Reviewer's report

Title: Statins and the risk of type 2 diabetes mellitus: cohort study using the UK Clinical Practice Research Datalink

Version: 1 Date: 20 January 2014

Reviewer: Carol Coupland

Reviewer's report:

This paper reports on the analysis of a large cohort study to assess the association between statin use and risk of type 2 diabetes. There have been several studies addressing this issue in the last few years, but this study adds to the overall evidence since it is large, representative of the general population of statin users, and has long follow-up. The analysis is extensive with detailed analyses of subgroups, and time periods of follow-up.

Major Compulsory Revisions

1. Information is needed in the Statistical analysis section in the Methods on how missing data were treated in the analysis. The Discussion should also cover this aspect and how it might influence the results.
2. The analysis section should also clarify whether the exposure variables were treated as time-varying exposures in the analysis (e.g. duration of use).
3. The Results show a striking decrease in risk with age. This should be highlighted more in the Discussion, including discussion of possible reasons for this decrease and comparisons with other studies. It would also be helpful to have NNH by ageband.

Minor Essential Revisions

4. It would be useful to have details on how many of the non-users were prescribed statins after the index date. It is not clear how these are treated in the primary analysis, and whether for example they are included in both columns in Table 1.
5. The duration categories given in the Methods don’t match with the categories in the Results /Tables 4 and 5.
6. The NNH and/or excess risk values should be added to the Abstract.
7. The Abstract should also mention the large decrease in hazard ratios with age.
8. A few things to check:
   - Table 1. Although cardiovascular disease is much higher in new users cardiovascular drug use is lower which seems strange.
   - Table 1. Annual consultation rates and prescription rates look high in both groups. Also there’s a big difference between the two groups for annual prescription rate – what drugs explain this difference as there is not much
difference for the individual drugs listed?

Table 3. I wouldn’t have thought the number of subjects in the first 6 months and after 6 months analysis would be the same. Haven’t some subjects been censored (e.g. died, diagnosed with diabetes) in the first 6 months, so they wouldn’t contribute to the analysis after 6 months?

Table 3. Nearly 30% of subjects are excluded in the PS[5-95%] analysis. I would have expected it to be around 10%, based on the percentile values.

9. Table 4. Add numbers of subjects at baseline and number of events (diabetes in follow-up) in each subgroup.

10. Table 5. This is a very complex table and would be easier to read if it was simplified, perhaps by reducing the number of time periods to match the ones in the Methods section, particularly since numbers were too small to estimate values in the 20-25 year band. Otherwise the incidence rate columns could be left out, or put in a supplementary table.

11. List S1. Several of the codes don’t seem to indicate type 2 diabetes, for example:

- 44T1000 RANDOM BLOOD SUGAR NORMAL
- 44U8.00 BLOOD GLUCOSE NORMAL
- 4661.00 URINE GLUCOSE TEST NOT DONE
- L180811 GESTATIONAL DIABETES MELLITUS

This needs clarification.

12. Table S2. Add numbers in the groups. Also relabel the CVD or hypertension row (or split into 2 to avoid confusion).

Minor issues not for publication

13. The 3rd sentence of the 4th paragraph of the Results doesn’t make sense (“an association of OAD an insulin”).

Discretionary Revisions

14. The authors speculate in the Results and Discussion sections that statin initiation is likely to be associated with having blood tests including glucose. It would be helpful if they could use their data to see whether this is the case, comparing rates of glucose tests over time after the index date in statin users and non-users.

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests.