Reviewer’s report

Title: Statins and risk of gastric cancer in diabetes patients

Version: 1 Date: 16 June 2011

Reviewer: Patricia Coogan

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Overall Comments:

The research question needs to be clarified (see point 1 in Major Compulsory revisions). The analysis methods are appropriate to the matched data. The writing is confusing, and the English usage requires correction in many places. The discussion needs to give more consideration to negative studies of statin and cancer, and to alternate explanations, rather than casual, for the reduced risk of gastric cancer among statin users.

Major Compulsory Revisions:

1. The reason for addressing the hypothesis in a cohort of diabetic patients needs to be elaborated in the introduction and the discussion. Why is a protective effect of statins expected to be more pronounced in people with diabetes compared to the general population? It is stated that the mechanism may involve the IGF pathway, but more description of why this would be of particular importance in diabetics is needed. If a diabetic cohort was chosen for logistical reasons, please state this.

2. The literature reviewed in the introduction and the discussion does not give enough consideration to the many negative studies of statin use and cancer that have been published. For example, in the introduction (paragraph 2), why focus on the Poynter study that found a 50% reduction in colorectal cancer among statin users, when colorectal cancer is not the subject of the present study? Give a more general overview of studies relating to all cancer types, and focus on results for gastric cancer. If studies on gastric cancer are few and/or small, state this. It seems likely the present study is by far the largest of gastric cancer yet published, so this point should be stated in the introduction.

3. There are many redundancies in the paper. For example, the beginning of the second paragraph of the introduction is essentially repeated in the discussion paragraph 2. The description of the duration categories of statin use given in section 3.2. repeats what has already been said in the methods. Removing redundancies will make for a more concise manuscript that does not tire the reader.

4. Description of the Hong Kong study in the third paragraph of the introduction is very confusing (i.e., "interaction between nonuse of statins and co-presence of low LDL").

5. Section 2.: “Controls could not have a diagnosis of gastric cancer within 6 months of the matched cases . . .” Does this mean controls could have a
diagnosis of gastric cancer at some time? Please clarify.

6. Section 2.1: It is very confusing how – or whether - you ascertained use of statin prescriptions prior to enrollment at the Samsung Medical Center. It is not clear if statin use NOT in your database was available to you or not. Please clarify.

7. Was any consideration given to lag time between initiation of statin therapy and cancer diagnosis? It is traditional to ignore statin use that was initiated within, say, 6 months of cancer diagnosis since it is not likely that such use would be related to the development of cancer. If such consideration was given, please state so. If not, redo analysis censoring exposure initiated in the 6 months prior to diagnosis, as either the main analysis or a sensitivity analysis.

8. Duration of statin use: it is surprising, given that cases were ascertained from 1999-2008, that there are not longer durations of statin use to consider. The first statin was approved in the US in 1989 – perhaps it was approved later in Korea. Due to lack of real long term category the duration analysis is not particularly informative. It shows that using is for 1 year of 2 or more has essentially the same effect.

9. Tables 2 and 3: It is not necessary to show the beta, SE, and p-value; the OR and 95% CI tell the whole story. It would be informative to give the numbers of case and controls in each use category in tables 2 and 3 rather than table 1.

10. Figure 1 – if you are going to show figure 1, explain the methods used to generate it in statistical methods. Also, since figure 1 is showing survival of cases among statin users and nonusers, why is “control” given on the figure? This is confusing.

11. Discussion: The last sentence of the first paragraph is not true according to table 2 (“There were no significant correlations between gastric cancer risk and prescriptions for aspirin”). In table 2, both univariate and multivariate analysis, there is a statistically significant decrease in the OR for aspirin use.

12. The discussion needs to expand the paragraph given to alternate explanations for the reduced risk for gastric cancer observed among statin users. It is crucial to address the fact that, in table 2, there are major reductions in the OR for the three drug groups presented: statins, aspirin, and other lipid lowering agents. This suggests that it is not, in fact, a causal effect of statins. Rather, there is some bias. We can speculate, for example, that persons who go on to be diagnosed with gastric cancer are less likely to use aspirin in the months/years prior to diagnosis due to greater likelihood of gastric pain or bleeding. Is some similar bias operating with statins? This is a very important point to address.

Minor Essential Revisions
All my comments are given in the above section.

Discretionary Revisions
Nothing.

Level of interest: An article whose findings are important to those with closely
related research interests

Quality of written English: Not suitable for publication unless extensively edited

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'