Reviewer's report

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

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Reviewer: Gregory A Nichols

Reviewer's report:

This manuscript uses data from the CPRD to assess the association between statin use and incident diabetes. In general it is well-designed containing only minor flaws. However, the findings are not novel, except to the extent that they are much stronger than previously reported. Yet this was not addressed. I don’t think this adds much to the current literature.

Major Compulsory:

1. As noted in the background section, the risk of developing diabetes is strongly associated with baseline fasting glucose. This is true regardless of statin use. The major shortcoming of previous studies is the inability to account for FPG level. Apparently lab data aren’t available. If there are read codes for pre-diabetes, impaired glucose regulation, impaired glucose tolerance or impaired fasting glucose, you should use these to try to account those at greatest risk of developing diabetes. Many researchers suspect that the statin effect is minimal and that it merely pushes people over the diagnostic threshold of diabetes and that it is likely these people would have eventually crossed that threshold anyway. The current manuscript does nothing to close this critical knowledge gap so the findings as presented are of limited value.

2. Consistent with the above, the first conclusion is that statins increase risk with longer duration of use and higher BMI. BMI is of course a very strong risk factor for incident diabetes, and high BMI is associated with dysglycemia, so this suggests to me that the statin effect is probably marginal at best. And longer duration of use is probably impossible to separate from worsening beta cell function/decreased insulin sensitivity over time that is the real cause of diabetes.

3. The hazard ratios reported are substantially higher than the ~9% increased risk in previous meta-analyses. In the discussion, the authors merely state that their findings confirm clinical trials and are consistent with higher hazard in WHI, but the findings are considerably higher than WHI. An increased risk of about 2-fold deserves much more discussion and explanation.

4. I may be confused about the methods, but it appears that censoring those in the unexposed group once they initiated a statin was only done as a sensitivity analysis. This should have been included in the primary design, otherwise it confounds the results (although it biases toward the null).
5. It is curious that <7% of those exposed to statins have hyperlipidemia and <23% have CVD. Obviously this means that indications for statins are not being fully recorded. Thus it is unclear what you stratification by CVD really means. Only the most severe cases?

6. Why aren’t anti-hypertensives (many of which effect glycemic levels) included?

Minor Essential:

7. There are several places in the results text where the authors attempt to explain their findings (e.g., “the hazard ratios were higher in the first 6 months of exposure which might indicate a possible detection bias…”). Such statements should be saved for the discussion.

8. Tables 1 & 2, with this sample size I imagine nearly everything is significant but you should include p values anyway or if everything is indeed statistically significant, add a footnote to that effect.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.