Author's response to reviews

Title: Statins and risk of gastric cancer in diabetes patients

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Version: 4 Date: 29 October 2012

Author's response to reviews: see over
Reviewer's report

Title: Statins and risk of gastric cancer in diabetes patients

Version: 3 Date: 25 March 2012

Reviewer: Patricia Coogan

Reviewer's report:

The paper is much improved in terms of writing. However, two errors pointed out in my most recent review persist: 1. Delete the second sentence in the first paragraph of the discussion that states that gastric cancer risk and statin use has not yet been evaluated. This is NOT TRUE. The authors describe previous analyses of statin use and gastric cancer incidence in the introduction.

→ It was deleted as recommended.

2. Discussion, bottom of page 9: the authors discuss a bias in using diabetes patients for the study. This will not introduce a bias since BOTH CASES AND CONTROLS ARE DIABETES PATIENTS. This issue of their study including only diabetes patients may affect generalizability (i.e., external validity), but NOT internal validity.

→ It was deleted as recommended. In addition, the following sentence was added in order to clarify the bias we were referring to: “Another potential bias for our observations would be the inherent bias from our patient population, all of whom visited a larger tertiary hospital in Korea instead of a private clinic for diabetes control.”

3. It is standard practice to report ORs and 95% CIs only to 2 decimal places; 3 places implies a false precision. → As recommended, we revised the decimals accordingly.

Thank you very much for your helpful comments.

Reviewer's report

Title: Statins and risk of gastric cancer in diabetes patients

Version: 3 Date: 19 March 2012

Reviewer: shoji shimoyama

Reviewer's report:

I requested the authors that they should perform uni- and multivariate analyses by including ALL variables, such as smoking, Helicobacter pylori, etc., which potentially RELATED TO
gastric cancer, and I requested the ALL p-values irrespective of their statistical levels. In this regard, the authors did not understand my comment, and the authors misunderstand my comments twice. The authors should have presented ALL odds ratios and ALL p-values in Table 2 for ALL confounding factors.

The median time for endoscopy interval (2 years) and mean duration between the date of entry into the diabetes cohort and gastric cancer index (673 days) are nearly the same, suggesting that the possibility of preexisting cancer at the time of diabetes cohort registry can not be excluded. The authors did not mention this limitation. Furthermore, I requested in the initial comment that the endoscopy frequencies between statin users and nonusers should be compared, however, the authors did not mention this matter.

As recommended by the reviewer, we added the following paragraph to address the potential limitation of our study in Discussion section: “Another limitation of our study is that due to retrospective nature of the study, the interval of endoscopy was not controlled. In Korea and Japan, endoscopy is recommended as a nationwide cancer screening program after age of 40. In this particular cohort, the median time for endoscopy interval (2 years) and mean duration between the date of entry into the diabetes cohort and gastric cancer index (673 days) are nearly the same, suggesting that the possibility of preexisting cancer at the time of diabetes cohort registry cannot be excluded. There was no difference in endoscopy intervals between statin user and non-statin user in this cohort.”

Reviewer's report

Title: Statins and risk of gastric cancer in diabetes patients

Version: 3 Date: 13 September 2012

Reviewer: Xilin Yang

Reviewer's report:

Comments to authors:

First, this study aims to address a topical issue, with a relative large database (thus having enough power for testing statin usage and the risk of gastric cancer in patients with diabetes), so deserving publication. However, non-collection of clinical factors such as A1c, LDL cholesterol, HDL cholesterol and triglyceride, etc., makes it impossible to consider some potential biases such as prevalent user bias and drug use indication bias.
A recent review of the methodologies on addressing drug effects on cancer in diabetes in non-clinical trial setting has illustrated their impacts on the results in cohort studies (Diabetes Obes Metab. 2012 Jul;14(7):579-85). In the case of use of a nested case control study without important clinical factors, it is uncertain whether statin use indication and prevalent statin use have introduced substantial bias. The drug use in this study may be defined as any periods before diagnosis of gastric cancer and therefore any periods after the diagnosis was classified as non-use of statins. This definition of use of statins requests that gastric cancer could not happen. In other words, longer duration of use of statins itself was related with less chance of being diagnosed with gastric cancer. Thus, testing the duration-effect relationship may not mean more than the overall effect of statin use on the risk of gastric cancer. Confronted with these uncertainties, I wonder whether the authors can validate the “exact case control study” using statins and their effect on cardiovascular disease or coronary artery disease as called for in the review article (Diabetes Obes Metab. 2012 Jul;14(7):579-85).

➔ To address this aspect, we discussed and added the following limitation in discussion:

➔ In addition, the drug use in this study was defined as any periods before diagnosis of gastric cancer and therefore any periods after the diagnosis was classified as non-use of statins. Our definition of use of statins presumes that gastric cancer does not occur after the use of statin. Hence, longer duration of use of statins itself was related with less chance of being diagnosed with gastric cancer. Thus, testing the duration-effect relationship may not mean more than the overall effect of statin use on the risk of gastric cancer. To further validate the impact of duration of statin use on gastric cancer incidence would be to validate the “exact case control study” using statins and their effect on cardiovascular disease or coronary artery disease[30].

On behalf of the authors, we would like to express our gratitude for thoroughly reviewing our work and providing helpful comments.