Reviewer’s report

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

Version: 2  Date: 8 December 2011

Reviewer: David Atkins

Reviewer’s report:

This paper presents a network meta-analysis of available trials of anti-hypertensive drugs to attempt to answer questions about the relative efficacy of different drug classes in preventing different disease endpoints. The methods are appropriate and well described, the selection of trials is generally defensible (see below), the conclusions are generally cautious and the writing is clear. The paper updates previously published findings, including some using similar approaches and some using conventional meta-analysis, and the presentation places their findings in contrast to other similar analyses. While there are no particularly notable new conclusions from this review, the thoroughness of the review, inclusion of several new trials and inclusion of GRADE strength of evidence ratings probably make it worth publishing. Finally, a comprehensive set of supplementary documents provides a wealth of other information to place the results in context, including a comparison of the data from the network meta-analysis to results limited to meta-analysis of direct comparisons.

Minor Essential Revisions:

The primary concern is how much it adds to our understanding and whether the use of indirect comparisons enabled by a network meta-analysis improves on estimates based only on direct comparisons. The primary value is allowing inferences about relative comparisons between classes for which no direct data exist. It is notable that in Table 6, comparing results of direct meta-analysis vs. the network model, the confidence intervals are actually wider in several cases (more uncertainty) for the network model. This seems counterintuitive since the network model should incorporate all the direct comparisons as well as indirect comparisons and thus should produce a somewhat more precise estimate due to including more data. The authors should verify these results and consider explaining them.

Network meta-analyses and conventional direct meta-analyses share the same limitation that they are only useful if the assumption of homogeneity is correct. In a conventional meta-analysis one can test that assumption several ways: one can assess homogeneity of results using I squared and other statistics; one can graphically assess in a forest plot whether estimates are generally similar across studies or vary widely; and finally one can assess the basic elements of each trial (patient characteristics, duration, outcome rates, treatment responses) to assess
whether studies really are comparable enough to justify pooling. I am not an expert on network meta-analyses but since the authors do not present any statistical measures of homogeneity I assume these aren’t possible. Nonetheless some discussion of the patient populations, baseline risk estimates, etc. would provide some reassurance that the trials really were assessing roughly comparable populations in terms of risk. (These are in the supplemental tables but some key elements could be brought into the discussion). A key issue which would invalidate assumption of homogeneity would be if mean blood pressure reduction was different across trials, especially in the 6 placebo controlled trials, since Law has argued that the risk reduction is dependent directly on level of BP change. Underlying patient risk may or may not make a difference, depending on whether the relative risk reduction is constant across risk groups, but since the paper has decided to select out a primary prevention population (excluding those with prior CVD events) they should discuss whether the risk levels were comparable across the different trials.

All cause mortality is an especially problematic outcome to pool across primary prevention trials when an intervention is only acting on some causes of death. The ability for a drug that only prevents CVD to lower all cause mortality depends on what proportion of all deaths are due to CVD. This may vary across the trials included. Thus some agents may appear more effective against all cause mortality than others only because they have been tested in populations at highest risk of CVD (e.g. diabetics). This should be mentioned.

2. Discretionary revisions

I have some possible minor revisions aimed primarily at expanding the discussion of the limitations of network meta-analysis and some further attempts to place the findings in context. Specific comments:

The authors state that all the trials used atenolol as the beta blocker. This is technically true but several included metoproplol and atenolol as treatment options presumably at discretion / preference of physician.

Table 2 – the description of the stop 1 trial is confusing as to what the different arms were – the use of or and + make it unclear what are options within arms and which are distinct arms.

The authors should discuss the existence of different drug classes within the CCB class. It appears that most of the CCBs in these trials were dihydropyridines which may justify treating them as one class but that might not be true of all of them. Certainly different agents differ in their vasodilatory activity.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:

No competing interests