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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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Dipeptidyl peptidase-4 (DPP-4) inhibitors are now being widely used for the treatment of type 2 diabetes, and preclinical studies and short-term clinical studies suggested that DPP-4 inhibitors as well as GLP-1 receptor agonists have cardiovascular (CV) benefits beyond the glycemic effects [1]. However, two randomised clinical trials (RCTs) with saxagliptin [2] and alogliptin [3], separately, in patients with type 2 diabetes at high CV risk showed a rather disappointing neutral CV effect. In the saxagliptin RCT (saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction [SAVOR-TIMI]), more patients in the saxagliptin than in the placebo group were hospitalized for heart failure (HF), whereas in the Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care (EXAMINE) trial, alogliptin did not increase the risk of HF outcomes in patients with type 2 diabetes and recent acute coronary syndromes [4]. Then, concerns about HF associated with the use of DPP-4 inhibitors led to many systematic reviews and meta-analyses. In addition to many previous studies, the largest meta-analysis study of recent years showed that a long-term treatment with DPP-4 inhibitors significantly increased the risk of HF [5].

Another way of studying the risk of HF associated with DPP-4 inhibitors is to analyze real-world clinical data. In this issue, Suh et al. [6] report data entitled "Increased risk of hospitalization for heart failure with newly prescribed dipeptidyl peptidase-4 inhibitors and pioglitazone using the Korean Health Insurance Claims Database." They collected data from the Korean Health Insurance claims database about newly prescribed sitagliptin, vildagliptin, and pioglitazone between January 1, 2009 and December 31, 2012 (mean follow-up of 336.8 days). Interestingly, they used poisson regression to model the relationship and generate hazard ratios (HRs) and 95% confidence intervals comparing days 0 to 30 with days 31 to 360 after pioglitazone or DPP-4 inhibitor prescription. In another comparison, they used pioglitazone group as the reference group to compare the HRs rather than control. The hospitalization rate for new HF was greatest in the first 30 days after starting the medication, which corresponded to a significantly higher incidence at days 0 to 30 compared with days 31 to 360 for all three drugs. The HRs were 1.85 (pioglitazone), 2.00 (sitagliptin), and 1.79 (vildagliptin) without statistical differences between the three drugs. This study showed an increase in hospitalization for HF in the initial 30 days' use of the DPP-4 inhibitor and pioglitazone com-pared with the subsequent follow-up period.

The study has the merits of analyzing a large number of type 2 diabetic patients (n=233,790 for pioglitazone, n=481,255 for sitagliptin, and n=220,484 for vildagliptin) with a mean follow-up of 336.8 days. Furthermore, this study included the entire

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population of patients with type 2 diabetes receiving the Korean National Health Insurance Service, suggesting that the data are from the nearly representative Korean diabetic patients in real-world practice settings. Although these kinds of data may have intrinsically limited information on comorbidity, family history, past illness, duration of diabetes, and other CV risks, it has been suggested positive predictive values >70% for diabetes and CV diseases [7].

In accordance with this data, the rate of hospitalization for HF was also higher in the earlier period (≤180 days) of saxagliptin use [2]. Although major CV outcomes are not affected by DPP-4 inhibitors or even slightly decreased by the drug [8], the risk of HF seems to be real [2,7]. However, the presence of HF at baseline did not further increase the hospitalization for HF nor other major CV endpoints in SAVER-TIMI 53 trial [2].

Back to the Suh et al. [6], the risk of DPP-4 inhibitor for HF was similar to that of pioglitazone, a well-known positive control [9]. However, it would be better to determine adjusted HRs, because some studies showed only borderline risk of these drugs for HF after adjustment for risk factors [7,10]. A comparison with metformin is also important, because it is the drug of first choice and the most combined drug with other antidiabetic agents. If more data are accessible, it would be very interesting to evaluate the interaction with angiotensin-converting enzyme inhibitor, as the authors suggested.

In conclusion, this study suggested that vigilance in the early period of drug use may be helpful for the management of patients with type 2 diabetes if a DPP-4 inhibitor is added on to other drug(s) or is newly started on, until further information through RCTs, including Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study, is available in the near future (at the time of this writing).

CONFLICTS OF INTEREST

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

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