Reviewer’s report

Title: Predictors for major cardiovascular outcomes in stable ischaemic heart disease (PREMAC): Statistical analysis plan for data originating from the CLARICOR (clarithromycin for patients with stable coronary heart disease) trial

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Reviewer: Johanna Damen

Reviewer's report:

The authors describe a statistical analysis plan for the data that were obtained for the CLARICOR trial in patients with stable coronary heart disease (CHD). The availability of register data that cover 10 years follow-up allows the authors to study the incremental value of several biochemical quantities over standard clinical predictors to predict cardiovascular events and all-cause mortality in patients who already had a CHD event.

The use of existing data from a randomized controlled trial has some advantages such as the dedicated collection of blood samples and other data, although it may suffer some problems concerning generalizability because of selective inclusion of patients. In this specific trial, there are no data on a specific group of patients, namely those who entered the stable state and then died before the end of follow-up. This results in a selective group of patients and I believe this might affect the selection of biochemical quantities that have prognostic information on top of standard clinical predictors.

Besides that, the authors describe a very relevant topic where research is certainly necessary. An overview of what is already known on this topic is however lacking. This makes it difficult to put this research into the context of existing knowledge.

Furthermore, I am interested to read something about the availability of the advanced biochemical quantities in current (and future) medical settings.

With respect to their analysis plan, the main topic of this paper, I have some major concerns.

- I suggest the authors not to select the biomarkers only on significant changes in hazard ratio, but also on their predictive ability. For this they might look at changes in performance measures such as discrimination (e.g. c-statistic or D-statistic) and calibration (e.g. O/E ratio). Furthermore, relatively new performance measures such as net reclassification improvement (NRI) or integrated discrimination improvement (IDI) might be considered to select which biochemical quantities have incremental predictive value on top of standard predictors.
- The authors describe no efforts to validate their results, either internally or externally.

- Is it possible to obtain information on blood pressure? I think this is an important predictor of cardiovascular events and should definitely part of the standard clinical predictors.

- Treatment decisions are usually based on one prediction model. Do the authors also consider analyses in which they combine all outcomes into a composite outcome?

- The part about skewness in predictors is not completely clear to me. How can this explain the results of the trial and how will these analyses be done?

One apparently minor but very crucial point:

- I believe multiple biochemical quantities can be described in one publication instead of separate publications for every biochemical quantity. I hope the authors consider this and at least remove the sentence saying they plan to describe every separate biochemical quantity in an individual publication (page 8, row 42).

In summary, I believe the authors describe a relevant topic, although the methods they use are very basic and not up to date according to current standards.

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