



Effective Health Care Program

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

Executive Summary

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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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



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 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 Biochemistry¹⁹ 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 Question 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.

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.

Table C. Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Population and condition of interest	<ul style="list-style-type: none"> All studies included human subjects exclusively. We included studies of adult patients with CKD including ESRD. <ul style="list-style-type: none"> For KQs 1, 2, and 3, we included patients who also are clinically suspected of having ACS. For KQ 1.5, we only included patients with normal renal function if the studies made a direct comparison with CKD. For KQ 4, we included patients who are clinically stable and asymptomatic for ACS. 	
Interventions	<ul style="list-style-type: none"> We included studies that evaluated troponin I, troponin T, high-sensitivity troponin T, or high-sensitivity troponin I. 	
Comparisons of interest	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> All-cause mortality Cardiovascular mortality MACE Hospitalizations Other major adverse events 	
Type of study	<ul style="list-style-type: none"> We included randomized controlled trials and observational studies with a comparison group. We did not place any restrictions based on sample size or language. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

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 I² 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 test³² and Egger’s test³³ 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*

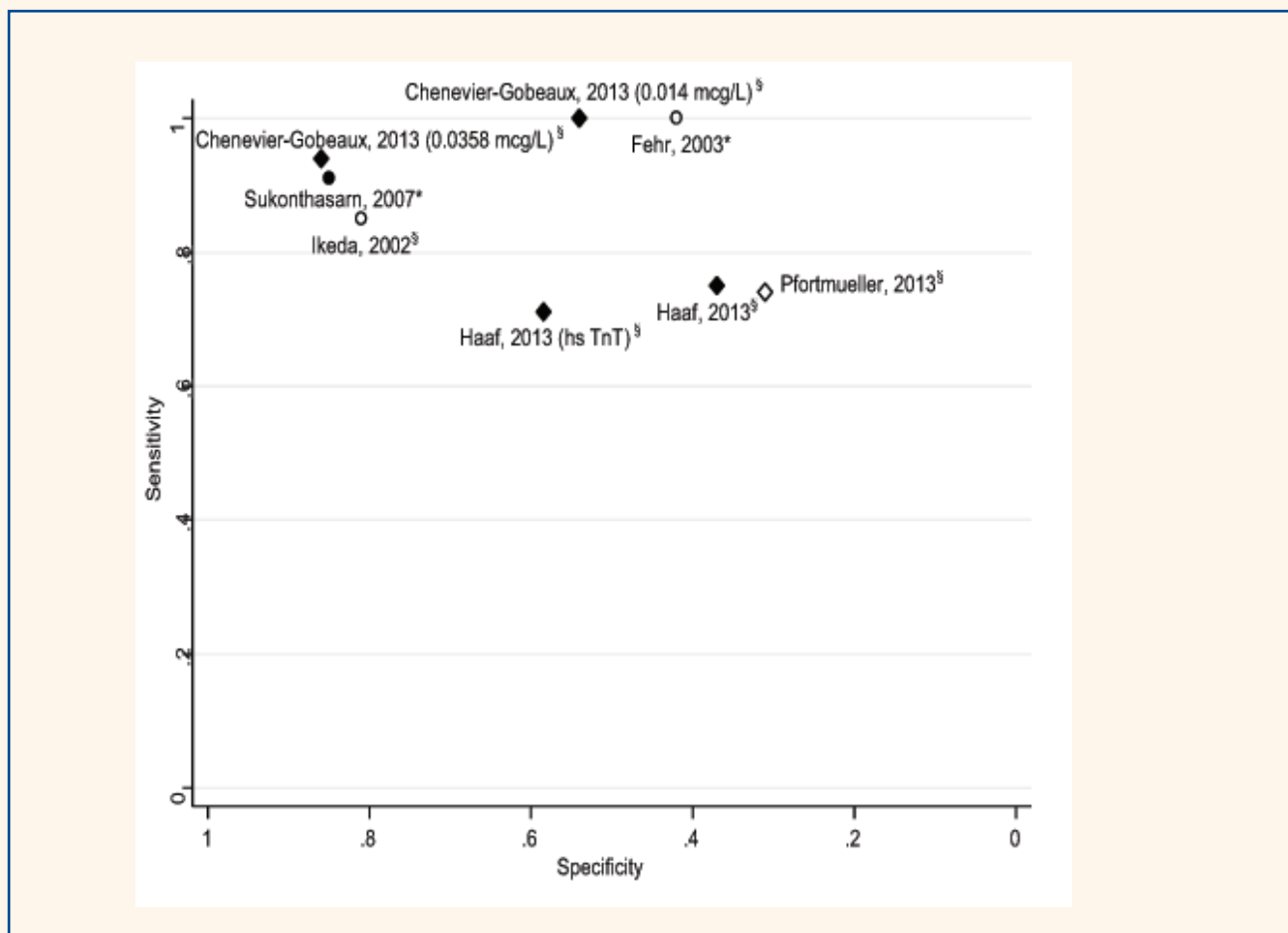
Key Question	Troponin Assay	Strength of Evidence (# of studies)	Summary and Conclusions
1.1, 1.1a: Operating characteristics (sensitivity, specificity, PPV, NPV) of a troponin elevation in diagnosing ACS	Troponin T	Low (6)	The sensitivity of the troponin T assay for ACS in patients with CKD ranged from 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.

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
1.2: 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.

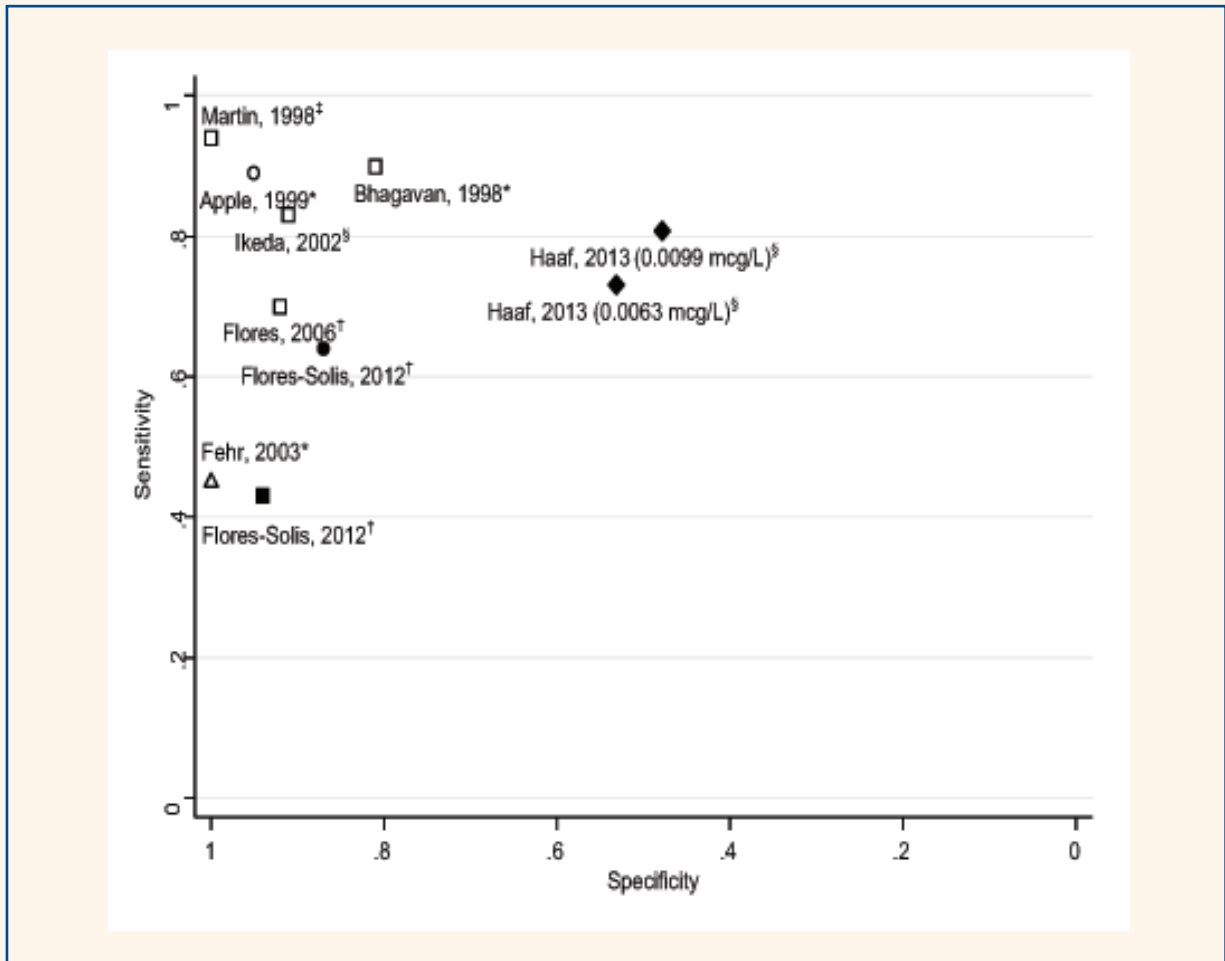
* Indicates a dialysis population.

† 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/1.73m². 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.

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 (continued)

Key Question and Outcome	Troponin Assay	Strength of Evidence* (# of studies)	Summary and Conclusions
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.

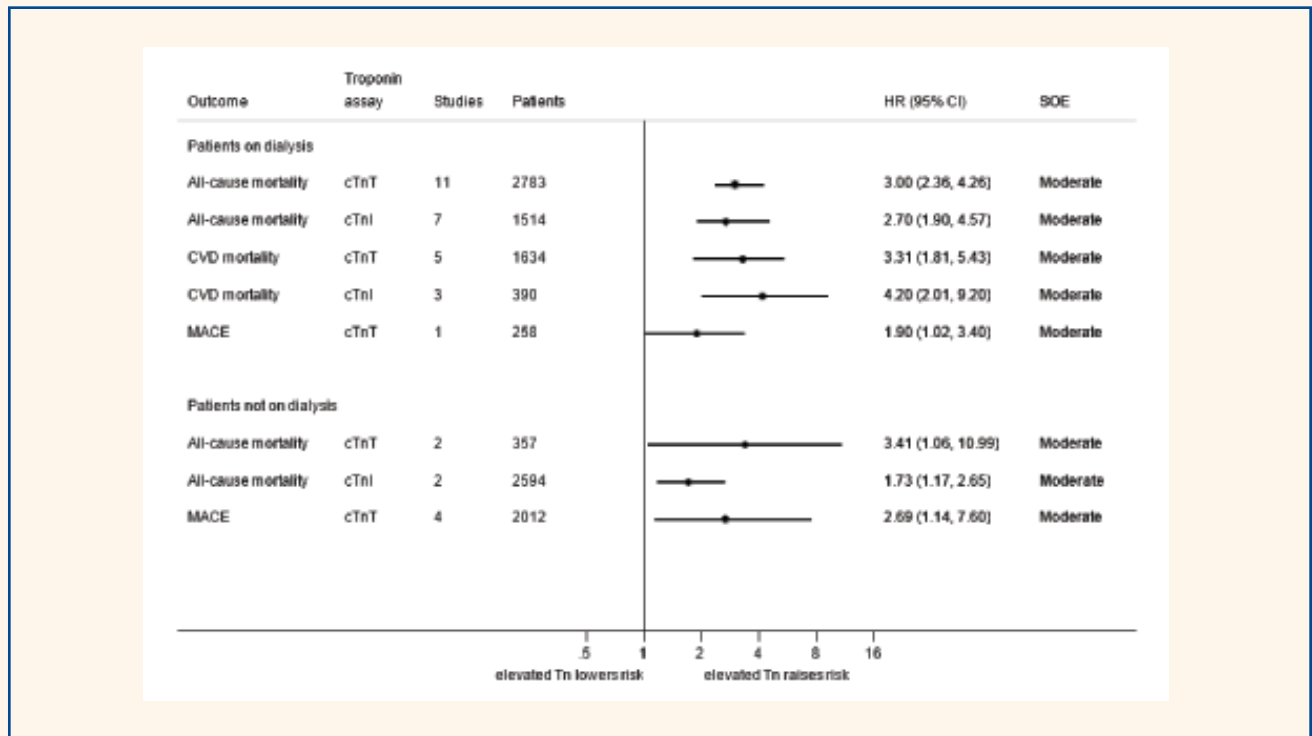
KQ 4.2: Risk Stratification Among Patients on Dialysis Without Symptoms of Acute Coronary Syndrome

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

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*
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
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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Full Report

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