Author’s response to reviews

Title: Can Cardiac Computed Tomography predict cardiovascular events in asymptomatic type-2 diabetics? Results of a long term follow-up

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Author’s response to reviews:

Dear Editor-in-Chief of the BMC Cardiovascular Disorders,

Following our original submission of the manuscript entitled “Can Cardiac Computed Tomography predict cardiovascular events in asymptomatic type-2 diabetics? Results of a long term follow-up”, some suggestions have been made by the Reviewer. According to those suggestions, a major revision was made to the manuscript. The corrections and changes performed to the manuscript are provided below, following each Reviewer’s comment.

Major Compulsory Revisions

1. The authors examine the additional value of CTA findings to those of the clinical risk scores SCORE and Framingham. As I understand it the European risk chart SCORE does not include diabetes mellitus since type 2 diabetics are considered to already be at increased risk and the instructions for its use state it is not for use in type 2 diabetics. Thus it does not seem to be a reasonable clinical risk assessor for this patient cohort while clinical risk assessors specifically for diabetics exist and would serve as a better comparison (UKPDS and American Diabetes Association).

CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- According to the comments made, SCORE has been removed from the manuscript. Statistical analysis was remade without the variable SCORE and the discussion was adapted to the new results.
- It was not possible to assess other scores such as UKPDS or American
Diabetes Association because information regarding the level of physical activity or previous history of gestational diabetes was not systematically evaluated.

2. In the Methods section it is stated that CT data were collected regarding calcium score, presence of calcified and non-calcified coronary plaque and luminal stenosis. It is not clearly stated how these were used in a predictive CT score as used in Table 9 and Figure 2.

CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
-We included in the Methods section a description of the variables used in each predictor model.

3. Table 8, as stated in the Statistical Methods, is a multivariate Cox regression with 9 independent variables. With only 10 outcome events it would seem that this is overfitting of the data.

CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
-Cox Regression was performed with the method Forward Conditional to perform multivariate analysis. Thus, we included all variables with statistical significance in univariate analysis.
- The method used for Cox regression was clarified in the Methods section.

4. In Figure 1 the hazard curves diverge markedly after 40 months. This might be related to a small number of patients remaining in follow-up in one of the cohorts at this time. I suggest adding the number in follow-up in each cohort under the follow-up time or curtailing the graph at 40 months if the numbers are particularly small.

CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
-The graphs were curtailed at 40 months.

5. Table 9 provides the data for areas under the curves in Figure 2. Although individual curves are significant predictors for an event it is not clear from the Table if there is any statistically significant difference between the curves.

CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
-Comparisons between ROC curves of the combined model and the other models and variables were added to Table 9.

Minor Essential Revisions

1. In the first paragraph of the Results section it is not clear what is implied by a “significant plaque” in relation to other plaques. Is the intention to refer to significant luminal narrowing above a cut-off value?
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- The term “significant” was replaced by “obstructive” (defined in the Methods section as a luminal narrowing > 50%).

2. Table 6 is referenced shortly after Table 3 without intervening reference to Tables 4 and 5.
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- References to Tables 4 and 5 were added.

3. In Table 5 the entries for the type of CV events are misplaced upwards by one line.
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- The table was reformatted.

4. In Table 6 the duration of diabetes follow-up is stated to be in years but is provided in months
REPLY:
- The values for duration of diabetes at the time of follow-up are stated and provided in years (the original value is correct). The duration of follow-up was provided in months.

5. In Table 6 the units for CRP are incorrect.
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- The units for CRP in Table 6 were corrected.

6. I do not understand the legend to Figure 2. Is it the case that the reciprocal of the creatinine clearance (1/clearance) was used? There is at least a problem in the use of English here.
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- The term “inverted GFR” was replaced by “reciprocal function of GFR (1/GFR)”.

7. In the last sentence of the paragraph on initial data collection SCORE is incorrectly cited to reference 8.
CORRECTIONS / CHANGES MADE TO THE MANUSCRIPT:
- SCORE and all related citations were removed from the manuscript.
Regarding the small size of the sample and the small number of events, we openly assume the need for validation in a larger sample. Thus, we remind that this is the first study focusing the prognostic value of CTA in asymptomatic diabetics without known heart disease. The great strength of this work is the reinforcement of the potential benefit of computer tomography, both with calcium score and coronary angiography, to provide information regarding cardiovascular risk of asymptomatic diabetics, something that is currently lacking.

Hospitalization for heart failure could not be included in the primary endpoint of this study because it was not systematically evaluated.

We hope to have addressed all of your concerns. Still, we will be looking forward to hearing news from you and completely receptive to other matters that you or the Reviewer may think pertinent to discuss or address.

Best regards,
The authors