Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: P:3, L: 85 - please provide the reference after "onset of symptoms" for the sentence

Reply 1: We have added the following references (9,10):

Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361(9):858-67.

Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361(9):868-77.

Comment 2: P:3 L 86 - please provide a reference after Figure 1

Reply 2: We have added the following references (11):

Neumann JT, Twerenbold R, Ojeda F, Sorensen NA, Chapman AR, Shah ASV, et al. Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. N Engl J Med. 2019;380(26):2529-40.

Comment 3: P: 6 L: 148-150 - please provide a reference for the statement

Reply 3: We agree with the reviewers that this statement was somewhat provocative and have deleted this sentence.

Comment 4. P:7/8 L:198-200 - please provide a reference for the sentence

Reply 4: We have moved the reference one sentence up:

46. Tolsma RT, Fokkert MJ, van Dongen DN, Badings EA, van der Sluis A, Slingerland RJ, et al. Referral decisions based on a pre-hospital HEART score in suspected non-ST-elevation acute coronary syndrome: final results of the FamouS Triage study. Eur Heart J Acute Cardiovasc Care. 2022;11(2):160-9.

Comment 5: P: 9, L: 230-231 - please provide a reference for the sentence " Second, troponin..."

Reply 5:

We have included a ref after this sentence (22):

Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-361.

Comment 6: P: 11, L: 286 "need" - to be consistent in grammar

Reply 6: Corrected, thank you.

Reviewer B

The article by Thulin et al. discusses the possibilities of a POCT hs-cTn implementation in health care. The authors considered the broad spectrum of issues that come along with the implementation of POCT that is of true added value to current literature. The authors concluded that before POCT implementation future studies are required to establish a new routine involving POCT.

I only have some minor suggestions to further improve the manuscript, as pointed out below:

General comments and issues:

Comment 1: What kind of hs-cTn assays do we have today: Here three different POCT tests are mentioned, all for cTnI. Can you elaborate on the status of POCT hs-cTnT?

Reply 1: To our knowledge there are no high sensitive cTnT POC instrument available. The IFCC Committee on Clinical Application of Cardiac Biomarkers aim to present "Biomarker Reference Tables" including all commercially available cTn assays, including POCT. These tables are updated 2-3 times a year. Information is provided by the manufacturers and all manufacturers that provide a package insert for they assay are allowed to submit it.

See (Ref 29): https://ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/biomarkers-reference-tables/

Comment 2: In line 142 the TAT is stated at 60-90 minutes. Is this median time or completion time of all tests since I know from our lab that median time is around 45 minutes and almost all samples are completed at 60 minutes. Please also clarify your definition of TAT: from sample drawing to result or sometimes from I notice the definition is used from registration at the lab to result. Most CLT tests require around 10-15 minutes of analysis time. Do you expect that the current trend of Total-Lab-Automation might further shorten TAT of CLT tests?

Reply 2: We agree with the reviewers that this statement was somewhat provocative as TAT has diminished substantially during the last years and have rephrased this sentence, see page 5-6 line 144-146

Underlined by one additional reference (37): Sanders JH, Karr T. Improving ED specimen TAT using Lean Six Sigma. Int J Health Care Qual Assur. 2015;28(5):428-40.

Regarding your last question our personal view is that it is likely that TAT may be reduced further in the future. As this statement may be somewhat speculative we have not included it in the ms.

Comment 3: In line 161 it is stated that the rule-out of hs-POCT assays is expected to be higher, but in the next sentence reports have found a similar rule-out ability as CLT. Maybe possibly rephrase, since now it reads as contradictory.

Reply 3: Thank you. We aimed to communicate that the rule-out ability of hs-POCT is

expected to be higher than what has been found in previous POCT studies. We have made changes that we hope clarify this, see page 6 line 162-164

Comment 4: Who would maintain the POCT? Do you expect any challenge on this regard when implementing POCT? Also include facilities such as mentioned in line 228.
Reply 4: Excellent point. We have included some statements about this in the section concerning "Institutional preparations before implementing POCT", see page 12, line 316-320.

Comment 5: Regarding the statement that the oncology center would benefit from POCT, do you expect it is clinically relevant to have the troponin results immediately in the case of cancer treatment? You probably need more biomarkers than solely troponin? (Line 230-236)
Reply 5: Thank you, this is correct. Also natriuretic peptide should be measured, we have updated the text accordingly. We think this could be relevant in some settings, when the cardiac markers are monitored between/before treatment cycles. Some oncology centers strive for the patients to spend as little unnecessary time as possible in contact with the health care service and therefor want to reduce time waiting in lines for taking blood samplings and receiving results. These samples typically have own facilities for measuring platelets/leucocytes/Hb if the central lab is too slow or crowded. Such facilities could be extended with POCT cardiac markers. We have rephrased the text somewhat to make this point clearer, see page 9 line 235-243

Comment 6: Line 292 – 296, it is stated that the frequency of IQA and EQA may be lower for the POCT than for CLT. Actually, this is quite remarkable and might be important when considering the cost-effectiveness. I believe this could be stressed even more clearly.
Reply 6: Thank you, we have included a sentence to make this point clearer, see page 11 line 307-309

Comment 7: 67: creatinine kinase -> creatine kinase
Reply 7: Corrected, thank you.

Comment 8: 77: a troponin assays -> a troponin assay
Reply 8: Corrected, thank you.

Comment 9: 79: Punctuation, add a comma after furthermore.
Reply 9: Corrected, thank you.

Comment 10: 103 – 114: outline paragraph same as other paragraphs.
Reply 10: Sorry, we are uncertain what is meant by this comment, we believe the outline of this paragraph is similar to the others.

Comment 11: 130: first time using the abbreviation ACS, write full out.
Reply 11: Corrected, thank you.

Comment 12: 223: either use abbreviation ACS throughout text or write full out.
Reply 12: Corrected, thank you.

Comment 13: 226: abbreviation PIM -> PMI.
Reply 13: Corrected, thank you.

Comment 14: 264: Typo, change dot into comma.
Reply 14: Corrected, thank you.

Comment 15: Figure 1: cronic -> chronic
Reply 15: Corrected, thank you.

Comment 16: Table 1: typo for PATHFAST, change comma into dot
Reply 16: Corrected, thank you.

Comment 17: Table 2: typo, change comma into dot
Reply 17: Corrected, thank you.

Reviewer C

These authors are from the three major stakeholders (emergency department, cardiology and the clinical laboratory) have reviewed the topic of point-of-care testing (POCT using high sensitivity troponin (hs-cTn). In addition to existing POC tests, there is ongoing interest among commercial manufacturers to produce and achieve regulatory approval for more POCT devices for hs-cTn, making this review relevant. Comments:

Comment 1:. Line 111, “Qudel” is misspelled. Should eliminate Alere as this company no longer exists.
Reply 1: Corrected, thank you.

Comment 2. Line 122, “just 8 minutes” sounds like an endorsement, the reader is able to know that this is superior to <20 min.
Reply 2: We removed the word “just” from the sentence, thank you.

Comment 3:. Line 130, the authors are all from Europe. The ACS rate in the US is half of what it is in Europe, as the ED practices are different (i.e., many more patients use the ED instead of primary or urgent care). This difference could influence the utility of POCT for hs-cTn.
Reply 3: Thank you. We agree and have added one sentence and two references (32-33) from USA, see page 5 line 132-133
Apple FS, Smith SW, Greenslade JH, Sandoval Y, Parsonage W, Ranasinghe I, et al.

Single High-Sensitivity Point-of-Care Whole-Blood Cardiac Troponin I Measurement to Rule Out Acute Myocardial Infarction at Low Risk. Circulation. 2022;146(25):1918-29.
Sandoval Y, Lewis BR, Mehta RA, Ola O, Knott JD, De Michieli L, et al. Rapid Exclusion of Acute Myocardial Injury and Infarction With a Single High-Sensitivity Cardiac Troponin T in the Emergency Department: A Multicenter United States Evaluation. Circulation. 2022;145(23):1708-19.

Comment 4: The discussion on desired turnaround time could be expanded. How is it defined, and what are the recommendations by international lab guidelines? What are the steps required to obtain a sample and perform testing from CLT and how is that reduced for POCT?
Reply 4: Thank you. We have included a definition and cited one key recommendation (5) suggesting a max TAT of 60 minutes, see page 5 line 142-14
Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem. 2018;64(4):645-55.
We have included more information regarding the different steps that are different for CLT and POC, see page 5-6 line 144-146:
Underlined by one additional reference (37):
Sanders JH, Karr T. Improving ED specimen TAT using Lean Six Sigma. Int J Health Care Qual Assur. 2015;28(5):428-40.

Comment 5:. Line 147. This needs expansion. Suggest, “Some protocols have suggested that AMI rule out can be achieved with after a single draw at baseline (if the symptoms history exceeds 3 h)(reference needed). If the CLT cannot produce a result for the admission sample within 1 hour, a decision cannot be made until after the 1-hour draw, obviating the advantage of rule out at presentation. Testing with POCT can enable early rule out for low ACS-risk patients.”
Reply 5: Thank you. We have rephrased accordingly, see page 6 line: 146-149

Comment 6: Line 184. In the U.S., testing is given waived, moderate and high complexity testing status. This dictates the qualifications required for testing. While there are POC tests waived for B-type natriuretic peptide, currently, there are no waived POC tests for troponin. Discussion and perhaps a call to manufacturers to seek waived status could be made in this manuscript. This will affect decisions to test in non-standard areas such as urgent care, nursing homes, ambulances, etc, which current is not possible in the US without qualified lab technologists.
Reply 6: We have included this information on page 10 line 278-280:

Comment 7: Line 230. Testing for cancer patients does not require rapid turnaround

time, therefore given the higher economic costs, it may be difficult to justify using POCT vs. CLT, even with "limited access" as stated. Do the authors anticipate that a change in chemotherapeutics drug or dosage could be made with receiving test results while the patient is still in the clinic (to perhaps justify POCT)?
Reply 7: We think this could be relevant in some settings, when the cardiac markers are monitored between/before treatment cycles. Some oncology centers strive for the patients to spend as little unnecessary time as possible in contact with the health care service and therefor want to reduce time waiting in lines for taking blood samplings and receiving results. These samples typically have own facilities for measuring platelets/leucocytes/Hb if the central lab is too slow or crowded (for patients that may experience neutropenia). Such facilities could be extended with POCT cardiac markers. We have rephrased the text somewhat to make this point clearer, see page 9 line 235-243

Comment 8: Line 250. A major issue for using POCT as a backup for CLT is the lack of standardization between manufacturers. Cutoff concentrations will change and affect medical decisions. For patients with positive results, continued testing of admitted patients will likely require continued POCT or retesting by CLT.
Reply 8: Excellent point, thank you. We have updated the text accordingly, see page 10 line 266-268

Comment 9: In this reviewer's opinion, POCT is most useful for AMI rule out, if ED physicians are comfortable with discharge of patients after an accelerated testing protocol. For patients who rule in, it could be argued that conventional sensitivity cTn could detect increases that exceed the 99th percentile. This review does not sufficiently highlight this advantage. Figure 2 does not state that this could be a major advantage.
Reply 9: We respectfully disagree with the reviewer that using conventional cTn is an advantage for detecting increases in cTn above the 99th percentile. The reason for this is that for many conventional assay the LOQ and the 99th percentile are quite similar. High analytical variation close to the 99th percentile may lead to a situation were assay imprecision leads to positive results in more patients who are measured with the conventional assay vs the high sensitive assay (since more patients might have an elevated concentration above the 99th percentile due to analytical variation). An example of this may be found in the following article:
High incidence of discrepancies in new Siemens assay – a comparison of cardiac troponin I assays. Rasmus Bo Hasselbalch, Jonas Henrik Kristensen, Nicoline Jørgensen, Nina Strandkjær, Bashir Alaour, Shoaib Afzal, Michael Marber, Henning Bundgaard and Kasper Karmark Iversen. Clinical Chemistry and Laboratory Medicine (CCLM). https://doi.org/10.1515/cclm-2022-0034
Our view is that the improved precision obtained by using hs-cTn assays will be an advantage in nearly all clinical situations.

Comment 10: The authors discussed combining risk scores (line 133). Are they advocating encoding an algorithm that includes these scores along with the hs-cTn

result within an electronic medical record?
Reply 11: This could be an option in the future yes, however todays recommendations are either clinical gestalt (using ACS criteria suggested by ESC or a validated clinical risk score). Since machine learning algorithms are not implemented in clinical practice yet we have not included a discussion of that in the current paper.

Reviewer D
In the presented manuscript, Thulin et al. depict the currently available point-of-care testing hs-CTn assays, their possible areas of application and necessary prerequisites for their introduction into routine diagnostics. The work is of interest for JLPM's readership and presented in an adequate, structured format. However, some important topics concerning the application of POCT devices in the ED setting are missing yet. Before publication in JMPM, the manuscript therefore requires thorough modifications: Major concerns are:

Comment 1: On page 5 it is stated that the TAT of the determination of cTn is 60-90 min. There should be, however, a description of a discrimination between hospitals with and without optimized sample transport systems to the central lab, e.g. by use of pneumatic tubing systems. For the labs with functioning tubing system, a TAT of approx. 45 min can be achieved. This situation makes it easier for the clinicians to act promptly, even without POCT. This TAT is demanded by several European guidelines. In this context it is also unclear what the term "delays before samples are taken" (line 143) means. Please clarify.
Reply 1: This is pointed out by several reviewers and we do agree. The paragraph has been rewritten, and also include some new references, see page 5-6 line 144-146
New references (5, 37):
Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem. 2018;64(4):645-55.
Sanders JH, Karr T. Improving ED specimen TAT using Lean Six Sigma. Int J Health Care Qual Assur. 2015;28(5):428-40.

Comment 2: Chapter "Institutional preparations before implementing POCT": In terms of quality assurance, the authors should mention the pivotal role of POCT coordinators who are found very often in smaller and bigger European hospitals. These coordinators are also successfully using POCT middleware IT-solutions for documenting IQA and EQA as well as the postanalytical result management. This positive development should definitely be mentioned and should be given adequate wide scope.
Reply 2: Excellent point, we do agree and the text has been updated accordingly, see page 12 line 315-320

Comment 3: In the same chapter the authors are encouraged to give also a statement to the extremely important topic of hygiene requirements when using POCT devices in high-workload ED settings. An effective and complete decontamination of the devices must be required.
Reply 3: Thank you, we do agree and this has been included, see page 12 line 318-319

Comment 4: Under "Increased availability", there should be a more detailed discussion about the conflicting topic in the ED of many bigger hospitals that the shift of biochemical analyses from the laboratory personnel directly to care-givers is problematic in particular against the backdrop of the shortage of skilled care-givers all over Europe. In this context, one can also speak of misrouting of nurse-specific work tasks. On page 11 this topic is insufficiently addressed by only a few sentences. An accordingly revised statement for hospital settings should be transferred to page 7.
Reply 4: We do agree, however, respectfully we would also highlight that the recruitment situation for laboratory staff is also under large pressure in some regions so the local situation should be taken into account. We have elaborated this issue, see page 12 line 321-326.

Minor modifications are:
Comment 5: page 3, line 65: The term "precision" has a clear definition in laboratory medicine, which I assume was not meant by the authors in this context. Please rephrase.
Reply 5: Agree, this has been changed to "diagnostic accuracy".

Comment 6: p. 3, line 65: The references 1 and 2 are misleading, since they are not the original first description of cTn as cardiac marker. Please add reference.
Reply 6: Thank you. The references have been replaced by the following:
Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. Am Heart J. 1987;113(6):1333-44.
Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kubler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. J Mol Cell Cardiol. 1989;21(12):1349-53.

Comment 7: p. 3, l 67: The parameter CK-MB should also be mentioned here!
Reply 7: This has been corrected, thank you.

Comment 8: p. 4, l. 105: Please add "…sample preparation such as centrifugation and pipetting steps".
Reply 8: This has been corrected, thank you.

Comment 9: p. 4, l. 110 - 111: Please add city and country of the respective manufacturers. Change "form" to "from" and "Qudel" to "Quidel".
Reply 9: Thank you, this information has been added, and corrected.

Comment 10: P. 4, l. 112: For Table 1 there should be an additional explanation that the given %CV at 99th percentile data were obtained under optimized laboratory conditions. For POCT one must always be aware that one device is used by numerous operators. This increases the result imprecision on a routine basis.
Reply 10: Thank you. We have added the following statement to the table legend:
«*%CV at 99th percentile data were obtained under optimized laboratory conditions. As POCT devices are generally used by multiple operators, the result imprecisions will be expected to be higher on a routine basis.“

Comment 11: p. 4, l. 117: Please correct “PATFAST” to “PATHFAST”.
Reply 11: This has been corrected, thank you.

Comment 12: P.5, l. 123: The last sentence can be omitted since there are far more than two undergoing developments of other cTn POCT prototype methods.
Reply 12: Agree, the sentence has been rephrased, see page 5 line 125-126

Comment 13: p. 5, l. 130: Please explain abbreviation ”ACS”.
Reply 13: This has been corrected, thank you

Comment 14: p. 5, l. 143: Please explain what is meant by “STAT assays”.
Reply 14: STAT is an abbreviation of statim that means "immediately" typically interpreted as “emergency”, this is a term implemented world-wide. However, if the editors think this is necessary we could include the following:
“STAT (STAT is an abbreviation of statim that means "immediately") assays”

Comment 15: p. 6, l. 167 and l. 170: It is not clear to which device the term “cut-off” refers. Please clarify!
Reply 15: Thank you, rephrased and clarified, see page 6 line 168-169 and 171-172

Comment 16: p. 8, l. 201 - 203: The authors claim, that the 0/1-h-algorithm in an outpatient setting using central laboratory hs-cTn has “acceptable safety and better cost effectiveness”, but miss to state as compared to which procedures / algorithms. Please clarify!
Reply 16: Thank you, rephrased and clarified, see page 8 line 205-208

Comment 17: p. 8, l. 208: Please clarify whether the “venous hs-cTn results” were measured with a POCT device or in the central laboratory!
Reply 17: Thank you, this have been replaced by “venous CLT hs-Tn results”

Comment 18: P. 9, starting with l. 237: It is controversial whether a troponin screening should be performed by use of POCT. Due to the fact that the results would not be time critical, measurements could also be performed in central labs. This opinion should be given in the text.

Reply 18: We agree and have rephrased the text to make it clear that this is probably only applicable in regions were POCT already is implemented in primary care, eg for follow-up/monitoring of diabetes patients (very common in Scandinavia for instance), see page….line…

Comment 19: P. 10, l. 264: The point after "includes …" should be omitted.
Reply 19: This has been corrected, thank you

Comment 20: P. 10, l. 267: What is the meaning of "organizations"?
Reply 20: Thank you, the word "organizations" has been deleted.

Comment 21: p. 11, l. 294: Please amend the important fact, that national legal requirements have also to be considered in determining the frequency of IQA!
Reply 21: Thank you, this information has been added, see page 9 line 249-252

Comment 22: Reference No. 25: The referenced website was last accessed in February 2020, i.e. two years ago. Please access the website again and update the manuscript in case new information is available!
Reply 22: Thank you, the reference has been updated.

Comment 23: Figure 1: "Chronic" instead of "Cronic".
Reply 23: This has been corrected, thank you

Comment 24: Tables 1+2: Which measurement means "hs-cTn"? cTnT or cTnI? Please clarify!
Reply 24: Thank you, this has been added, see table legend.

Comment 25: Table 1: Please amend the explanations of the abbreviations "LoB" and "WB"!
Reply: Thank you, this has been added.

Comment 26: Table 2: Why are exact "times for results" given for the PATHFAST and the VTli, but not for the TriageTrue? Can the exact time for the TriageTrue figured out from the manufacturer directly? If yes, please amend the exact time.
Reply 26: We have not found any information about the exact time for the TriageTrue assay. We have also contacted the manufacturer without response.

Comment 27: Table 2: Please explain the abbreviations "NPV" and "PPV"! Please also clarify to which event the given NPVs and the PPV refer! What do the numbers in parentheses in the NPV- and PPV-columns mean – confidence intervals? Please explain!
Reply 27: Thank you, this information has been included.

Reviewer E
This paper reviews the currently available high-sensitivity cTn device, the benefit of

using POCT high-sensitivity cTn assays, and gives perspectives on what should be done before implementing these novel POCT high-sensitivity cTn assays in daily practice. This paper has information suitable for a broad range of audiences and organizes the information in a clear structure. Here are a few points that need to be addressed:

Comment 1:. Page 3 Line 73, "The UDMI bases the diagnosis of AMI on clinical evidence of myocardial ischemia along with a detection of a rise and/or fall of cTn with at least one value above the 99th upper reference limit of the assay." There is still no consensus about specific criteria for how the 99th percentile URL should be defined. To avoid confusion, the author should remove "of the assay" from the sentence.
Reply 1: This has been corrected, thank you

Comment 2: In Table 1 and Table 2, the values should use"." instead of ",". For example, it should be 21.6 instead of 21,6
Reply 2: This has been corrected, thank you

Comment 3:. On Page 9 Line 238, the author mentions, " If the oncology centre has limited access to central laboratory facilities or the service provided is slow, using…". The benefit of POCT hs-cTn assay in cardiotoxic cancer treatment is not so evident for these well-equipped hospitals with cancer treatment capability. The author may rephrase it as "home use tracking between cancer treatment cycles", or may remove this small section.
Reply 3 Thank you. We think testing during outpatient consultation could be relevant in some settings, when the cardiac markers are monitored between/before treatment cycles. Some oncology centers strive for the patients to spend as little unnecessary time as possible in contact with the health care service and therefor want to reduce time waiting in lines for taking blood samplings and receiving results. These samples typically have own facilities for measuring platelets/leucocytes/Hb if the central lab is too slow or too crowded (e.g. for patients who may develop neutropenia). Such facilities could be extended with POCT cardiac markers. We have rephrased the text somewhat to make this point clearer, see page 9 line 235-243

Comment 4:. On Page 10 Line 264, "and includes. limits of blank," should be corrected to ", which includes limits of blank,"
Reply 4: This has been corrected, thank you

Comment 5:. On Page 2 Line 38, "were hs-cTn measurements are…" should be corrected to "where hs-cTn…"
Reply 5: This has been corrected, thank you

Reviewer F
Comment 1: L87: I would argue this application is diagnostic, not predictive; please rephrase.

Reply 1: We respectfully disagree. An AMI diagnosis should be made based on the UDMI. The 0/1 hour or 0/2 hour algorithms used in the ED is not suitable for making a diagnosis but for allocating patients to low, intermediate, or high risk of eventually having a UDMI-based diagnosis of AMI.

Comment 2: the link does not work for reference 25.
Reply 2: This has been corrected, thank you.

Comment 3: L115-123: can the authors provide more information on these assays? For example: Are they available in the US, Europe, or elsewhere?
Reply 3: Good question. To our knowledge, these instruments are available in Europe but we are uncertain about Asia, America, and other parts of the world. We have added some information about this, see page 4 lines 112-114

Comment 4: L264-266: please also include 'reportable range/linearity' and 'accuracy' in addition to the assay characteristics listed
Reply 4: This has been included, see page 10 line 275.

Comment 5: L301: 'personal' should be 'personnel'
Reply 5: This has been corrected, thank you.

Comment 6: L306-309 (and L253-257): please consider including a statement around the importance of analytical concordance of the hs-cTn POC assay with the central laboratory assay.
Reply 6: Excellent point, the text has been rephrased accordingly, see page 10 line 266-268 and page 12 line 330-334

Comment 7: Table 2: Please provide references for the information provided.
Reply 7: We have added the references to the table legend.

RE-Review

Reviewer B
Comment 1: There were some typing errors left though, someone should please have a final look to that e.g. p6 physician, p11 feasible and p12 requiring.
Reply 1: Thank you, these errors have been corrected.

Reviewer C
Comment 1: They misinterpreted my statement on comment #8. I did not state that conventional assays is an advantage, but that the advantage of hs-cTn of conventional assays was not as present.
Reply 1: Sorry for the misinterpretation. After the clarification we certainly do agree with the reviewer that conventional assays are good for ruling-in NSTEMI. The reason why we did not highlight the advantages of conventional cardiac troponins in this

review is that the focus was on hs assays. We fear that including some statements related to conventional assays may in fact confuse the readers. However, if the editor strongly wish that this should be added we are happy to include it.