Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease*

Draft review available for public comment from November 6, 2013 to December 4, 2013.

Research Review Citation: Michos ED, Berger Z, Yeh HC, Suarez-Cuervo C, Wilson LM, Stacy S, Bass EB. Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease. Comparative Effectiveness Review No. 135. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 14-EHC030-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Executive Summary	Change title to: "Critical Review of Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients with Kidney Disease"	We changed the title to "Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients with Chronic Kidney Disease."
Peer Reviewer #1	Methods	Specify where troponin was measured, in the ED or in the office.	We looked through a subset of the papers and location of troponin assay was not mentioned in the majority, so we were not able to add this information to the report.
Peer Reviewer #1	Results	Specifically mention that Roche, Inc., has the FDA clearance for office measurement of Troponin T in the assessment of prognosis of patients with ESRD	We discuss Food and Drug Administration (FDA) approval for troponin T for prognosis in patients with end-stage renal disease (ESRD) in the Discussion chapter, but we did not specifically mention Roche. We have added this to background section for KQ4. On page 5, we now state, "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)."
Peer Reviewer #1	Discussion	Be sure to emphasize that with ED measurement of modern generation troponins, that levels are positive in the majority of patients so we must observe a characteristic rise of serial troponins and have consistent clinical information to diagnose AMI	Yes, we have diagnosis of MI (using clinical information and serial rise/fall of troponin or other cardiac biomarker) in Tables B and 2 of our background section. We brought this point back home in the discussion especially in the context of high sensitivity assays (see the Key Findings section for KQ1 and the Research Gaps section)
Peer reviewer #2	Introduction	In their introduction, the authors nicely summarize information about the cardiac troponin assays, including 1) its detection in normal and abnormal states, 2) cut points that define an abnormal level, 3) role of the newer, high sensitivity assays, 4) and renal mechanisms underlying elevated troponin levels in chronic kidney disease. Beyond addressing the 4 key questions, the authors also briefly review the different types of troponin assays (troponin T, troponin I, high-sensitivity troponin T and high-sensitivity troponin I). They conclude that limited data precludes them from determining whether differences exist in the diagnostic and prognostic abilities of these assays in patients with chronic kidney disease	Thank you for reviewing our report.

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Peer reviewer #2	Methods	The authors had very broad inclusion criteria and relatively few exclusion criteria that were both appropriate and justified. In spite of "casting a wide net", the authors were unable to identify large numbers of high quality studies for inclusion in the analysis.	Thank you for reviewing our report!
Peer reviewer #2	Methods	This left 114 studies (with 121 publications), of which nearly 80% addressed the 4th key question. The remaining 20% of publications were evenly split between those that addressed the 1st and 3rd key questions. No publications directly addressed the 2nd key question. It is important to note, though, that many of the ACS trials evaluating the efficacy and safety of antithrombotic agents excluded patients with more advanced forms of CKD (Page 15, KQ2).	Yes, this is a problem that likely contributed to why we did not find any studies that addressed KQ2. We have added this comment about the exclusion of patients with severe chronic kidney disease (CKD) from trials. We now state in the Discussion chapter, Key Findings section for KQ2, "Furthermore, many RCTs that tested therapeutic agents for ACS management excluded patients with advanced CKD."
Peer reviewer #2	Methods	Both the diagnostic criteria for the outcomes measures and the statistical methods used were sound and appropriate for the analyses performed.	Thank you for reviewing our report!
Peer reviewer #2	Results	Page 21 ES—For conducted meta-analyses, did the authors request and/or have access to patient level data from the individual studies.	No, we did not have nor request individual patient level data from the individual studies. Due to our time and budget constraints, we were unable to collect individual patient-level data from all of the included studies.
Peer reviewer #2	Results	Unfortunately, the authors were limited by the relative paucity of data related to key questions 1, 2, and 3. Furthermore, all of the studies included in the analysis were observational in design with moderate bias due to confounding. Finally, there was notable heterogeneity as to the assays used.	Thank you for reviewing our report. We agree with this assessment of our work.
Peer reviewer #2	Results	In spite of this, the authors went to great detail to appropriately present the results in the body of the review, as well as, in the figures, tables, and appendices. They identified numerous research gaps in each of the 4 key question areas that are very clinically relevant.	Thank you for reviewing our report!
Peer reviewer #2	Results	They appropriately concluded that even minor elevations in cardiac troponin levels carry a worse prognosis in patients with and without an acute coronary syndrome.	Thank you for reviewing our report!

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Peer reviewer #2	Results	Areas to be addressed in the results section include: 1. Page 15, KQ4—Is the increased cardiovascular risk associated with chronic kidney disease proportionate to the severity of chronic kidney disease or is there a threshold effect?	Since dialysis patients are presented separately, we did not have any direct comparison with CKD stages 1-4, only indirect comparisons could be made. We found limited evidence presented by CKD staging. We were unable to determine a threshold effect. We acknowledged this limitation in the first paragraph of the section on Applicability in the Discussion chapter.
Peer reviewer #2	Results	Page 19—The analysis included studies that were published over the course of 23 years (1990-2013). Were there were any temporal differences in the findings for the 4 key questions among studies evaluating non-high (non-ultra) sensitivity troponin assays (e.g., did study findings differ between those published early vs. late during the 23 year period)?	We ran our meta-analysis figures in order by year to see if there was any evidence for a temporal difference across years, but did not find any. We decided to keep the meta-analysis figures sorted by cutpoints but mentioned the lack of temporal differences in the results.
Peer reviewer #2	Results	Page 24, Table D—The authors should note (even as a footnote) that none of the studies evaluating troponin assays (column 2) included high (ultra) sensitive assays.	Two of the studies, found in our updated search, now do include high-sensitivity assays, and we note this in the revised text.
Peer reviewer #2	Results	Page 26, 27, Table E— The authors should note (even as a footnote) that none of the studies evaluating troponin assays (column 2) included high (ultra) sensitive assays.	We added this footnote.
Peer reviewer #2	Discussion	The authors describe well the implications of the major findings. They also did an excellent job outlining the limitations of the studies included in the review and used this to highlight areas for future research.	Thank you for reviewing our report.
Peer reviewer #2	Conclusion	Given the paucity of available high quality data (particularly related to key questions 1, 2, and 3), it comes as no surprise that there are several gaps identified in the conclusion of the review that deserve further attention. These include: 1. Defining the operating characteristics of troponin T and I assays in patients with chronic kidney disease, both with and without an underlying acute coronary syndrome. 2. Determining whether troponin levels in patients with chronic kidney disease help to determine the relative effectiveness of specific therapies. 3. Evaluating prognosis after an acute coronary syndrome based on the troponin level in patients with chronic kidney disease. 4. Stratifying risk based on the mechanism underlying the elevated troponin level.	Thank you for reviewing our report.

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Peer reviewer #2	Figure	Figure 3 (page 17) nicely summarizes their literature search strategy. After identifying 6081 original publications, nearly 1/2 were excluded based on title review, an additional 1/2 were excluded at the abstract level, and another nearly 2/3 were excluded at the article level. Reasons for exclusions at three levels were appropriate and well described.	Thank you for reviewing our report!
Peer reviewer #2	General	A common challenge for inpatient providers is what to make of an elevated isolated troponin level in patients with chronic kidney disease. Is this diagnostic of an acute coronary syndrome? Is this due to kidney disease alone? Does this portend increased cardiovascular risk? The submitted review is an important contribution to the literature on this subject. The authors did an excellent job explicitly defining the studied population and also clearly state appropriate key questions. Specifically, they review the implications of an elevated troponin level in chronic kidney disease with regard to 1) diagnosis (KQ1) 2) management (KQ2), 3) prognosis (KQ3), and 4) risk stratification (KQ4). The review is well structured. The primary takeaway is that even minor elevations of cardiac troponin are associated with a worse prognosis in patients with and without a suspected acute coronary syndrome. Given the limited availability of high quality data in the literature related to this topic, no other definitive conclusions can be generated that help to inform policy and/or practice decisions.	Thank you.
Peer reviewer #3	Introduction	The introduction is comprehensive and clearly details the current knowledge of troponin assays and the problems associated with their implementation, interpretation, and application. This should relay to the reader how complex troponin interpretation is.	Thank you for reading our report. Yes, the introduction is a bit long but hopefully sets the stage for how complex troponin interpretation is.
Peer reviewer #3	Introduction	I have concerns about the statement 'This does not mean that 1 percent of the population has acute myocardial damage, but must be interpreted in the context of a high pre-test probability suspected ACS.' If that is true, the authors must follow with a statement defining what it does mean for 1% of the population. The authors have reported evidence indicating that the selection of the 99th percentile is all but arbitrary. A clear summary statement on the selection of the 99th percentile as a cutoff and the meaning of the 1% based on current evidence is needed to clarify matters for readers who might otherwise interpret these values as being perfectly valid.	We removed this confusing statement. We meant that the 1% above the 99th percentile could include patients with myocardial damage from non-ACS causes or can be the outliers of the extreme of the normal reference population. All elevated troponins have to be taken in context with high pre-test probability for suspected ACS.

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Peer reviewer #3	Methods	The search methods are comprehensive and without sample size or language restrictions. Also to their credit, they have appropriately limited their search to studies with clinical outcomes. Although the authors state that they included studies that evaluated sensitivity, specificity, and positive and negative predictive values. Likelihood ratios are not mentioned but no explanation of this is given although it is unlikely that a study would report likelihood ratios without also reporting sensitivity and specificity. As the authors (but possibly not the readers) well know, predictive values are subject to the prevalence of the disease and so can be misleading. For this reason I would suggest avoiding these measures. The search methods, study selection quality assessment and data abstraction appear to be free of any systematic bias. The data analysis and synthesis are appropriate for this type of meta-analysis.	We did not find information regarding likelihood ratios.
Peer reviewer #3	Results	The results highlight the lack of quality evidence to answer the research questions. My concerns about predictive values have been mentioned already. The results are detailed in the study selection and characteristics. The tables allow for easy reading and interpretation. There are no missing studies that I am aware of.	Thank you for your comment and for reviewing the report!
Peer reviewer #3	Discussion	As with the rest of the document, the Discussion is comprehensive and clearly describes all of the challenges of interpreting the current evidence for the clinical application of troponin assays. The limitations are a reflection of the quality of the available evidence rather than the review itself and quite appropriate.	Thank you for your comment and for reviewing the report!
Peer reviewer #3	General	I would like to thank the authors for undertaking such a complex and arduous task and congratulate them on their excellent efforts. The research questions are clearly stated and highly clinically relevant. The manuscript is very well written and provides and comprehensive picture of the current state of knowledge of the topic. My only recommendation is that this same review be repeated in 3-4 years when more information is available especially concerning high sensitivity troponin assays which will soon be ubiquitous.	Thank you for reviewing our report! While the report was being peer reviewed, we updated our search and included a few more studies that evaluate the high sensitivity troponin assays. Additionally, the Agency for Healthcare Research and Quality has a system for identifying reviews that need to be updated. We sincerely hope to have the opportunity to update the review in the future.
Peer reviewer #3	General	This paper is clearly written and could not be more so. As the authors state repeatedly, the challenge is the 'paucity' of quality studies on the subject. This of course limits the clinical usability of the paper. However, this is a highly valuable document that provides both detailed description and summaries of the current evidence to guide policy and practice decisions. As equally important, the authors provide guidance for future research on the topic.	Thank you for reading our report.

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Peer reviewer #4	Executive Summary	Page ES 16, Table E - 3.3 - do the authors mean comparing troponin T with troponin I?	This has been corrected.
Peer reviewer #4	Introduction	The introduction is good. I believe that since this review started there are new guidelines about the classification of CKD which also incorporates albuminuria. See www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf page x. I'm sure none of the studies that you evaluated used this new classification (or even had data on albuminuria), but it may be good to acknowledge these new guidelines and suggest that further investigations incorporate albuminuria if possible.	We updated to acknowledge the new guidelines. This is now included in the Troponin Elevation in Chronic Kidney Disease section of the Background.
Peer reviewer #4	Methods	The methods are appropriate.	Thank you for reviewing our report!
Peer reviewer #4	Results	The results are appropriate in detail. Throughout the report, it is unclear whether the authors are reporting a creatinine clearance or an estimated GFR. For example ES 14 says that renal failure was defined as creatinine clearance less than 60 ml/min/1.73m2. These are generally eGFR units not creatinine clearance (which are usually ml/min). This is also a pretty standard definition of kidney disease using eGFR (from either MDRD or CKD-EPI equations). Creatinine clearance is again used in the last row of Table E. Is this meant to be eGFR?	We reviewed and revised the report to make sure GFR units of measurement are listed correctly.
Peer reviewer #4	Results	Why do tables F and G have different columns when they are showing basically the same data? This is confusing for the reader.	Table F was for results of patients on dialysis. This has now been converted to a figure. Table G was results for non-dialysis CKD patients (generally CKD stages 1-4, or stage 5 not on dialysis).
Peer reviewer #4	Discussion	The discussion and conclusions are adequate. The future research section is clear.	Thank you for this comment.
Peer reviewer #4	Conclusion	The report is well structured and the main points are clearly presented. KQ1-In the conclusion about the first question, the authors state that there is evidence of moderate quality about the outcome but in Table D, they say that the strength of the evidence is low. So the SOE is low but the quality is moderate? This is confusing.	Thank you for this comment. We corrected the reference to "moderate" in the Executive Summary to "low."

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Peer reviewer #4	Figures	In figure 3, page 17- why are there 24 articles awaiting review?	At the time we submitted the draft, there were 24 articles awaiting review. We were either waiting to receive the full text of the article or were trying to find a reviewer who can read the language in which the article was published. We resolved the status of all articles for the final report.
Peer reviewer #4	General	The report does a very thorough job with its assigned task of reviewing the literature about the use of troponin T and I in patients with CKD. The report is clinically meaningful but unfortunately brings up more questions than answers. The key questions are explicitly stated. The report is well structured and the main points are clearly presented.	Thank you for reviewing our report!
TEP #1	Introduction	Some items to consider: Page ES1. The notion that troponin T is cardiac specific has been challenged recently (JACC 2011;58:1819 and JACC 2013;61:1466-7).	We have updated the background section and have added that reference.
TEP #1	Introduction	Page ES1. The discussion on high-sensitivity troponin should be based on objective measures. What is written does not differentiate between conventional and high sensitivity measures. Apple suggest a labeling scheme based on the percentage of troponin values that can be detected above the limit of detection in a healthy population. The authors cite the Apple article (Clin Chem 2009, 55:1303-6, reference 6) but don't discuss the critera for troponin assay labeling. According to this scheme, the hs-cTnT assay and the Siemens Ultra assay are in fact not high sensitivity troponin assays. There have not been other schemes published.	We added the labeling schemes to the Background chapter under the High Sensitivity Assays section. We state, "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," and cite Apple's paper. We no longer consider the Siemens Ultra assay as a high sensitivity troponin assay in the report.

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TEP #1	Methods	Meta-analysis was not conducted for the diagnostic criteria, key question 1, because the studies were too heterogeneous. Nevertheless, the citation of clinical sensitivity and specificity for each study is of limited value. Therefore a meta-analysis could have been conducted with the limitations cited. Other published meta-analyses have been conducted that have used even more heterogeneous criteria, e.g., use of different beta-blockers for the secondary prevention of AMI (e.g., JAMA 1999;281:1927-36). Recognizing that there is no harmonization among assays, comparing results against an assays pre-defined cutoff concentration is one way to combine data, assuming that the strategy for the cutoff level assignment was consistent (i.e., the 99th percentile).	We believe it is inappropriate to conduct meta-analyses for the diagnostic criteria because there were too few studies that reported a sufficient amount of data to conduct a meta-analysis. We would have needed at least five studies to have reported the number of true positives, true negatives, false positives, and false negatives. However, most studies only reported on the sensitivity/specificity. To display the trends in sensitivity and specificity better, we revised Figures 4 and 5. We attempted to show the heterogeneity in the data by (1) having closed/open markers to show adjudicated/unadjudicated outcomes and (2) having different markers for the varying cutoffs.
TEP #1	Methods	For KQ 3 and 4, the authors could consider using cumulative meta-analysis, i.e., to determine when statistical significance had been reached, obviating the need for subsequent trials on the same subject. The number of subjects enrolled in to each trial could also be shown in the meta-analysis.	We do not think a cumulative meta-analysis will help to address our Key Questions. To determine if there are any temporal trends, we sorted the studies included in the meta-analyses by date. Since we did not see any temporal trends, we decided to leave our figures sorted by cutpoint. We discussed the lack of temporal trends in the report text.
TEP #1	Methods	The authors apparently have not attempted to apply the STARD guidelines as a criteria for quality of clinical trials. This 25-item checklist could provide a quantitative assessment of publication and clinical trial quality. While it would be a tremendous effort to now apply this standard to the thousands of papers cited, AHRQ should consider this approach in the future (or document why this isn't appropriate).	Although the STARD statement is a very thorough checklist of items for the reporting of diagnostic accuracy tests, it does not assess study quality. We chose the Downs and Black quality assessment tool because it assesses study quality as well as study reporting, and is an appropriate tool for assessing observational studies (which was the bulk of included studies). We refer to use of the Downs and Black tool in the Quality Assessment section of the Methods chapter.

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TEP #1	Methods	Was there any attempt to see if there are differences in results between "registry" studies that used different local labs under routine testing versus clinical trials where a core lab may have been used?	We did not collect data on the number of laboratories used in our initial data collection. We reviewed a sample of 21 articles to collect this data. None of the 21 articles reported if they used different local laboratories or if there was a core laboratory. We decided not to add any corresponding text to the report.
TEP #1	Results	As a matter of convention, this reviewer believes that units should be expressed as ng/L and not mcg/L, resulting in whole numbers, recognizing that this was not the prevailing view when most of these papers were written, but is now the prevailing view in light of high sensitivity assays (Thygesen et al. Eur Heart J 2012, doi: 10.1093/eurheartj/ehs154.) This reviewer also prefers the use of "concentration" to "levels" and "increased" to "elevated"	Most of the included studies evaluated regular troponin assays, not the high sensitivity assays. We prefer to keep the units expressed as mcg/L. However, since most of the newer studies are evaluating the high sensitivity assays, we added in a conversion metric into the Methods chapter. We added the following statements to the end of the Data Analysis and Synthesis section of the main report, "We report troponin levels in terms of mcg/L, because most studies used this unit. However, some of the newer high sensitivity troponin assays report troponin levels in terms of ng/L. To convert from mcg/L to ng/L, multiply by 1000."
TEP #1	Discussion	KQ 3 and 4, Risk stratification-An important control population is acute coronary syndromes with renal disease. This is the primary use of troponin for risk stratification. The odds and hazards ratios presented for renal disease, with and without ACS are difficult to interpret when not taken this into context.	For KQ4, all patients were stable patients without suspected ACS. A control population of ACS patients with renal disease was not provided in the individual studies for KQ4, so no direct comparison can be made. Similarly for KQ3, all patients had suspected ACS, so direct comparisons with a stable population could not be made. In the Limitations section of the Discussion (in the Executive Summary and main report), we acknowledge the inability to make such direct comparisons.
TEP #1	Conclusion	From this review, are there any recommendations as to what is considered standard of care for measuring troponin in patients with renal disease, if any? If so, when should blood be collected and how often?	We were not able to answer this question with our review. However we do have this listed as a research gap.

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TEP #1	General	The key questions are appropriate. The report is only somewhat clinically meaningful as the strength of the evidence is most cases is poor in many cases, and only fair in others. The most disappointing part of the conclusions (no fault of the systematic review) is the lack of therapeutics that can be engaged to reduce cardiovascular risks.	Thank you for reviewing our report.
TEP #1	General	The target audience for this article is not defined. It is presumed to be cardiologists, nephrologists, laboratory medicine specialists and emergency department physicians. Should pharmacologists be a target despite the fact that there are no therapeutic trials that reduce risk? What about epidemiologists? Dialysis units?	The target audience has now been defined under the Scope and Key Questions section of the Introduction. We state, "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."
TEP #1	General	The report is well structured, organized and main points are clear. However, this systematic review is not likely to change regulatory policy or alter medical practice decisions particularly due to the absence of trials that examine outcomes of appropriate therapeutics.	Yes, we were limited by the available data. But hopefully this report will bring strong attention to the research gaps and the need for data to show how measuring troponin in patients without suspected acute coronary syndrome (ACS) can guide appropriate therapeutics.
TEP #2	Executive Summary	Page1,Troponin Detection in Normal And Disease states-There may be some lack of clinical specificity for cTnT - see Jaffe, JACC 2011. The 99th Percentile Cutpoint-Challenges-In addition, present day assays, hscTn ones excluded are not close to normal values so there is no worry about false positive rates from that perspective. It is guideline acceptable that many current assays have a coefficient of variation between 10 and 20 percent at the 99th percentile. See Clin Chem, Jaffe et al "Being Rational about imprecision."	We added this reference and clarified the concerns for false positives of high-sensitivity troponin assays.
TEP #2	Executive Summary	Page 2,High Sensitivity Troponin Assays-Actually all of these assays(newer high-sensitivity troponin assay) have good imprecision at the 99th%. Companies have dealt with that.	We updated the report to indicate manufacturers are developing assays that are even more precise at very low concentrations such as 1 ng/L. Please see the first paragraph under the High-Sensitivity Troponin Assays section of the Introduction chapter.

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TEP #2	Executive Summary	Page 3,KQ 1-Not all patients with CKD have elevated values so high cut off values will disadvantage those who do not have elevated values.It is not a great idea to have an alternative threshold other than the 99th percentile of cardiac troponin elevation in patient with CKD. Read the recommendation by The National Academy of Clinical Biochemistry carefully. It is only for those who have elevated baseline values. In that setting, it accounts for analytical variation.	We have added the concept about the disadvantages of using higher cutpoints. We have emphasized that the rise/fall pattern for diagnosis is only for those who have at least one value above the 99th percentile. We meant this before, but apologize if this was not clear.
TEP #2	Executive Summary	Page 4,KQ 4-See work by Cosio and colleagues regarding chronic elevation of cardiac troponin identifying patients with CKD who are at increased risk for cardiovascular morbidity and mortality. Elevations predict even after correction for other variables	We have cited studies where the association of chronic troponin elevation is associated with increased risk for cardiovascular morbidity and mortality after adjustment for other variables in multivariate models. Still this is not the same thing when critically evaluating a biomarker in how much it discriminates and re-classifies individuals into higher and lower risks compared with existing models.
TEP #2	Executive Summary	Page 5,Scope and Key Questions,KQ1(1.1b)-You are out on a limb on the question, Does a significant delta of change (such as greater than 20% within 9hours) better discriminate between ACS and non-ACS compared with a single troponin elevation? A 20% change below the 99th% value will not work.	We reworded this section. We meant the delta of change to refer to only those that have at least one value above the 99th percentile.
TEP #2	Executive summary	Page 9, Table C-Need to do this by cut off values used or it would be easy to be misled. We indicated that on initial call.	Thank you for this comment. The results tables are currently organized by assay (troponin T and troponin I), and then by cutoff value.
TEP #2	Discussion	Page 22 ES, KQ 1- You cannot use the recommendation by The National Academy of Clinical Biochemistry in those without elevated values. You are off base here. KQ 1-Don't disagree with principle that findings must be in context of what we already know about the use of troponin for diagnosis of ACS in the general population, but many ESRD patients are diabetic and those many are "at high risk." How to define this better for this population is unclear.	We rewrote this section. We meant the delta of change to refer to only those that have at least one value above the 99th percentile. We are sorry this was not clear.

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TEP #2	Discussion	Page 25 ES, KQ 4 Kahn et al used very high cut off value of .1 ng/ml to include studies.	We have added a comment about this. In the Discussion chapter under the Key Findings section for KQ4 where we discuss the Khan 2005 meta-analysis, we state, "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."
TEP #2	Discussion	Page 27 ES, KQ1-4, On heterogeneity with assay platforms and many papers not reporting which generation of assay was used being a limitation of our analyses-OK but how this measure is handled will effect all the results and you need to make people aware of that. No analysis can correct totally for this but the magnitude of this confound should be expressed.	We have added reference to the proposed "scorecard" for troponin assay per Apple's 2009 paper. This was added to the Background chapter under the High Sensitivity Assays section.
TEP #3	Introduction	The Introduction is adequate. Page ES-1-The report states that troponin is low but measurable in normal individuals. This is true for newer high sensitivity assays, however many assays commercially available in the US cannot measure troponin in normal individuals or can measure it only at levels below the LoQ or measuring range of the assay.	We clarified this in the Background sections of the Executive Summary and main report. In the first paragraph, we state, "Blood from healthy individuals with no evidence of cardiac disease contains very low amounts of cardiac troponin. 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."
TEP #3	Introduction	As additional background, FDA sent a letter to manufacturers of troponin assays in 2010 which is public and posted on FDA's website at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm230118.htm which provides some additional perspective from FDA's viewpoint.	We added this to the background in the main document.
TEP #3	Methods	The search strategies and criteria appear to be appropriate as well as the statistical methods.	Thank you for reviewing our report!
TEP #3	Results	The amount of detail is certainly adequate - if possible briefer summaries could be provided which may be easier to interpret.	Thank you for reviewing our report!

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TEP #3	Discussion	The findings are clearly stated. The limitations section describes some of the issues with troponin which make the studies difficult to interpret or draw conclusions from such as lack of harmonization, inconsistencies in determining 99th %. Also some older studies have used earlier generation assays which are much less analytically sensitive that newer assays.	Thank you for reviewing our report!
TEP #3	General	The report is meaningful - but long and somewhat cumbersome to follow The report is well structured but much information is presented so I found it a bit cumbersome to read. The conclusions can be used but since troponin assays are evolving newer studies should provide additional information in the future.	It is a difficult topic to summarize succinctly. Hopefully the revisions will make it somewhat clearer. Hopefully the Executive Summary by itself should be succinct enough to read on its own, without the entire report.
TEP #4	Introduction	Well done.	Thank you for reviewing our report!
TEP #4	Methods	Well conceived and performed.	Thank you for reviewing our report!
TEP #4	Results	Comprehensive and clear.	Thank you for reviewing our report!
TEP #4	Discussion	This section is most impressive. The consideration given to the implications and limitations of the available data is very thoughtful and appropriate. Given the assay issues, beginning recommendations for future work with assay characterization is spot on. The point that measurement of these biomarkers does is not yet linked to additional specific therapies (beyond risk stratification of already high risk patients) is exceptionally important. The other recommendations are also appropriate.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP #4	Conclusion	Page119-There's only one sentence I thought didn't make sense, the first in the last paragraph of the conclusion on page 119 (similarly at the end of the ES): "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." In fact, this seems contradictory to the first conclusion paragraph that states no conclusive evidence for risk stratification. I would recommend deleting this sentence and the "However" that follows. A modified second sentence could then begin a final paragraph with the most important message.	Yes, there is an FDA approval for the use of Troponin T for prognosis in ESRD. Elevation of this biomarker is associated with an increased risk. We have now introduced this in the background (it was previously already in the discussion). The issue is whether troponin T adds additional incremental prognostic information over other clinical factors is not as clear. Many studies did not adjust for age, history of coronary artery disease, comorbidities, etc. So whether troponin T is better than existing clinical models is unclear.
TEP #4	General	This is a comprehensive review that in my opinion was exceptionally done. Though it took a long time to get through, I learned a lot! An extensive body of literature was reviewed aptly to answer appropriate questions. Moreover, the interpretation of the results are accurate and do not stretch beyond the data. It's unfortunate that there are insufficient data to more completely address thresholds to apply to existing practice in diagnosing ACS, but the data are what the data are, and this comes through as an important next direction. Yes, clear and usable.	Thank you for reviewing our report!