Author’s response to reviews

Title: Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomised, double blind trials

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Response to Reviewers

We wish to thank the reviewers for their hard work in ploughing through this necessarily lengthy paper, and for their helpful comments. Our responses are as follows:

Paul Hopkins

1. Are the inclusion criteria too narrow so that dose response trials are limited? This is a sensible question, and Paul asks whether including trials of six weeks' duration might not be sensible. We did consider this, but rejected it because six weeks, in our judgement, was too short in relation to a life long treatment. It actually asks a different question, about whether there is a dose response in dose-response studies, and in longer studies where dose response was not the primary object of the study.

Fortunately we have our answer, because Law et al have subsequently published a meta-analysis of the dose response for statins in short term studies up to six weeks (BMJ 2003 326: 1423). What is interesting is that in 164 studies with about 24,000 patients on statin and 14,000 on placebo they found a strong dose-response for all statins. In our analysis of studies of 12 weeks or longer with 43,000 on statins and 25,000 on placebo (effectively the studies not in the Law meta-analysis), we come to a different conclusion.

We think that the distinction between studies by duration is interesting, and, in addition, that our analysis speaks more clearly to the clinical reality of long term treatment with statins. We also think that this strengthens our decision to examine trials more related to real world use of statins, and the publication of the Law meta-analysis is a big help as a post-hoc justification. We now address the issue in a new section in the discussion.

2. Should we have included open studies? We chose not to because of the known bias inherent in open studies. It could be argued that study design might not affect cholesterol measurement, but we would have needed to perform sensitivity analyses for double-blind and open studies, putting in an additional layer of complexity. Whether the inclusion criteria were too restrictive is answered in part by the fact that we had about 68,000 patients included, almost twice as many as the 38,000 in the Law short-term meta-analysis.
3. We judged it right to separate studies in which there was a fixed dose of statin from those in which
dose-titration occurred. The Figures clearly separate them. There is no indication from our reading
that titration studies have selected resistant patients for study, or that patients in those studies have
any initial difference from those where a fixed dose was used. One might expect that a dose titration
study should result in larger reductions in cholesterol and LDL cholesterol. By and large this was not
the case, but that was not because any particular patients had been preselected. We now mention
this in the discussion.

The results in the meta-analysis already clearly separate titration from fixed dose studies, as in the
Figures. The tables generally show comparisons of commonly used fixed doses. Our reading of the
text does not see the confusion.

Minor points:

References for the included studies are now in additional file 1. [Note we have made a very small
change to additional file 2]

The abstract has been altered to improve the language.

On page 8 we now expand dispersion to explain what we mean.

On page 10 the change has been made.

We agree about atorvastatin, but the simple fact is that we could find no other studies of duration of
12 weeks or longer.

The data for drugs on pages 12-20 are in tables and additional files, but a description of the results
is also provided in the results section; they are not exclusive.

We agree with the point made about initial concentration, and have amended the language to reflect
this.

Regarding the Kong and Herbert meta-analyses, Sheldon's analysis certainly looked at different
drugs and doses, though Hebert’s did not, though it reported mean changes in cholesterol. We have
altered the language to make it less likely that we could misrepresent what they did.

We have expanded the discussion to include fixed dose versus titration effects.

On the suggested sentence change on page 28, we just can't see where this applies. We have
changed page, paragraph and sentence combinations, and still cannot see where this applies. Sorry.

We can see no changes in the conclusions on page 28 that are justified, and the point about
included studies has been made. What have done is to change the language to reflect that the
duration of treatment of which we speak is at least 12 weeks, and also into the longer term. That is,
of course, justified by the inclusion criteria.

The second sentence of the conclusion has been changed. We don't this is because of the inclusion
criteria, but rather a change in judgement made earlier about the fact that 25-50% reductions are
hardly similar. We agree, and can't now see how that slipped in.

HTT Ong

These are helpful comments, and the reviewer is perhaps right in spotting that we have been a bit
reticent in coming forward with advice. In part that is because we feel that the knowledge gained from meta-analysis of clinical trials has to be interpreted for each individual patient, or in making guidelines or care pathways based on the evidence. That is where the wisdom of each doctor comes in, and we hesitate to extrapolate into these areas. After all, equal on average is not equal for everyone. But we can be a bit more definitive, and have done so without leaving what we feel is a comfort zone.

Abstract conclusion: Agreed, this has been changed.

Exclusion and inclusion: We have expanded the results section to better describe excluded and included studies, and make particular reference to the mega-trials.

We are asked to make a strong concluding statement about what dose of each statin would be needed to lower cholesterol by 20%. We have done this, but added the proviso that these are average results, and that individual patients may have different response to the average.