Author’s response to reviews

Title: Prognostic Implications of Statin Intolerance in Stable Coronary Artery Disease Patients with Different Levels of High-Sensitive Troponin

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Responses to reviewers

John Beilby (Reviewer 1):
This is an interesting and well written paper.
Authors’ responses: Thank you very much for your kind comment.

Major issue:

The authors should comment in the text on the role of possible interferences with the Abbott hs-cTnI method due to antibody-mediated interferences Circulation 2018; 138:989-99. These interferences could significantly skew the conclusions drawn in this study if they have not be ruled out as having an effect.
Authors’ responses: Thank you very much for your insightful comment. We agreed that this is a significant limitation of our study and have addressed this in the limitations accordingly.

While we are aware of the limitations of direct measurement of cTnI in stored serum sample using immunoassays, how the presence of absence of antibodies and other molecules interfere with the prognostic significance of hs-cTnI values remain unknown. For example, studies have suggested that some anti-cTnI antibodies predict MACE after ACS. While the presence of those anti-cTnI antibodies may result in erroneously low cTnI value, low cTnI value has remained predictive of good clinical outcomes in a variety of cardiovascular conditions.

Despite these limitations, the findings of our study showed that hs-cTnI values predicted clinical outcomes. Before the development of a simple and low-cost test that is negatively influenced by all antibodies, we believe that our findings is still of clinical value since hs-cTnI measured by immunoassays is one of the most readily available test in the clinical setting.

‘…the presence of heterophile or anti-TnI antibodies, may lead to erroneous hs-cTnI values.’ Page 12, paragraph 2, lines 15-16.

‘Moreover, how the presence or absence of antibodies interfere with the prognostic significance of hs-cTnI values remain unknown. Despite these limitations, hs-cTnI has been shown to predict clinical outcomes in a variety of cardiovascular conditions, which is consistent with the findings of this study. Before the development of a simple and low-cost test that is negatively influenced by those antibodies, our findings is still of significant value as hs-cTnI measured by immunoassays is widely available in the clinical setting.’ Page 13, paragraph 1, lines 4-10.

Other points;

Methods

Page 5; line 54 .. The authors should change creatine to read creatine kinase.

Authors’ responses: Thank you very much. We have amended it accordingly. Page 5, paragraph 2, line 2.

Page 6; line 10 ..The authors should comment on the stability of plasma troponin stored at -80C for a number of years.

Authors’ responses: Thank you very much for your comment. We agreed that this is a significant limitation of this study and have addressed this in the Limitations session accordingly.
Currently, the long-term stability of cTnI in frozen sample remains debatable. While early studies have shown a non-negligible time-dependent degradation in the initial few days, more recent studies have found that the magnitude of degradation in the longer-term may be small compared with the actual cTnI values. More importantly, studies have consistently shown that retrospective cTnI assessment predict clinical outcomes in various cardiovascular conditions, consistent with our findings.

‘Third, retrospective assessment of hs-cTnI in stored serum samples using immunoassays may result in random measurement errors. It is because the long-term stability of cTnI in frozen sample has remained debatable, …, may lead to erroneous hs-cTnI values. Nevertheless, in a recent study that assessed cTnI levels using the Architect STAT hs-cTnI assay (Abbott Laboratories, IL, USA) in serum samples that were stored for 0.8 to 82.0 months, the mean cTnI value in the quartile of samples with the longest storage time did not differ significantly from those with the shortest storage time, suggesting that the magnitude of cTnI degradation over a long period of storage time may be small compared with the actual cTnI value.’ – Page 12 paragraph 2, line 12 to page 13, paragraph 1, line 4.

‘Despite these limitations, hs-cTnI has been shown to predict clinical outcomes in a variety of cardiovascular conditions, which is consistent with the findings of this study.’ – Page 13, paragraph 1, lines 6-8.

line 15 ..The units used for hs-cTnI are ng/L. Elsewhere in the manuscript eg table 1 gp/mL are used. The authors need to make sure the units are consistent.

Authors’ responses: Thank you very much for your comment. We have changed all unit for cTnI in this manuscript to ng/L accordingly.

Results

Page 8; line 55..Could the authors please clarify that this statement is correct ie 'was significantly higher in patients with than those without SI (2.0 △ 0.8 vs. 1.9 △ 0.6 mmol/L, P=0.01). The lipid values appear to be the same as in line 54.

Authors’ responses: Thank you very much for your comment. We understand that the numbers appeared similar numerically but they are significantly different statistically.

Conclusion

Page 14; Line 11.. ‘...our findings suggested that hs-cTnI is useful to stratify patients with stable CAD’... Can the authors come up with a more definitive statement as to how this study could be clinically useful. Since there is a statistically significant difference in LDL levels between SI and
statin tolerant patients but it is not clinically significant, and the fact that the cut-off used for hs-TnI of 5.2ng/L is within the 99th percentile value of serum hs-cTnI level in male and female control subjects of 8.5 ng/L and 7.6 ng/L, respectively.

Authors’ responses: Thank you very much for your insightful comment. We have amended the conclusion to include our cut-off value accordingly.

‘The results of this study showed that SI independently predicted MACE in patients with stable CAD and hs-cTnI >5.2 ng/L, but not in those with low hs-cTnI. Our findings suggested that a cut-off value of hs-cTnI >5.2 ng/L is useful to stratify patients with stable CAD to more aggressive non-statin lipid lowering treatment.’ Page 14, paragraph 1, lines 1-4.

Surbhi Chamaria, MD (Reviewer 2):
Overview and general recommendation

Statin intolerance in patients with CAD is an ever-increasing problem and a cause of MACE. Most patients on statin therapy are either not at optimal doses or are intolerant and hence not on statins.

This study looks at implications of statin intolerance in patients with CAD who also have hs-TnI levels.

I found the paper to be overall well written and much of it to be well described. The authors have done a thorough search.

Authors’ responses: Thank you very much for your kind comment.

Major Comments:

a. Why was hs-TnI levels checked in patients with stable CAD? Were there other reasons for the levels to be elevated besides CAD?

Authors’ responses: Thank you very much for your comment. We determined the hs-cTnI level retrospectively for study purpose. We have clarified this in the Methods session accordingly.

‘Serum level of hs-cTnI was retrospectively determined for this study after completion of patient recruitment…’ Page 6, paragraph 2, lines 1-2.
b. Why are a significant number of patients with no statin intolerance on lower doses of statin and lowest potency statin?

Authors’ responses: Thank you very much for your enquiries. Some patients in this study were recruited over 15 years ago, when the benefit of high-dose statin and low LDL-C in stable CAD was less well-established. As shown in previous studies, stable patients with CAD are often continued with the same dose of medications after discharge, which was also observed in this study.

We have addressed this limitation in the Limitations session accordingly.

‘Second, some patients in this study were recruited over 15 years ago, when the benefit of high-dose statin and low LDL-C in stable CAD was less well-established. Since stable patients are often continued with the same statin dose after initial prescription, a significant proportion of patients in this study remained on low dose statin. In fact, only 43% of patients without SI in this study achieved a target LDL-C level of <1.8 mmol/L on follow-up, which was similar to those observed in other Asian countries including Taiwan and Japan. As the latest guidelines recommended titration of both statin and non-statin therapies to achieve a 30-49% reduction in LDL-C, it remains unclear whether the adoption of this approach will alter the results of this study.’ Page 12, paragraph 2, lines 4-12.

c. Why were patients who did not have statin intolerance on other lipid lowering drugs such as ezetimibe and fibrates?

Authors’ responses: Thank you very much for your enquiries. Some patients might receive ezetimibe and fibrates for high LDL-C or high Tg not controlled with statin.

d. Among the patients who had a major adverse cardiac event how many of these were patients who had statin intolerance and who did not?

Authors’ responses: Thank you very much for your enquiries. Moreover, patients who developed a MACE were more likely to have SI [41 (27.7%) vs. 97 (12.1%), P<0.01] than those who did not. This data was presented in the Results session. We have added this in Table 2 accordingly.