Author's response to reviews

Title: Identification of acute myocardial infarction in patients with atrial fibrillation and chest pain with a contemporary sensitive troponin I assay

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Author's response to reviews:

The authors thank the editor and the reviewers for attentively reading our manuscript and for the helpful and constructive comments. We have thoroughly revised the manuscript according to the suggestions.

In the following we provide a point-to-point reply to the questions raised by the reviewer. Changes in the manuscript are highlighted in red. The authors hope that the amended manuscript is now suitable for publication in BMC Medicine.

Comments to Reviewer 1:

1. “As stated above, the statistics is a bit behind my understanding and as presented, that is a major point. The manuscript would greatly benefit from a more complete description of the basis for the models used, especially how the cut-off values were arrived at. I am not disputing the logic or results, merely the underlying principles and what they actually mean in real terms for potential clinical use. This becomes very apparent with Figure 2. I understand what this Figure is saying but it is hard to readily translate this into practical clin. chem. use.”
Thank you for this sophisticated suggestion, which identifies some important points of our manuscript that could be improved. We have now expanded the statistical methods section to clarify how the different cut-offs were calculated and to better describe the background of figure 2. The corresponding paragraphs of the manuscript now read as follows:

Methods (Page 11, Line 14; Page 12, Line 4)

“In the derivation cohort of 90 patients with AF optimized thresholds were computed by determining the cut-offs that maximized (i) the sum of specificity and sensitivity (Youden-optimized cutoff, named “unweighted”), and those that yielded (ii) 90 % sensitivity and (iii) 90 % specificity, respectively. In addition we have considered the 99th percentile of the assay as cut-off. The uncertainty of choices (i) – (iii) is reflected by 95% confidence intervals that were obtained nonparametrically by taking the 2.5% and 97.5% percentiles from 2000 bootstrap replications of these evaluations.”

and

“Relative and absolute changes in the concentration between admission and after 3 h (i.e. absolute differences and differences divided by the baseline value times 100%) in the validation cohort were regarded as new biomarkers that gave rise to analogously defined cut-offs. Empirical kernel density estimations of these absolute and relative changes have been plotted for both subgroups, MI and non-MI patients (Figure 2), where the bandwidths have been chosen as to provide optimal insight into the qualitative distribution of values.”

Furthermore, reference of figure 2 in the manuscript reads now as follows:

“Troponin I kinetics represented by absolute and relative changes in troponin I concentration within the first three hours after admission are visualized in Figure 2 with respect to final diagnosis of type 1 MI.”

As from a clinical perspective for application of a biomarker (or its kinetics) a simple approach, e.g. use of cut-offs to dichotomize the continuous values (here of change in TnI concentration within 3h) is of utmost importance, we now rephrased the respective sentence on threshold application as follows:

“In respect to a clinical application, based on these data concerning changes in troponin I concentration an unweighted optimized diagnostic threshold of 0.011 ng/mL […] for the absolute change and of 0.3 % […] for the relative change […]”

2. “It strikes me that percentage presence of AF in the derivation cohort is almost 6x higher than the validation cohort. Does this influence the cut-offs used? One suspects it might, but this is not considered openly in the discussion. It should be as it is clear in Table 1 that there is a much smaller average presentation time (1/2) and lower percentage of Type 1 MI in the validation cohort.”

We agree with the reviewer, that the two cohorts indeed differ in various aspects. The derivation cohort is a cohort with high risk and with high pretest probability of
ACS. This is reflected by the high percentage of patients with final diagnosis of MI type 1, the high number pts. with TnI levels above the 99th percentile threshold on admission and the low number of AF (90 out of 1574 pts.) compared to the validation cohort (e.g. 314 pts with AF out of 1818) representing an unselected population as seen in many European chest pain observations units. As several of the patients in the derivation cohort have been transferred from a e.g. tertiary hospital the time between onset of symptoms and presentation differs between the two cohorts.

These aspects indeed might have a relevant influence on threshold derivation (e.g. calculating the unweighted threshold in the validation cohort would lead to cut-off of 0.028 ng/mL compared to 0.040 ng/mL if calculated in the derivation cohort, which is lower than the 99. percentile of the used assay). This important aspect is now discussed in more detail in the manuscript as suggested and implemented as part in the limitation section as follow:

Discussion (Page 19, Line 18)

“Several patients in the derivation cohort have been transferred from a tertiary hospital leading to higher median time between onset of symptoms and presentation which might have an influence on troponin concentrations upon admission and therefore on threshold calculation. In contrast, the high percentage of coronary angiography confirmed type 1 MI in the derivation cohort demonstrates the low percentage of other causes of troponin elevation by parameters influencing ischemic myocardial injury. These are important aspects which need to be reflected by interpreting the data.

In addition, the proportion of MI in the validation cohort is comparable to other European all-comer studies but higher than in non-European cohorts, which might limit the generalizability of the result.”

3.

• pg. 7 last line. Please insert reference for benefit of aggressive MI treatment.
• pg. 15, line 7: insert "of" prior to AF, ie. to read "diagnosis of AF [20]."
• pg. 15, para. 2, line 4: remove "considerably". 0.04 is not considerably higher than 0.032.
• Table 1: Derivation cohort, Troponin I n=311? Shouldn't this be n=90?

The authors appreciate these comments and the respective sentences have been rephrased and clarified as well as the number of patients in table 1 has been corrected.

Comments to Reviewer 2:

1. Most important and essential issue: validation of type 1 MI in the present study. There was no concrete (detail) description regarding validation of the type 1 MI in the present study. The concrete and detail conditions for the validation of type 1 MI in the present study should be described, especially their CAG or coronary CT/MRI findings (detail findings and corresponding patient numbers)
and/or myocardial RI/MRI findings (detail findings and corresponding patient numbers) should be shown in the new table or added in table 1, which should clarify backgrounds of patients with validated type 1 MI in the present study.

Thank you for your suggestions identifying some important points of our study that deserve further description. Identified potential culprit lesions in the CAG were classified according to the Ambrose criteria used as basis for final gold-standard diagnosis of MI type 1. This is now stated within the methods section of the manuscript as follows:

Methods (Page 9, Line 15)

“[…] type 1 MI was diagnosed when there was evidence of myocardial necrosis that was consistent with myocardial ischemia together with clinical symptoms of ischemia or electrocardiographic changes indicative of new ischemia […] or imaging evidence of new loss of viable myocardium or detection of a culprit lesion on coronary angiography classified according to the Ambrose criteria”

and

“The final diagnosis MI type 1 was made by 2 independent cardiologists based on all available clinical, laboratory, and imaging findings blinded to the investigational troponin I measurements. In case of disagreement a third cardiologist was consulted.”

Furthermore, as suggested, we have added data on CAG finding to the description of the cohorts as follows:

Results (Page 13, Line 3)

“The derivation cohort included a total of n=90 patients with AF […]. Based on coronary angiography findings, 67 patients with type 1 MI and AF needed a percutaneous coronary intervention or a coronary artery bypass grafting.”

and

“The validation cohort consisted of n=314 patients with documented AF […]. Of those 63 patients with type 1 MI, 52 needed a percutaneous coronary intervention or coronary artery bypass grafting. The median Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score in MI type 1 patients was calculated with 12.25 (IQR 6-22.12).”

2. New onset (or paroxysmal) atrial fibrillation versus chronic atrial fibrillation:
Both patients with new onset (paroxysmal?) atrial fibrillation and persistent atrial fibrillation were included in the present study. The reviewer guess that there were some differences in the troponin release-kinetics between the two groups, which might be more important rather than type 1 plaque rupture? Comparative analysis are expected. Duration of atrial fibrillation, heart rate and BP at the onset also significantly influence (relate to) the occurrence of ischemic myocardial injury and troponin release kinetics. Additional analyses regarding these points are also expected.
We fully agree with the reviewer that new onset vs. chronic AF might have a relevant influence on our analyses. During the structured assessment of patients enrolled in the validation cohort, we asked if the individual patient was aware of arrhythmias / atrial fibrillation or if this information was given in previous medical documents provided by the patient. This was the case in 66 individuals of the 314 patients presenting with AF documented in the ECG obtained on admission. We therefore performed a sub-group analysis excluding these 66 patients leading to a group of 248 pts. with presumably new onset AF. This group is now referenced in the manuscript as follows:

Results (Page 13, Line 17)

“In these 314 patients presenting with AF, data on previously known arrhythmias, based on information given by the patients, was available in 66 patients leading to a sub-cohort of 248 individuals with presumably new onset AF of whom 52 had the final diagnosis MI type 1.”

Furthermore, we calculated the respective NPV and PPVs after cut-off application in this sub-cohort in comparison to the overall validation cohort (supplementary table 1 compared to table 2) showing a comparable diagnostic performance of TnI in both groups referenced in the manuscript as follows:

Results (Page 14, Line 22)

“If restricting these analyses of the diagnostic performance of different thresholds to patients with presumably new onset AF comparable diagnostic performance was observed (Supplemental Table 1).”

To account for potential factors influencing ischemic myocardial injury (e.g. heart rate, blood pressure, CVRF, …) we have additionally calculated a multivariate model as suggested (presented as supplementary table 3) showing that troponin I is independently associated with MI type 1 in patients with AF. Of note, we did not include CAG findings in this multivariate model, as these findings are part of the definition of MI used to classify patients in our study. This aspect and the respective table is now referenced within the main manuscript as follows:

Results (Page 14, Line 1)

“Furthermore, this discriminatory information of TnI to identify MI type 1 in patients presenting with AF was independent of parameters that might influence ischemic myocardial injury such as blood pressure, heart rate, new onset of AF as well as cardiovascular risk factors (Supplemental Table 2).”

3. Statistical analyses were adequate in the submitted manuscript, and the reviewer expects further analyses regarding the issues described above (#1, #2). The reviewer would like to propose a multivariable analysis for the prediction of the occurrence of type-1 MI in these particular patients, new or paroxysmal onset atrial fibrillation? HR and BP? CAG findings? coronary risk factors?
See also our answers to comment 1 and 2 of this reviewer. The suggested multivariate analyses is now included as suppl. table 2 (including new onset vs. chronic AF). Data on CAG findings are presented within the manuscript. Analyses regarding a subgroup of patients with presumably new onset AF are included (e.g. suppl. table 1).