Reviewer's report

Title: Comparative effectiveness of antihypertensive mediation for primary prevention of cardiovascular disease. Systematic review and multiple treatments meta-analysis.

Version: 2 Date: 7 November 2011

Reviewer: Milo Puhan

Fretheim and colleagues report about a systematic review and network meta-analysis. This review focuses entirely on methodological aspects as requested by the editor. The paper is well written except and the results appear to be valid overall. But providing some more detail on some issues would further improve the paper.

Major comments
- Some eligibility criteria are not clear. For example, it is unclear what it means that only trials with CVD mortality and morbidity were included. How was a primary outcome defined? Often, the primary outcome is not well defined in trials or there are, although not recommended, several primary outcomes or none. Also, why would a trial that had myocardial infarction as an outcome be excluded for the analysis on all-cause mortality? Just because it was not the primary outcome? This should be clarified.
- Also, only including trials with CVD mortality and morbidity as primary outcome does not necessarily mean that smaller trials were excluded. Also, trial size is not generally regarded as a marker for study quality because it is not associated with bias per se but with greater sampling variability. Thus the authors should explain how they defined “smaller” trials and justify why they excluded them.
- Later in the results section the authors say that trials of “sufficient quality” were included in the review. It is not stated anywhere in the methods section that quality of trials was a criterion for inclusion and how this was assessed. This requires an explanation.
- The authors should be applauded that they are one of the very few groups that report about strength of evidence when it comes to network meta-analysis. I am very familiar with the GRADE approach but it is unclear how the evidence was graded. This is very challenging in network meta-analyses since the quality of direct and indirect evidence needs to be judged as well as their combination (for those comparisons where both is available). Thus there should be a more detailed explanation how the assessment of the strength of evidence was done. Please also note that the GRADE working group has released an approach for network meta-analysis yet although this is currently under development.

Minor comments:
- The authors had, as in any study, to take some arbitrary decisions as for example that one primary or mixed primary and secondary prevention populations. I do not challenge these decisions but since they are arbitrary some sensitivity analyses would be informative. For example, what happens to the result if just primary prevention populations are included?

- Please explain how inconsistency was assessed. Was it assessed based on statistical significance or on some judgment on how much of a difference between direct and indirect evidence was acceptable? Just using statistical significance can be very misleading in network meta-analysis because the power to detect still relevant differences is often low.

- Please provide more details on the statistical model and how justifiable some assumptions were (distribution of random effects, priors).

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

none