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Reviewer 00060494

Comment 1: "*What is the benefits and clinical applications of the different Tn rise and fall distribution announced in your article? I mean that will it change the MI treatment strategies even with different types of MI?"*

Response: We thank the reviewer for this question. Our research provides a first insight in the differences in the kinetics of troponin (Tn) for the different types of myocardial infarction (MI). Understanding these differences could be beneficial in clinical practice, because it may allow for optimization of the diagnostic criteria per type of MI in the future. In addition, knowing the expected kinetics of Tn after the different types of MI could potentially also allow for better monitoring of treatment effectiveness. We have changed the paragraph regarding clinical applications in the *discussion* section as follows: "The results of this systematic review give insight in the typical rise and fall of Tn in different types of MI. This systematic review is a first step in understanding the similarities and differences in the Tn kinetics between the different types of MI. The different types of MI each seem to result in a unique rise and fall pattern of Tn. In the future this may allow for optimization of the diagnostic criteria per type of MI. Potentially, understanding the kinetics of Tn can also help in monitoring treatment effectiveness."

Comment 2: *"Many factors may interfere the Tn level, such as renal function, sepsis, shock, or unstable hemo-dynamic status…etc. The paper had not well declaration of the included 34 analysis articles about these impacts on these factors. I think that it may put in the limitation section."*

Response: We agree with the reviewer that many factors interfere with Tn levels. Unfortunately, the included articles do not report on all these factors to fully overcome this limitation. We have revised the limitation paragraph in the discussion section accordingly: "Fourth, Tn levels can be influenced by several patient related factors. For instance, impaired renal function is associated with higher Tn levels. Insufficient patient specific data was available to correct for such patient related factors. However, these

批注 **[W&C1]:** Ook even aanpassen in je artikel

factors are likely affecting the absolute levels of Tn and not the shape of the rise-and-fall curve."

Comment 3: *"The topic of this article: The typical rise and fall of troponin in (peri-procedural) myocardial infarction. A systematic review…I think that it be confused to readers. In fact, it is not a review article."*

Response: We understand that confusion regarding the type of article can arise due to the extensive analysis we conducted on the acquired data. However, we do believe that this indeed is a systematic review. As described in the methodology section; we conducted a systematic search and screened systematically for to include all relevant articles.

Reviewer 00424947

Comment 1: "*Abstract: some mention should be made of a lack of data for determining patterns for Type 2 MI, since these were not addressed in the abstract."*
Response: We thank the reviewer for this comment. Type 2 MI was not a focus of this research. To clarify this we have rewritten the *methods* section of the *abstract* as follows: "We conducted a systematic search in PubMed and EMBASE including all studies which focused on the kinetics of Tn in MI type 1, type 4 and type 5."

Comment 2: "*It would be helpful to clarify the type I MI patients - were these spontaneous MI that were not treated with reperfusion therapies?"*
Response: We apologize for the confusion regarding the type 1 MI patients included in this study. This subgroup consists of the patients diagnosed with MI type 1 who received no reperfusion intervention or who did receive reperfusion intervention with an unclear effect. This means that only patients in who the effect of reperfusion was not evaluated or in who reperfusion was not initiated are included in the type 1 MI subgroup. The patients with type 1 MI in which reperfusion was evaluated and was successful were analyzed in a separate subgroup: the successful reperfusion group. To clarify this we have extended the first paragraph of the *statistical analysis* paragraph of the *methods* section: "Studies were divided into four subgroups based on the focus of the articles: studies on type 1 spontaneous MI (where reperfusion was not initiated or its effect not evaluated), studies that focused on successful reperfusion in the setting of an acute MI, studies on MI associated with PCI (type 4a MI), and studies on MI associated with CABG (type 5 MI) ."

Comment 3: "*Why was there no information provided regarding Type II MI? Is there no data available on this subset?"*
Response: We thank the reviewer for this question. We focused on the three types of MI that results from coronary artery disease (type I) or that are associated with coronary artery intervention (type 4 and 5). Since type 2 MI results from a different aetiology, namely the miss-match between demand and supply, we did not focus on this type of MI in this systematic review. We added the following sentence to our *methods* section: "Type 2 MI studies were not included in this systematic review as the etiology behind this type of MI is distinctly different."

Reviewer 01919991

Comment 1: "*the title is somewhat confusing for the presence of the notation "peri procedural" (although it is indicated in brackets)"*
Response: We apologize for the confusion. We have added the words 'peri-procedural' because, in addition to type 1 spontaneous MI, we also focus on two types of peri-procedural MI; type 4 (MI associated with PCI) and type 5 (MI associated with CABG). We believe that since a significant part of this systemic review concerns peri-procedural MI, it is acceptable to include it in the title.

Comment 2: *"it would be better to be consistent in the unit of measure of troponin concentration in table 1, both in the choice of it (e.g., ng/ml vs ng/l or microg/l) and in typography (l vs L)."*
Response: We agree with the reviewer that the typography should be consistent and we have changed table 1 accordingly. However, since we report in the table the cut-off level for troponin as published in that particular included article, we believe that it is appropriate to report it in our table with the same units as in that article. For the analysis part all troponin levels have been standardized according to the methods described in the *statistical analysis* paragraph in the *methodology* section.

We thank the reviewers for their useful responses. We hope that this revised version is now acceptable for publication.

Yours sincerely,
On behalf of all co-authors,

Dianne van Beek