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Increased Risk of Hospitalization for Heart Failure with Newly Prescribed Dipeptidyl Peptidase-4 Inhibitors and Pioglitazone Using the Korean Health Insurance Claims Database (*Diabetes Metab J* 2015;39:247-52)

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We appreciate your interest and comments on our article entitled "Dipeptidyl peptidase-4 inhibitors and hospitalization for heart failure using the Korean Health Insurance Claims Database" which was published in *Diabetes and Metabolism Journal* [1].

The objective of this study was to assess the association of the most widely used dipeptidyl peptidase-4 inhibitors (DPP4i) and thiazolidinediones (TZDs) with heart failure (HF) hospitalization using the National Health Insurance System (NHIS) database. We observed a 1.8- to 2.0-fold increase in hospitalization for HF in the initial 30 days of medication (pioglitazone, sitagliptin, and vildagliptin) compared with the subsequent follow-up period.

The strengths of this study include the large population of patients with type 2 diabetes mellitus (T2DM) with a mean follow-up of 337 days. These data were taken from the database of representative Korean diabetic patients in real-world clinical settings because the NHIS is a compulsory and universal health care system in Korea [2]. We acknowledge that we could not adjust for confounding variables because of limited information on known HF risk factors. As we already mentioned in the paper, further study with full data regarding medications and co-existing illness is needed.

Recent re-analysis of saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 found that the increased risk of HF hospitalization was heightened among patients with elevated levels of natriuretic peptides, previous HF, or chronic kidney disease [3]. Sitagliptin also showed significantly increased risk of HF-related hospitalizations among patients with T2DM and HF [4]. Thus, one may suspect that undiagnosed HF might have given rise to the increase in HF hospitalization during the initial 30 days. However, we reduced these possibilities by eliminating those with a prior diagnosis of HF.

We agree with Lee DH that the comparison with metformin is important because it is the drug of first choice and is used the most in combination with other antidiabetic agents. However, characteristics of diabetic patients on metformin alone group and those on metformin along with DPP4i or TZD group are

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different. On the other hand, characteristics of groups treated with metformin and DPP4i or TZD are similar because NHIS allows reimbursement of these drug combinations in the same clinical settings. Therefore, we have chosen pioglitazone as a comparator for the analysis which is known to increase the risk of edema and HF [5,6]. In addition, we used a poisson regression to model the relationship and generate hazard ratios and 95% confidence intervals comparing days 0 to 30 with days 31 to 360 after prescription because these groups share the same baseline characteristics. However, we did not find a significant difference of HF hospitalization between the DPP4i and TZD. Collectively, our results indicate a class effect and a relatively acute drug effect on HF during the earlier period of medication.

In conclusion, our study suggested that vigilance in the early period of DPP4i prescription may be helpful for the management of patients with T2DM. We are awaiting the results of the ongoing trials with cardiovascular disease as a main endpoint. We sincerely appreciate Lee DH for his interest in our study and knowledgeable comments.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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