Comments on the paper authored by group 14 as refereed by group 13

Group 14 investigated the association between two inflammatory biomarkers, CRP and fibrinogen, and all cause and cardiovascular mortality. We have read this paper and provide our summary of comments below. Generally, to improve the clarity of your analyses, we recommend that you proofread your paper and make sure there are no structural, punctuation and grammatical errors. We also recommend that you reformat your tables and graphs so that they are readable. In addition, please consider adding a discussion section addressing limitations of your analysis and a paragraph interpreting important conclusions. It is difficult to know what important conclusions are gained from these analyses. More specific comments and suggestion are listed below by section of your paper.

List of Comments by Section:

Summary:
-Please specify the cardiovascular risk factors adjusted for, not XXX.
-Please specify the direction of effects (e.g. 16.3% higher or lower risk of death?).
-Consider using "unadjusted" instead of "crude" to describe secondary analyses.
-Final conclusions are unclear. Please clarify the associations found between CRP and fibrinogen and CVD-specific, early, and late mortality. Consider adding estimates of effect (HR) for these models for comparison.
-Consider including the cardiovascular risk factors that were associated with inflammatory biomarkers in univariable analyses.
-In general, results should be reported as associations rather than predictive abilities, as this model is not truly a prediction model.
-Please include any significant problems you encountered in this study.

Background:
-Consider association rather than prediction in the description of the objective of the analysis as this model is not truly a prediction model developed in the same way as FRS and TIMI.

Questions of interest:
-Consider specifying which Specific Aims correspond to which Questions of Interest.
-Investigation of effect modification by sex is not included in the Specific Aims.
-Consider using "unadjusted" instead of "crude" in your description of your aims.

Statistical Methods:
-Please specify what it means to be in the low, normal, and high fibrinogen categories and the low, normal and high, CRP categories.
-Please explain why you log transformed CRP.
-In the final paragraph, your interpretation of your interaction term or terms is convoluted. Please clarify.
-Please explain the data are you referring to when you state "cases with available data".
-Please explain why early you used (<= 3 years) vs. late (>3 years).

Results:

-Please provide text describing the descriptive statistics presented in tables, highlighting important trends or differences that led to identification of the confounders included in your model adjusting for other CVD risk factors. Description of Kaplan Meier figures would also be helpful.

-The third paragraph of the Association between short and long term prediction section is unclear and reports conflicting results. It reports a higher HR for CRP in the long term, while the confidence interval reports a higher HR in the short term. It is also unclear what the parenthetical references to CRP mean. This paragraph could benefit from careful editing to ensure correct variables and associations are reported.

-In the fourth paragraph, it is unclear how a model with CRP as the predictor can be additionally adjusted for CRP. The rest of the paragraph suggests this sentence is in reference to fibrinogen with adjustment for CRP, however this needs to be clarified.

-In the forth paragraph, please include the p-value for the result, even if it is not significant.

-In the fifth paragraph, the p-value presented for the parameter estimate of fibrinogen from a model adjusting for CRP and additional risk factors is 0.01214 and this is considered non-significant. This is <0.05 and should be considered significant. Please double check your numbers in the text are accurate.

-In the last paragraph of the results section, hazard ratios are presented for interaction terms. Generally these terms are not interpreted and only p-values are reported and interpreted.

-It is unclear if results of Secondary Aim 4 are presented in this section.

-In the results, you refer both to a doubling and an absolute increase in CRP and fibrinogen when interpreting the Cox PH regression estimates. These are not synonymous in Cox proportional hazards regression. Doubling may not be the correct word. You should use a comparison involving a proportion or percentage, not an absolute term, and be consistent in the results you present for clarity.

-On page 5, when comparing the hazard ratios of models looking at the association between short-term death and long term death, was an inferential test performed? Please explain as this is not clear from your statistical methods.

-Do you mean short term and long term 'survival' (vs. short term and long term 'death')?

-Please include a 0 before decimal points.

-You have included many graphs and tables that are not referenced in your text. Please state in the text the tables and figures in which your discussed results are presented. Please exclude any tables or figures that are not discussed.

-Please display the results in the tables in a way that is legible (font size 4 is too small).

-In table 2, there are only 59 subjects in the 'low' fibrinogen category, and 4293 and 563 in the mid and high groups. Your analysis may benefit by more evenly distributing the number of subjects in each category. If these categories were specifically selected for a scientific reason, please explain in the text.