Reviewer's report

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

Authors:

Dr Jayne E Edwards (jayne.edwards@pru.ox.ac.uk)
Dr Robert Andrew Moore (andrew.moore@pru.ox.ac.uk)

Version: 2 Date: 22 Jul 2003

Reviewer: Paul Hopkins

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Dear Editor,

This is a well-written review of lipid changes with statins in various clinical trials. The authors have done an admirable job in assembling and considering a large number of trials. For the trials they have chosen to include, the data appears to be competently extracted, analyzed and presented. There are, however, a few issues that limit the utility of this meta-analysis. First, the inclusion criteria are so narrow as to severely limit the number of dose-response trials. Several key dose-response trials are omitted. As a result, only a single dose for atorvastatin is included. It is not at all clear that 12 weeks are necessary to achieve reliable information regarding long-term efficacy as the authors assert. In fact, the authors themselves found no effect of duration in the analysis of the trials included for their meta-analysis. Stable plasma total and LDL cholesterol levels are probably achieved within 2 weeks of starting a statin and certainly 6 weeks is adequate to demonstrate the percent reduction for any dose. Multiple longer-term studies are available that show no reduction in efficacy if compliance is maintained. Therefore, if dose-response is the outcome most desired (and most useful to clinicians), I see no reason not to include trials of 6 weeks or longer duration. Since the authors already examine duration as a determinant, this seems particularly reasonable.

Similarly, it would be useful to see whether open-label versus blinded design made any difference in the assessments of efficacy. Because of excluding open-label studies several notable and widely cited studies were excluded including the CURVES study by Jones, et al and ACCESS (Brown AS, 1998). Undoubtedly, these two points would greatly increase the number of trials to be considered. However, if the criteria remain so restrictive, the review becomes extremely limiting and not very useful for the clinician. Further, because of the very limited number of trials and doses included, the conclusion that most of the statins yield similar percent reduction in lipids becomes unjustifiable. At the very least, any conclusions regarding efficacy or comparisons of dose response must be highly guarded with limitations more clearly spelled out.

While the authors analyze randomized dose-response studies separately from titration to target LDL trials, the emphasis in the main body of the review is on the combination of these types of trials together. This is particularly problematic as the titration studies naturally select out more resistant patients for higher doses. This greatly distorts (flattens) the apparent dose response as compared with patients randomized from the outset to all doses. It seems reasonable to keep these types of trials separate from the main presentation (except possibly data for the initial dose since all patients would receive this dose). It makes little sense to combine higher doses in the meta-analysis as this would clearly bias higher doses in the titration trials to look more like the lower doses. Therefore, results presented in the main body of the paper (apart from the supplemental data files) should
clearly separate these types of studies.

Minor Points (but all constitute compulsory revisions)
* The full references for the included trials does not appear in the main paper or any of the supplemental files.
* In the abstract - Results, 2nd sentence. 25-50% is hardly "similar" (2-fold range of efficacy). Also, the cholesterol lowering effect of the statins is quite different and the conclusion should not be that they are "similar" for reasons noted above.
* Page 8 - by dispersion I assume you mean S.D. or S.E. This should be stated for clarity. The lack of such data in most trials is surprising.
* Page 10, last paragraph. Change "strict diet" to "defined diet" as none of the studies enforced anything close to what most clinicians would consider a truly strict diet.
* The data for atorvastatin (p 12-13) is most unfortunate as much more information on dose-response is available (and I suspect equally valid to the few studies included here).
* Data for individual drugs on pages 12-20 would probably be better in a table. (discretionary)
* Page 22 - It seems difficult to justify the statement "Initial concentration of total cholesterol had no effect on the ability of statins to reduce total cholesterol" since only mean baseline cholesterol levels were presumably available. Unless individual cholesterol levels were available, this statement must be expressed with appropriate cautions as to the limitations of analysis. The same may be said for age and gender (unless the trials report gender-specific results).
* The conclusions in the last paragraph should be greatly toned down and are probably not justifiable given the method of the meta-analysis and studies included (actually a major point).
* Page 29 - Conclusions - 2nd sentence - very misleading given the limitations of the studies included (actually a major point).

Competing interests:

During the past 5 years I have received honoraria for speaking in behalf of several manufacturers of statin medications including Merck, Astra-Zeneca, and Pfizer. I have also served on advisory boards for these companies and have been involved in research studies with them.