Author's response to reviews

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

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Author's response to reviews: see over
Revised manuscript (2nd re-submission):

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

We are grateful for further positive comments and constructive critique from the reviewers.

In essence there is only one issue remaining: Reviewer 1 wants a more thorough analysis of inconsistencies in our model. We have therefore conducted new analyses in line with what the reviewer suggests (see detailed description in the “point by point response” below).

Our responses are written in italics.

We hope the manuscript is now acceptable for publication in BMC Medicine.

Regards,
Atle Fretheim (on behalf of the authors)
1st Reviewer: Milo Puhan

The authors have addressed most of the comments. I may not agree with some decisions made by the authors but I acknowledge that some decisions are arbitrary in this area where a number of methodological questions remains.

The only point that I would like to raise is the assessment of inconsistency. I think this should be addressed in the main body of the manuscript (show appendix 6 as a main table) because one of the key questions of this work how much indirect evidence adds to direct evidence. There is not other way to show this than by putting appendix table 6 into the main body of the paper.

Finally, I disagree with assessing inconsistency by comparing direct estimates and MTC estimates because these estimates are not independent and underestimate inconsistency, Ideally, direct, indirect and MTC estimates would be reported.

Response:

*We consider this comment important and have calculated both direct and indirect effect-estimates, in addition to the main MTM-estimates. We have added the following paragraph to the methods section:*

“We checked for inconsistency between direct and indirect evidence by “node-splitting” [23]. We calculated the direct and indirect estimates of effect and the corresponding Bayesian “p-values” for inconsistency.”

*(Ref 23 is added since the previous version of the manuscript: Dias S, Welton N, Caldwell D, Ades A: Checking consistency in mixed treatment comparison meta-analysis. Statistics in Medicine 2010, 29: 932-944)*

*We have added the following in the Results section:*

“We did not find any statistically significant inconsistencies in the network when comparing effect estimates based on direct vs. indirect evidence. However, there were some inconsistencies that we should point out (Table 6):

In three instances the inclusion of indirect evidence shifted the effect estimate from “non-significant” (i.e. the CrI included the value 1) to “significant”, or vice versa. Firstly, for beta-blockers vs. ARB the direct comparison-analysis yielded a significant increased risk of stroke with beta-blockers (RR 1.34, CrI 1.03 to 1.74) whereas the result from the MTM did not (RR 1.23, CrI 0.96 to 1.49) (Bayesian p-value for inconsistency = 0.17). Secondly, also for beta-blockers vs. ARB, the results for diabetes incidence based on direct evidence was not significant (RR posterior median 1.32, CrI 0.97 to 1.82), while in the MTM it was (RR 1.46, CrI 1.15 to 1.98) (Bayesian p-value for inconsistency = 0.13). Thirdly, for the comparison of ACE-inhibitors vs. placebo the direct evidence-analysis yielded an insignificant difference for all-cause mortality (RR 1.30, CrI 0.82 to 2.14) which became a significant in

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favour of ACE-inhibitors in the MTM (RR posterior median 0.87, CrI 0.79 to 0.96) (Bayesian p-value for inconsistency = 0.08).

The lowest p-value (0.06) for inconsistency was seen for all-cause mortality in the diuretics and/or beta-blockers vs. placebo-comparison. In this case both estimates favoured diuretics and/or beta-blockers significantly, but the effect size estimates differed (direct evidence: RR 0.57, CrI 0.34 to 0.84; MTM: RR 0.82, CrI 0.73 to 0.93).

The absence of clear inconsistencies in the network suggests that our model is trustworthy, but some caution is warranted when interpreting the findings that changed substantially after the inclusion of indirect evidence. The full table of comparisons between results from MTM and results based on direct and indirect evidence are shown in Additional file 6.”

The reviewer suggested that we present the full table of comparisons between MTM-results and results based on direct evidence, in the article proper. As we now have complied with the reviewer’s main criticism (lack of comparison between direct and indirect findings), the full table comprising both MTM, direct and indirect evidence is 25 columns wide and 38 rows long. We have no principled objections to including this table in the article proper, but we think having such an enormous table will be inappropriate, mainly lay-out wise. Also, we believe having this information available as an Additional file is sufficient for the vast majority of potential readers. We therefore maintain our suggestion to have the full table as an Additional file, but have prepared a smaller table where we display the selection of cases where there is some degree of inconsistency between the findings (table 6 – added to the current version of the manuscript).

If the Editor prefers to include the full table in the article proper, we will not object – of course!

Here is the new table we suggest (instead of including the full 25x38 table):
Table 6. Estimates of effect from multiple-treatment meta-analysis (MTM) compared to the direct and indirect estimates of effect based on node-splitting [23], for comparisons with Bayesian “p-values” for inconsistency < 0.3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MTM-estimate (95% Crl)</th>
<th>Direct estimate (95% Crl)</th>
<th>Indirect estimate (95% Crl)</th>
<th>P-value for inconsistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics vs beta-blockers</td>
<td>Diabetes-incidence</td>
<td>1.09 (0.80 to 1.44)</td>
<td>0.88 (0.59 to 1.32)</td>
<td>1.31 (0.88 to 2.17)</td>
</tr>
<tr>
<td>Diuretics vs ACE-inhibitors</td>
<td>Diabetes-incidence</td>
<td>1.43 (1.12 to 1.83)</td>
<td>1.54 (1.14 to 2.10)</td>
<td>1.25 (0.89 to 1.79)</td>
</tr>
<tr>
<td>Diuretics vs placebo</td>
<td>All-cause mortality</td>
<td>0.88 (0.80 to 0.95)</td>
<td>0.89 (0.82 to 0.97)</td>
<td>0.80 (0.68 to 0.96)</td>
</tr>
<tr>
<td>Beta-blockers vs ARB</td>
<td>Stroke</td>
<td>1.23 (0.96 to 1.49)</td>
<td>1.34 (1.03 to 1.74)</td>
<td>1.00 (0.69 to 1.41)</td>
</tr>
<tr>
<td>Beta-blockers vs ARB</td>
<td>Diabetes-incidence</td>
<td>1.46 (1.15 to 1.98)</td>
<td>1.32 (0.97 to 1.82)</td>
<td>1.98 (1.26 to 3.40)</td>
</tr>
<tr>
<td>ACE-inhibitors vs CCB</td>
<td>All-cause mortality</td>
<td>1.02 (0.95 to 1.10)</td>
<td>1.05 (0.96 to 1.13)</td>
<td>0.95 (0.82 to 1.09)</td>
</tr>
<tr>
<td>ACE-inhibitors vs CCB</td>
<td>Heart failure</td>
<td>0.82 (0.69 to 0.94)</td>
<td>0.79 (0.67 to 0.95)</td>
<td>0.68 (0.52 to 0.90)</td>
</tr>
<tr>
<td>ACE-inhibitors vs placebo</td>
<td>All-cause mortality</td>
<td>0.87 (0.79 to 0.96)</td>
<td>1.30 (0.82 to 2.14)</td>
<td>0.86 (0.77 to 0.95)</td>
</tr>
<tr>
<td>Diuretics and/or beta-blockers vs placebo</td>
<td>All-cause mortality</td>
<td>0.82 (0.73 to 0.92)</td>
<td>0.57 (0.34 to 0.84)</td>
<td>0.85 (0.75 to 0.96)</td>
</tr>
<tr>
<td>CCB vs ARB</td>
<td>Stroke</td>
<td>0.91 (0.75 to 1.11)</td>
<td>0.86 (0.69 to 1.05)</td>
<td>1.15 (0.78 to 1.70)</td>
</tr>
<tr>
<td>CCB vs ARB</td>
<td>Diabetes-incidence</td>
<td>1.25 (1.02 to 1.56)</td>
<td>1.29 (1.07 to 1.71)</td>
<td>0.86 (0.49 to 1.49)</td>
</tr>
</tbody>
</table>