Evidence-based Practice Center Systematic Review Protocol

Project Title: Troponin Cardiac Marker Interpretation During Renal Function Impairment

I. Background and Objectives for the Systematic Review

Troponin is a protein complex of three subunits, T (TnT), I (TnI), and C (TnC), that is involved in the contractile process of skeletal and cardiac muscle. TnC is expressed in both cardiac and skeletal muscle; under normal conditions, cardiomyocytes express cardiac specific forms of TnT and TnI (cTnI and cTnT). Due to the cardiac specificity of cTnT and cTnI, they have the potential to be specific markers of cardiac damage and indeed are currently recommended by various international societies as a diagnostic indicator for acute myocardial infarction (AMI).1-3

Blood from healthy individuals with no evidence of cardiac disease contain very low, but detectable, amounts of cTn.4 Upon cardiac injury, resulting from ischemia or various other causes, cTn is released from cardiomyocytes into the blood in proportion to the degree of damage.5 Troponin levels increase within 3 to 4 hours after the onset of damage and remain high for up to 4 to 7 days (cTnI) or 10 to 14 days (cTnT). A clinically relevant increase is defined as a level that exceeds the 99th percentile of a normal reference population.6 In patients with clinical symptoms of acute coronary syndrome (ACS) and without other causes for an elevated troponin, the Third Universal Definition of Myocardial Infarction endorses a rising/falling pattern of cardiac biomarkers (preferably cTn) with at least one value above the 99th percentile to diagnose an AMI in junction with at least one clinical feature (symptoms, electrocardiogram [EKG], imaging, or pathological) supportive of ischemia.1

Currently, there is no universally adopted 99th percentile value because there is no reference standard preparation of either cTnT or cTnI, and each diagnostic manufacturer independently develops its own assays. There is no consensus 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 are taken from diverse and poorly defined study participants.7 When 19 cTnI and cTnT assays were compared in the same presumably healthy population, there was substantial variability between assays regarding troponin concentrations at the 99th percentile. The high sensitivity assays detected measurable troponin levels in a larger percent of these presumably healthy people.7 Precision recommendations state that cTn assays should be able to achieve ≤10 percent total imprecision (i.e., 10 percent coefficient of variation [CV]) at the 99th percentile cut point, however, many current assays have a CV between 10 and 20 percent at the 99th percentile.8 Furthermore, newer high sensitivity (hs) troponin assays have a detection limit 10 to 100 fold lower than currently available commercial troponin assays which challenge this precision guideline.9

Source: www.effectivehealthcare.ahrq.gov
Published online: June 13, 2013
Patients with chronic kidney disease (CKD) [including those with end stage renal disease (ESRD)] have a greater prevalence of persistently elevated cTn compared with non-CKD patients. Although the mechanism is not known for certain, kidney disease-related subclinical cardiac damage is likely the cause, possibly exacerbated by reduced clearance.\textsuperscript{10} Ellis et al. did not observe a statistically significant difference in the half-life and the elimination rate constant of cTnI in patients with AMI and ESRD when compared with patients with AMI and normal kidney function.\textsuperscript{11} Increased troponin levels in patients with kidney disease may be due to cardiac injury associated with chronic structural heart disease (e.g., coronary artery disease, heart failure, etc.) rather than acute ischemia, especially when the levels are not changing rapidly over time.\textsuperscript{12} Furthermore, the previous reviews have not provided a link between degree of kidney failure and cTn elevation. Whether baseline troponin elevation reduces diagnostic ability for ACS detection only in ESRD but not milder forms of CKD is also unclear. Given that the prevalence of CKD in the US reached 15 percent in 2008, how to interpret troponin in this population is an important issue.\textsuperscript{13,14}

Discerning ACS from non-ACS conditions in symptomatic CKD patients

Patients presenting with suspected ACS must be rapidly and accurately assessed because of serious clinical consequences. Recommended diagnostic strategies include clinical evaluation, 12-lead ECG, and biomarker determination.\textsuperscript{15} Patients with characteristic ST elevation myocardial infarction (STEMI) can be evaluated for emergent reperfusion therapy. In situations where there is no definitive ST elevation, a decision is made between ACS [non-STEMI (NSTEMI)/unstable angina (UA)] and non-ACS conditions. The Third Universal Definition of Myocardial Infarction distinguishes between spontaneous myocardial infarction (MI) due to atherosclerotic plaque rupture (Type I MI) from an MI resultant from supply/demand ischemic imbalance (Type 2 MI).

In the spectrum of ACS, both UA and NSTEMI (Type I MI) share similar pathogenesis and are diagnosed by electrocardiographic evidence of ischemia and/or positive biomarkers of necrosis (e.g., cTn) in an appropriate clinical setting (chest discomfort or other symptoms that may occur with myocardial ischemia).\textsuperscript{16} Most patients who die from UA/NSTEMI do so from sudden cardiac death or myocardial infarction (MI). Thus, it is imperative to recognize ACS so that prompt and appropriate treatment can be implemented. In the absence of clear ECG findings, troponin levels are often a key factor in making the correct diagnosis.

On the other hand, elevations of cTn also occur in individuals with non-ACS conditions, such as kidney disease, sepsis, congestive heart failure, myocarditis, and pulmonary embolism.\textsuperscript{17} Non-ACS conditions can include non-coronary causes (hypoxia, 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 II MI. Many symptoms associated with non-ACS conditions may overlap with symptoms of ACS (chest pain or dyspnea for example). This presents a diagnostic dilemma to the clinician and often requires an extended evaluation before an accurate diagnosis can be made. Appropriate diagnosis is critical as ACS and non-ACS conditions are managed quite differently. For example, therapy for type II MIs is most often directed at treating the underlying medical condition that led to the supply/demand mismatch, rather than urgent revascularization.
In addition to the harm in missing a diagnosis of ACS, harm may result from erroneously diagnosing ACS when a non-ACS condition is present. This may subject patients to unnecessary coronary angiography and its potential risks (i.e., contrast dye, radiation exposure, bleeding, MI, stroke, emergent coronary artery bypass grafting [CABG], or death) and potentially unnecessary revascularization/stenting.

The diagnosis of ACS among patients with CKD (including those with ESRD) can be particularly challenging. EKGs are frequently abnormal in patients with ESRD due to a higher prevalence of left ventricular hypertrophy and electrolyte imbalances. Furthermore, there is a higher prevalence of persistent elevation of cTn in patients with reduced kidney function, which may reduce the specificity of troponin for diagnosing acute MI. To manage this uncertainty around the interpretation of cTn, additional indicators are sometimes used to help diagnose ACS in CKD patients. Baseline troponin levels are often not known in patients with CKD upon initial presentation, but elevated troponin levels are considered along with symptoms and other clinical factors in diagnosing ACS. Whether an alternative threshold other than the 99th percentile of cTn elevation should be used in CKD patients is unknown. Patterns of troponin change (rise, fall, magnitude of troponin change) can be very helpful for clinicians in determining ACS from non-ACS in patients. However, no consensus exists about whether the diagnostic criteria for MI using the troponin assay should be approached differently for CKD versus non-CKD patients. The National Academy of Clinical Biochemistry (NACB) has recommended that for patients with ESRD and suspected ACS a dynamic change in troponin levels of greater than 20 percent within 9 hours should be required for diagnosis of AMI; but some evidence suggests each individual assay should be evaluated to establish its own specific delta value.

Currently, diagnostic guidelines for MI using cTn are the same for patients with CKD compared with those without CKD. Thus, given the higher prevalence of baseline elevated troponin levels among individuals with CKD, this population may have a higher risk of having false positive diagnoses of MI. An evidence-based cutoff or change from baseline measure for the diagnosis of ACS in patients with CKD might allow clinicians to better diagnose and treat ACS in this population.

Use of troponin for management strategies in CKD patients with ACS
Cardiac biomarkers, such as cTn, also play a role in differentiating UA from NSTEMI in ACS patients. Frequently, clinicians use levels of troponin elevation, along with clinical factors, to risk stratify patients when the diagnosis of NSTEMI/UA is likely. High-risk ACS patients are generally recommended for an “early invasive” strategy (i.e., diagnostic angiography with the intent of revascularization) while low-to-intermediate risk ACS patients may be treated with an “initially conservative” (i.e., selectively invasive) management strategy. As with the initial diagnosis of ACS, there is a concern that elevated background troponin levels in CKD patients may limit the applicability of treatment algorithms that are based on troponin levels in non-CKD populations. Whether troponin results in CKD patients with suspected ACS are associated with differences in the comparative effectiveness of interventions or management strategies is unknown.

Use of troponin for prognosis in CKD patients following ACS

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In addition to their use for the diagnosis and management of ACS, the troponin subunits T and I and the high sensitivity troponin assays have also been investigated as 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 frequently excluded studies on patients with ACS. Therefore, the prognostic significance of cTn elevation in regards to short and long term major adverse cardiovascular events for patients with both CKD and ACS remains uncertain.

Use of troponins in adults with CKD who do not have symptoms of ACS: role for risk stratification
Among asymptomatic patients without suspected ACS, chronic elevation of cTn identifies patients with CKD at increased risk for cardiovascular morbidity and mortality. However, it is unknown whether measuring troponins improve risk prediction compared with or supplementing existing models. Furthermore, whether asymptomatic CKD patients with chronically elevated cTn levels should be managed differently compared with patients with CKD having normal cTn levels is unclear. In the absence of myocardial ischemia, there are no specific interventions recommended to reduce cardiovascular disease risk in patients with CKD based solely on a troponin elevation. Without evidence-based guidelines, clinicians will be uncertain about the role of screening asymptomatic individuals, the interpretation of elevated cTn results, and how that affects patient management and outcomes in the context of kidney disease.

Types of troponin assays and special subgroups of CKD patients
As mentioned previously, there are multiple commercially available troponin assays including cTnT, cTnI, hs cTnT, and hs cTnI. Whether all of these troponin assays have equal ability for discerning ACS from non-ACS and equal utility for prognostication and risk stratification of CKD patients with and without ACS is unclear. Furthermore, whether troponin testing leads to changes in management and outcomes among certain subgroups of CKD patients is also unknown.

The purpose of the review will be to present information for the appropriate use of troponin levels to guide evidence-based management decisions for patients with kidney disease.

II. The Key Questions
The Key Questions were posted on the Agency for Healthcare Research and Quality’s Website between February 29 and March 28, 2012 for public comment. We present below the revised Key Questions based on feedback received.

Key Question 1: DIAGNOSIS OF ACS
What is the diagnostic performance of a troponin elevation (troponin I, troponin T, hs troponin T, or hs troponin I) >99th percentile (compared to no elevation) for the detection of ACS in adult patients with CKD (including those with ESRD)?

-ACS will be defined by a gold standard outcome [e.g., clinically diagnosed ACS adjudicated by formal criteria such as the Third Universal Definition of MI or the American Heart Association/American College of Cardiology ACS Guidelines].
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?
   a. How do the positive predictive value and the negative predictive value vary with the population’s pretest probability for ACS?
   b. Does a significant delta of change (such as greater than 20% within 9 hours) better discriminate between ACS and non-ACS compared with a single troponin elevation?
2. What are the operating characteristics of troponin elevation for distinguishing ACS from non-ACS among the following subgroups?
   a. Gender
   b. Age
   c. Ethnicity
   d. Stage of kidney disease (CKD stages I-IV or ESRD on dialysis)
   e. Status post renal transplant
   f. Presence of baseline or prior elevated troponins
   g. Presence of ischemic EKG changes
   h. Comorbidities (e.g., diabetes, hypertension)
   i. Smoking status
   j. 10-year coronary heart disease (CHD) risk
   k. History of CAD
3. What are the harms associated with a false positive diagnosis of ACS based on an elevated troponin level?
4. Among studies that directly compared one type of troponin assays (troponin I, troponin T, hs troponin T, or hs 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?
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?

**Key Question 2: MANAGEMENT IN ACS**

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

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. 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?
   a. Gender
   b. Age
   c. Ethnicity
   d. Stage of kidney disease (CKD stages I-IV or ESRD on dialysis)
   e. Status post renal transplant
   f. Presence of baseline or prior elevated troponins
   g. Presence of ischemic EKG changes
   h. Comorbidities (e.g., diabetes, hypertension)
   i. Smoking status
   j. 10-year coronary heart disease (CHD) risk
   k. History of CAD

Key Question 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?

1. Do troponin results relate to:
   a. 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 follow-up)?
   b. Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of follow-up)?

2. Does a troponin elevation help to estimate prognosis after ACS in the following subgroups?
   a. Gender
   b. Age
   c. Ethnicity
   d. Stage of kidney disease (CKD stages I-IV or ESRD on dialysis)
   e. Status post renal transplant
   f. Presence of baseline or prior elevated troponins
   g. Presence of ischemic EKG changes
   h. Comorbidities (e.g., diabetes, hypertension)
   i. Smoking status
j. 10-year CHD risk
k. History of CAD

3. Among studies that **directly** compared one type of troponin assays (troponin I, troponin T, hs troponin T, or hs troponin I) against another type of troponin assay, does a certain type of troponin test estimate prognosis better after ACS?

**Key Question 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?**

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?
   i. What is the distribution by CKD stages I-IV and in ESRD?

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?

3. Does troponin elevation improve CHD risk prediction for the following subgroups:
   a. Gender
   b. Age
   c. Ethnicity
   d. Stage of kidney disease (CKD stages I-IV or ESRD on dialysis)
   e. Status post renal transplant
   f. Presence of baseline or prior elevated troponins
   g. Presence of ischemic EKG changes
   h. Comorbidities (e.g., diabetes, hypertension)
   i. Smoking status
   j. 10-year CHD risk
   k. History of CAD

4. Among studies that **directly** compared one type of troponin assays (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?
Population(s):
For all Key Questions, the population of interest is adult patients with CKD (this includes those with ESRD).

- For Key Questions 1, 2, and 3, we will focus on patients with clinically suspected ACS.
- For Key Question 4, we will focus on the general population of adult patients with CKD (including those with ESRD) without suspected ACS.
- The subgroups of interest are listed in Key Questions 1.2, 2.2, 3.2, and 4.3. One subgroup of particular interest is patients with ESRD on dialysis.
- For Key Question 1.5, we will focus on studies that directly compare patients with CKD and patients with normal renal function.

Interventions:
The test of interest is troponin testing, including troponin T, troponin I, high sensitivity troponin T, and high sensitivity troponin I.

Comparators:
For all Key Questions, the comparisons of interest will compare troponin elevation (generally >99th percentile) vs. no elevation.

If there are studies that directly compared different types of troponin assays with each other, we will report these findings (KQ 1.4, 3.3, 4.4); however we will not study this indirectly in our methodologic approach.

If there are studies that directly compared the utility of troponin elevation for diagnosis of ACS in CKD vs. non-CKD patients, we will report these findings (KQ 1.5) but we will not study this indirectly in our methodologic approach.

Note that for the population with suspected ACS (KQ 1-3), biomarker testing is done so routinely as part of standard care that “no testing” is not a realistic comparator.

In our subgroup analysis (KQ 1.2, 2.2, 3.2, 4.3), we will stratify results by milder forms of CKD (stages I-IV) versus ESRD on dialysis.

In KQ4, one comparator of interest would be “no testing” beyond use of a standard risk predictor model using traditional risk factors such as the Framingham Risk Score.

The comparisons of interest for each KQ are outlined in Table 1.
### Table 1. Comparisons of interest for each Key Question

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Outcome</th>
<th>Elevated troponin level vs. normal troponin level</th>
<th>Troponin T vs. troponin I vs. hs troponin T vs. hs troponin I</th>
<th>Troponin testing in CKD vs non-CKD</th>
<th>Troponin testing vs. other risk prediction models</th>
<th>No comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1.1</td>
<td>Diagnosis of ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>KQ1.2</td>
<td>Diagnosis of ACS</td>
<td>X (by subgroups)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ1.3</td>
<td>Diagnosis of ACS</td>
<td>X (regarding harms)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ1.4</td>
<td>Diagnosis of ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ1.5</td>
<td>Diagnosis of ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ2.1</td>
<td>Management of ACS</td>
<td>X Interaction with intervention and management strategies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ2.2</td>
<td>Management of ACS</td>
<td>X (by subgroups)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>KQ3.1a&amp;b</td>
<td>MACE after ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>KQ3.2</td>
<td>MACE after ACS</td>
<td>X (by subgroups)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ3.3</td>
<td>MACE after ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>KQ4.1</td>
<td>Prevalence troponin elevation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>KQ4.2</td>
<td>MACE in non-ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>KQ4.3</td>
<td>MACE in non-ACS</td>
<td>X (by subgroups)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>KQ4.4</td>
<td>MACE in non-ACS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tbody>
</table>

ACS = acute coronary syndrome; KQ = key question; vs = versus
Outcomes for each question:

For Key Question 1, the outcomes of interest are sensitivity, specificity, and positive and negative predictive value against a clinical diagnosis of ACS as the reference standard. ACS is largely a clinical diagnosis, which can lend itself to some subjectivity. As defined by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, ACS has three major components: (1) chest pain or anginal equivalent, (2) ischemic EKG changes, and/or (3) positive biomarkers of cardiac injury. Positive biomarkers can include creatine kinase (CK) or CK-MB, but most often troponin. Therefore, troponin is not only the diagnostic assay but considered as one clinical factor for definition for ACS in Key Question 1. However, by itself, troponin is neither required nor sufficient for a diagnosis of ACS. Furthermore, a patient can have negative biomarkers and still be diagnosed with ACS (i.e., troponin negative ACS), a situation where a negative troponin value represents a “false negative” for ACS. We will likely find that patients with ACS, for the purposes of the studies included in our review, will be selected based on billing records with ACS diagnostic codes. As stated in our method plan below, we will scrutinize the studies to determine how rigorously the outcome of ACS/MI was diagnosed. Our primary results will focus on studies that used a formal adjudication process for ACS diagnosis using strict criteria as established by the Third Universal Definition of Myocardial Infarction consensus or the ACC/AHA guidelines.

Harms of interest are associated with over-diagnosing ACS.

For Key Question 2, the outcome is differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds.

However, based on our preliminary literature search, we think it is unlikely that there are studies that have tested this question as the primary study hypothesis. If there is limited information on studies that address KQ2, subquestions on subgroups and types of troponin assays will be impossible to answer.

For Key Questions 3 and 4, the outcomes of interest are:

- Long-term outcomes (all-cause mortality and MACE over at least 1 year of follow-up)
- Short-term outcomes (all-cause mortality and MACE during the initial hospitalization or within 1 year of follow-up).

Timing:

We will consider studies with any length of followup. For Key Questions 1 and 2, which considers ACS, the included studies will likely involve a length of followup appropriate for the diagnosis and treatment of ACS (i.e., hours to days), while for Key Questions 3 and 4, which involve short- and long-term outcomes, the length of followup might vary but could be weeks, months, or years.

Because troponin started to be used as a cardiac marker in the early 1990s, we will consider studies published after 1990.
Settings:
We will consider all settings.
III. Analytic Framework

Analytic Framework

Figure 1. Analytic framework of the interpretation of troponin as a cardiac marker among patients with chronic kidney disease (including those with end-stage renal disease) and suspected acute coronary syndrome

ACS = acute coronary syndrome; CKD = chronic kidney disease; KQ = key question; MACE = major adverse cardiovascular event
Figure 2. Analytic framework for the interpretation of troponin as a cardiac marker during renal function impairment among patients with chronic kidney disease (including those with end stage renal disease) without symptoms of acute coronary syndrome

ACS = acute coronary syndrome; CKD = chronic kidney disease; KQ = key question; MACE = major adverse cardiovascular event
### IV. Methods

**Criteria for Inclusion/Exclusion of Studies in the Review**

We present the inclusion/exclusion criteria in Table 2.

<table>
<thead>
<tr>
<th>PICOTS</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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</table>
| Population and condition of interest | • All studies will include human subjects exclusively.  
  • We will include studies of adult patients with CKD including ESRD.  
  o For Key Questions 1.2, and 3, we will include patients who also are clinically suspected of having ACS  
  o For KQ 1.5, we will only include patients with normal renal function if the studies made a direct comparison with CKD.  
  o For Key Question 4, we will include patients who are clinically stable and asymptomatic for ACS.  
  o In Key Question 1.2, 2.2, 3.2, and 4.3, we will evaluate subgroups of patients based on:  
    ▪ Gender  
    ▪ Age  
    ▪ Ethnicity  
    ▪ Stage of kidney disease (CKD 1-4 or ESRD on dialysis)  
    ▪ Status post renal transplant  
    ▪ Presence of baseline or prior elevated troponins  
    ▪ Presence of ischemic EKG changes (for patients with clinically suspected ACS only)  
    ▪ Comorbidities (e.g., diabetes, hypertension)  
    ▪ Smoking status  
    ▪ 10-year CHD risk  
    ▪ History of CAD | | |
| Interventions          | • We will include studies that evaluate troponin I, troponin T, high sensitivity troponin T, or high sensitivity troponin I.                                                                                             | | |
| Comparisons of interest | • The comparisons of interest for each KQ are outlined in Table 1.  
  • For all Key Questions, the comparisons of interest will compare troponin elevation (generally >99th percentile) vs. no elevation.  
  • If there are studies that directly compared different types of troponin assays with each other, we will report these findings (KQ 1.4, 3.3, 4.4); however we will not study this indirectly in our methodologic approach.  
  • If there are studies that directly compared the utility of troponin elevation for diagnosis of ACS in CKD vs. non-CKD patients, we will report these findings (KQ 1.5) but we will not study this indirectly in our methodologic approach.  
  • For the population with suspected ACS (KQ 1-3), biomarker testing is done so routinely as part of | • We will exclude studies that do not have a comparison group. |
standard card that “no testing” is not a realistic comparator and thus will not be evaluated.  
• In our subgroup analysis (KQ 1.2, 2.2, 3.2, 4.3), we will stratify results by milder forms of CKD (I-IV) vs ESRD.  
• In KQ4, one comparator of interest is “no testing” beyond use of a standard risk predictor model using traditional risk factors such as the Framingham Risk Score.

### Outcomes

- For Key Question 1, the outcomes of interest are sensitivity, specificity, and positive and negative predictive values compared with clinical diagnosis of ACS (adjudicated using strict criteria per guidelines).
- For Key Question 2a, the outcome is differences in the effects of patient management strategies, interventions, or treatments for ACS by troponin level thresholds
- For Key Questions 3 and 4, the outcomes of interest are:
  - Short-term outcomes:  
    - All-cause mortality  
    - <1 year MACE  
  - Long-term outcomes:  
    - All-cause mortality  
    - ≥1 year MACE rates

### Type of Study

- We will include randomized controlled trials and observational studies with a comparison group.
- We will not place any restrictions based on sample size or language.

- We will exclude articles with no original data (reviews, editorials, and commentaries).
- We will exclude studies published before 1990 because troponin started being used a cardiac marker in the early 1990s.

### Timing and Setting

- We will include studies regardless of the length of followup.
- We will include all study settings.

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

**Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

We will search the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials from January 1, 1990 through January 2013 and we will update the search during peer review. We will develop a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text words of key articles identified a priori. Our search strategy for MEDLINE is presented in Table 3. The search will be updated during the peer review process. We will handsearch the reference lists of all included articles and other relevant systematic reviews.
Additionally, the team will search clinicaltrials.gov to identify relevant registered trials. We will review the Scientific Information Packets provided by the troponin assay manufacturers.

Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, which is abstract review.

The abstract review phase will be designed to identify studies reporting the effects of troponin testing. Abstracts will be reviewed independently by two investigators and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 2). Differences between investigators regarding the inclusion or exclusion of abstracts will be tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication.

**Data Abstraction and Data Management**

We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we seek to maximize consistency in identifying all pertinent data available for synthesis.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer’s abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, dialysis status, smoking status), interventions (including type of troponin assay and cut-offs used), comparisons, outcome measures, definitions, and the results of each outcome, including measures of variability.

For all articles, we will pay attention to the troponin assay used and the troponin cut-off value used. There is a concern that in some of the older studies, very high cut-off values were used and not the 99th percentile. Furthermore, many assays do not have clinical studies associated with it to establish the 99% upper reference limit. We will be sensitive to this issue when synthesizing the data and may need to report results separately for studies not using the 99th percentile. If there is ambiguity in the cut-off used for the

Source: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)
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troponin assay, we will attempt to contact the manufacturer of the assay or the study authors to get more details.

For Key Questions 1, 2, and 3, we will collect information on how the ACS outcome was defined in the studies. While troponin is one factor often considered in evaluation of MI/ACS, by itself, troponin is neither necessary nor sufficient for diagnosis. We are using a clinical diagnosis of ACS for our gold standard outcome for KQ1; however there is a concern that the literature varies greatly in the definitions of ACS. In some papers, the outcome of ACS versus non-ACS may be defined by billing or diagnostic codes rather than using the strict criteria as established by the Third Universal Definition of Myocardial Infarction consensus and/or a formal adjudication process. This may lead to misclassification and reduce the utility of the diagnostic test. While we plan to include all relevant papers in the initial literature search, primary results will be limited to only studies were ACS was defined by rigorous criteria and adjudicated.

We will collect data on subgroups of interest, including gender, age, ethnicity, stage of kidney disease, dialysis status, pre/post dialysis (in dialysis patients), status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic EKG changes (for patients with clinically suspected ACS only), comorbidities (e.g., diabetes, hypertension), smoking status, 10-year CHD risk, and history of CAD.

All information from the article review process will be entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data and to create detailed evidence tables and summary tables. We may contact authors for additional data, if necessary.

Assessment of Methodological Risk of Bias of Individual Studies
Article quality will be assessed independently by two reviewers. We will use separate quality assessment tools for studies evaluating diagnostic performance and for studies evaluating prognostication and risk stratification. For studies evaluating diagnostic performance, we will use the closed-ended questions from the QUADAS-2 quality assessment tool. For studies evaluating prognostication or risk stratification, we will use the Downs and Black quality assessment tool. We will supplement these tools with additional quality-assessment questions based on recommendations in the Methods Guide for Medical Test Review and the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.

For all studies, the overall study quality will be assessed as:

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

• **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Differences between reviewers will be resolved through consensus adjudication.

**Data Synthesis**

For Key Questions 1, 2, and 3 we will focus our main analysis on the studies that provided a rigorous definition of ACS (i.e., studies that adjudicated ACS as an outcome).

We will conduct meta-analyses when there are sufficient data and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For Key Question 1, we will follow the meta-analytic methods for when there is an imperfect reference standard.\(^{29}\) We will construct 2x2 tables and calculate sensitivity, specificity, and positive and negative predictive values where possible. If we find at least five studies that are sufficiently homogenous, we will conduct a hierarchical summary receiver operator curve meta-analysis to analyze sensitivity and specificity. For comparing studies that used different troponin assays from different manufacturers, we will use an index reference such as 99\(^{th}\) percentile for that assay rather than the absolute troponin value. If papers did not use the standardized cut-off of the 99\(^{th}\) percentile, these results likely will need to be presented separately as they may not be directly comparable with studies that did use the 99\(^{th}\) percentile.

Given the nature of the topic, we anticipate the studies to be predominantly observational in nature, including post-hoc analyses of randomized controlled trials that studied ACS interventions. In addition to including studies that compare threshold levels of cTn elevation compared with no elevation (for diagnosis and prognosis), we will also be searching for studies that directly compared elevated cTn in CKD patients with elevated cTn in non-CKD populations for ACS diagnosis.

For continuous outcomes, we will calculate a weighted mean difference by using a random-effects model with the DerSimonian and Laird formula.\(^{30}\) For dichotomous outcomes, we will calculate a pooled effect estimate of the relative risk, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.\(^{30}\)

Heterogeneity among the trials in all the meta-analyses will be tested by using a standard chi-squared test with a significance level of alpha \(\leq 0.10\). Heterogeneity will also be examined among studies by using an \(I^2\) statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.\(^{31}\) A value greater than 50 percent may be considered to connote substantial variability. If we find substantial
heterogeneity, we will attempt to determine potential reasons for this by conducting meta-regression analyses using study-level variables.

Publication bias will be examined by using Begg’s test and Egger’s test, including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.32, 33

STATA statistical software (Intercooled, version 12.1, StataCorp, College Station, TX) will be used for all meta-analyses.

Studies that are not amenable to pooling will be summarized qualitatively.

Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes
At the completion of our review, at least two reviewers will independently assign evidence grades. Conflicts will be resolved through consensus or third-party adjudication. We will grade the strength of evidence based on the quantity, quality, and consistency of the best available evidence, addressing KQs 1, 2, 3, and 4 by adapting an evidence grading scheme recommended in the Methods Guide.28, 29 We will apply evidence grades to the bodies of evidence about each intervention comparison for each outcome. We will assess the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We will assess the strength of the best available evidence by assessing the limitations to individual study quality (using individual quality scores), consistency, directness, precision, publication bias, and the magnitude of the effect.

We will classify evidence pertaining to the KQs into four basic categories: 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).

Assessing Applicability
We will assess the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings are typical for adult patients with CKD or ESRD. Factors that may limit applicability include gender, age, ethnicity, stage of kidney disease, dialysis status, status post renal transplant, presence of baseline or prior elevated troponins, presence of ischemic EKG changes (for patients with suspected ACS only), comorbidity, smoking status, 10-year coronary heart disease risk, and history of coronary artery disease.
V. References


12. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? J Am Coll Cardiol. 2006 Nov 7;48(9):1763-4. PMID: 17084246.


VI. Definition of Terms
ACS = acute coronary syndrome
AMI = acute myocardial infarction
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CHD = coronary heart disease
CK = creatine kinase
CKD = chronic kidney disease
CT = computed tomography
cTn = cardiac specific form of troponin
CV = coefficient of variation  
EKG = electrocardiogram  
ESRD = end stage renal disease  
KQ = key question  
MACE = major adverse cardiovascular event  
MI = myocardial infarction  
NACB = National Academy of Clinical Biochemistry  
NSTEMI = non-ST elevation myocardial infarction  
STEMI = ST elevation myocardial infarction  
Tn = troponin  
UA = unstable angina  

VII. Summary of Protocol Amendments
In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions
For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants
Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts
Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under
development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers
Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures
EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder
This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.
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Publication date from 1990/01/01