Reviewer’s report

Title: N-Terminal Pro-B-type Natriuretic Peptide and Microsize Myocardial Infarction Risk in the Reasons for Geographic and Racial Differences in Stroke Study

Version: 0 Date: 19 Sep 2017

Reviewer: Chris Pemberton

Reviewer's report:

This manuscript by Sterling et al. raises a potentially interesting point regarding "micro-MI's" as they defined by peak cTn <0.5ng/mL (=0.5ug/L). Because of hs-cTn assays there is is a well described shift from non-MI to MI Dx.

The authors now suggest that a single community obtained NT-proBNP at up to 5.9 years PRIOR can more strongly predict a micro-MI compared with a "standard" or larger MI. The statistics seem appropriate and models adjusted for logical and contributory variables, but they do seem underpowered when they have a good base of sample (REGARDS) to choose from. Some major issues which, to my mind, need to be resolved.

1. How IMPORTANT or ACCURATE is the prediction of NT-proBNP for micro-MI? This is not discussed. ie. Did the authors determine a NT-proBNP cut-off for micro - versus larger MI? I admit to struggling with the practicality of implementing this and just what it really means.

2. Following on from point 1, the authors suggest that multiple microvascular issues over a period of time may be contributing to micro-MI's and the fact that NT-proBNP can detect micro-vasculcar issues in a variety of organs might explain why its predictive power is so strong. This doesn't make sense from the point of view that significant CHD is also obviously picked up by NT-proBNP and that if anything, the predictive power of NT-proBNP should be stronger in a group that has both major and minor vessel disturbance?

3. Given the ability of micro-MI's to now be detected by hs-cTn assays and also used as criterion by the authors to define micro-MI, shouldn't the cTn result be used a a covariate in their model to counter definition induced artifacts?

4. The number of events seems underpowered eg. n=10 or n=16 for the reference groups in Tables 2 and 3

5. Finally, the definition of micro-MI seems somewhat haphazard and does not refer to a guideline or accepted definition?
Minor issues to be assessed are:

1. More data on the Elecsys assay performance are required. LOD, LOB, QC results at various concentrations.

2. What blood sampling tubes were NT-proBNP samples drawn into? Were they chilled immediately? How long before they were processed and stored? What temperature were they stored at and for how long?

3. What cTn assay was used to assist Dx of MI and MI size?

4. Spelling on line 29, pg. 3. >? does not need to be there.

5. Spelling on line 24. p7, referent should be reference.

6. Nomenclature of the cTn needs to be consistent. Suggest they adopt the IFCC and accepted standard of ng/L.

7. Conclusion. NT-proBNP is not a novel CHD risk factor. Its been known for nearly 20 years.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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