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

Version: 1  Date: 11 Dec 2016

Reviewer: Ben Van Calster

Reviewer’s report:

I thank the authors for their clarifications and additions, which improved the paper. A few things remain unclear for me.

- What will be done with treatment arm should be discussed more at the beginning. Now it is only mentioned just before the discussion. What is the key analysis: the one using only patients in the placebo arm, or the one including all patients? What do you mean with the comment on out-of-hospital vs in-hospital deaths?

- PH and linearity assumptions: will you perform 1 joint PH test, or will you perform a separate test for each covariate? Will you then perform a supremum test for linear functional form for each continuous covariate?

- Definition of C statistic: the authors reply that C is a frequency of correct triage, but their explanation then correctly shows that it is a probability (not a frequency). I still think that the description 'frequency of correct two-patient triage decisions' is very confusing. It is the proportion of all patient pairs where the predicted survival is better for the patient who survived longer (Royston & Altman 2013; Steyerberg 2009). I struggle with seeing this in the context of a triage decision, because it is a clinically irrelevant situation (as often indicated by Pepe’s group).

- The new section about interaction between sex and other risk factors is not clear. What do you mean with 'in these situations'? Are this based on known interactions from the literature, or is it based on interactions terms added to the models? If so, will you only assess interaction terms for new markers?

- About the combined analysis: the authors state that "consequences of leaving out some of the selected quantities will be examined". What does this mean? Will some sort of variable selection be done on the identified biochemical markers?

- The authors mention P<0.01 as a criterion: is this only for the combined analysis, or is 1% the alpha level used for all tests?
Calibration checks: what are 'subpopulations of interest'? More generally, I do not think that calibration is very relevant for exploratory work to identify potentially prognostic markers.

Net benefit paragraph in discussion: the authors state that they are "not able to measure the two types of benefit using the same unit of measurement". However they will calculate change in true positives and false positives using a risk cut-off of 25%. Then, using the Net Benefit measure from Vickers and Elkin (Med Decis Making 2006; see also Vickers et al, BMJ 2016) this cut-off can be used to combine true and false positives into a single number.

'wasteful of insight' is a strange formulation. Also, Bonferroni does not 'disregard all but the lowest p-value'?

Regarding missing values: Little's MCAR test will be used. I'm not very familiar with this test, but it seems to assume multivariate normality? Which variables will you include? Irrespective of the result, would it not be better to perform imputation to avoid loss of data?

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