

# 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).<sup>1</sup> 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.<sup>2</sup> 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 MedDRA<sup>1</sup> 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.<sup>3</sup> A pooled odds ratio (OR) with 95% CI was calculated using a fixed effects model and an  $I^2$  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  $p$ -

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value < 0.05 as statistically significant. The meta-analysis was performed with STATA (Version 14; Stata Corp., College Station, Texas, United States).

Finally, five CVOTs were included in this meta-analysis.<sup>4-8</sup> The basic characteristics of the included trials are summarized in ►Table 1. A total of 47,714 patients with type 2 diabetes and established or at high risk of cardiovascular disease were randomly allocated to the DPP-4 inhibitor group (23,899 patients) and the placebo group (23,815 patients). The median duration of follow-up ranged from 1.8 to 3 years. The mean age, baseline HbA1c%, and baseline body mass index on included patients were 64.2 years, 7.8%, and 30.5 kg/m<sup>2</sup>, respectively. The risk of bias of each trial was judged as low (►Table 1). Results of individual trials as well as meta-analysis are presented in ►Fig. 1. For risk of VTE, 79 events in the DPP-4 inhibitor group and 70 events in the placebo group were reported. Meta-analysis of the five trials did not find a significant association between DPP-4 inhibitors and risk of VTE (OR: 1.12; 95% CI: 0.81–1.55). Furthermore, there was no significant difference between DPP-4 inhibitors ( $p = 0.50$ ). 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: 0.68–1.90). 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 placebo (OR: 2.98; 95% CI: 0.31–28.70). No statistical heterogeneity was observed in the meta-analysis with an  $I^2$  ranged from 0 to 26.7%. There was no evidence of publication bias in the meta-analysis based on funnel plot (figures not shown) and Egger's test ( $p > 0.05$ ).

To our knowledge, this is the first meta-analysis of placebo-controlled CVOTs to assess the risk of VTE associated with DPP-4 inhibitors among patients with type 2 diabetes. Some evidence from spontaneous reporting databases indicated that DPP-4 inhibitors were associated with an increased risk of VTE.<sup>1,9</sup> However, we found no significant difference in the risk of VTE between DPP-4 inhibitors and placebo, which was also consistent with our previous study.<sup>2</sup> It has been proposed that DPP-4 inhibitors may have protective mechanisms against thrombosis effects by inhibiting platelet aggregation through their inhibitory effect on intracellular free calcium and tyrosine phosphorylation<sup>10</sup> and improving endothelium-dependent vasodilatation through increasing circulating levels of GLP-1.<sup>11</sup> An increase in events of VTE at the gastrointestinal levels was observed in previous studies,<sup>1,2</sup> while in this study only two events were reported in the DPP-4 inhibitor group, which requires further investigation including their underlying mechanisms.

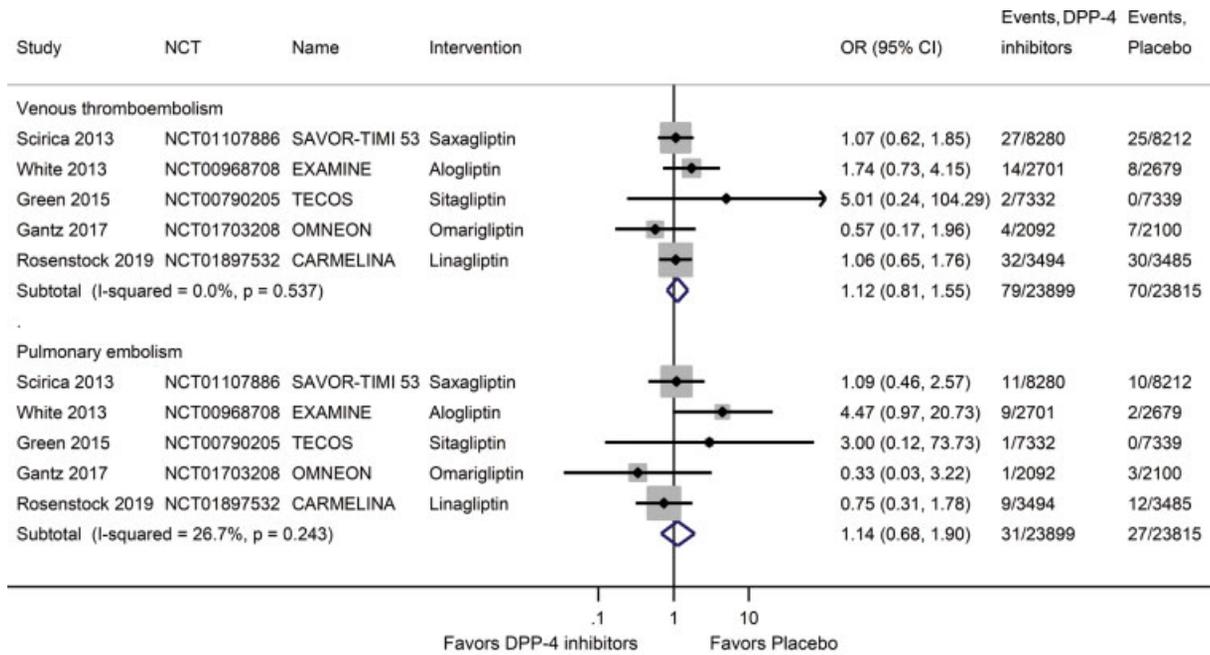
This study has several strengths including meta-analysis of available strong evidence and only considering randomized placebo-controlled trials that balanced the background therapy as well as other confounders. However, some limitations in this study should be considered. First, the events of VTE were not the predefined outcomes in these trials that the numbers of VTE are likely underestimated as only serious

**Table 1** Basic characteristics of included studies

Study	NCT	Name	No. of patients	Populations	Intervention	Age (y)	Baseline HbA1c (%)	Baseline BMI (kg/m <sup>2</sup> )	Duration of diabetes (y)	Median follow-up (y)	Risk of bias <sup>a</sup>
Scirica et al (2013) <sup>4</sup>	NCT01107886	SAVOR-TIMI 53	16,492	T2D patients with a history of or were at risk for CV events	Saxagliptin	65.1	8	31.2	10.3	2.1	Low
White et al (2013) <sup>8</sup>	NCT00968708	EXAMINE	5,380	T2D patients with either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15–90 days	Alogliptin	61	8	28.7	7.2	1.5	Low
Green et al (2015) <sup>6</sup>	NCT00790205	TECOS	14,671	T2D patients with established CV disease	Sitagliptin	65.5	7.2	30.2	11.6	3	Low
Gantz et al (2017) <sup>5</sup>	NCT01703208	OMNEON	4,192	T2D patients with established CV disease	Omarigliptin	63.6	8	31.3	12	1.8	Low
Rosenstock et al (2019) <sup>7</sup>	NCT01897532	CARMELINA	6,979	T2D patients with high CV risk	Linagliptin	65.9	7.9	31.3	14.8	2.2	Low

Abbreviations: BMI, body mass index; CV, cardiovascular; T2D, type 2 diabetes.

<sup>a</sup>Risk of bias of each trial was judged as low, high, or unclear according to Cochrane risk of bias tool.



**Fig. 1** Meta-analysis of the association between DPP-4 inhibitors and risk of venous thromboembolism and pulmonary embolism.

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.

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