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Editorial

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Effect of Dipeptidyl Peptidase-4 Inhibitors on Cardiovascular Outcome

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▸ See the article "Comparative Cardiovascular Risks of Dipeptidyl Peptidase-4 Inhibitors: Analyses of Real-world Data in Korea" in volume 48 on page 395.

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Diabetes is a key risk factor for cardiovascular disease (CVD) and is associated with a 2- to 4-fold higher risk of CVD. In addition, all-cause mortality among individuals with diabetes mellitus remain >2-fold higher compared with individuals without diabetes mellitus.[1] Although it has been well established that strict glycemic control reduces microvascular complications of diabetes mellitus (neuropathy, nephropathy, and retinopathy), the relationship between blood glucose control and reduction of macrovascular events is more challenging. In the United Kingdom Prospective Diabetes Study (UKPDS), intensive glucose lowering therapy significantly reduced microvascular complications than conventional dietary therapy, but the relative risk of myocardial infarction was not significantly decreased with intensive glucose lowering therapy.[2] However, risks of myocardial infarction and all-cause mortality were significantly lower in the intensive therapy group during 10 years of post-trial follow-up period.[3] On the contrary, intensive glucose control had no beneficial effect on cardiovascular events among veterans with longstanding type 2 diabetes mellitus.[4] Accordingly, intensive glucose control should be started at the time of diagnosis for the substantial improvement of cardiovascular prognosis.

Interestingly, there was a debate whether the benefit of glucose lowering therapy was different according to the class of anti-diabetic drug. Especially, the issue was provoked by the report of Nissen and Wolski,[5] which showed that rosiglitazone was associated with a significant increase in the risk of myocardial infarction. Subsequent study showed that rosiglitazone did not increase the risk of overall cardiovascular morbidity or mortality compared with other glucose-lowering drugs.[6] Finally, U.S. Food and Drug Administration (FDA) eliminate the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone. But, many clinicians are still reluctant to prescribe rosiglitazone to control blood glucose. Anyway, due to the controversy regarding cardiovascular safety of diabetic drug, the FDA issued guidance defining pre/post-approval requirements for the demonstration of cardiovascular safety for all new medications developed for glucose control in type 2 diabetic patients.[7]

In this issue, Ha et al.[8] reported a very interesting result regarding CVD risk associated with 5 different dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with type 2 diabetes using claims database of the Korean National Health Insurance System. They showed that saxagliptin, linagliptin, and gemigliptin therapies were associated with a lower risk of

kcj Korean Circulation Journal

cardiovascular events compared to sitagliptin therapy. Previous cardiovascular outcome trials examining the safety of the DPP4i (saxagliptin, alogliptin, and sitagliptin) found that these agents neither increased nor decreased cardiovascular events. In the SAVOR-TIMI 53 trial, patients randomized to saxagliptin had a significant increased risk for heart failure hospitalization.[9] However, other studies and a meta-analysis did not show any harmful effect of DPP4i on congestive heart failure or other cardiovascular events.

This paper will open a new controversy regarding the safety of diabetic drug. However, before initiating a debate regarding the differential effect of DPP4i on CVD event and searching for underlying mechanism associated with increased risk with sitagliptin, several points should be considered with the results.

In recent years, lots of research interests have been focused on claims databases. Claims data can be derived from electronic health record, such as clinic visits, hospitalizations, prescriptions, and procedures, which are mainly for billing purpose. These databases are readily available to access and contain clinical information coded using accepted coding systems. Claims databases can provide large, demographically diverse, multicenter, real-world cohorts. However, these data have limitations because they are not collected for research purposes. For example, claims databases contain limited or lack of clinical information, especially laboratory data. In addition, there are doubts regarding the accuracy of billing codes used to classify diagnoses.

Despite its limitations, claims databases have been actively used for various researches. Claims data are used to conduct comparative effectiveness and safety research, which generally aims to compare alternative treatments where randomized controlled trials (RCTs) may never be performed or may be unfeasible. Thus, claims data analysis can add new information and provide hints regarding new drug development or post-marketing drug surveillance.

Although, this paper showed a differential cardiovascular effect among DPP4i, but there was no reasonable explanation supporting the difference. In addition, unmeasured bias associated with the selection of DPP4i or clinical characteristics might have an effect on the different effect of DPP4i. Thus, further studies or analysis should be performed for this topic.

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