Dipeptidyl Peptidase 4 Inhibitors and Venous Thromboembolism Risk in Patients with Type 2 Diabetes: A Meta-analysis of Cardiovascular Outcomes Trials

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Dipeptidyl peptidase 4 (DPP-4) inhibitors are commonly prescribed second-line oral glucose-lowering drugs in the treatment of type 2 diabetes, which have good safety profiles compared with other antidiabetic drugs, such as low risk of hypoglycemia and having neutral effects on cardiovascular outcomes. One recent pharmacovigilance study using World Health Organization Vigibase found a consistent signal of reporting of venous thromboembolism (VTE) associated with DPP-4 inhibitors (proportional reporting ratio [PRR]: 2; 95% confidence interval [CI]: 1.7–2.3) especially at the gastrointestinal levels (PRR: 13.4; 95% CI: 9.2–19.6).1 Our study using Food and Drug Administration adverse-event reporting system database found no association between DPP-4 inhibitors and VTE risk but with a moderate signal of VTE at gastrointestinal levels.2 However, spontaneous reporting databases have several limitations, such as reporting bias, lack of denominator data, and confounding; this association requires further investigation. Current evidence regarding the effect of DPP-4 inhibitors on VTE risk is very limited, we thus performed a meta-analysis of large cardiovascular outcomes trials (CVOTs) to evaluate the association between DPP-4 inhibitors and VTE risk among the patients with type 2 diabetes.

We systematically searched Pubmed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) up to May 1, 2020 to identify the large randomized, double-blind, placebo-controlled CVOTs. Two reviewers independently selected the trials according to the following inclusion criteria: (1) CVOTs involving patients with type 2 diabetes; (2) DPP-4 inhibitors versus placebo; (3) trials reported the events of VTE including pulmonary embolism and gastrointestinal VTE. The events of VTE, pulmonary embolism, or gastrointestinal VTE were defined based on the MedDRA1 and were retrieved from the results of serious adverse events reported on Clinicaltrials.gov. The risk of bias of included trials was judged as low, high, or unclear according to the Cochrane risk of bias tool.3 A pooled odds ratio (OR) with 95% CI was calculated using a fixed effects model and an I² statistic was used to assess the possible between-study heterogeneity. Furthermore, a meta-regression was performed to test the difference between the DPP-4 inhibitor and a funnel plot as well as the Egger’s test was performed to evaluate the publication bias. We considered p-
Ical heterogeneity was observed in the meta-analysis with an odds ratio of 2.98 (95% CI: 0.31 to 28.70). No statistical heterogeneity was observed in previous studies, which is consistent with our previous findings. However, we found no significant difference between DPP-4 inhibitors and placebo (OR: 1.12; 95% CI: 0.81 to 1.55). Furthermore, there was no significant difference between DPP-4 inhibitors and placebo (p = 0.50). Similarly, no significant difference between DPP-4 inhibitors (31 events) and placebo (27 events) was observed regarding the risk of pulmonary embolism (OR: 1.14; 95% CI: 0.68 to 1.90). For risk of gastrointestinal VTE, only two events were reported in patients taking DPP-4 inhibitors and none were reported in the placebo group. There was no significant association between DPP-4 inhibitors and risk of VTE (OR: 1.14; 95% CI: 0.68 to 1.90) and improving endothelium-dependent vasodilatation through increasing circulating levels of GLP-1.

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adverse events of VTE were reported on the Clinicaltrials.gov. Second, given the low incidence of VTE in this study, the study might be underpowered to detect that difference as significant. For example, only two events of VTE were identified at the gastrointestinal levels. Therefore, we cannot fully exclude the increased risk of VTE associated with DPP-4 inhibitors among the patients with type 2 diabetes. Third, due to lack of information regarding the co-medication in individual patients from trials, we cannot evaluate the potential drug–drug interaction in this study.

In conclusion, based on current available evidence from CVOTs, we did not find a significant difference between DPP-4 inhibitors and risk of VTE. However, further meta-analyses of individual data from all randomized controlled trials as well as well-designed large prospective observational studies are warranted to confirm our findings.

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Conflict of Interest
None declared.

References