mcg/L	% Pts with event: 52.9% / 17 persons Results: unadjusted	NR	NR
Sahinarslan, 2008[103]	MACE ≥ 1 year	Years: 5	Assay: cTnT Mfg: NR; NR	< 0.1 mcg/L	% Pts with event: 24.6% / 61 persons Results: adjusted	N: 61 OR: 1	NR
Sahinarslan, 2008[103]	MACE ≥ 1 year	Years: 5	Assay: cTnT Mfg: NR; NR	> 0.1 mcg/L	% Pts with event: 64.7% / 17 persons Results: adjusted	N: 17 OR: 3.215 95% CI: 0.405 to 25.53 p value: 0.269; ref group: Grp1	NR
Satyan, 2007[104]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.022 mcg/L	Results: adjusted	N: 38 RH: 1	NR
Satyan, 2007[104]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.022 mcg/L< 0.056 mcg/L	Results: adjusted	N: 38 RH: 1.57 95% CI: 0.46 to 5.35 p value: 0.5; ref group: Grp1	NR
Satyan, 2007[104]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.056 mcg/L< 0.106 mcg/L	Results: adjusted	N: 37 RH: 2.32 95% CI: 0.69 to 7.86 p value: 0.2; ref group: Grp1	NR
Satyan, 2007[104]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.106 mcg/L< 0.569 mcg/L	Results: adjusted	N: 37 RH: 3.39 95% CI: 1.04 to 11.07 p value: 0.04; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Satyan, 2007[104]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.022 mcg/L	Results: adjusted	N: 38 RH: 1	NR
Satyan, 2007[104]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.022 mcg/L< 0.056 mcg/L	Results: adjusted	N: 38 RH: 0.81 95% CI: 0.16 to 4.06 p value: 0.8; ref group: Grp1	NR
Satyan, 2007[104]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.056 mcg/L< 0.106 mcg/L	Results: adjusted	N: 37 RH: 2.12 95% CI: 0.47 to 9.54 p value: 0.34; ref group: Grp1	NR
Satyan, 2007[104]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.106 mcg/L< 0.569 mcg/L	Results: adjusted	N: 37 RH: 2.14 95% CI: 0.48 to 9.6 p value: 0.32; ref group: Grp1	NR
Scott, 2003[106]	All-cause mortality	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; Cardiac reader	< 0.1 mcg/L	Pts with event: % Pts with event: 17% / 42 persons Results: unadjusted	N: 42 Coefficient: REF SE: 2.185	NR
Scott, 2003[106]	All-cause mortality	Years: 1	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; other; Cardiac reader	> 0.1 mcg/L	% Pts with event: 41% / 29 persons Results: unadjusted	N: 29 (40.8%) Coefficient: 4.988 SE: 2.185 95% CI: 10645.93 to 2.023 p value: 0.0025; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Sharma, 2005[107]	All-cause mortality	Years: 2.12	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 0 / 87 persons Results: unadjusted	N: 87	AUC: 0.76 p value: 0.02 95% CI: 0.617 to 0.935
Sharma, 2005[107]	All-cause mortality	Years: 2.12	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 5 / 31 persons Results: unadjusted	N: 31 AUC: 0.76 95% CI: 0.617 to 0.935 p value: 0.02; ref group: Grp1	NR
Sharma, 2006[108]	All-cause mortality	Years: 2.25	NR	NR	Results: unadjusted	NR	AUC: 0.82 p value: 0.02 95% CI: 0.99 to 0.64 Sens: 75 Spec: 72
Sharma, 2006[108]	All-cause mortality	Years: 2.25	NR	NR	Results: unadjusted	NR	AUC: 0.82 p value: 0.02 95% CI: 0.99 to 0.64 Sens: 75 Spec: 72
Sharma, 2006[108]	All-cause mortality	Years: 2.25	NR	NR	Results: unadjusted	NR	AUC: 0.82 p value: 0.02 95% CI: 0.99 to 0.64 Sens: 75 Spec: 72
Sharma, 2006[108]	All-cause mortality	Years: 2.25	Assay: cTnT Mfg: Roche; Elecsys	> 0.06 mcg/L	Results: unadjusted	N: 51 OR: 7.14 95% CI: 5.71 to 10.22 p value: 0.004; ref group: Grp2	AUC: 0.82 p value: 0.02 95% CI: 0.99 to 0.64 Sens: 75 Spec: 72
Sharma, 2006[108]	All-cause mortality	Years: 2.25	Assay: cTnT Mfg: Roche; Elecsys	> 0.06 mcg/L	Results: unadjusted	N: 62	AUC: 0.82 p value: 0.02 95% CI: 0.99 to 0.64 Sens: 75 Spec: 72

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Sharma, 2006[109]	All-cause mortality	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	< 0.04 mcg/L	Pts with event: 3 / 74 persons Results: unadjusted	NR	NR
Sharma, 2006[109]	All-cause mortality	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 6 / 88 persons Results: unadjusted	NR	NR
Sharma, 2006[109]	All-cause mortality	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	> 0.04 mcg/L	Pts with event: 17 / 52 persons Results: unadjusted	NR	NR
Sharma, 2006[109]	All-cause mortality	Years: 2.5	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 14 / 38 persons Results: unadjusted	NR	NR
Shroff, 2012[110]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: Ortho Clinical Diagnostics ; Vitros	<0.04 ng/mL	Pts with event: 5 / 281 persons Results: unadjusted	NR	NR
Shroff, 2012[110]	All-cause mortality	Years: 1	Assay: cTnI Mfg: other Mfg: Ortho Clinical Diagnostics ; Vitros	>0.04 ng>mL	Pts with event: 3 / 95 persons Results: unadjusted	NR	NR
Shroff, 2012[110]	MACE < 1 year	Years: 1	Assay: cTnI Mfg: other Mfg: Ortho Clinical Diagnostics ; Vitros	<0.04 ng/mL	No. of events: 4 / 281 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Shroff, 2012[110]	MACE < 1 year	Years: 1	Assay: cTnI Mfg: other Mfg: Ortho Clinical Diagnostics ; Vitros	>0.04 ng>mL	No. of events: 5 / 95 persons Results: unadjusted	NR	NR
Sommerer, 2007[111]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: Roche; Elecsys	> 0.026 mcg/L	Results: adjusted	N: 53 (39.6%) OR: 2.12 SE: NR 95% CI: 1.24 to 3.62 p value: 0.006; ref group: Grp1	NR
Sommerer, 2007[111]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.026 mcg/L	Results: adjusted	N: 81 OR: REF SE: NR	NR
Stolear, 1999[112]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	< 0.1 mcg/L	Pts with event: 6 % Pts with event: 13% / 47 persons Results: adjusted	N: 47	NR
Stolear, 1999[112]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer Mannheim; Elecsys	> 0.1 mcg/L	Pts with event: 18 % Pts with event: 38% / 47 persons Results: adjusted	N: 47 beta coefficient in Cox model: 2.74 SE: 0.69 p value: 0.0001; ref group: Grp1	NR
Stolear, 1999[112]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; TROP T RA -rapid beside assay	< 0.2 mcg/L	Pts with event: 2 / 44 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Stolear, 1999[112]	All-cause mortality	NR	Assay: cTnT Mfg: other Mfg: Boehringer; other; TROP TRA - rapid assay	> 0.2 mcg/L	Pts with event: 22 / 50 persons Results: adjusted	NR	NR
Stolear, 1999[112]	Subs. MI		Assay: cTnT Mfg: other Mfg: Boehringer; Elecsys	< 0.1 mcg/L	Pts with event: 0 / 47 persons Results: unadjusted	NR	NR
Stolear, 1999[112]	Subs. MI		Assay: cTnT Mfg: other Mfg: Boehringer; Elecsys	> 0.1 mcg/L	Pts with event: 2 / 47 persons Results: unadjusted	NR	NR
Svensson, 2009[114]	All-cause mortality	Years: 2	Assay: cTnT Mfg: NR; NR	NR	Results: adjusted	N: 206 HR: 1.76 95% CI: 0.32 to 9.69 p value: 0.52; ref group: other; ref group: Total sample	NR
Trape, 2008[115]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 4 / 39 persons Results: unadjusted	NR	NR
Trape, 2008[115]	All-cause mortality	Years: 1	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 5 / 13 persons Results: unadjusted	NR	NR
Trape, 2008[115]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 11 / 39 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Trape, 2008[115]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 8 / 13 persons Results: unadjusted	NR	NR
Trape, 2008[115]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	Pts with event: 18 / 39 persons Results: unadjusted	NR	NR
Trape, 2008[115]	All-cause mortality	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 10 / 13 persons Results: unadjusted	NR	NR
Troyanov, 2005[116]	Other composite (ACS occurrence)	Years: 3	Assay: cTnT Mfg: Roche; Elecsys	> 0.4 mcg/L	NR	N: 29 Unadjusted HR: 2.98 95% CI: 8.57 to 1.04 p value: 0.04	NR
Troyanov, 2005[116]	Other composite (ACS occurrence)	Years: 3	Assay: cTnI Mfg: other Mfg: Abbot Laboratories; other; MEIA, AxSYM	> 0.3 mcg/L	NR	N: 29 unadjusted HR: 3.37 95% CI: 7.25 to 1.56 p value: 0.001	NR
Van Lente, 1999[117]	MACE < 1 year-Revascularization		NR		Results: unadjusted	NR	AUC: 0.59 p value: <0.01 Sens: 0.45 Spec: 0.72
Van Lente, 1999[117]	MACE < 1 year-Revascularization		NR		Results: unadjusted	NR	AUC: 0.53 p value: <0.02 Sens: 0.33 Spec: 0.78
Van Lente, 1999[117]	MACE < 1 year-Revascularization		Assay: cTnI Mfg: Dade Behring; stratus	Threshold 0.6 mcg/L	Results: unadjusted	NR	AUC: 0.53 p value: <0.02 Sens: 0.33 Spec: 0.78

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Van Lente, 1999[117]	MACE < 1 year-Revascularization		Assay: cTnT Mfg: other Mfg: Boehringer; other; Enzymun	Threshold 0.10 mcg/L	Results: unadjusted	NR	AUC: 0.59 p value: <0.01 Sens: 0.45 Spec: 0.72
Vichairuangthum, 2006[118]	Cardio mortality		Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.08 mcg/L	Pts with event: 0 / 16 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Cardio mortality	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.4 mcg/L	Pts with event: 2 / 49 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Cardio mortality	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.08 mcg/L	Pts with event: 2 / 47 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Cardio mortality	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.4 mcg/L	Pts with event: 0 / 14 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.08 mcg/L	Pts with event: 0 / 16 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Vichairuangthum, 2006[118]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.4 mcg/L	Pts with event: 5 / 49 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.08 mcg/L	Pts with event: 10 / 47 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	MACE ≥ 1 year	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.4 mcg/L	Pts with event: 5 / 14 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Subs. MI	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.08 mcg/L	Pts with event: 0 / 16 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Subs. MI	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	< 0.4 mcg/L	Pts with event: 0 / 49 persons Results: unadjusted	NR	NR
Vichairuangthum, 2006[118]	Subs. MI	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.08 mcg/L	Pts with event: 1 / 47 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Vichairuangthum, 2006[118]	Subs. MI	NR	Assay: cTnI Mfg: other Mfg: Johnson & Johnson; other; Vitros ECi	> 0.4 mcg/L	Pts with event: 1 / 14 persons Results: unadjusted	NR	NR
Wang, 2006[119]	Other composite (cardio congestion)	Years: 3	Assay: cTnT Mfg: Roche; other; Roche Modular Analyzer	per 1 ug/L increase (cont.)	Pts with event: 85 / 222 persons Results: adjusted	N: 85 RH: 2.98 95% CI: 1.19 to 7.42 p value: 0.019; ref group: other; ref group: total population	NR
Wang, 2007[120]	All-cause mortality	NR	NR	NR	Results: adjusted	NR	Sens: 0.76 95% CI: 0.64 to 0.85 Spec: 0.71 95% CI: 0.63 to 0.78
Wang, 2007[120]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 9 / 77 persons Results: adjusted	NR	Sens: 0.76 95% CI: 0.64 to 0.85 Spec: 0.71 95% CI: 0.63 to 0.78
Wang, 2007[120]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Pts with event: 15 / 78 persons Results: adjusted	NR	Sens: 0.76 95% CI: 0.64 to 0.85 Spec: 0.71 95% CI: 0.63 to 0.78
Wang, 2007[120]	All-cause mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 46 / 83 persons Results: adjusted	NR	Sens: 0.76 95% CI: 0.64 to 0.85 Spec: 0.71 95% CI: 0.63 to 0.78
Wang, 2007[120]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 6 / 77 persons Results: adjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Wang, 2007[120]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Pts with event: 9 / 78 persons Results: adjusted	NR	NR
Wang, 2007[120]	Cardio mortality	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 29 / 83 persons Results: adjusted	NR	NR
Wang, 2007[120]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Pts with event: 37 / 78 persons Results: adjusted	NR	Sens: 0.61 95% CI: 0.52 to 0.69 Spec: 0.78 95% CI: 0.69 to 0.85
Wang, 2007[120]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Pts with event: 66 / 83 persons Results: adjusted	NR	Sens: 0.61 95% CI: 0.52 to 0.69 Spec: 0.78 95% CI: 0.69 to 0.85
Wang, 2007[120]	MACE ≥ 1 year	NR	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Pts with event: 26 / 77 persons Results: adjusted	NR	Sens: 0.61 95% CI: 0.52 to 0.69 Spec: 0.78 95% CI: 0.69 to 0.85
Wang, 2007[120]	MACE ≥ 1 year	NR	NR	NR	Results: adjusted	NR	Sens: 0.61 95% CI: 0.52 to 0.69 Spec: 0.78 95% CI: 0.69 to 0.85
Wang, 2010[121]	Cardio mortality	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	Results: adjusted	N: 81 RH: 1	NR
Wang, 2010[121]	Cardio mortality	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	Results: adjusted	N: 79 RH: 2.58 95% CI: 0.78 to 8.57 p value: 0.13; ref group: Grp1	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Wang, 2010[121]	Cardio mortality	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	Results: adjusted	N: 70 RH: 1.91 95% CI: 0.58 to 6.32 p value: 0.29; ref group: Grp1	NR
Wang, 2010[122]	Other composite	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	< 0.01 mcg/L	% Pts with event: 8.1% / 81 persons	NR	NR
Wang, 2010[122]	Other composite	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	> 0.01 mcg/L< 0.099 mcg/L	% Pts with event: 18.7% / 70 persons	NR	NR
Wang, 2010[122]	Other composite	Years: 5	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 28.5% / 79 persons	NR	NR
Wayand, 2000[123]	All-cause mortality	Years: 2	NR	NR	NR	NR	AUC: 0.477 Sens: 0.57 Spec: 0.67
Wayand, 2000[123]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; stratus	< 0.4 mcg/L	Pts with event: 3 / 31 persons	NR	AUC: 0.477 Sens: 0.57 Spec: 0.67
Wayand, 2000[123]	All-cause mortality	Years: 2	Assay: cTnI Mfg: Dade Behring; stratus	> 0.4 mcg/L	Pts with event: 2 / 28 persons	NR	AUC: 0.477 Sens: 0.57 Spec: 0.67
Wayand, 2000[123]	All-cause mortality	Years: 2	NR	NR	NR	NR	AUC: 0.703 p value: 0.213 Sens: 0.57 Spec: 0.88

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Wayand, 2000[123]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; other; Enzymum Troponin T - ES700	< 0.1 mcg/L	Pts with event: 1 / 31 persons	NR	AUC: 0.703 p value: 0.213 Sens: 0.57 Spec: 0.88
Wayand, 2000[123]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; other; Enzymum Troponin T - ES700	> 0.1 mcg/L	Pts with event: 4 / 28 persons	NR	AUC: 0.703 p value: 0.213 Sens: 0.57 Spec: 0.88
Wolley, 2013[124]	Cardio mortality	NR	Assay: hcTnT Mfg: Roche; other; Automated Chemiluminescent Immunoassay	< 14 ng/L	Results: unadjusted	OR: 1	NR
Wolley, 2013[124]	Cardio mortality	NR	Assay: hcTnT Mfg: Roche; other; Automated Chemiluminescent Immunoassay	> 14 ng/L	Results: unadjusted	OR: 1.506 95% CI: 1.182 to 1.918 ref group: cont.	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Wood, 2003[125]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	% Pts with event: 14% No. of events: 10 / 71 persons Results: adjusted	N: 71 RH:	NR
Wood, 2003[125]	All-cause mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	% Pts with event: 52% No. of events: 11 / 25 persons Results: adjusted	N: 25 RH: 1.72 95% CI: 1.08 to 2.74 p value: 0.02; ref group: Grp1	NR
Wood, 2003[125]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	< 0.1 mcg/L	No. of events: 5 / 71 persons	NR	NR
Wood, 2003[125]	Cardio mortality	Years: 2	Assay: cTnT Mfg: Roche; Elecsys	> 0.1 mcg/L	No. of events: 6 / 25 persons	NR	NR
Yakupoglu, 2002[126]	Cardio mortality	NR	Assay: cTnI Mfg: other Mfg: Diagnostic Products; immulite	< 2.3 mcg/L	Pts with event: 10 % Pts with event: 33% / 30 persons Results: unadjusted	NR	NR
Yakupoglu, 2002[126]	Cardio mortality	NR	Assay: cTnI Mfg: other Mfg: Diagnostic Products; immulite	> 2.3 mcg/L	Pts with event: 6 % Pts with event: 75% / 8 persons Results: unadjusted	NR	NR
Yakupoglu, 2002[126]	Other composite (survival)	NR	Assay: cTnI Mfg: other Mfg: Diagnostic Products; immulite	< 2.3 mcg/L	% Pts with event: 66.1% / 30 persons Results: unadjusted	NR	NR

Author, Year	Outcome	Followup Time	Assay	Cutpoint	Incidence of Outcome	Measures of Association	AUC
Yakupoglu, 2002[126]	Other composite (survival)	NR	Assay: cTnI Mfg: other Mfg: Diagnostic Products; immulite	> 2.3 mcg/L	% Pts with event: 25% / 8 persons Results: unadjusted	NR	NR

Abbreviations: ACE=adverse cardiovascular event; AUC=area under the curve; cardio=cardiovascular; CI=confidence interval; cont.=continuous; cTnI=cardiac troponin I; cTnT=cardian troponin T; Grp=group; HR=hazard ratio; hs=high sensitivity; lab=laboratory; LR=likelihood ratio; MACE=major adverse cardiac events; mcg/L=micrograms per liter; Mfg=manufacturer; MI=myocardial infarction; N=number; ng/mL=nanograms per liter; ng/L=nanograms per liter; NR=not reported; ns=not specified; pts=patients; ref=reference; OR=odds ratio; revasc=revascularization; RH=relative;RR=relative risk; hazard; sd=standard deviation; se=standard error; sens=sensitivity; spec=specificity; subs.=subsequent

Table 5a. Study quality data for articles included in KQ1

Reporting

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Alcalai, 2007[4]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Alcalai, 2007[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apple,1999[6]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Apple,1999[6]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
Bhagavan, 1998[16]	Yes	Yes	No	Yes	No	Yes	Yes	No	No
Bhagavan, 1998[16]	Yes	Yes	No	Yes	No	Yes	No	No	No
Chenevier-Gobeaux, 2013[127]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Chenevier-Gobeaux, 2013[127]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Fehr, 2003[34]	Yes	No	No	Yes	No	Yes	Yes	No	Yes
Fehr, 2003[34]	Yes	No	No	Yes	No	Yes	No	No	No
Flores, 2006[37]	Yes	No	Yes	Yes	No	Yes	No	Yes	No
Flores, 2006[37]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Flores-Solis, 2012[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Flores-Solis, 2012[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Haaf, 2013[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haaf, 2013[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ikeda, 2002[62]	Yes	Yes	No	Yes	No	Yes	No	No	No
Ikeda, 2002[62]	Yes	Yes	No	Yes	No	Yes	No	No	No
Martin, 1998[83]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Martin, 1998[83]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No
McCullough, 2002[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McCullough, 2002[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Noeller, 2003[91]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Noeller, 2003[91]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roppolo, 1999[102]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Roppolo, 1999[102]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Sukonthasarn, 2007[113]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Sukonthasarn, 2007[113]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Troyanov, 2005[116]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Troyanov, 2005[116]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Abbreviation: KQ=key question

Internal Validity -Bias

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Alcalai, 2007[4]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Alcalai, 2007[4]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Unable to determine	Yes
Apple, 1999[6]	Yes	Yes	Unable to determine	Yes	Yes	No	Yes	Yes	Unable to determine
Apple, 1999[6]	Unable to determine	Yes	Unable to determine	Yes	Yes	No	Yes	Yes	Unable to determine
Bhagavan, 1998[16]	No	Yes	Unable to determine	Yes	Yes	Unable to determine	Unable to determine	No	Unable to determine
Bhagavan, 1998[16]	Unable to determine	Yes	Unable to determine	Yes	Yes	Unable to determine	Unable to determine	Unable to determine	Unable to determine

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Chenevier-Gobeaux, 2013[127]	Yes	Yes	No	Yes	Yes	Yes	Unable to determine	Yes some	Yes
Chenevier-Gobeaux, 2013[127]	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	NA
Fehr, 2003[34]	Not feasible	Yes	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	No	No
Fehr, 2003[34]	Unable to determine	Yes	Unable to determine	Yes	Yes	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Flores, 2006[37]	Unable to determine	Unable to determine	NA	Yes	Yes	Yes	Yes	Unable to determine	NA
Flores, 2006[37]	Not feasible	Yes	NA	Yes	Yes	Yes	Yes	No	Yes
Flores-Solis, 2012[38]	Not feasible	Yes	NA	Yes	Yes	Yes	Yes	NA	NA
Flores-Solis, 2012[38]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes
Haaf, 2013[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Haaf, 2013[43]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Ikeda, 2002[62]	Unable to determine	No	NA	Yes	Yes	Yes	Yes	No	NA
Ikeda, 2002[62]	Unable to determine	No	NA	Yes	Yes	Yes	Yes	No	NA
Martin, 1998[83]	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes	NA	Yes
Martin, 1998[83]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	NA	Yes
McCullough, 2002[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
McCullough, 2002[84]	Yes	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes
Noeller, 2003[91]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Noeller, 2003[91]	Yes	Yes	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes some	Yes
Roppolo, 1999[102]	No	Yes	NA	Yes	Yes	Yes	Yes	No	Yes
Roppolo, 1999[102]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Unable to determine	NA	Yes
Sukonthasarn, 2007[113]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Unable to determine
Sukonthasarn, 2007[113]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	Unable to determine	Unable to determine
Troyanov, 2005[116]	No	Yes	No	Yes	Yes	Yes	Yes	Yes some	Unable to determine
Troyanov, 2005[116]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes some	Yes

External validity - Power

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Alcalai, 2007[4]	Yes	Yes	Yes	No	NR support	Fair
Alcalai, 2007[4]	Yes	Yes	Yes	No	NR support	Good
Apple, 1999[6]	Yes	Yes	Unable to determine	No	Yes industry support	Fair
Apple, 1999[6]	Unable to determine	Yes	Unable to determine	No	NR support	Fair
Bhagavan, 1998[16]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Bhagavan, 1998[16]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Chenevier-Gobeaux, 2013[127]	Unable to determine	Yes	Unable to determine	No	Yes industry support	Fair

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Chenevier-Gobeaux, 2013[127]	Unable to determine	Yes	Unable to determine	No	Yes industry support	Fair
Fehr, 2003[34]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Poor
Fehr, 2003[34]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Poor
Flores, 2006[37]	No	No	Unable to determine	No	NR support	Poor
Flores, 2006[37]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Flores-Solis, 2012[38]	Yes	Yes	Yes	Yes	No industry support	Fair
Flores-Solis, 2012[38]	Unable to determine	Unable to determine	Yes	Yes	No industry support	Good
Haaf, 2013[43]	Yes	Yes	Yes	No	Yes industry support	Good
Haaf, 2013[43]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Ikeda, 2002[62]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Ikeda, 2002[62]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Martin, 1998[83]	Yes	Yes	Unable to determine	No	NR support	Fair
Martin, 1998[83]	Yes	Yes	Yes	No	NR support	Fair
McCullough, 2002[84]	Yes	Yes	Yes	No	Yes industry support	Good
McCullough, 2002[84]	Yes	Yes	Unable to determine	No	NR support	Good
Noeller, 2003[91]	Yes	Yes	Yes	Yes	NR support	Fair
Noeller, 2003[91]	Yes	Yes	Unable to determine	Yes	NR support	Good

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Roppolo, 1999[102]	Yes	Unable to determine	Unable to determine	No	NR support	Good
Roppolo,1999[102]	Yes	Yes	Unable to determine	No	NR support	Poor
Sukonthasarn, 2007[113]	Yes	Unable to determine	Yes	No	No industry support	Fair
Sukonthasarn, 2007[113]	Yes	Yes	Yes	No	Yes industry support	Good
Troyanov, 2005[116]	Unable to determine	Unable to determine	Yes	No	Yes industry support	Fair
Troyanov, 2005[116]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair

NA=not applicable; NR=not reported

Table 5b. Study quality data for articles included in KQ2 and KQ3

Reporting

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Acharji, 2012[3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Chew, 2008[21]	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
Kontos, 2008[75]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Melloni, 2008[87]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Apple, 2007[9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Flores, 2006[37]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Bueti, 2006[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kontos, 2005[73]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Kontos, 2005[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Han, 2005[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Aviles, 2002[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gruberg, 2002[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wayand, 2000[123]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Van Lente, 1999[117]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviation: KQ=key question

Internal Validity -Bias

Author, year	Blinding those measuring outcomes	Data dredging	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Acharji, 2012[3]	Not feasible	Yes	Yes	Yes	Yes	Yes	Yes
Chew, 2008[21]	Not feasible	Yes	Yes	Yes	Yes	No	Yes
Kontos, 2008[75]	No	Yes	Yes	Yes	Yes	No	Yes
Melloni, 2008[87]	No	Yes	Yes	Yes	Yes	Yes	Yes
Apple, 2007[9]	No	Yes	Yes	Yes	Yes	No	Yes
Flores, 2006[37]	Not feasible	Yes	Yes	Yes	Yes	No	Yes
Bueti, 2006[20]	No	Yes	Yes	Yes	Yes	Yes	Yes
Kontos, 2005[73]	Not feasible	Yes	Yes	Yes	Yes	Yes	Yes
Kontos, 2005[74]	No	Yes	Yes	Yes	Yes	No	Yes
Han, 2005[45]	Not feasible	Yes	Yes	Yes	Yes	Yes	Yes
Aviles, 2002[12]	Yes	Yes	Yes	Yes	Yes	No	Yes
Gruberg, 2002[42]	No	No	Yes	Yes	Yes	No	Yes
Wayand, 2000[123]	Yes	Yes	Yes	Yes	Yes	No	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Van Lente, 1999[117]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

External validity - Power

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Acharji, 2012[3]	Yes	Yes	Unable to determine	Yes (in original RCT)	Yes	Good
Chew, 2008[21]	Unable to determine	Unable to determine	Unable to determine	No	NR	Poor
Kontos, 2008[75]	Yes	Unable to determine	Unable to determine	No	NR	Good
Melloni, 2008[87]	Yes	Yes	Yes	No	Yes	Good
Apple, 2007[9]	Yes	Yes	Unable to determine	No	Yes	Fair
Flores, 2006[37]	Unable to determine	Unable to determine	Unable to determine	No	NR	Poor
Bueti, 2006[20]	Yes	Yes	Yes	No	No	Good
Kontos, 2005[73]	Yes	Yes	Yes	No	NR	Fair
Kontos, 2005[74]	Yes	Unable to dtermine	Yes	No	NR	Good
Han, 2005[45]	Yes	Yes	Unable to determine	No	NR	Fair
Aviles, 2002[12]	Yes	Yes	Yes	No	Yes	Good
Gruberg, 2002[42]	Yes	Yes	Yes	No	NR	Good
Wayand, 2000[123]	Unable to determine	Unable to determine	Yes	No	NR	Fair

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Van Lente, 1999[117]	Yes	Yes	Yes	No	Yes	Good

Table 5c. Study quality data for articles included in KQ4

Reporting

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics Described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Abaci, 2004[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abbas, 2005[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apple, 1997[5]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Apple, 2002[7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apple, 2004[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Artunc, 2012[10]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Assa, 2013[11]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Bagheri, 2009[13]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Boulier, 2004[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bozbas, 2004[18]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Brunet, 2008[19]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Choy, 2003[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chrysochou, 2009[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Claes, 2010[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Codognotto, 2010[25]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Connolly, 2008[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conway, 2005[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Deegan, 2001[28]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
deFilippi, 2003[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics Described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Dierkes, 2000[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Duman, 2005[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Farkouh, 2003[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feringa, 2006[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fernandez-Reyes, 2004[36]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Gaiki, 2012[39]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Geerse, 2012[40]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Goicoechea, 2004[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hallen, 2011[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han, 2009[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Hasegawa, 2012[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Havekes, 2006[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Helleskov Madsen, 2008[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickman, 2009[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickson, 2008[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickson, 2009[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hocher, 2003[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hocher, 2004[55]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hocher, 2008[56]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hojs, 2005[57]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Holden, 2012[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Hussein, 2004[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Ie, 2004[61]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Iliou, 2003[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Ilva, 2008[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ishii, 2001[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kalaji, 2012[67]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Kang, 2009[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kanwar, 2006[69]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Katerinis, 2008[70]	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Kertai, 2004[71]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Khan, 2001[72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics Described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Lamb, 2007[77]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lang, 2001[78]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Le Goff, 2007[79]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Lowbeer, 2002[80]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lowbeer, 2003[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Mallamaci, 2002[82]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McGill, 2010[85]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
McMurray,2011[86]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Mockel, 1999[88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Morton, 1998[89]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Musso,1999[90]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Ooi, 1999[92]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Ooi, 2001[93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Orea-Tejeda, 2010[94]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Petrovic, 2009[96]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Porter, 1998[97]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Porter, 2000[98]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Quiroga, 2013[99]	Yes	Yes	Yes	No	Yes	No	No	No	No
Roberts,2009[101]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Sahinarslan, 2008[103]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Satyan, 2007[104]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scheven, 2012[105]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Scott, 2003[106]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sharma, 2005[107]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sharma, 2006[108]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Sharma, 2006[109]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shroff, 2012[110]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sommerer, 2007[111]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Stolear, 1999[112]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Svensson, 2009[114]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trape, 2008[115]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

Author, year	Main hypothesis/ objective described	Main outcome described	Patient characteristics Described	Interventions of interest described	Principal confounders described	Main findings described	Random variability estimate	Loss to follow up described	Actual probability values
Troyanov, 2005[116]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Vichairuangthum, 2006[118]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2006[119]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2007[120]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2010[121]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wolley, 2013[124]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Wood, 2003[125]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yakupoglu, 2002[126]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes

Abbreviation: KQ=key question

Internal Validity -Bias

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Abaci, 2004[1]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Abbas, 2005[2]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Apple, 1997[5]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Apple, 2002[7]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Apple, 2004[8]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Artunc, 2012[10]	Unable to determine	Yes	Yes	Yes	Unable to determine	Yes	Yes	Unable to determine	Yes
Assa, 2013[11]	No	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Unable to determine
Bagheri, 2009[13]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Boulier, 2004[17]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bozbas, 2004[18]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Brunet, 2008[19]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Choy, 2003[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chrysochou, 2009[23]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Claes, 2010[24]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Codognotto, 2010[25]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Connolly, 2008[26]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conway, 2005[27]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Deegan, 2001[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
deFilippi, 2003[29]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dierkes, 2000[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Duman, 2005[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Farkouh, 2003[33]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Feringa, 2006[35]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Fernandez-Reyes, 2004[36]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	No	Unable to determine
Gaiki, 2012[39]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Geerse, 2012[40]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Goicoechea, 2004[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hallen, 2011[44]	o	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han, 2009[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Hasegawa, 2012[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Havekes, 2006[48]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Helleskov Madsen, 2008[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Hickman, 2009[51]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickson, 2008[52]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickson, 2009[53]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hocher, 2003[54]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hocher, 2004[55]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hocher, 2008[56]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hojs, 2005[57]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Unable to determine	No	Yes
Holden, 2012[58]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hussein, 2004[60]	No	Yes	No	Yes	Yes	Yes	Yes	No	No
Ie, 2004[61]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Iliou, 2003[63]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ilva, 2008[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Ishii, 2001[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Kalaji, 2012[67]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kang, 2009[68]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kanwar, 2006[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Katerinis, 2008[70]	Unable to determine	Yes	Yes	Unable to determine	Yes	Yes	Yes	No	Yes
Kertai, 2004[71]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Khan, 2001[72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lamb, 2007[77]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lang, 2001[78]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	No	Yes
Le Goff, 2007[79]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes some	Unable to determine
Lowbeer, 2002[80]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lowbeer, 2003[81]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mallamaci, 2003[82]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McGill, 2010[85]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
McMurray, 2011[86]	No	Yes	Yes	Yes	Unable to determine	Yes	Yes	Yes some	Yes
Mockel, 1999[88]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unable to determine
Morton, 1998[89]	No	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes some	Unable to determine
Musso, 1999[90]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Unable to determine	No	No
Ooi, 1999[92]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ooi, 2001[93]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Orea-Tejeda, 2010[94]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Petrovic, 2009[96]	Unable to determine	No	Yes	Yes	Yes	Yes	Yes	Unable to determine	Unable to determine
Porter, 1998[97]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Porter, 2000[98]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	Unable to determine	Yes
Quiroga, 2013[99]	No	Unable to determine	No	No	No	Yes	Yes	Yes some	Unable to determine
Roberts, 2009[101]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sahinarslan, 2008[103]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Yes	Yes	Unable to determine
Satyan, 2007[104]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scheven, 2012[105]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scott, 2003[106]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Sharma, 2005[107]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Sharma, 2006[108]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sharma, 2006[109]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Shroff, 2012[110]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	No	Unable to determine
Sommerer, 2007[111]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Unable to determine	Yes
Stolear, 1999[112]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Svensson, 2009[114]	Unable to determine	Yes	Yes	Yes	Yes	Unable to determine	Unable to determine	Yes some	Yes
Trape, 2008[115]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, year	Blinding those measuring outcomes	Data dredging	Adjust for different followup	Appropriate statistical tests used	Main outcome measures accurate	Intervention groups from same population	Intervention groups recruited same time	Adequate adjustment for confounding in analyses	Losses to followup taken into account
Troyanov, 2005[116]	No	Yes	No	Yes	Yes	Yes	Yes	Yes some	Unable to determine
Vichairuangthum, 2006[118]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2006[119]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2007[120]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes some	Yes
Wang, 2010[121]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wolley, 2013[124]	Unable to determine	Unable to determine	No	Yes	Yes	Yes	Yes	Yes some	Unable to determine
Wood, 2003[125]	Unable to determine	Yes	Yes	Yes	Yes	Yes	Unable to determine	Yes some	Yes
Yakupoglu, 2002[126]	Unable to determine	Yes	Unable to determine	Yes	Yes	Yes	Unable to determine	No	Yes

External validity - Power

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Abaci, 2004[1]	Unable to determine	Yes	Yes	No	NR support	Fair
Abbas, 2005[2]	Unable to determine	Unable to determine	Yes	No	Yes industry support	Fair
Apple, 1997[5]	Yes	Yes	Unable to determine	No	Yes industry support	Fair
Apple, 2002[7]	Unable to determine	Unable to determine	Yes	No	Yes industry support	Fair
Apple, 2004[8]	Yes	Yes	Yes	No	Yes industry support	Good
Artunc, 2012[10]	Yes	Yes	Unable to determine	No	NR support	Fair
Assa, 2013[11]	Yes	Unable to determine	Unable to determine	No	NR support	Fair

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Bagheri, 2009[13]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Boulier, 2004[17]	Yes	Unable to determine	Unable to determine	No	Yes industry support	Good
Bozbas, 2004[18]	Unable to determine	Unable to determine	Yes	No	NR support	Poor
Brunet, 2008[19]	Yes	Yes	Yes	No	Yes industry support	Good
Choy, 2003[22]	Yes	Unable to determine	Yes	No	Yes industry support	Good
Chrysochou, 2009[23]	Yes	Unable to determine	Yes	No	NR support	Fair
Claes, 2010[24]	Yes	Unable to determine	Yes	No	NR support	Good
Codognotto, 2010[25]	Unable to determine	Unable to determine	Yes	No	No industry support	Fair
Connolly, 2008[26]	Yes	Yes	Yes	No	No industry support	Good
Conway, 2005[27]	Yes	Unable to determine	Unable to determine	No	NR support	Fair
Deegan, 2001[28]	Yes	Yes	Yes	No	NR support	Fair
deFilippi, 2003[29]	Yes	Yes	Unable to determine	No	Yes industry support	Fair
Dierkes, 2000[31]	Unable to determine	Yes	Yes	No	NR support	Good
Duman, 2005[32]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Farkouh, 2003[33]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Feringa, 2006[35]	Yes	Unable to determine	Yes	No	NR support	Good
Fernandez-Reyes, 2004[36]	Yes	Unable to determine	Unable to determine	No	NR support	Fair
Gaiki, 2012[39]	Yes	Unable to determine	Unable to determine	No	NR support	Fair
Geerse, 2012[40]	Yes	Yes	Yes	No	NR support	Fair
Goicoechea, 2004[41]	Unable to determine	Unable to determine	Yes	No	NR support	Good
Hallen, 2011[44]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Han, 2009[46]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Hasegawa, 2012[47]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Havekes, 2006[48]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Helleskov Madsen, 2008[50]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Good
Hickman, 2009[51]	Yes	Yes	Yes	Yes	NR support	Good
Hickson, 2008[52]	Unable to determine	Unable to determine	Yes	No	No industry support	Good
Hickson, 2009[53]	Unable to determine	Unable to determine	Yes	No	No industry support	Good

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Hocher, 2003[54]	Yes	Yes	Yes	No	No industry support	Good
Hocher, 2004[55]	Unable to determine	Unable to determine	Yes	No	No industry support	Good
Hocher, 2008[56]	Unable to determine	Unable to determine	Yes	No	No industry support	Good
Hojs, 2005[57]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Poor
Holden, 2012[58]	Yes	Yes	Yes	No	NR support	Good
Hussein, 2004[60]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Ie, 2004[61]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Iliou, 2003[63]	Unable to determine	Unable to determine	Yes	No	Yes industry support	Good
Ilva, 2008[64]	Yes	Unable to determine	Yes	No	Yes industry support	Good
Ishii, 2001[65]	Yes	Yes	Unable to determine	No	Yes industry support	Good
Kalaji, 2012[67]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Kang, 2009[68]	Unable to determine	Yes	Unable to determine	No	No industry support	Fair
Kanwar, 2006[69]	Yes	Yes	Yes	No	Yes industry support	Good
Katerinis, 2008[70]	Yes	Yes	Yes	No	NR support	Poor
Kertai, 2004[71]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Khan, 2001[72]	Unable to determine	Yes	Yes	No	NR support	Good
Lamb, 2007[77]	Yes	Yes	Yes	No	Yes industry support	Good
Lang, 2001[78]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Fair
Le Goff, 2007[79]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Lowbeer, 2002[80]	Unable to determine	Unable to determine	Yes	No	No industry support	Fair
Lowbeer, 2003[81]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Mallamaci, 2002[82]	Unable to determine	Yes	Yes	No	NR support	Good
McGill, 2010[85]	Yes	Unable to determine	Yes	No	No industry support	Fair
McMurray, 2011[86]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Fair
Mockel, 1999[88]	Unable to determine	Unable to determine	Yes	No	Yes industry support	Fair

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Morton, 1998[89]	Yes	Yes	Yes	No	No industry support	Good
Musso, 1999[90]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Ooi, 1999[92]	Yes	Unable to determine	Unable to determine	No	NR support	Fair
Ooi, 2001[93]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Good
Orea-Tejeda, 2010[94]	Yes	Unable to determine	Yes	No	No industry support	Fair
Petrovic, 2009[96]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Porter, 1998[97]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Porter, 2000[98]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Fair
Quiroga, 2013[99]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Roberts, 2009[101]	Yes	Unable to determine	Yes	No	Yes industry support	Fair
Sahinarslan, 2008[103]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair
Satyan, 2007[104]	Yes	Yes	Yes	No	No industry support	Good
Scheven, 2012[105]	Yes	Unable to determine	Unable to determine	No	No industry support	Fair
Scott, 2003[106]	Yes	Unable to determine	Unable to determine	No	No industry support	Good
Sharma, 2005[107]	Yes	Yes	Yes	No	NR support	Good
Sharma, 2006[108]	Yes	Yes	Yes	No	NR support	Fair
Sharma, 2006[109]	Yes	Yes	Unable to determine	No	No industry support	Fair
Shroff, 2012[110]	Yes	Unable to determine	Unable to determine	No	Yes industry support	Fair
Sommerer, 2007[111]	Unable to determine	Yes	Unable to determine	No	NR support	Fair
Stolear, 1999[112]	Yes	Yes	Unable to determine	No	Yes industry support	Good
Svensson, 2009[114]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Fair
Trape, 2008[115]	Unable to determine	Unable to determine	Yes	No	NR support	Good
Troyanov, 2005[116]	Unable to determine	Unable to determine	Unable to determine	No	Yes industry support	Fair
Vichairuangthum, 2006[118]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair

Author, year	Population asked representative	Population prepared participate representative	Staff places facilities representative	Power calculation reported	Industry support	Overall quality
Wang, 2006[119]	Yes	Yes	Yes	No	No industry support	Good
Wang, 2007[120]	Yes	Yes	Yes	No	No industry support	Good
Wang, 2010[121]	Yes	Yes	Yes	No	No industry support	Good
Wolley, 2013[124]	Unable to determine	Unable to determine	Unable to determine	No	No industry support	Fair
Wood, 2003[125]	Unable to determine	Unable to determine	Yes	No	NR support	Fair
Yakupoglu, 2002[126]	Unable to determine	Unable to determine	Unable to determine	No	NR support	Fair

Abbreviations: NA = not applicable; NR = not reported

Appendix E. Overview of Studies Included in the Meta-Analyses

Table 1. Studies included/excluded for cTnT and all-cause mortality for dialysis patients

Author, Year	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Kalaji, 2012[67]	X	X		
Holden, 2012[58]	X			
Hallen, 2011[44]	X	X		
Codognotto, 2010[25]	Derived			
Hickman, 2009[51]		X		Not included in HR meta-analysis because presented OR and not enough data to derive HR
Petrovic, 2009[96]			X	Insufficient information to derive any HR or OR
Chrysochou, 2009[23]			X	Belongs in non-dialysis group.
Bagheri, 2009[13]			X	Very poor quality study; unclear measures, did not provide data for all participants
Roberts, 2009[101]			X	Definition of a troponin qualitatively different (number of times troponin was elevated)
Trape, 2008[115]		X		
Sahinarslan, 2008[103]		X		
Helleskov Madsen, 2008[50]	X	X		
Satyan, 2007[104]	X			
Wang, 2007[120]		X-Choose 0.1 cutpoint to dichotomize data		
Havekes, 2006[48]	X			
Sharma, 2006[109]**,** Sharma, 2005[107]		X		
Duman, 2005[32]		X-used same cutpoint as HR meta-analysis		Not included in HR meta-analysis because presented OR and not enough data to derive HR
Abaci, 2004[1]		X-Choose 0.1 cutpoint to dichotomize data		
Fernandez-Reyes, 2004[36]	X			
Ie, 2004[61]		X		
Iliou, 2003[63]	X	X		

Author, Year	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Choy, 2003[22]		X		Not included in HR meta-analysis because presented OR and not enough data to derive HR
deFilippi, 2003[29]	X	X-Choose 0.117 cutpoint to dichotomize data		
Scott, 2003[106]			X	Study provided a coefficient for a log rank test; Insufficient information to derive other statistics
Lowbeer, 2002[80]	X	X		
Mallamaci, 2002[82]	X			
Deegan, 2001[28]	Derived	X		
Ishii, 2001[65]	X	X		
Lang, 2001[78]		X		
Dierkes, 2000[31]	X	X-choose same cutpoint as HR meta-analysis		
Stolear, 1999[112]	X	X		
Mockel, 1999[88]			X	Does not report results for dialysis patients separately
Musso, 1999[90]			X	Results are not reported separately for a dialysis population
Apple, 2002[7], Apple, 2004[8]	X	X		
Ooi, 1999[92], **Ooi, 2001**[93]	*X*	**X-Choose 0.1 cutpoint to dichotomize data**		
Porter, 1998[97], **Porter, 2000**[98]		X		
Hocher, 2003[54], Hocher, 2004[55]**, Hocher, 2008**[56]	X			
Svensson, 2009[114]			X	Unclear cut-point
Le Goff, 2007[79]			X	Only included patients with NT proBNP >5000
Brunet, 2008[19]		X		
Artunc, 2012[10]	X			
McGill, 2010[85]			X	Data presented as a continuous variable.

Table 2. Studies included/excluded in the meta-analysis for cTnI and all-cause mortality for dialysis patients

Study	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Geerse, 2012[40]	X	X-dichotomized data at 0.1 cutpoint		
Artunc, 2012[10]			X	High sensitivity assay
Kalaji, 2012[67]	X	X		
Codognotto, 2010[25]			X	Insufficient data reported
Hickman, 2009[51]		X		Not included in HR meta-analysis because study reported an OR, not HR
Petrovic, 2009[96]			X	Insufficient data to be included in meta-analysis
Kang, 2009[68]	X	X		
Helleskov Madsen, 2008[50]	X	X		
Katerinis, 2008[70]		X		
Brunet, 2008[19]		X-Beckman Access 0.06 cutpoint		
Kanwar, 2006[69]		X-used CHD(-) group		
Duman, 2005[32]		X		
Abaci, 2004[1]		X		
Hussein, 2004[60]		X		
Boulier, 2004[17]	X			
Choy, 2003[22]		X		
Farkouh, 2003[33]	X	X		
Apple, 2002[7]**,** Apple, 2004[8]	X			
Lowbeer, 2002[80]			X	No data reported for cTnI –just qualitative statement of no difference
Khan, 2001[72]		X		
Ishii, 2001[65]		X		
Lang, 2001[78]		X-Dade Stratus data		
Mockel, 1999[88]			X	Results are not separated by dialysis patients.
Musso, 1999[90]			X	Results are not separated by dialysis patients
Porter, 1998[97]		X-Dade data		
Morton, 1998[89]			X	No data for analysis
Iliou, 2003[63]	X			
Assa, 2013[11]			X	Data presented as a continuous variable.
Artunc, 2012[10]	X			

Study	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Gaiki, 2012[39]		X		

Table 3. Studies included/excluded for cTnT and cardiovascular mortality for dialysis patients

Study	Included in HR meta-analysis	Included in OR meta-analysis	Excluded from both meta-analyses	Reason for exclusion
Abaci, 2004[1]		X-dichotomized on >0.1 cutpoint		
Apple, 1997[5]		X		
Deegan, 2001[28]		X		
Duman, 2005[32]		X		I ran the OR analysis with and without this study. The problem is that it does not report number of events and sample sizes, just an adjusted OR.
Havekes, 2006[48]	X			
Hocher, 2003[54]; Hocher, 2004[55]; **Hocher, 2008**[56]	X			
Hojs, 2005[57]		X		
Iliou, 2003[63]	X	X-used >0.1 cutpoint		
Ishii, 2001[65]	X	X		
Lang, 2001[78]		X-Used ELISA data		
Le Goff, 2007[79]			X	
Mallamaci, 2002[82]	X			
Ooi, 1999[92], *Ooi, 2001*[93]	**X**	*X*		
Satyan, 2007[104]	X			
Wang, 2007[120], Wang, 2010[122]		X-dichotomized on >0.1 cutpoint		The 2 Wang publications were excluded from the HR meta-analysis because 1743 did not provide a clear cut-point and 6702 had a narrow definition of CVD mortality
Wolley, 2013[124]			X	Data analyzed as a continuous variable.

Table 4. Studies included/excluded for cTnI and cardiovascular mortality for dialysis patients

Study	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Abaci, 2004[1]		X		
Apple, 1997[5]		X		
Boulier, 2004[17]	X			
Duman, 2005[32]			X	Insufficient information to derive any values.
Ishii, 2001[65]		X		
Kang, 2009[68]	X			
Khan, 2001[72]		X		
Lang, 2001[78]		X		

Study	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Vichairuangthum, 2006		X		
Yakupoglu, 2002[126]		X-excluded in sensitivity analysis		
Geerse, 2012[40]		X-used 0.1 cutpoint		
Gaiki, 2012[39]		X		

Table 5. Studies included/excluded for cTnT and MACE >1 year for dialysis patients

Study	Included in HR Meta-Analysis	Included in OR Meta-Analysis	Excluded From Both Meta-Analyses	Reason for Exclusion
Sahinarslan, 2008[103]		X		
Brunet, 2008[19]		X		
Han, 2005[45]	X	X		
Sommerer, 2007[111]		X-analysis ran with and without study		Sommerer only presents an adjusted odds ratio.
Wang, 2007[120]		X		
Conway, 2005[27]		X		
Iliou, 2003[63]	X	X		
Porter, 2000[98]		X		
Apple, 1997[5]		X		
Assa, 2013[11]			X	Data analyzed as a continuous variable.

Table 6. Studies included/excluded for cTnI and MACE >1 year for dialysis patients

Study	Included in OR Meta-Analysis	Included in Sensitivity Analysis #1	Included in Sensitivity Analysis #2	Excluded From Meta-Analyses & Reason for Exclusion
Katerinis, 2008[70]			X	
Brunet, 2008[19]	X-Used Beckman 0.06 cutpoint	X	X	
Vichairuangthum, 2006[118]	X-Used 0.4 cutpoint	X	X	
Troyanov, 2005[116]	X-abstracted data from KM curve	X	X	
Hung, 2004[59]		X		
Beciani, 2003[15]			X	
Yakupoglu, 2002[126]				X – This is cardiovascular mortality.
Porter, 2000[98]	X-Used Dade 0.4 cutpoint	X	X	
Apple, 1997[5]	X	X	X	
Gaiki, 2012[39]	X	X	X	

Table 7. Studies included/excluded for cTnI and MACE <1 year for dialysis patients

Study	Included in OR Meta-Analysis	Excluded From Meta-Analyses & Reason for Exclusion
Roberts, 2004[100]	X	
Peetz, 2003[95]		X – I don't think there is sufficient data to derive an odds ratio. Using DigitizeIt, we were able to get the point estimate and the upper bound of the confidence interval. However, we are not able to abstract the lower bound of the CI. These numbers are very imprecise, so I would be reluctant to use them.
Heeschen, 2000[49]	X	
Roppolo, 1999[102]	X	

Appendix F. List of Covariate Adjustment per Individual Studies

CAD Risk Equivalents included: CAD, cerebrovascular disease, vascular disease, PVD, reduced LVEF, heart failure, or diabetes

Study	Dialysis (D) or non-D (ND)	Troponin Assay	Outcome	Variables Adjusted for	Included in meta-analysis (yes, no)
Abbas, 2005[2]	ND	Troponin I	All-cause mortality	Age, sex, eGFR, diabetes	NO for HR Gives adjusted OR but not HR
Abbas, 2005[2]	ND	Troponin T	All-cause mortality	Age, sex, eGFR, diabetes	NO for HR Gives OR but not HR
Alam, 2013[129]	D	Troponin I	All-cause mortality	Adjusted for age, time of dialysis, diabetes, history of CAD, CRP	YES-HR
Alam, 2013[129]	D	Troponin I	CVD mortality	Adjusted for age, time of dialysis, diabetes, history of CAD, CRP	YES-HR
Apple, 2002[7] Apple, 2004[8]	D	Troponin T	All-cause mortality	Age, history of CAD, time since first dialysis	YES-HR
Apple, 2002[7]	D	Troponin I	All-cause mortality	Age, history of CAD,	YES-HR
Bayes-Genis, 2013[130]	ND	Troponin T	All-cause mortality	Age, sex, diabetes, ischemic etiology of HF, LVEF, others	NO HR for troponin presented as continuous variable; unclear if dialysis patients excluded
Boulier, 2004[17]	D	Troponin I	All-cause mortality Total sample	Age, sex, diabetes, smoking, cholesterol/TG, time in dialysis, dialysis center/ modality, hypertension (*although the authors present stratified results by CHD or non-CHD status, main analyses not adjusted for CHD)	YES-HR
Boulier, 2004[17]	D	Troponin I	CVD mortality	Age, sex, diabetes, smoking, cholesterol/TG, time in dialysis, dialysis center/ modality, hypertension	YES-HR
Choy, 2003[22]	D	Troponin T	All-cause mortality	Age, sex, history of CAD, diabetes, years on dialysis	NO for HR. Presented adjusted OR only and not enough data to derive a HR.
Claes, 2010[24]	ND- post renal transplant	Troponin I	Other composite: AMI, revascularization, or death due to an ischemic event	Age, hematocrit, history of cardiovascular disease	NO for HR Special population - only post renal transplant group
Connolly, 2008[26]	ND – post renal transplant	Troponin T	All-cause mortality	Age, sex, smoking, diabetes, systolic BP, diastolic BP, total cholesterol, HDL, BMI, hemoglobin, serum phosphate, parathyroid hormone	NO - special population of post renal transplant
Conway, 2005[27]	D	Troponin T	MACE	Age, sex, history of CAD, PVD, diabetes,	NO for HR – troponin

				length of time of HD	presented continuously
Dierkes, 2000[31]	D	Troponin T	All-cause mortality	Age, time of dialysis, diabetes, cerebrovascular disease	YES-HR
Farkouh, 2003[33]	D	Troponin I	All-cause mortality	Age, sex, history of CAD, Diabetes, smoking, angina or MI, hypertension, cholesterol levels, CK,CK-MB levels	YES-HR
Farshid, 2013[131]	Mixed D and ND	Troponin T	All-cause mortality	Age, sex, diabetes, history of MI, LVEF, diastology	NO (HR were not presented separately for dialysis and non-dialysis status, mixed population)
Feringa, 2006[35]	ND	Troponin T	MACE	Age, sex, history of CAD	YES-HR
Feringa, 2006[35]	ND	Troponin T	All-cause mortality	Age, sex, history of CAD, eGFR	YES-HR
Hallen, 2011[44]	D	Troponin T	All-cause mortality	Age, sex, creatinine, duration of disease, CHF, diabetes, albumin, LVEF	YES-HR
Hasegawa, 2012[47]	ND	Troponin T	Composite: MACE	Age, History of CAD, Diabetes, eGFR	YES-HR
Hassan, 2014[132]	D	Troponin T	All-cause mortality	Age, history of cardiac disease, prior cardiac events, CRP, albumin	NO HR presented for troponin as a continuous variable only
Hassan, 2014[132]	D	Troponin T	MACE	Age, history of cardiac disease, prior cardiac events, CRP, albumin	NO for HR. HR presented for troponin as a continuous variable only
Havekes, 2006[48]	D	Troponin T	All-cause mortality	Age, sex, comorbidity, primary renal disease, smoking, BMI, GFR, BP, hemoglobin, albumin, cholesterol, comorbidity includes history of CAD, PVD, cerebrovascular disease, LVEF	YES-HR
Havekes, 2006[48]	D	Troponin T	CVD Mortality	Age, sex, cormorbidity, primary renal disease, smoking, BMI, GFR, BP, hemoglobin, albumin, cholesterol, comorbidity includes history of CAD, PVD, cerebrovascular disease, LVEF	YES-HR
Helleskov Madsen, 2008[50]	D	Troponin T	All-cause mortality	Age, reduced LVEF, diabetes	YES-HR
Helleskov Madsen, 2008[50]	D	Troponin I	All-cause mortality	Age, reduced LVEF, diabetes	YES-HR
Hickson, 2008[52]	ND and D mixed – waiting for renal transplant	Troponin T	All-cause mortality	Age, sex, race, serum albumin, history of stroke, BMI, smoking, creatinine, dialysis use, time of dialysis, cholesterol, hemoglobin, history of previous transplant	NO for HR – mixed population of non-dialysis and dialysis
Hickson, 2009[53]	ND – post renal transplant	Troponin T	MACE	Age, dialysis time, low ejection fraction, delayed graft function	NO -Special population kidney transplant recipients
Hocher, 2008[56]	D	Troponin T	All-cause mortality	Age, history of CAD, diabetes	YES-HR
Hocher, 2008[56]	D	Troponin T	CVD mortality	Age, History of CAD, diabetes	YES-HR
Hung, 2004[59]	D	Troponin I	MACE	Age, sex, ECG findings (suggestive of	NO

			Hypertension prone patients	previous MI, ischemic changes, LVH)	Adjusted OR only – for subgroup of hypotension prone patients
Iliou, 2003[63]	D	Troponin T	CVD mortality	Age, history of CAD, hematocrit	YES-HR
Iliou, 2003[63]	D	Troponin T	MACE	Age, history of CAD	YES-HR
Ishii, 2001[65]	D	Troponin T	CVD mortality	Hypercholesterolemia, history of heart failure	YES-HR
Ishii, 2001[65]	D	Troponin T	All-cause mortality	Age, history of heart failure	YES-HR
Kalaji, 2012[67]	D	Troponin T	All-cause mortality	Age, history of CAD, time of dialysis, Diabetes, LV ejection fraction	YES-HR
Kalaji, 2012[67]	D	Troponin I	All-cause mortality	Age, history of CAD, diabetes, time of Dialysis	YES-HR
Kang, 2009[68]	D	Troponin I	All-cause mortality	Age, history of CAD, History of CVD, Diabetes, presence of septic shock, serum CRP, albumin	YES-HR
Kang, 2009[68]	D	Troponin I	CVD mortality	Age, history of CAD, Diabetes	YES-HR
Lamb, 2007[77]	ND	Troponin T	All-cause mortality	Age, hemoglobin concentration, vascular disease	YES-HR
Lamb, 2007[77]	ND	Troponin I	All-cause mortality	Age, hemoglobin concentration, vascular disease	YES-HR
Levin, 2013[133]	ND	Troponin I	All-cause mortality	age, sex, eGFR, history of CVD, serum phosphate, and albumin	YES-HR
Lowbeer, 2003[81]	D	Troponin T	All-cause mortality	Age, sex, cardiovascular disease, malnutrition, diabetes, IL-6	YES-HR
Mallamaci, 2002[82]	D	Troponin T	All-cause mortality	Age, sex, diabetes, smoking, previous CVD events, LVM,	YES-HR
Mallamaci, 2002[82]	D	Troponin T	CVD mortality	Age, sex, diabetes, smoking, previous CVD events, LVM,	YES-HR
McMurray, 2011[86]	ND	Troponin T	MACE	Age, CHF, smoking, CHD, CVD, PAD, HbA1c	YES-HR
Sahinarslan, 2008[103]	D	Troponin T	MACE	Age, sex, hypertension, diabetes, hemoglobin, creatinine, albumin	No for HR – presents only adjusted OR.
Scheven, 2012[105]	ND	Troponin T	MACE	Age, sex, history of cardiovascular disease, smoking, BMI,SBP, cholesterol level, Diabetes	YES-HR
Sommerer, 2007[111]	D	Troponin T	MACE	Age, sex, history of CAD, NTpro BNP, dialysis >36 months, diabetes	NO Only adjusted OR not adjusted HR
Stolear, 1999[112]	D	Troponin T	All-cause mortality	Age, sex, history CAD, CRP hematocrit, pre-albumin	YES-HR
Wang, 2007[120]	D	Troponin T	All-cause mortality	Age, history of CAD	NO – not enough info for HR. Unclear if HR presented by troponin cutpoint or continuously
Wang, 2007[120]	D	Troponin T	CVD mortality	Age, history of CAD	NO – not enough info for HR. Unclear if HR presented by troponin cutpoint or continuously

Wang, 2007[120]	D	Troponin T	MACE	Age, history of CAD	NO – not enough info for HR. Unclear if HR presented by troponin cutpoint or continuously
Wood, 2003[125]	ND	Troponin T	All-cause mortality	Age, sex, diabetes, history of CAD, creatinine	No for HR - Troponin as continuous
deFilippi, 2003[29]	D	Troponin T	All-cause mortality	Age, sex	YES-HR
Duman, 2005[32]	D	Troponin T	All-cause mortality	Age	NO for HR Adjusted OR only
Duman, 2005[32]	D	Troponin I	All-cause mortality	Age	No for HR Adjusted OR only
Duman, 2005[32]	D	Troponin T	CVD mortality	Age	NO for HR Adjusted OR only
Geerse, 2012[40]	D	Troponin I	All-cause mortality	Age, Sex	YES-HR
Han, 2009[46]	D	Troponin T	MACE	Age, IL-6, CRP	YES-HR
Holden, 2012[58]	D	Troponin T	All-cause mortality	Age	YES-HR
Iliou, 2003[63]	D	Troponin T	All-cause mortality	Age, hematocrit *(Note: For the CVD mortality outcome, history of CAD is adjusted for but not for all-cause mortality outcome)*	YES-HR
Iliou, 2003[63]	D	Troponin I	All-cause mortality	Age, hematocrit	YES-HR
McGill, 2010[85]	D	Troponin T	All-cause mortality	Adjusted- but no details	NO- Troponin presented as continuous
Satyan, 2007[104]	D	Troponin T	All-cause mortality	Age, sex, race, serum albumin, ESRD cause	YES-HR
Satyan, 2007[104]	D	Troponin T	CVD mortality	Age, sex, race, serum albumin, ESRD cause	YES-HR
Svensson, 2009[114]	D	Troponin T	All-cause mortality	Age, sex, BP	NO. Troponin as continuous
Abaci, 2004[1]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Abaci, 2004[1]	D	Troponin I	All-cause mortality Cardio mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Abaci, 2004[1]	D	Troponin T	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Apple, 1997[5]	D	Troponin T Troponin I	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Apple, 1997[5]	D	Troponin T	MACE	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Artunc, 2012[10]	D	Troponin T	All-cause mortality	Unadjusted	YES-HR
Artunc, 2012[10]	D	Troponin I	All-cause mortality	Unadjusted	YES-HR
Bagheri, 2009[13]	D	Troponin T	All-cause mortality	Unadjusted	NO, Insufficient data, unclear measures, did not provide data for all participants
Brunet, 2008[19]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Brunet, 2008[19]	D	Troponin T	MACE	Unadjusted	NO – not enough info for HR

					Included in OR meta-analysis
Choy, 2003[22]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Chrysochou, 2009[23]	Mixed ND and D	Troponin T	All-cause mortality	Unadjusted	NO – population is selective for renal artery stenosis patients, not separated by dialysis and non-dialysis, unclear if HR for troponin is continuous or cutpoint
Codognotto, 2010[25]	D	Troponin T	All-cause mortality	Adjusted –details NS (adjusted for ProBNP and CRP, unclear if adjusted for age or other variables).	YES-HR
Deegan, 2001[28]	D	Troponin T	All-cause mortality	Unadjusted	YES-HR
Deegan, 2001[28]	D	Troponin T	CVD mortality	Unadjusted	NO – not enough information for HR Included in OR meta-analysis
Duman, 2005[32]	D	Troponin I	CVD mortality	Unadjusted	NO – insufficient information to derive any values
Fernandez-Reyes, 2004[36]	D	Troponin T	All-cause mortality	Unadjusted	YES-HR
Gaiki, 2012[39]	D	Troponin I	MACE	Unadjusted	NO – insufficient information for analyses
Giocoechea, 2004[41]	ND	Troponin T	MACE	Unadjusted	YES-HR
Heeschen, 2000[49]	D	Troponin I	MACE	Unadjusted	NO – insufficient information for analyses
Hickman, 2009[51]	D	Troponin T	All-cause mortality	Unadjusted	NO for HR (not enough information to derive a HR) YES for OR
Hojs, 2005[57]	D	Troponin T	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Hussein, 2004[60]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Ishii, 2001[65]	D	Troponin I	All-cause mortality CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Kanwar, 2006[69]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis Separated into CAD+ and CAD- groups; used CHD-group
Katerinis, 2008[70]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Kertai, 2004[71]	ND	Troponin T	All-cause mortality	Unadjusted	YES-HR
Khan, 2001[72]	D	Troponin I	All-cause mortality CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis

Lang, 2001[78]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Lang, 2001[78]	D	Troponin T Troponin I	All-cause mortality CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Le Goff, 2007[79]	D	Troponin T	All-cause mortality CVD mortality	Unadjusted	NO not enough info for HR Troponin results combined with NT-proBNP levels, not troponin alone.
Ie, 2004[61]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Lowbeer, 2002[81]	D	Troponin T	All-cause mortality	Unadjusted	YES-HR
Mockel, 1999[88]	D and ND	Troponin T, Troponin I	All-cause mortality	Unadjusted	NO- Mixed D and ND, no statistical measures of association given
Morton, 1998[89]	D	Troponin I	All-cause mortality	Unadjusted	NO – no data for analysis
Musso, 1999[90]	D and ND	Troponin T, Troponin I	All-cause mortality	Unadjusted	NO-Results are not reported separately for a dialysis population
Ooi, 1999[92] Ooi, 2001[93]	D	Troponin T	All-cause mortality	Unadjusted	YES-HR
Ooi, 1999[92]	D	Troponin T	CVD mortality	Unadjusted	YES-HR
Peetz, 2003[95]	D	Troponin I	MACE	Unadjusted	NO – OR given, but no CI or number of events in each arm
Petrovic, 2009[96]	D	Troponin T	All-cause mortality	Unadjusted	NO Insufficient information to derive any HR or OR
Petrovic, 2009[96]	D	Troponin I	All-cause mortality	Unadjusted	NO – insufficient data to be included in meta-analysis
Porter, 1998[97]	D	Troponin I	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Porter, 1998;[97] Porter, 2000[98]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Porter, 2000[98]	D	Troponin T	MACE	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Roberts, 2004[100]	D	Troponin I	MACE	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Roberts, 2009[101]	D	Troponin T	All-cause mortality	Unadjusted	NO: Definition of troponin elevation is qualitatively different (# of times troponin was elevated)
Roberts, 2009[101]	D	Troponin T	CVD mortality	Unadjusted	NO: Definition of troponin elevation is qualitatively different (# of times troponin was elevated)

Roppolo, 1999[102]	D	Troponin I	MACE	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Sahinarslan, 2008[103]	D	Troponin T	All-cause mortality MACE	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Scott, 2003[106]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR. Study provided a coefficient for a long rank test; insufficient information to derive other statistics.
Sharma, 2006;[108] Sharma, 2005[107]	D	Troponin T	All-cause mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Trape, 2008[115]	D	Troponin T	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Vichairuangthum, 2006[118]	D	Troponin I	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis
Yakupoglu, 2002[126]	D	Troponin I	CVD mortality	Unadjusted	NO – not enough info for HR Included in OR meta-analysis Excluded in a sensitivity analysis

AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHD = coronary heart disease; CRP = C-reactive protein; CVD = cardiovascular disease; D = dialysis; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; HF = heart failure; HR = hazard ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; ND = nondialysis; OR = odds ratio; PAD = peripheral arterial disease; PVD = peripheral vascular disease; TG = triglycerides

Appendix G. Troponin Assays for Background Reference

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
cTnI	Abbot Laboratories	ADV AxSYM cTnI Immunoassay	NR	0.4	0.04	NR	Storti S, Prontera C, Parri MS, et al. Evaluation of the analytical performance of the advanced method for cardiac troponin I for the AxSYM platform: comparison with the old method and the Access system. Clin Chem Lab Med 2006;44(8):1022-29 PMID: 16879072
cTnI	Abbot Laboratories	Architect ci8200	2nd	0.032	0.012	NR	Tate JR, Ferguson W, Bais R, et al. The determination of the 99th centile level for troponin assays in an Australian reference population. Ann Clin BIochem. 2008;45(Pt 3):275-88 PMID:18482916
cTnI	Abbot Laboratories	Architect STAT	NR	0.03	0.012	N: 480 Age: 16 to 82	Lam Q, Black M, Youdell O, et al. Performance evaluation and subsequent clinical experience with the Abbott Automated Architect STAT Troponin-I assay. Clin CHem. 2006;52(2):298-300 PMID: 16449210
cTnI	Abbot Laboratories	AxSYM	NR	0.8	0.5	NR	Apple FS, Quist HE, Doyle PJ, et al. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-6
cTnI	Astra	Cardiac STATus Troponin I Rapid Test					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnI	Baxter	Stratus					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnI	Bayer	ACS: 180	NR	0.37	0.1	Eight serum pool samples (details NR)	Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentration. Clin Chem. 2004;50(2):327-32 PMID: 14656904

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
cTnI	Bayer	ADVIA Centaur	NR	0.35	0.1	NR	Apple FS, Quist HE, Doyle PJ, et al. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-6
cTnI	Bayer	Immuno1	NR	0.34	0.1	Eight serum pool samples (details NR)	Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentration. Clin Chem. 2004;50(2):327-32 PMID: 14656904
hscTnI	Bayer	Advia Cenatur (Ultra)	NR	0.33	0.07	NR	Foohey L, Neighbor S, Buchmelter T, et al. Troponin clinical applications. Bayer Healthcare Diagnostics Division. 2006 (http://www.medical.siemens.com/siemens/en_GLOBAL/gg_diag_FBAs/files/brochures/TnI_Assay/tni_wp2.pdf)
cTnI	Beckman Coulter	Access Acu	NR	0.06	0.04	NR	IFCC Troponin tables
cTnI	Beckman Coulter	AccuTnI	NR	0.06	0.04	NR	Morrow DA, Rifai N, Sabatine MS, et al. Evaluation of the Accu TnI cardiac troponin I assay for risk assessment in acute coronary syndromes. Clin Chem. 2003;49(8):1396-8 PMID: 12881457
cTnI	Beckman Coulter	Chemiluminescent Immunoenzymatic Assay					"Chemiluminescent Immunoenzymatic Assay" is too broad of a term, need more specific assay name.
cTnI	Bio-Merieux	Vidas	NR	0.11	0.01	N: 747 Age: 20 to 81	IFCC Troponin tables
cTnI	BioSite Diagnostics	Triage Cardiac Panel	NR	0.05	0.05	NR	http://emj.bmj.com/content/suppl/2012/03/21/emermed-2011-200667.DC1/emermed-2011-200667-s6.pdf
hscTnI	Boehringer Mannheim (company bought by Roche)	Elecsys	NR	0.005	0.014	NR	Hoeller R, Rubini Gimenez M, Reichlin T, et al. Normal presenting levels of high-sensitivity troponin and myocardial infarction. Heart. 2013: Epub ahead of print PMID: 23604180

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
cTnT	Boehringer Mannheim	Elecsys	3	0.035	0.01	NR	Fesmire FM, Decker WW, Diercks DB, et al. Clinical policy: critical issues in the evaluation and management of adult patients with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2006;48(30:270-301 PMID: 16934648
cTnT	Boehringer Mannheim	Cardiac Reader					"Cardiac Reader" is too broad of a term, need more specific assay name.
cTnT	Boehringer Mannheim	ELISA	2	0.01	0.1	N: 323, with suspected AMI	Muller-Bardoff M, Hallermayer K, Schroder A, et al. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. Clin Chem. 1997;43(3):458-66 PMID: 9068589
cTnT	Boehringer Mannheim	TropT-sensitive Rapid Test					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnT	Boehringer Mannheim	Enzymun					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnT	Boehringer Mannheim	TROP TRA-Rapid Beside Assay					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnI	Dade Behring	Opus	NR	0.9	0.1	Eight serum pool samples (details NR)	Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentration. Clin Chem. 2004;50(2):327-32 PMID: 14656904
cTnI	Dade Behring	OPUS Plus	1	0.3	0.1	NR	Fesmire FM, Decker WW, Diercks DB, et al. Clinical policy: critical issues in the evaluation and management of adult patients with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2006;48(30:270-301 PMID: 16934648
cTnI	Dade Behring	Opus Magnum Analyzer	NR	3.0 (12% CV)	0.5	NR	Kontos MC, Shah R, Fritz LM, et al. Implication of different cardiac troponin I levels for clinical outcomes and prognosis of acute chest pain patients. J AM Coll Cardiol. 2004;43(6):958-65 PMID: 15028350

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
cTnI	Dade Behring	Stratus	NR	0.1	0.07	Eight serum pool samples (details NR)	Panteghini M, Pagani F, Yeo KT, et al. Evaluation of imprecision for cardiac troponin assays at low-range concentration. Clin Chem. 2004;50(2):327-32 PMID: 14656904
cTnI	Dade Behring	Stratus-II Enzyme Immunoassay	NR	0.6	<0.35 (97.5 percentile, 99th% NR)	NR	Boriani G, Biffi M, Cervi V, et al. Evaluation of myocardial injury following repeated internal atrial shocks by monitoring serum cardiac troponin I levels. Chest. 2000;118(2):342-7 PMID: 10936122
cTnI	Diagnostic Product Corp	Immulite	1st	0.6	0.2	NR	Fesmire FM, Decker WW, Diercks DB, et al. Clinical policy: critical issues in the evaluation and management of adult patients with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2006;48(30:270-301 PMID: 16934648
cTnI	Johnson and Johnson	Vitros ECi	1st	0.12	0.08	NR	Fesmire FM, Decker WW, Diercks DB, et al. Clinical policy: critical issues in the evaluation and management of adult patients with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2006;48(30:270-301 PMID: 16934648
cTnI	Ortho Clinical Diagnostics	Vitros					Search for "Vitros" brings up every assay in the Vitros assay series.
hscTnI	Ortho Clinical Diagnostics	Vitro ES	NR	0.034	0.034	NR	IFCC Troponin tables (from Erin)
cTnT	Roche	Cardiac-ELISA ES300	2nd	0.06	0.01	N: 750 Age: 58 to 78	Jernberg T, Venge P, Lindahl B. Comparison between second and third generation troponin T assay in patients with symptoms suggestive of an acute coronary syndrome but without ST segment elevation. Cardiology. 2003;100(1):29-35 PMID: 12975543
cTnT	Roche	Immunochemical test					"Immunochemical test" is not a specific assay, refers to broad range of assay types that use immunochemical technology.

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
cTnT	Roche	ECLIA (electrochemiluminescence immunoassay, used in Elecsys)	NR	0.013	0.014	N: 294, with chest pain and suspected AMI	Roche Diagnostics GmbH. Troponin T hs instruction insert for Elecsys and Cobas analyzers (05199620001V4 English). REF 05092744 190;2011 – 02, V4:1 – 5.
cTnT	Roche	ECLusys					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnT	Roche	Enzymun Troponin T – ES700					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnT	Roche	Modular Analyzer					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnT	Roche	Trop T					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnI	Siemens	Dimensional RxL CTNI	NR	0.14	0.07	N: 342 Age: 18 to 83	IFCC Troponin tables (from Erin)
cTnI	Siemens	Lithium-Heparin Plasma					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.
cTnI	Siemens	Advia Centaur	NR	0.4	0.4	NR	Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33(18):2252-7 PMID: 22723599
cTnI	Siemens	Heterogeneous Immunoassay					"Heterogeneous Immunoassay" is too broad of a term, need more specific assay name.
cTnI	Siemens	Immulite 1000 Troponin I Kit	NR	0.22	0.19	N: 300	IFCC Troponin tables (from Erin)
hscTnI	Siemens	Advia Centaur	NR	0.03	0.04	N: 838, patients with chest pain and non-diagnostic electrocardiogram	Collinson PO, Gaze D, Thokala P, et al. What is the diagnostic accuracy of highly sensitive troponin assays in the emergency room population. Clin Chem. 2012:58(10):A4-A5 (abstract only)

Troponin assay (cTnI, cTnT, hscTnI, hsCTnT)	Manufacturer	Assay name	Assay Generation	CV (mcg/L)	99th percentile (mcg/L)	Reference population for 99th%tile	Source reference
hscTnI	Siemens	Dimension Vista 1500	NR	0.003	0.009	NR	Hoeller R, Rubini Gimenez M, Reichlin T, et al. Normal presenting levels of high-sensitivity troponin and myocardial infarction. Heart. 2013: Epub ahead of print PMID: 23604180
cTnI	Tosoh	AIA-600II	2nd	0.06	<0.06	NR	Apple FS, Quist HE, Doyle PJ, et al. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase MB mass for use with European Society of Cardiology/American College of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-6
cTnI	Tosoh	AIA	2	0.06	0.06	NR	Fesmire FM, Decker WW, Diercks DB, et al. Clinical policy: critical issues in the evaluation and management of adult patients with non-ST-segment elevation acute coronary syndromes. Ann Emerg Med. 2006;48(30:270-301 PMID: 16934648
cTnI	Tosoh	AIA200					Unable to find single source providing CV in mcg/L and 99th percentile for same reference group.

Appendix H. References for Appendixes

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