Author's response to reviews

Title: Elevated troponin I levels but not low grade chronic inflammation is associated with and cardiac-specific mortality in stable hemodialysis patients

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Version: 3 Date: 17 September 2013

Author's response to reviews: see over
September 16, 2013

Dear Editors,

Thank you very much for considering our manuscript for publication in your journal. We now submit a revised version that incorporates the changes that were suggested.

We hope that you find our manuscript in its current revised form now satisfactory for publication in your journal.

Sincerely,

Ahsan Alam MD

Referee 1:

1) “Methods”: Tn can be altered, even lowered, for several weeks after an acute cardiac event, above all when the renal function is compromised. Patients with recent (at least 3 months) clinical cardiac and not cardiac event must be excluded… Please provide some details (in addition to the phrases declared in the discussion)

We agree that kinetics of troponin I are relevant when assessing ‘baseline’ levels. After a myocardial event, cardiac troponin I remains elevated for 1-2 weeks (Cummins et al. Am Heart J. 1987 Jun;113(6):1333-44.), and our patients were defined as ‘stable’ with this principle in mind.

Nonetheless, we re-reviewed our cohort to determine those that had any medical event in the prior 2 months. Ten patients had hospital visits that could be classified as minor or unrelated to any cardiac cause, and thus no troponin value was measured. Sixteen patients had a troponin value measured in the prior 2 months, with only 5 patients showing any elevation, but all returned to within normal-range by study initiation. One of the 5 individuals was admitted to the coronary care unit within the prior 2 months. This individual’s TnI was normal-range at study inclusion (TnI level <0.06). Excluding this individual did not change the magnitude or significance of our results, and if anything slightly strengthened its association.

As we did not pre-specify the exclusion of patients with a medical event in the prior 2 months, we have maintained our analysis as presented. We have included the information above in the results and discussion to address any concerns. We would also suggest that even in the presence of a possible recent cardiac event, particularly one that was subclinical, the prognostic information of a ‘routine’ or unbiased troponin level is more useful clinically.
2) “Methods”. In addition, a low non specific increased level of Tn may be present during serious infections, lung, peripheral artery, and muscle disease. Please provide some details in “methods” and in the “discussion”, where you talk about the other cardiac not ischemic accidents (pap 11, paragraph 1)

We agree that there are other circumstances where Tn may be elevated due to non-ischemic myocardial injury (e.g. sepsis). Since our null hypothesis was that TnI was not in fact related to cardiac-specific mortality, we did not exclude the possibility that other causes could be related to elevated TnI. In fact, we demonstrate that TnI elevations are also predictive of all-cause mortality, which may reflect these other processes, and not simply cardiac-specific events. Our study; however, was not designed to capture non-fatal events, as we felt these outcomes would not be as ‘hard’ an outcome as death, and more difficult to adjudicate. We have included this in our limitation section.

3) “Methods” The normal range for Tn I levels is <0.06 mcg/l in your laboratory, but which is the cut off for considering an acute ischemic injury?

There is no absolute cut-off that is diagnostic for acute myocardial ischemia, although a value above 0.10-0.30 mcg/L would be suspicious for an acute coronary syndrome in the appropriate clinical context (i.e. clinical symptoms, ECG changes, etc). Our laboratory cutoff for an elevated value was 0.06 mcg/L, but as sensitivity analyses we also used a cutoff of 0.10 mcg/L as well as tertiles, which provided similar trends.

4) 27% out of patients have “high” Tn I levels. How is the mean (median) value in this group? Did you consider other cardiac parameters (e.g. CK-MB, repeated Tn test) to really exclude a cardiac event and to confirm the “stable” condition?

The mean (SD) TnI level was 0.06 (0.11) and median (IQR) was 0.03 (0.02-0.06). We measured TnI monthly, but this was not repeated between monthly labs. We did not screen for other cardiac parameters, as our study was not designed to change clinical management in otherwise asymptomatic patients. We do not routinely measure CK-MB. We have mentioned this in our discussion. We do plan to examine other cardiac parameters in a future prospective study.

5) The lack of information about dialysis session, above all the intradialytic hypotension episodes, is pointed out by the Authors… another interesting parameters could be the post dialytic values of TnI. Some paper found a correlation between intradialytic increase levels of Tn and the mortality. I suggest to some more data on this issue.

We agree with the reviewer that examining troponin before and after dialysis would be of value. Our study did not sample post-dialysis troponin levels, however, we plan to study this in a prospective cohort. We have acknowledged this in our discussion.
6) **In your study the age doesn’t correlate with the mortality. This is unclear and unlikely. Can this be explained in the discussion?**

   We agree that patient age is an important factor associated with mortality, and thus we adjusted for age in our models. Patients who died were indeed older (mean age 70.4±15.1 vs. 66.5 ±14.8, p=0.17) than those who remained alive, but this did not reach statistical significance. The lack of association may in part be related to our exclusion of hospitalized/unstable patients, which we suspect excluded older patients. Also, the age of our cohort ranged from 26-93 years of age. These extremes of age may represent a lower risk population with respect to cardiac disease, due to selection and survival bias. We have included this potential explanation in our discussion.

7) **The same consideration about the lack of association between CAD history and the cardiac mortality… How do you justify it?**

   There was an association of CAD with death, but this was not significant in our analysis, perhaps due to limited power. We characterize the CAD history from chart review, which may is limited by physician reporting. Furthermore, severity and treatment of CAD were not captured, and these factors may be more discriminating as compared to CAD history alone. We have included this issue in our discussion section.

8) **In accordance to the age (mean 65 years), do you suggest some clinical interventions, diagnostic procedures, monitoring algorithms in patient with persistent “high” Tn I levels? Please argue this, as important message of your study**

   Similar to other observational studies, ours cannot relate elevated troponins as biomarker on a causal pathway leading to cardiac-specific mortality. We are cautious in suggesting changes to any existing clinical practice patterns. However, with further study, we can foresee the use of routine troponin levels to risk stratify patients to undergo further cardiac evaluation, such as exercise or pharmacologic stress testing. The benefits of this intervention require separate study. We have made mention of this in our discussion.

Reviewer 1: Andreana De Mauri

9) **Quality of written English: Not suitable for publication unless extensively edited**

   We regret any errors in language that may be present, and we are open to make any modifications to improve readability if detailed examples can be provided.

Reviewer 2: Fabrizio Grosjean
Minor essential revisions

10) Low grade inflammation is involved in development of diabetes mellitus and likely in its complications. Surprisingly the authors show that also diabetes mellitus, such as TNI, is independently associated to cardiac specific mortality and is associated with higher levels of TNI. This finding should be further discussed in the manuscript.

We acknowledge the association of diabetes and inflammation. We adjusted for the presence of diabetes to adjust for its association (confounding) with all-cause and cardiac mortality. The presence of diabetes likely captures many factors in addition to inflammation in dialysis patients, thus is likely more powerful a predictor of mortality than CRP alone.

11) Please specify in the text when data reported in supplementary materials are cited

We have included a citation to supplementary tables.

Discretionary revisions

12) I would suggest to change the title in: Elevated TNI levels but not low grade chronic inflammation markers are associated with cardiac specific mortality in stable hemodialysis patients

We agree with the reviewer and have modified our title.

Editorial Comments:

13) First of all as stated by one of the reviewers Tn can be altered for several weeks after an acute cardiac events so it is important to exclude any events prior the beginning of the study. even more important is to know the cut off for TnI in the hospital where the study was carried out. The authors should also indicate the mean of TnI values and it may be important to know if other parameters commonly used to discriminate for acute cardiac events were used to exclude minor ischemic events.

We have addressed these issues in our comments to referee 1.

14) Since mortality in dialysis patients also correlate with hypotension and other features of dialysis session it may be important to add more data on these topics The more important issue about this article is the contrast with the majority of papers which indicate that age
a very important risk factor for all cause mortality and also the fact that mild elevation of TnI correlate also with all cause mortality. How can the authors explain these results? The authors should at least speculate on this issue and also on the lack of association with CAD.

We have addressed this issue in our comments to referee 1.

15) It may be important to suggest a clinical algorithm in order to treat patients with persistent increase of TNI levels.

We have addressed this issue in our comments to referee 1.

16) Finally since the most important results is the apparent dissociation between elevation of TnI and inflammation I would as the second reviewer suggested change the title of the paper.

We have changed the title as suggested.

17) Editorial Request: Please upload Supplementary Tables as Additional Files

Supplementary tables are provided as a separate file.