Author’s response to reviews

Title: All-cause mortality of insulin plus dipeptidyl peptidase-4 inhibitors in persons with type 2 diabetes

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Author’s response to reviews:

Mr. Joselito A costa
Editor
BMC Endocrine Disorders

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Dear Dr. Mr. Joselito A costa:

Re: Document reference No. BEND-D-18-00249R1

Please find attached a revised version of our document “All-cause mortality of insulin plus dipeptidyl peptidase-4 inhibitors in persons with type 2 diabetes”. We would like to resubmit for publication as an original article, in BMC Endocrine Disorders.

Your comments and those of the reviewers were highly insightful and enabled us to improve the quality of our document. In the following pages are our responses to each comment from the reviewer(s) as well as your own comments.
Revisions in the text are shown yellow highlights. We hope that our revisions to the document combined with our accompanying responses will be sufficient to render our document suitable for publication in BMC Endocrine Disorders.

We look forward to hearing from you soon.

Yours sincerely,

James Cheng-Chung Wei

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Responses to the comments of Reviewer #1 (Dr. Indulekha Karunakaran)

1. The methodology section should include more details on the methods of measurement. For instance, what criteria was used to diagnose diabetes, hypertension etc.

Response: Dear Dr. Indulekha Karunakaran, thank you for your review of our manuscript and suggestions. The methods of measurement were depicted on Methods section, line 114-117, “newly diagnosed type 2 patients with diabetes (T2DM; ICD-9-CM: 250.x) in the age range of 18–100 years were selected. Only those patients diagnosed with T2DM at least twice in outpatient claims or at least once in inpatient claims were included to ensure diagnostic accuracy.” Line 119-121, “diagnosis of type 1 diabetes (250.1x), rheumatic heart failure (rheumatic HF, 398.91), stroke (430–438), peripheral arterial occlusive disease (443.9 440–444), or HF (428) before the index date of the study.” Line 145-146, “Risk factor–related comorbidities analyzed in this study include ischemic heart disease (411–414), dyslipidemia (272, A code: A182) and hypertension (401–405, A code: A260 and A269).”

2. Data on obesity parameters like BMI or waist could be helpful to assesses if these factors have any influence over the mortality from DPP-4 inhibitor users and non-users.

Response: Our research database, based on the reimbursement archives of a national health insurance program, doesn’t have the records of body weight, BMI or waist, so we can’t assess these factors. We have described this limitation in our manuscript on Discussions section, line 257-259, “Secondly, the NHIRD does not include data on life styles, smoking habits, body weights, and economic conditions, all of which could influence mortality risks.”
3. The methods section could list the DDP-4 inhibitors used by the study participants.

Response: We have listed the analyzed DDP-4 inhibitors on Methods section, line 126-127, “The DPP-4 inhibitors prescribed were saxagliptin, sitagliptin, vildagliptin, and linagliptin.”


DOI: https://doi.org/10.1016/j.diabres.2018.04.012~the authors have used stroke, CAD and Heart failure as major outcomes. This study shows an incidence rates per 1000 PYs of CAD and heart failure of control versus users were 19.85 versus 13.54. The present study has excluded subjects with stroke and heart failure, but not CAD, there were 0 CVD deaths in the subjects using DPP-4 inhibitor users. This should be explained

Response: We explain this result in the Discussions section, line 224-228, “There were 0 CV death in the insulin plus DPP-4 inhibitors users and only 3 CV deaths in the non-users in our study. The low number of CV death might be because we had excluded the high-risk patients, such as those with heart failure, stroke or peripheral arterial occlusive disease, from the study cohort. The mean follow-up time in our study is less than 2 years, which also might lead to few cases of CV death.”

5. The present report of the authors used the population-based National Health Insurance Research Database of Taiwan from 2000-2010. Was data from the previous study conducted from 1997-2000 also from National Health Insurance Research Database?

Response: Yes, it was also from the National Health Insurance Research Database.

Responses to the comments of Reviewer #2 (Dr. Marc Evans)

1. This is fairly well conducted database study, my main suggestion here would be a more detailed discussion on approaches to address factors such as prescriber bias and immortality survival bias.

Response: Dear Dr. Marc Evans, thank you for your encouragement and suggestions. We discussed this issue in the Discussions section, line 237-248, “In conducting the observational studies there are several methodological issues should be addressed, such as selection bias, immortal time bias and confounding by indication. Because our database is from the National Health Insurance program, which covers 99% of the whole residents of Taiwan, selection bias could be avoided. The first date of concurrent use of insulin and DPP-4 inhibitors was defined as the index date; so, we didn’t create a follow-up period (i.e., immortal time window) within which the investigated outcomes could not happen; the chance of immortal time bias is low. The
prescription of medication in the clinical practice is influenced by indications, contraindications, side effects and the preferences of patients and doctors. This might lead to the bias of “cofounding by indication”; however, we performed a 1:1 propensity score match to balance the 13 clinically relevant covariates between the users and non-users. We believe the two study groups were comparable and the bias of cofounding by indication could be minimized as much as possible.”