Author’s response to reviews

Title: Routine Creatine Kinase Testing Does Not Provide Clinical Utility in the Emergency Department for Diagnosis of Acute Coronary Syndromes

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1. Did you evaluate CK or CK-MB? I'm assuming CK-MB, but please specify. If CK, then this should be properly addressed in the limitations section. If it was CK-MB, please change "CK" to "CK-MB" throughout the manuscript.
   • Our region uses unfractionated CK as a screening test for patients presenting to the emergency department. This is consistent with practice patterns known to us in many institutions across Canada. This has been clarified and addressed in Paragraph 4 of the Discussion section.

2. You mention "bloodwork as per a regional protocol". Please describe the protocol used in your institution: Do you recommend 1h, 2h, or 3h hs-cTnT and CK testing? How do you define a significant change in hs-cTnT in your protocol?
   • This is addressed in Paragraph 3 of the Method section, and has been clarified. The regional protocol involves nurse-initiated cardiac biomarker testing for patients presenting with CEDIS complaints suggestive of ACS (chest pain, shortness of breath, etc.). There is no standardized time at which serial tests are ordered; this is at the discretion of the physician. For the majority of patients, this is between 2 and 4 hours. What is the cut-off you use for CK? Since you are relying on diagnoses made by the attending cardiologist, it would be helpful for the reader to get a better understanding of how the diagnoses were made.
   • The upper limit of normal in our institution is 175 U/L for females, and 190 U/L for males. This has been specified in paragraph 4 of the Methods section.

3. Please specify the characteristics of the assays used (hs-cTnT and CK) such as the upper reference limit of the assay and if you have a institutional specific decision limits.
   • This has been addressed in paragraphs 3 and 4 of the Methods section. The assays used are commercially available Roche hs-cTnT and CK assays. The upper limits of normal have been specified
4. You specified a significant change as an increase of $\geq 5$ ng/L. Although this is the preferred delta for a 1h hs-cTnT measurement, it is lower than recommended delta values for 2h, 3h, or 6h hs-cTnT (Mueller et al. Clinical chemistry. Jan 2012;58(1):209-218; Biener et al. International journal of cardiology. 2013;167(4):1134-1140; Reichlin et al. The American Journal of Medicine. 2015;128:369-379). You could have thereby possibly missed patients with a non-significant change on a 2h, 3h or 6h hs-cTnT who should have been included with the 2012 patients you assessed as TnT-/CK+. You should consider addressing this in the limitations section.

- We have addressed this in detail in the limitations as suggested (Paragraph 8 of discussion), as well as in Paragraph 4 of the methods.

5. As per my previous comment, you defined a significant change as an increase $\geq 5$ ng/L. Did you not consider an elevated hs-cTnT showing a significant fall on serial testing as significant and were these patients not diagnosed with acute myocardial injury or AMI?

- This has been addressed in Paragraph 4 of the Methods as well as Paragraph 2 of the Results section. Serially decreasing hsTnT was not considered to be diagnostic so as to include as many situations in which CK might be useful as possible. Serially decreasing hsTnT with positive CK prompted a detailed chart review. No such patients were diagnosed with AMI.

6. The primary outcome of index visit AMI, was this based on the discharge diagnosis?

- This has been clarified in Paragraph 5 of the methods.

7. For both the primary and secondary outcomes, you describe a process of thorough chart review. Did the reviewers adjudicate the final diagnoses, or just extract specific discharge diagnoses? If diagnoses were adjudicated, were the reviewers blinded to the CK levels? I'm assuming they were not, which would then introduce potential bias in the adjudication process.

- This has been clarified in Paragraph 6 of the methods.

8. Do you have any data on baseline characteristics for the patients? Age, gender and especially AMI prevalence at least would be helpful.

- Although this data would be informative, it was not collected due to feasibility. The nature of the hospital is described in Paragraph 1 of the Methods, and aggregate data regarding the frequency of various presenting complaints is shown in Table 1.

- In addition, to further help characterize the sample, we have added a column to Table 1 showing the prevalence of each presenting complaint in the total sample. We have added to Paragraph 1 of the results the total proportion of the sample that was discharged from the ED vs admitted to hospital.

- The sample included all patients who presented to an urban tertiary care center in a major Canadian city, and baseline characteristics would be reflective of the population. It was felt that collection and description of this data would be beyond the scope of the current project, and would not significantly contribute to the validity of the conclusions. This has been addressed in Paragraph 3 and 6 of the Discussion.

- The recently reported baseline characteristics of the population with respect to CKD, CHF, IHD, and yearly incidence of AMI have been added to Paragraph 6 of the Discussion.

9. A total of 2012 patients had a non-diagnostic hs-cTnT and positive CK. How many of these had a hs-cTnT $>14$ ng/L? One could argue that this is the group were it would be most important to evaluate whether CK has a role. Among these 2012 patients, some patients must have had negative serial hs-
cTnT, and in these patients AMI is ruled out with a very high negative predictive value and CK is not needed. It's those with elevated hs-cTnT without significant change where the evaluation of the potential role of CK (-MB) is most interesting. Since only 1 patient among these 2012 was diagnosed with AMI, I'm wondering whether the proportion of patients with a hs-cTnT >14 was actually very small? Do you also have data on renal function on these patients?

• This has been addressed in the Limitations section. Although we do not have this baseline data, qualitatively, the presence of elevated baseline hsTnT and presence of CKD was not uncommon. As above, we have added the reported prevalence of CKD in the local population.

10. You state in your discussion that, except for the 1 missed AMI, all patients with AMI had a trending hs-cTnT. Does that mean that patients with elevated hs-cTnT without significant change as a rule were never diagnosed with AMI? It is not completely uncommon to see this pattern in late presenters and in some studies they constitute 10-25% of all AMIs (Morrow et al. J Am Coll Cardiol. Oct 1 2013;62(14):1239-1241). It therefore makes me wonder if there could be some misdiagnosed patients in your TnT-/Ck+ group?

• We have rephrased this part in Paragraph 2 of the discussion- this one patient did indeed have an elevated but non-trending hsTnT. In addition, it is possible that patients with elevated but non-trending hsTnT and negative CK would have been diagnosed with AMI, but they would not have been included in our chart review as they were not of interest for our study. We have rephrased to state that no patients with truly negative hsTnT and positive CK were diagnosed with AMI, and have clarified the details of the one patient who was included as possibly having an AMI with non-diagnostic hsTnT/ +CK by our study definitions.

11. Among the 2012 patients, what was the most common final diagnoses?

• We did not collect data regarding non-cardiac diagnoses, as this was beyond the scope of our study looking at the role of CK in the diagnosis of AMI. However, we have added a clarification that states explicitly that almost all were diagnosed with non-cardiac causes of chest pain in Paragraph 2 of the Results.