Article details: 2013-0074	
Title	A systematic review and meta-analysis of diagnostic performance of high sensitivity troponin in acute myocardial infarction
Authors	Ayman Al-Saleh, Ashraf Alazzoni, Saleh Al Shalash, Chenglin Ye, Lawrence Mbuagbaw, Lehana Thabane, Sanjit Jolly
Reviewer 1	**Sally Aldous**
Institution	None given.
General comments	I have reviewed the above article. In summary, this is a metaanalysis of 12 studies in patients presenting with chest pain comparing the sensitivity and specificity of hsTnT with conventional cTn. At presentation, sensitivity is significantly higher in hsTnT but not significantly higher at later time points. Specificity is significantly lower. The introduction and methods are well written. The aim of the study is clear. Although the statistical analysis is comprehensive, the results achieved gave only a small amount of information (sensitivity and specificity plus a little bit of ROC analysis). Discussion was very brief. It was not mentioned that the sensitivity of hsTnT is still not high enough at presentation to warrant discharge in those with negative results. Given that at later time points, there does not appear to be a significant difference, there should be a discussion regarding the benefit of using a hs assay. It is also not mentioned that MI is adjudicated by a conventional troponin. We know that more patients are diganosed with MI when a hs assay is used for adjudication, therefore using a conventional cTn for adjudication will miss some MIs picked up by the hsTnT, this will underestimate the sensitivity and specificity of hsTnT and over-estimate them for the conventional troponin. This should have been acknowledged.
Reviewer 2	**P. Nagele**
Institution	None given.
General comments	This manuscript reports the findings of a systematic review and meta-analysis of the performance of novel high-sensitivity cardiac troponin assays in the diagnosis of acute MI. Generally, the topic is of interest to the greater medical community and currently a hot topic in cardiovascular medicine. However, just within the last months, several reviews, systematic reviews and meta-analyses about this topic have been published [Clin Cardiol. 2013 Aug 27. doi: 10.1002/clc.22196; Clinical Biochemistry 46, Issues 1–2, January 2013, Pages 26–30, among others]. Before I provide a few specific comments regarding the study, I would like to provide some candid feedback, particularly since the first author appears to be an international trainee: this manuscript should have never been submitted the way it is written and presented. It resembles a rough draft that requires substantial refinement, error and spelling check, to get it to an acceptable – and publishable – level. This is not the fault of the junior trainee but the senior author and mentor. Was there no quality check before submission? Specific comments: 1. The authors include very heterogeneous studies, some that used TnT and others that used TnI, some that used this cutoff and some that used other cutoffs. It is in my opinion very important to pool the results from studies that closely resemble each other to provide a meaningful comparison. 2. How was acute MI defined in each study? Was the universal definition of acute MI followed? What were the criteria? What edition of the universal definition (1st, 2nd, or 3rd)? It is very important to point out that a single cTn value above the 99th percentile is not sufficient to diagnose an acute MI. What about a rising/falling pattern? What about the type of MI (STEMI, NSTEMI, type IVb)? There are so many important differentiations within acute coronary syndromes that lumping them together may not be ideal. 3. Regarding the diagnosis of acute MI using hs-cTn assays, several aspects deserve consideration: different cutoff values, different change values (delta), e.g. 5/7/9 ng/L – I suggest that the authors provide more stratified analyses using different approaches. 4. Please use ONE scientific notation for concentration throughout: I would recommend ng/L since this will become the standard for hs-cTn reporting.

	5. In the methods section, the authors write about 12 included studies, but the rest of the paper lists 9. Please clarify. 6. Please provide a detailed list – akin to table 1 – for all 38 excluded studies. 7. The whole section labeled "biochemical assays" should be completely revised. Perhaps a table is better. 8. Figure 2 is barely readable. 9. Table 2: there seem to be some errors – how can the Alsous 2012 paper use Roche Elecsys with a cTnI assay when Roche only makes hs-cTnT and has the patent for TnT? 10. Who is the corresponding author?
Author response	We would like to thank you for reviewing our manuscript and providing us with helpful comments and suggestions. We did edit the article as per your suggestions and here is a detailed description of our responses and the changes we made (the responses are arranged as per the list of comments we received from you). Response to Editors' comments: 1. Please structure the Interpretation section (discussion) into the following 4 main categories: Main findings; explanation and comparison with other studies; limitations; and conclusions and implications for practice and future research. Response: We did edit the discussion section and acknowledged the mentioned format as follows: "Interpretation: Main Findings The results of our meta-analysis of hs-Tn shows that the use of hs-Tn at presentation to ED to diagnose AMI resulted in a significantly higher sensitivity compared to c-Tn, however, with reduced specificity. However, the AUC values for repeated measurements over 6 hours were similar between hs-Tn-T and c-Tn. Thus, the major advantage of hs-Tn is early diagnosis and treatment of non ST elevation myocardial infarction. The heterogeneity in our meta-analysis based on I2 was in the low to moderate range with , I2 for sensitivity was 32.53% (9 and for specificity 32.35.(10,11) This is explained by the use of different control standard troponin assays for comparison with different cut-off values. Explanation and Comparison with Other Studies To our knowledge, there are no published systematic reviews and meta-analyses that compared sensitivity and specificity of hs-Tn to standard troponin in patients presenting with chest pain. This is important as clinicians are uncertain of how to react clinically when an institution adopts hs-Tn. A prognosis based systematic review of hs-Tn (26) demonstrated that in patients presenting with chest pain who have a negative c-Tn but positive hs-Tn have a significantly higher mortality than if both assays are negative. This is important as nearly a third of patients presenting with chest pain in their study had positive hs Tn but negative c-Tn. This indicates a possibly higher frequency of AMI diagnosis when hs-Tn is used instead of c-Tn but importantly these events are associated with an adverse prognosis. Further data is needed to determine the effect of hs-Tn on outcomes and costs in the treatment of patients with suspected AMI. Another aspect to consider is the serial measurement of cardiac troponin and its ability in enhancing AMI diagnosis. The National Academy of Clinical Biochemistry recommends a 20% increase in serial troponin measurements.(27) For hs-Tn, large relative changes may occur despite minor absolute level increase which is partially due to the high sensitivity nature of hs-Tn and its ability to detect levels even in the normal range.(28) Irfan et al (2013) studied the absolutes and relative changes in hs-Tn levels at presentation and 1, 2 hours. Absolute changes in hs-Tn T levels had significantly higher diagnostic accuracy as compared to relative changes. (29) Despite the increased sensitivity of hs-Tn at presentation, guideline committees have been reluctant to endorse the use of hs-Tn to rule out at AMI with a single value. An algorithim to expedite patient discharge was studied in patients presenting to ED with chest pain. In this study (30), AMI was ruled out in patients with hs-Tn T lower than 12ng/L at presentation and a change of less than 3 ng/L over the first hour. The sensitivity of rule out group was 100% supporting the concept that 2 hs-Tn T values over an hour are safe enough to rule out AMI. An algorithm such as this would allow patients' time in ED to

	be reduced from 6-8 hours to potentially 1-2 hours. Finally, using hs-Tn in ED has other pros and cons that need consideration. For example, the early diagnosis of AMI will allow earlier initiation of anticoagulant and antiplatelet therapy and potentially more efficient care. Triaging of patients presenting with chest pain may be improved with hs-Tn. On the other hand, reduced specificity may result in prolonged hospital stays, increased use of invasive tests such as angiography in patients with normal coronary arteries. Randomized trials comparing the systematic use of hs-Tn vs. c-Tn in patients presenting with chest pain would be able to determine the potential benefit of early initiation of therapies on clinical outcomes and time to safe discharge from hospital. Limitations: hs-Tn I has multiple analyzers and different cut-off points that precludes attempts to meta-analyze the data due to significant heterogeneity. Another limitation was that all studies assessed the diagnostic accuracy of hs-Tn T at different time intervals from symptom onset which limits the ability to assess the diagnostic accuracy of hs-Tn T at different time intervals except at presentation where the data was available from all trials. Furthermore, the reference standard for AMI adjudication was c-Tn, which will eventually underestimate the sensitivity and specificity of hs-TnT and over-estimate them for c-Tn. Also, the included studies used different c-Tn assays and cut points as a reference standard for AMI adjudication which can be a source of bias. Finally, English language studies were only included in this study which raises the possibility of not including other relevant studies in other languages. Conclusion: For patients presenting to the emergency department, hs-Tn compared to c-Tn has improved sensitivity but reduced specificity which may be useful in triaging patients. Over a period of 6 hours, AUC of both hs-Tn T and c-Tn are similar. Future studies are needed to determine potential benefits of earlier treatment and health economic consequences of use of hs-Tn." 2. Please include some discussion on the heterogeneity you found in your study. Response: We acknowledge that point and we did add the following to the discussion section: "The heterogeneity in our meta-analysis based on I2 was in the low to moderate range with , I2 for sensitivity was 32.53% (9 and for specificity 32.35.(10,11) This is explained by the use of different control standard troponin assays for comparison with different cut-off values." 3. Please include a brief interpretation of the risk of bias as per the Cochrane Risk of Bias/QUADAS that was employed in the study. Response: We acknowledge that point and we did add the following section: "Methodological quality of included studies: The QUADAS tool demonstrates a generally high quality validity assessment (Figure 1). All studies used acceptable reference standard test and delay between tests were appropriate. A second or third reference standard was not used to verify diagnosis, thereby partial and differential verification bias was avoided in all studies. Majority of the studies satisfied target population. Incorporation bias was not present in any of the studies since hs-Tn was not incorporated in a composite reference standard. Blinding of reference standard results was unclear in five studies while the index test results blinding was unclear in only one study. Withdrawals were unclear in one study. Sponsoring was adequately precluded in 3 studies while four remained unclear." 4. Please clarify the reference standard used for myocardial infarction in the various studies you included, and if the reference standards are different, please address in the limitations subsection of the discussion how these differences may have affected your results. Response: Table 2 lists the type, assay and cut point of cTn used in each study as a reference standard. It was mainly cTnT, fourth generation assay (Roche Diagnostic, 0.04 ng/ml) but few studies used a different cut point and/or cTnI as illustrated in Table 2. We did add the following to the limitations section to acknowledge that: "Also, the included studies used different c-Tn assays and cut points as a reference standard for AMI adjudication which can be a source of bias." 5. Please remove Table 3 and ensure that the content is included in the text of the paper itself. Response: Table 3 was removed and its content added to the paper

	6. Please include a comment in your limitations section as to the implications of searching English literature only. Response: We acknowledge that point and we did add the following to limitations section: "Finally, English language studies were only included in this study which raises the possibility of not including other relevant studies in other languages." 7. We have attached a link to a systematic review / meta-analysis recently published in CMAJ for you to reference with respect to the format and standards of publication. Response: We acknowledge that example and have followed its format and standards of publications Other points: 1. Please ensure your final word count is below 2500 words and the abstract is about 250 words. Response: We acknowledge that and did edit the contents of the paper to comply with the word limits mentioned. 2. Abbreviations: For only the most standard abbreviations (i.e., 95% CI, SD, OR, RR, HR), please spell out at first mention and include the abbreviation in parentheses. The abbreviations may be used throughout the remainder of the manuscript. Please remove all other abbreviations. Response: We acknowledge that and used standard abbreviations after spelling out at first mention throughout the manuscript. 3. Please include up to 1 academic and 1 professional degree after each author's name. Response: Each author's name was edited as mentioned. 4. Please structure the abstract into 4 main sections: Background, Methods, Results and Interpretation. Response: We acknowledge and formatted the abstract as requested: "Background: High Sensitivity Troponin (hs-Tn) has been adopted by many clinical centers worldwide. Clinicians are uncertain how to interpret the results of hs-Tn. Our aim is to assess the diagnostic abilities of hs-Tn to diagnose acute myocardial infarction (AMI) in a systematic review. Methods: We performed a systematic review and meta-analysis of comparative studies of hs-Tn versus c-Tn in adults with suspected AMI in the emergency department (ER). We searched PubMed, Embase and Cochrane up to April 2013. Bivariate random-effects modeling were used to obtain summary diagnostic accuracy parameters. Results: A systematic search yielded 9 studies that assessed the use of hs-Tn T (9186 patients). At presentation to ED, in diagnosing AMI, the summary sensitivity was estimated to be 0.94 (95% CI: 0.89, 0.97) and 0.72 (95% CI: 0.63, 0.79) for hs-Tn T and c-Tn test, respectively. At presentation to ED, the summary specificity was estimated to be 0.73 (95% CI: 0.64, 0.81) and 0.95 (95% CI: 0.93, 0.97) for hs-Tn T and c-Tn test, respectively. The difference of the summary sensitivity or specificity between both hs-Tn T and c-Tn test was statistically significant ($p < 0.01$). At 3-6 hours from presentation, AUC were similar between hs-Tn T vs c-Tn. Interpretation At presentation to ER, hs-Tn has improved sensitivity but reduced specificity when compared to c-Tn. With repeated measurements over 6 hours, AUC are similar between hs-Tn T and cT-n and so the major advantage of hs-Tn T is early diagnosis." 5. Please use plain numbers in brackets for your references and do not use automatic numbering of field codes as these do not carry over well into our publishing software. Response: We did change the automatic numbering of field codes for references to plain numbers in brackets as per your request. 6. Please be sure to include a completed PRISMA reporting guideline checklist. Response: We did include a completed PRISMA reporting guideline checklist as per your request.

	Response to Dr. Sally Aldous comments: 1. Discussion was very brief. It was not mentioned that the sensitivity of hsTnT is still not high enough at presentation to warrant discharge in those with negative results. Given that at later time points, there does not appear to be a significant difference, there should be a discussion regarding the benefit of using a hs assay. Response: We did edit the discussion section and has acknowledged that. 2. It is also not mentioned that MI is adjudicated by a conventional troponin. We know that more patients are diganosed with MI when a hs assay is used for adjudication, therefore using a conventional cTn for adjudication will miss some MIs picked up by the hsTnT, this will underestimate the sensitivity and specificity of hsTnT and over-estimate them for the conventional troponin. This should have been acknowledged. Response: We did edit the limitations section and has acknowledged that by adding the following: "Furthermore, the reference standard for AMI adjudication was c-Tn, which will eventually underestimate the sensitivity and specificity of hs-TnT and over-estimate them for c-Tn." Response to Dr. P. Nagele comments: 1. The authors include very heterogeneous studies, some that used TnT and others that used TnI, some that used this cutoff and some that used other cutoffs. It is, in my opinion, very important to pool the results from studies that closely resemble each other to provide a meaningful comparison. Response: We agree about the importance of pooling results from studies that resemble each other. That was the main reason because of which we divided studies into two groups: studies that used hs-TnT and the ones that used hs-TnI. Then we analyzed the hs-TnT studies that used the same cut-off point (14 ng/L) and we presented the results in the paragraph entitled "Sensitivity and Specificity of hs-Tn T: At presentation". We added a sentence to that paragraph to make it clearer that we only analyzed the hs-TnT studies that used the same cut-off point. With regards to hs-TnI, we specified that given the different assays and cut-offs that have been utilized for studies, it wasn't possible to combine the results for analysis. Therefore, we presented the results of each study without analysis in Table 4. 2. How was acute MI defined in each study? Was the universal definition of acute MI followed? Response: Yes, the most up to date universal definition of acute MI as per ESC/ACCF/AHA was used in the included studies. We did add the following paragraph to clarify that and to explain how acute MI was defined in each study: "Studies population and outcomes definition: The included studies enrolled patients who presented to the ED with symptoms, such as chest pain, that were suggestive of AMI. Patients underwent the usual initial clinical assessment that included history taking, physical examination and 12-lead ECG. The c-Tn was measured at presentation to ED and was repeated 2-24 hours later (Table 1). hs-TnT was measured at presentation in nine studies (14-22) while hs-TnI was measured in three studies(20,23-24). The final diagnosis for each patient was determined by event adjudicators after they reviewed all available medical records from the time of the patient's arrival in the ED to the end of the follow-up period (Table 1). AMI was defined in accordance with the 2007 ESC/ACCF/AHA guidelines(25) in seven studies.(14-20) In brief, AMI was diagnosed when there were typical clinical signs of myocardial ischemia and evidence of myocardial necrosis. Myocardial necrosis was diagnosed on the basis of a rising and/or falling c-Tn pattern (>20% or <20% compared to the c-Tn levels at admission) with at least one value above the 99th percentile and an imprecision of ≤ 10%. Similar but previous 2000 and 2001 ACC guidelines where used in two studies.(21-22) " 3. Regarding the diagnosis of acute MI using hs-cTn assays, several aspects deserve consideration: different cutoff values, different change values (delta), e.g. 5/7/9 ng/L. Response: We did edit the discussion section and has acknowledged that by adding the following: "Another aspect to consider is the serial measurement of cardiac troponin and its ability in enhancing AMI diagnosis. The National Academy of Clinical Biochemistry recommends a 20% increase in serial troponin measurements.(27) For hs-Tn, large relative changes may occur despite minor absolute level increase which is partially due to the high sensitivity nature of hs-Tn and its ability to detect levels even in the normal range.(28) Irfan et al (2013) studied the absolutes and relative changes in hs-Tn levels at presentation and 1, 2 hours. Absolute changes in hs-Tn T levels had significantly higher diagnostic accuracy as compared to relative changes. (29) Despite the increased

	sensitivity of hs-Tn at presentation, guideline committees have been reluctant to endorse the use of hs-Tn to rule out at AMI with a single value. An algorithim to expedite patient discharge was studied in patients presenting to ED with chest pain. In this study (30), AMI was ruled out in patients with hs-Tn T lower than 12ng/L at presentation and a change of less than 3 ng/L over the first hour. The sensitivity of rule out group was 100% supporting the concept that 2 hs-Tn T values over an hour are safe enough to rule out AMI. An algorithm such as this would allow patients' time in ED to be reduced from 6-8 hours to potentially 1-2 hours." and the following: "hs-Tn I has multiple analyzers and different cut-off points that precludes attempts to meta-analyze the data due to significant heterogeneity." 4. Please use ONE scientific notation for concentration throughout: I would recommend ng/L since this will become the standard for hs-cTn reporting. Response: We did edit the article and changed the units to ng/L for hs-Tn T and I (the changes were made in the paragraph entitled "Sensitivity and Specificity of hs-Tn I" and in Table 4). With regards to conventional troponin, we used ng/ml throughout the article since this is the most commonly used unit currently. 5. In the methods section, the authors write about 12 included studies, but the rest of the paper lists 9. Please clarify. Response: Out of the 12 included studies, 9 assessed hs-TnT and 3 studies assessed hs-TnI. We presented the results of these studies in the paragraphs entitled "Sensitivity and Specificity of hs-Tn T" and "Sensitivity and Specificity of hs-Tn I" respectively. The 3 studies for hs-Tn I were included in systematic review but due to different assay could not be included in quantitative analysis. 6. Please provide a detailed list – akin to table 1 – for all 38 excluded studies. Response: We did add a summary table of excluded articles to the appendix. 7. The whole section labeled "biochemical assays" should be completely revised. Perhaps a table is better. Response: We agree and since we have all the information pertaining to the biochemical assays used already in Tables 2 and 4, we did delete the "biochemical assays used" paragraph. 8. Figure 2 is barely readable. Response: We did edit figure 2 to increase it is resolution. 9. Table 2: there seem to be some errors – how can the Aldous 2012 paper use Roche Elecsys with a cTnI assay when Roche only makes hs-cTnT and has the patent for TnT? Response: With regards to table 2, Aldous 2012: the hs-TnT assay used was the Elecsys system (Roche diagnostics) as written in the table while the reference test was the conventional troponin I assay (Abbott Diagnostics). We did use the "track changes" function to highlight the changes we made as per your suggestions. Yours sincerely, Dr. Sanjit Jolly, MD, FRCP(C) Assistant Professor McMaster University Interventional Cardiologist Hamilton Health Sciences Corporation Hamilton, Ontario, Canada