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ORIGINAL RESEARCH

Glucagon-Like Peptide-1 Receptor Agonists and Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Limited data exist on the association of glucagon-like peptide 1 receptor agonists (GLP-1RAs) with the risk of venous thromboembolism. This meta-analysis aimed to investigate the association between GLP-1RAs and the risk of venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism.

METHODS AND RESULTS: A systematic search of PubMed, Web of Science, EMBASE, and Cochrane library was conducted from inception until July 3, 2024, to identify randomized controlled trials comparing GLP-1RAs with placebo or other anti-iabetic drugs, with reported data on DVT and pulmonary embolism. The primary outcome was venous thromboembolism, and secondary outcomes included DVT and pulmonary embolism. Pooled odds ratios (ORs) were calculated using fixed-effects models with Mantel–Haenszel method and treatment arm continuity correction for zero-event trials. A total of 39 randomized controlled trials involving 70 499 participants were included. A nonsignificant upward trend in the risk of venous thromboembolism was observed among participants using GLP-1RAs (OR, 1.19 [95% CI, 0.94–1.50]). GLP-1RAs were significantly associated with an increased risk of DVT (OR, 1.64 [95% CI, 1.14–2.36]); risk difference 25 (5–52) more events per 10 000 person-years). Subgroup analyses revealed that increased risk of DVT was particularly prominent in randomized controlled trials with treatment duration >1.5 years (OR, 2.32 [95% CI, 1.49–3.60]) and in cardiovascular outcome trials (OR, 2.18 [95% CI, 1.36–3.49]). No significant association was observed between GLP-1RAs and risk of pulmonary embolism.

CONCLUSIONS: GLP-1RAs might increase the risk of DVT, especially for long-term use of GLP-1RAs. Clinicians should be aware of this potential risk when prescribing GLP-1RAs.

Key Words: adverse events ■ deep vein thrombosis ■ glucagon-like peptide 1 receptor agonists ■ pulmonary embolism

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have garnered significant attention as a promising treatment for diabetes and obesity due to their metabolic and cardiorenal benefits.[1–3] With their growing global use,[4] comprehensively understanding their safety profiles is crucial. GLP-1RAs are associated with gastrointestinal adverse events, ranging from common gastrointestinal disturbances including nausea, vomiting, and diarrhea to serious adverse events including gallbladder or biliary diseases,[5] pancreatitis, bowel obstruction, and gastroparesis.[6] However, comprehensive safety data remain limited.

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major global health issue and a leading cause of morbidity and mortality.[7,8] Established risk factors

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CLINICAL PERSPECTIVES

What Is New?

- Glucagon-like peptide-1 receptor agonists are significantly associated with an increased risk of deep vein thrombosis, especially among individuals with long-term use.

What Are the Clinical Implications?

- Clinicians should be vigilant regarding the increased risk of deep vein thrombosis in patients using glucagon-like peptide-1 receptor agonists, especially in those with risk factors of deep vein thrombosis or those requiring long-term treatment.
- Future researchers should place greater emphasis on deep vein thrombosis in clinical studies focusing on glucagon-like peptide-1 receptor agonists, ensuring comprehensive reporting of adverse events related to deep vein thrombosis to avoid underreporting.

Nonstandard Abbreviations and Acronyms

CVOTs	cardiovascular outcome trials
GLP-1RAs	glucagon-like peptide 1 receptor agonists

include surgery, hospitalization, immobilization, cancer, obesity, and oral contraceptive use.[7–9] Although GLP-1RAs have demonstrated benefits for atherosclerotic cardiovascular diseases[10] through inhibiting arterial thromboembolism via multiple mechanisms such as antiplatelet properties, antioxidant and anti-inflammation function, and protective effect on endothelial function,[11,12] the pathophysiology of VTE differs from that of arterial thromboembolism, involving stasis and hypercoagulability rather than vascular wall lesions and high-shear stress. Therefore, VTE and arterial thromboembolism are traditionally considered 2 different entities.[13] Despite some overlapping risk factors such as obesity, older age, and inactivity, conditions such as hypertension, hyperlipidemia, and diabetes, strongly linked to atherosclerotic cardiovascular diseases, are not independently associated with VTE.[14] The potential link between GLP-1RAs and VTE risk remains largely unexplored. Previous data, including a World Health Organization reporting database analysis, associated dipeptidyl peptidase-4 inhibitors—mechanistically related to GLP-1—with increased VTE risk,[15] which raised our concerns about the association of GLP-1RAs use and risk of VTE. Additionally, a meta-analysis of the SUSTAIN (Efficacy and Safety of Semaglutide Once-Weekly Versus Sitagliptin Once-Daily as Add-on to Metformin and/or TZD in Subjects With Type 2 Diabetes) and PIONEER (Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes Mellitus Treated With Diet and Exercise Only) trials, which explored adverse events associated with semaglutide,[16] found a significantly increased risk of DVT with semaglutide. However, limited data exist on the association of GLP-1RAs with the risk of VTE. To address these gaps, we conducted a comprehensive meta-analysis of randomized controlled trials (RCTs) to systematically evaluate the association between GLP-1RAs and VTE risk.

METHODS

All authors declare that all supporting data are available in the article, its online supplementary files or clinicaltrials.gov; the papers we included, and their supplementary files were found on online data bank (mainly PubMed).

We performed the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] The study protocol has been previously registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD42023450109).

Data Sources, Evidence Searches, and Identification

We comprehensively searched databases including PubMed, EMBASE, Cochrane Library, and Web of Science for RCTs of GLP-1RAs with no restrictions on language up to July 3, 2024. The literature searches were conducted by 2 reviewers (Y.L., L.H.) independently (Table S1). We also manually screened additional gray literature in Google Scholar, the references of eligible studies and relevant reviews, and other resources.

Study Selection

Studies fulfilling the eligibility criteria (Table S2) were included: (1) RCTs investigating the efficacy or safety of GLP-1RAs for adults >18 years old with type 2 diabetes, prediabetes, obesity, overweight, nonalcoholic steatohepatitis, or metabolic syndrome; and (2) the number of DVT or PE were reported. Studies including patients with type 1 diabetes, investigating coformulation of fixed-dose combinations of GLP-1RAs and other antidiabetic drugs (eg, IDegLira), with crossover design or post hoc analysis, or without non-GLP-1RAs comparators were excluded. Conference abstracts, reviews, and animal experiments were also excluded. When multiple articles reporting results from the same RCT, only the

one with the most comprehensive data was included. The titles and abstracts of the literature were screened by 2 independent reviewers (Y.L. and L.H.) in the preliminary screening. Subsequently, full text of the potentially relevant articles was retrieved to confirm eligibility. The disagreement was resolved through discussion with 2 senior authors (H.Z. and Y.L.).

Data Extraction, Risk of Bias, and Quality Assessment

The following data were extracted from the published articles, supporting information, and clinicaltrials.gov or the European Union Clinical Trials Register: first author, year of publication, clinical trial identifier, treatment duration, baseline characteristics of participants (sample size, age, sex, body mass index, hemoglobin A1c), interventions, controls, and outcomes of interest (the number of DVTs, PEs, and VTEs [calculated as the sum of DVT and PE cases]). The risk of bias of the eligible studies was assessed according to the revised Cochrane risk of bias tool for randomized trials.[18] The quality of evidence for all outcomes was assessed through the Grading of Recommendations, Assessment, Development and Evaluations framework.[19]

Definition of Outcomes

In RCTs, DVTs or PEs were reported as serious adverse events. We identified the outcomes based on the terms from *Medical Dictionary for Regulatory Activities* (MedDRA) version 26.1. DVT and PE were captured with the preferred terms. The total number of VTE events was calculated as the sum of DVT and PE cases. We retrieved outcomes from the results of serious adverse events reported on Clinicaltrials.gov. The primary outcome was VTE calculated as the sum of DVT and PE cases. The secondary outcomes were defined as DVT and PE, both of which were captured with the preferred terms directly.

Statistical Analysis

To identify the association of GLP-1RAs use with risk of outcomes, odds ratios (ORs) and the corresponding 95% CIs were pooled by fixed-effects models with the Mantel–Haenszel method, and treatment arm continuity correction was applied to deal with the zero events.[20,21] The heterogeneity was assessed by Q statistic and χ^2 tests (statistical heterogeneity was set at P value <0.10).[22] To test the robustness of the results, sensitivity analysis was conducted by multiple

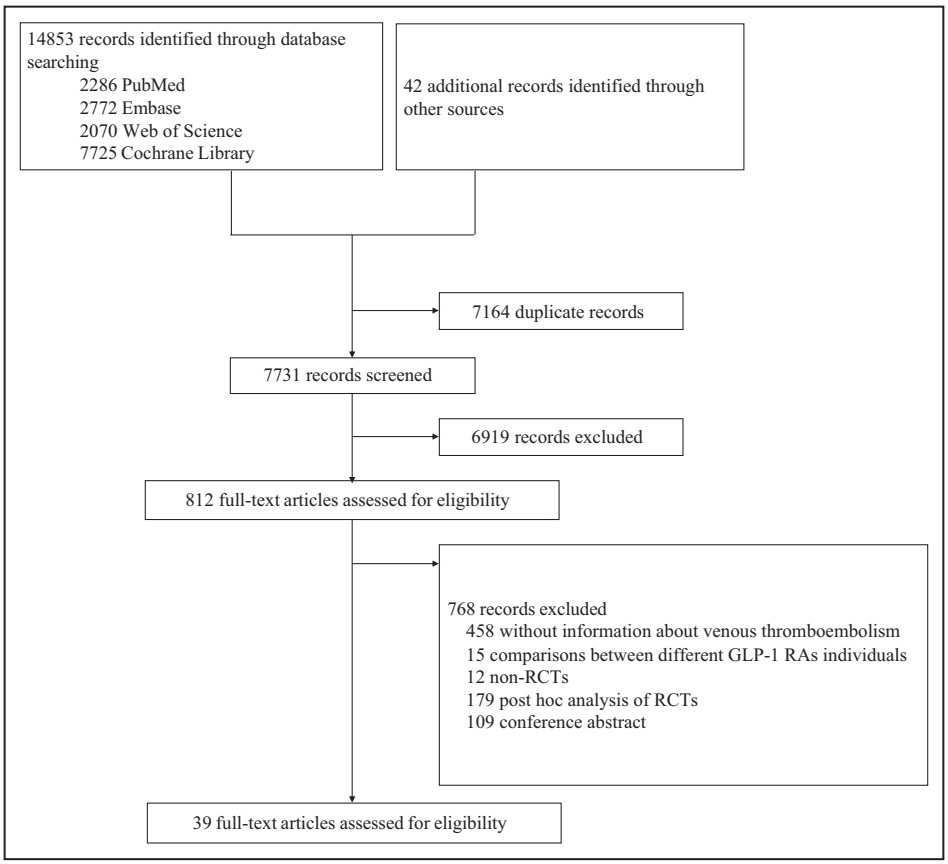

Figure 1. PRISMA flow diagram.
GLP-1Ras indicates glucagon-like peptide 1 receptor agonists; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and RCTs, randomized controlled trials.

Table 1. Baseline Characteristics of Studies Included

Trials	No. of participants	Treatment duration	Age, y	No. (%) of women	BMI, kg/m^2	HbA1c, %	Interventions	Controls
Rosenstock et al. (2009)	356	16 wks	54	186 (52.2%)	32.1	8	Albiglutide (weekly [4–15, or 30 mg], biweekly [15–30, or 50 mg], or monthly [50 or 100 mg]); Exenatide twice daily	Placebo
LEAD-2 (2009)	1087	26 wks	56.6	454 (41.8%)	31.1	8.4	Liraglutide 0.6 mg/day+metformin; Liraglutide 1.2 mg/day+metformin; Liraglutide 1.8 mg/day+metformin; Glimepiride 4 mg/day+metformin	Liraglutide placebo+metformin
Buse et al. (2011)	259	30 wks	59	111 (42.9%)	33.5	8.4	Exenatide 10 g; twice daily	Placebo
LEAD-3 Mon (2011)	745	104 wks	53	375 (50.3%)	33.1	8.4	Liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Glimepiride
European Exenatide Study (2012)	1019	4.5 y	56	457 (46.4%)	32	7.5	Exenatide 10 μg, twice daily	Glimepiride
GETGOAL-Duo1 (2013)	446	24 wks	56	224 (50%)	31.8	7.6	Lixisenatide 20 μg+insulin glargine+metformin, daily	Placebo +insulin glargine+ metformin
GETGOAL-L (2013)	495	24 wks	57	267 (53.9%)	32.1	8.4	Lixisenatide 20 mg+basal insulin±metformin; daily	Placebo+basal insulin ± metformin
AWARD-1 (2014)	976	26 wks	56	406 (41.6%)	33	8.1	Dulaglutide 0.75 mg; dulaglutide 1.5 mg; weekly	Placebo
HARMONY-1 (2014)	301	52 wks	55	121 (40.2%)	34.1	8.1	Albiglutide 30 mg+pioglitazone; weekly	Placebo +pioglitazone
HARMONY-3 (2014)	1012	104 wks	54.8	530 (52.4%)	32.6	8.1	Albiglutide 30–50 mg; weekly	Placebo; sitagliptin; glimepiride
HARMONY-4 (2014)	745	52 wks	55.5	327 (43.9%)	33.1	8.3	Albiglutide 30 mg weekly+metformin	Insulin glargine+ metformin
Leiter et al. (2014)	495	52 wks	63.3	229 (46.3%)	30.4	8.2	Albiglutide 30 mg, weekly	Sitagliptin
AWARD-5 (2015)	1098	104 wks	54	577 (52.5%)	31	8.1	Dulaglutide 0.75 mg; dulaglutide 1.5 mg; weekly	Sitagliptin; placebo
Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (2015)	6063	225 wks	59.8	1861 (30.7%)	30.1	7.7	Lixisenatide 20 μg daily	Placebo
HARMONY-5 (2015)	663	52 wks	55.2	310 (46.8%)	32.2	8.2	Albiglutide 30 mg, weekly	Placebo; pioglitazone
Jaiswal et al. (2015)	46	78 wks	53	20 (43.5%)	36.5	8.3	Exenatide 10 μg, twice daily	Insulin glargine
SCALE Diabetes (2015)	844	58 wks	54.9	421 (49.9%)	37.2	7.9	Liraglutide 1.8 mg; liraglutide 3.0 mg; daily	Placebo
SCALE Obesity and Prediabetes (2015)	3731	56 wks	41.5	2928 (78.5%)	37.4	5.3	Liraglutide 3.0 mg, daily	Placebo

(*Continued*)

Table 1. Continued

Trials	No. of participants	Treatment duration	Age, y	No. (%) of women	BMI, kg/m^2	HbA1c, %	Interventions	Controls
Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (2016)	9340	3.8 y	64.3	3337 (35.7%)	32.5	8.7	Liraglutide 1.8 mg, daily	Placebo
SUSTAIN-2 (2017)	1225	56 wks	55.1	605 (49.4%)	32.5	8.1	Semaglutide 0.5 mg; semaglutide 1.0 mg; weekly	Sitagliptin
SUSTAIN-6 (2017)	3297	104 wks	64.6	1295 (39.3%)	32.8	8.7	Semaglutide 0.5 mg; semaglutide 1.0 mg; weekly	Placebo
AWARD-7 (2018)	576	52 wks	64.5	275 (47.7%)	32.5	8.6	Dulaglutide 0.75 mg; dulaglutide 1.5 mg; weekly	Insulin glargine
HARMONY outcome (2018)	9432	1.5 y	64.1	2894 (30.3%)	32.3	8.7	Albiglutide 30–50 mg, weekly	Placebo
O'Neil et al. (2018)	957	52 wks	47	619 (64.7%)	39.3	5.5	Semaglutide 0·05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg; daily	Placebo
PIONEER-1 (2019)	703	26 wks	55	346 (49.2%)	31.8	8	Oral semaglutide 14 mg; daily	Placebo
PIONEER-2 (2019)	819	52 wks	58	406 (49.5%)	32.8	8.1	Oral semaglutide 3 mg, 7 mg, 14 mg; daily	Empagliflozin
PIONEER-3 (2019)	1861	78 wks	58	879 (47.2%)	32.4	8.3	Oral semaglutide 3 mg, 7 mg, 14 mg; daily	Sitagliptin
PIONEER-6 (2019)	3183	82 wks	66	1007 (31.6%)	32.3	8.2	Oral semaglutide 3 mg, 7 mg, 14 mg; daily	Placebo
PIONEER-8 (2019)	730	52 wks	61	336 (46%)	31	8.2	Oral semaglutide 3 mg, 7 mg, 14 mg; daily	Placebo
Researching Cardiovascular Events With a Weekly Incretin in Diabetes (2019)	9892	7 y	66.2	4589 (46.4%)	32.3	7.3	Dulaglutide 1.5 mg; weekly	Placebo
SUSTAIN-8 (2019)	786	52 wks	56.6	364 (46%)	32.3	8.3	Semaglutide 1.0 mg; weekly	Canagliflozin
SCALE Insulin (2020)	392	56 wks	56.7	207 (52.3%)	35.6	7.9	Liraglutide 3.0 mg+IBT+ insulin, daily	Placebo+IBT+insulin
STEP-1 (2021)	1961	68 wks	46.5	1453 (74.1%)	37.9	5.7	Semaglutide 2.4 mg; weekly	Placebo
STEP-3 (2021)	611	68 wks	46	495 (81.0%)	38	5.7	Semaglutide 2.4 mg; weekly	Placebo
Efficacy in Controlling Glycaemia With Victoza (Liraglutide) as Add-On to Metformin vs OADs as Add-On to Metformin After Up to 104 Weeks of Treatment in Subjects With Type 2 Diabetes (2022)	1991	104 wks	57.4	947 (47.6%)	33.5	8.2	Liraglutide 1.2 mg; daily liraglutide 1.8 mg; daily	Other oral anti-diabetic drugs
STEP-5 (2022)	304	104 wks	47.3	236 (77.6%)	38.5	5.7	Semaglutide 2.4 mg; weekly	Placebo
STEP-8 (2022)	338	68 wks	49	265 (78.4%)	37.5	5.5	Semaglutide, 2.4 mg; weekly; liraglutide, 3.0 mg; daily	Placebo
SUSTAIN-11 (2022)	1748	52 wks	61.2	854 (48.9%)	31.5	8.6	Semaglutide 1.0 mg, weekly	Insulin aspart

(*Continued*)

Table 1. Continued

Trials	No. of participants	Treatment duration	Age, y	No. (%) of women	BMI, kg/m^2	HbA1c, %	Interventions	Controls
Frias et al. (2023)	92	32 wks	58	33 (36%)	35.5	8.5	Semaglutide 2.4 mg, weekly+cagrilintide 2.4 mg, weekly; semaglutide 2.4 mg, weekly	Cagrilintide 2.4 mg, weekly

AWARD indicates A Study in Participants With Type 2 Diabetes Mellitus; BMI, body mass index; GETGOAL, 24-Week Treatment With Lixisenatide in Type 2 Diabetes Insufficiently Controlled With Metformin and Insulin Glargine; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; HbA1c, hemoglogin A1c; IBT, intensive behavioral therapy; LEAD, Liraglutide Effect and Action in Diabetes; PIONEER, Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes Mellitus Treated With Diet and Exercise Only; SCALE, Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes; STEP, Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity; and SUSTAIN, Efficacy and Safety of Semaglutide Once-Weekly Versus Sitagliptin Once-Daily as Add-On to Metformin and/or TZD in Subjects With Type 2 Diabetes.

types of pooling methods[23] (ie, exact method [exact inference for fixed effects meta-analysis],[24,25] Peto's method, Mantel–Haenszel without continuity correction, generalized linear mixed models, and random-effects model) to adjust the sparse events and omitting specific studies. To assess potential modifying factors, we conducted an exploratory subgroup analysis and meta-regression on the prespecified covariates. For continuous covariates (ie, treatment duration [using 78 weeks as a cutoff], baseline body mass index [using the median as a cutoff], weight loss [using the median as a cutoff]), both meta-regression with the residual maximum likelihood method and subgroup analysis were used. For categorial covariates (ie, drug dose, treatment indications, types of control, types of trials, specific GLP1-RA types), subgroup analysis was used. The high and low dose was defined as follows: high-dose groups included liraglutide ≥1.8 mg once daily, subcutaneous semaglutide ≥1.0 mg once weekly, oral semaglutide ≥7 mg once daily, dulaglutide ≥1.5 mg once weekly, exenatide ≥10 μg twice daily, lixisenatide 20 μg (≥20 μg) once daily, and albiglutide ≥50 mg once weekly; low dose of GLP-1RAs included liraglutide 0.6 to 1.2 mg (<1.8 mg) daily, subcutaneous semaglutide 0.5 mg (<1.0 mg) once weekly, oral semaglutide 3.0 mg (<7.0 mg) once daily, dulaglutide 0.75 mg (<1.5 mg) once weekly, exenatide <10 μg twice daily, lixisenatide 10 μg (<20 μg) once daily, and albiglutide 30 mg (<50 mg) once weekly. We evaluated the publication bias using Egger's and Begg's asymmetry tests, as well as the funnel plots.[26] We observed the development of evidence using a cumulative meta-analysis. All the analyses were performed with meta package in R studio (version 4.3.1). Statistical significance was set as at a *P* value of <0.05.

Data Sharing

The study-specific summary data included in the meta-analysis can be obtained from the corresponding author.

Dissemination to Participants and Related Patients and Public Communities

No patients were involved in setting the research question, outcome measures, or design and implementation of the study. We do not plan to disseminate results directly to patients beyond our general media communication plan.

Transparency

The article's corresponding authors (Huabing Zhang, and Yuxiu Li) affirm that the article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies of the study have been explained as originally planned (and, if relevant, registered).

RESULTS

Study Screening and Characteristics of Studies Included

A total of 39 RCTs with 70 499 participants were included in the meta-analysis following comprehensive screening[27–65] (Figure 1). The characteristics of the included studies were presented in Table 1. Female participants account for 44.2%. The mean age of participants was 60.0 years old, with an average body mass index of 32.9 kg/m^2, and an average hemoglobin A1c of 7.9%. All the DVT or PE events were documented in clinicaltrials.gov as serious adverse events.

Risk of Bias and Quality of Evidence

The details of risk of bias of the included studies were presented in Table S3 and summarized in Figure S1. Most of the studies had low risk of bias or some concerns of bias across the 5 domains. As illustrated in Table 2, the quality of evidence for the risk of all the outcomes was rated as moderate because of some

Table 2. Summary of Findings for VTE, DVT, and PE in the Meta-Analysis

Outcome	No. of patients (studies)	Study event rates		Relative effects (95% CI)	Anticipated absolute effect*		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence†
		With GLP1-RAs	With control		Risk with control	Risk difference (95%CI) with GLP-1RAs						
VTE	70 499 (39)	(0.39%) 151/38868	(0.36%) 114/31631	OR, 1.19 (0.94 to 1.50)	60	11 (−4 to 30)	Some concerns‡	Not serious	Not serious	Not serious	Not serious	Moderate ⊕⊕⊕?
DVT	63 798 (29)	(0.20%) 71/34824	(0.12%) 35/28974	OR, 1.64 (1.14 to 2.36)	38	25 (5 to 52)	Some concerns‡	Not serious	Not serious	Not serious	Not serious	Moderate ⊕⊕⊕?
PE	61 092 (29)	(0.24%) 80/32862	(0.28%) 79/28230	OR, 0.94 (0.69 to 1.26)	42	−3 (−13 to 11)	Some concerns‡	Not serious	Not serious	Not serious	Not serious	Moderate ⊕⊕⊕?

GRADE Working Group grades of evidence: high certainty=we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty=we are moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty=our confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect; very low certainty=we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect. DVT indicates deep vein thrombosis; GLP-1RAs, glucagon-like peptide 1 receptor agonists; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; OR, odds ratio; PE, pulmonary embolism; and VTE, venous thromboembolism.

*Anticipated absolute effect is event rate per 10 000 person-years.

†Quality of evidence was evaluated using noncontextualized GRADE approach.

‡All randomized controlled trials included in this analysis were designed to evaluate efficacy of GLP-1RAs and did not report DVT or PE as safety end points of interest. Concerns might arise about selective reporting of results, considering that occurrence of DVT or PE might not be fully reported in trials.

concerns on possible reporting bias (underreporting could not be excluded).

Association Between GLP-1RAs and Risk of VTE Events

We observed an increasing trend in the risk of VTE among participants using GLP-1RAs; however, this increase was not statistically significant (OR, 1.19 [95% CI, 0.94–1.50]) (Figure 2; Table 2). Notably, GLP-1RAs were associated with a significant increase in the risk of DVT compared with controls (OR, 1.64 [95% CI, 1.14–2.36]; absolute risk difference 25 [5 to 52] more events per 10 000 person-years) (Figure 3; Table 2). In contrast, the risk of PE (OR, 0.94 [95% CI, 0.69–1.26]) showed no significant difference between the GLP-1RA group and control group (Figure 4; Table 2).

Potential Modifiers for the Association of GLP-1RAs With Risk of DVT and PE

The summary of subgroup analysis of association between GLP-1RAs and risk of DVT was presented in Figure 3 and Figures S2 through S7, S9 through S15. As shown in Figure S8, the odds ratio for DVT in RCTs with a treatment duration longer than 78 weeks was consistently >1, whereas the OR for DVT in studies with a treatment duration <78 weeks was more variable and less certain. Based on these observations, we chose 78 weeks as the cutoff for subgroup analysis. Notably, GLP-1RAs were found to significantly increase the risk of DVT when used for longer duration (≥78 weeks) (OR, 2.32 [95% CI, 1.49–3.60]), which was not observed in those with shorter duration (<78 weeks) (OR, 0.66 [95% CI, 0.33–1.30]) (*P* for interaction=0.002, Figure 5; Figure S9). More importantly, ORs>1 were observed among all 12 RCTs with treatment duration >1.5 years (78 weeks) without exception, suggesting a possible treatment duration threshold for the prominent increase of DVT occurrence. Intriguingly, GLP-1RAs significantly increased the risk of DVT in cardiovascular outcome trials (CVOTs) (OR, 2.18 [95% CI, 1.36–3.49]), whereas we did not observe an increase in risk of DVT in non-CVOTs (OR, 1.02 [95% CI, 0.57–1.83]) (*P* for interaction=0.047) (Figure S10). The modified effects of drug dose, types of GLP-1RAs, baseline body mass index, weight loss, and type of control on the risk of DVT were not statistically significant (Figures S11 through S15). Similarly, a significantly increased risk of VTE was observed in participants with a treatment duration >78 weeks (OR, 1.38 [95% CI, 1.06–1.80]), whereas no such increase was found in those with a treatment duration of <78 weeks (OR, 0.67 [95% CI, 0.40–1.11]) (*P* for interaction=0.01, Figure S2). A significant association with an increased risk of overall VTE was observed exclusively in those treated with albiglutide (OR, 2.03 [95% CI, 1.03–3.99]) (Figure S5). In contrast, the

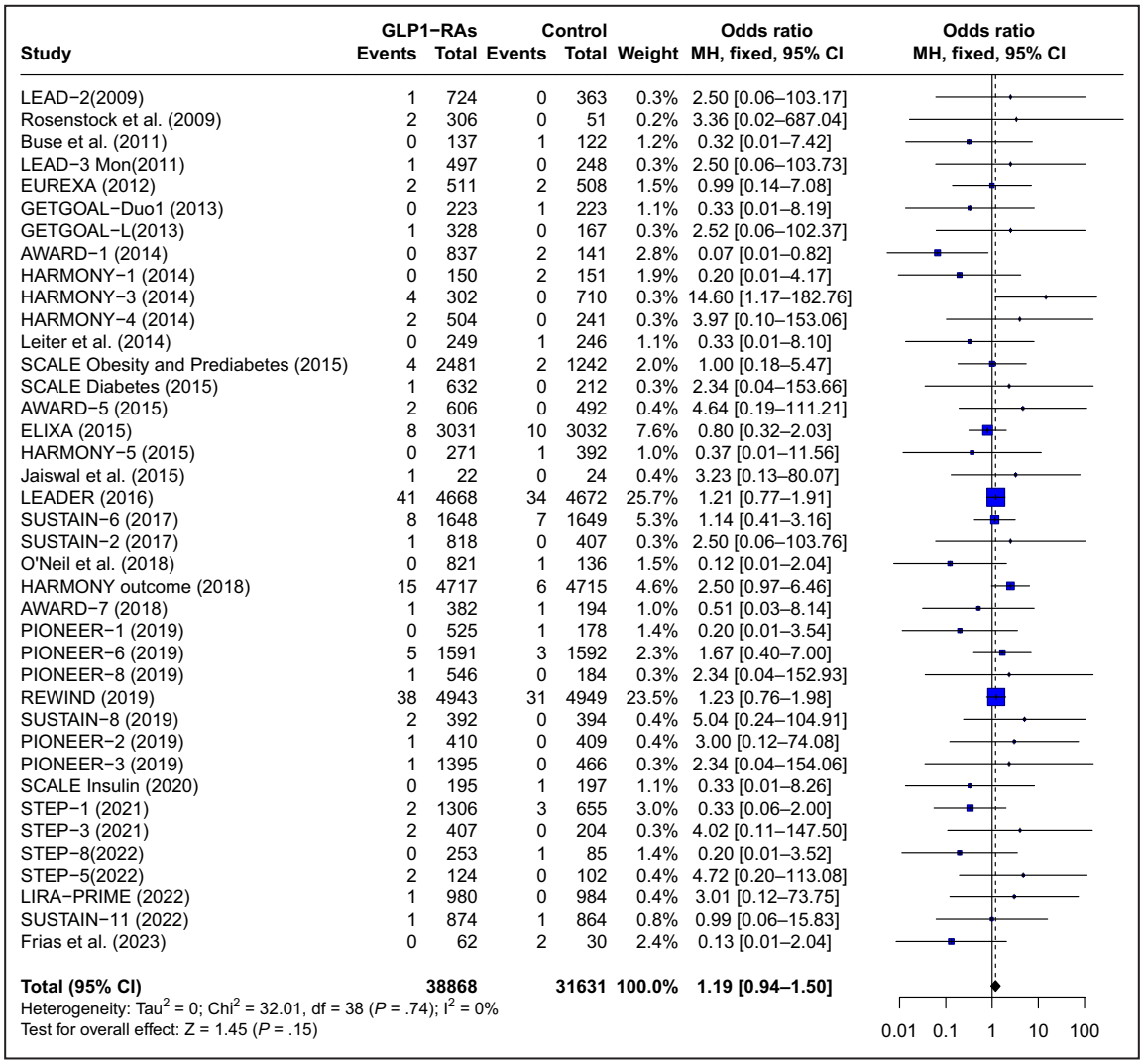

Figure 2. Association of GLP-1RAs with risk of VTE compared with placebo or non-GLP-1RAs drugs.
AWARD indicates A Study in Participants With Type 2 Diabetes Mellitus; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EUREXA, European Exenatide Study; GETGOAL, 24-Week Treatment With Lixisenatide in Type 2 Diabetes Insufficiently Controlled With Metformin and Insulin Glargine; GLP-1RAs, glucagon-like peptide 1 receptor agonists; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; LEAD-2, Liraglutide Effect and Action in Diabetes-2; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LIRA-PRIME, Efficacy in Controlling Glycaemia With Victoza (Liraglutide) as Add-On to Metformin vs OADs as Add-On to Metformin After Up to 104 Weeks of Treatment in Subjects With Type 2 Diabetes; MH, Mantel–Haenszel; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SCALE, Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes; STEP, Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity; and VTE, venous thromboembolism.

subgroup analysis of PE did not observe significant subgroup difference (Figures S16 through S21).

Sensitivity Analyses and Publication Bias

The robustness of the results was explored by multiple methods. Different pooling methods to handle the zero-events studies and use of random-effects model did not change the results of DVT and PE (Table S4). When a single study was omitted one by one (Figures S22 through S24), the results of VTE, DVT, and PE remained stable. The cumulative meta-analysis by year illustrated that the association between GLP-1RAs and increased risk of DVT has been increasingly significant over time and remained stable after 2017 (Figure S25). No publication bias was identified by funnel plot and asymmetry tests for VTE, DVT, and PE (Figures S26 through S28).

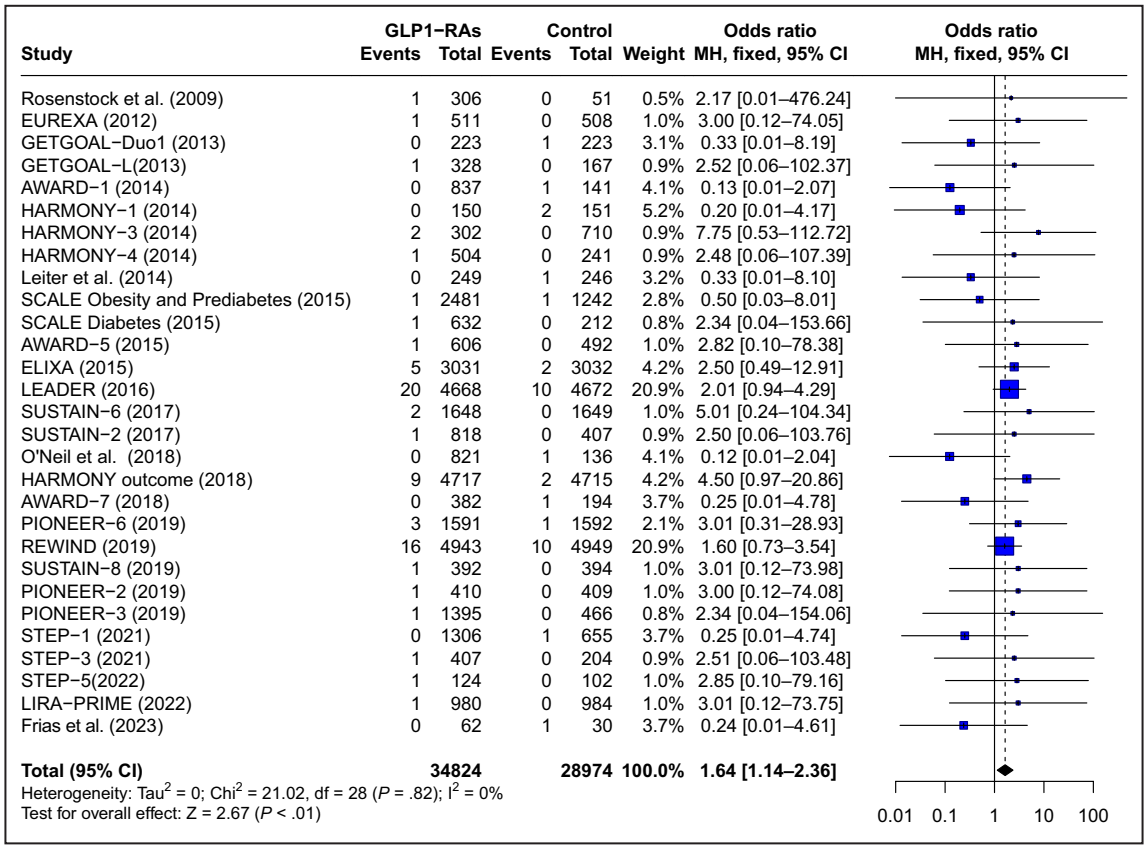

Figure 3. Association of GLP-1RAs with risk of DVT compared with placebo or non-GLP-1RAs drugs.
AWARD indicates A Study in Participants With Type 2 Diabetes Mellitus; DVT, deep vein thrombosis; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EUREXA, European Exenatide Study; GETGOAL, 24-Week Treatment With Lixisenatide in Type 2 Diabetes Insufficiently Controlled With Metformin and Insulin Glargine; GLP-1RAs, glucagon-like peptide 1 receptor agonists; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LIRA-PRIME, Efficacy in Controlling Glycaemia With Victoza (Liraglutide) as Add-On to Metformin vs OADs as Add-On to Metformin After Up to 104 Weeks of Treatment in Subjects With Type 2 Diabetes; MH, Mantel–Haenszel; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SCALE, Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes; and STEP, Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity.

DISCUSSION

To our knowledge, this is the first study to systematically investigate the association of GLP-1RAs use with risk of VTE. Our findings suggest that GLP-1RAs significantly increased the risk of DVT. It is noteworthy that the increased risk of DVT was particularly prominent among those treated with GLP-1RAs >1.5 years and CVOTs. No significant association was found between GLP-1RAs and risk of PE.

To date, few preclinical and clinical studies have focused on the association between GLP-1RAs and risk of DVT or PE. A previous publication reported a patient with type 2 diabetes suffering from cerebral venous thrombosis after using dulaglutide for 3 weeks and was experiencing nausea and vomiting.[66] The authors speculated that dehydration due to dulaglutide-associated nausea and vomiting was the provocative factor, which however could not be verified. Recently, a meta-analysis of the SUSTAIN and PIONEER trials investigated the safety profiles of semaglutide and intriguingly found that semaglutide was significantly associated with increased risk of DVT (6 RCTs with 13 339 participants included in the meta-analysis, risk ratio [RR], 3.66 [95% CI, 1.09–12.25]) but not significantly associated with risk of PE (9 RCTs with 12 868 participants included in the meta-analysis, RR, 0.97 [95% CI, 0.47–1.99]).[16] However, only semaglutide was investigated, with a limited number of RCTs included. In contrast, all currently clinically used GLP-1RAs and all eligible RCTs were comprehensively included in this meta-analysis (39 RCTs with 70 499 participants included in meta-analysis) to ensure systematic evaluation of association between GLP-1RAs use and risk of VTE. We found a significant but weaker association (OR, 1.64 [95% CI, 1.14–2.36]) between

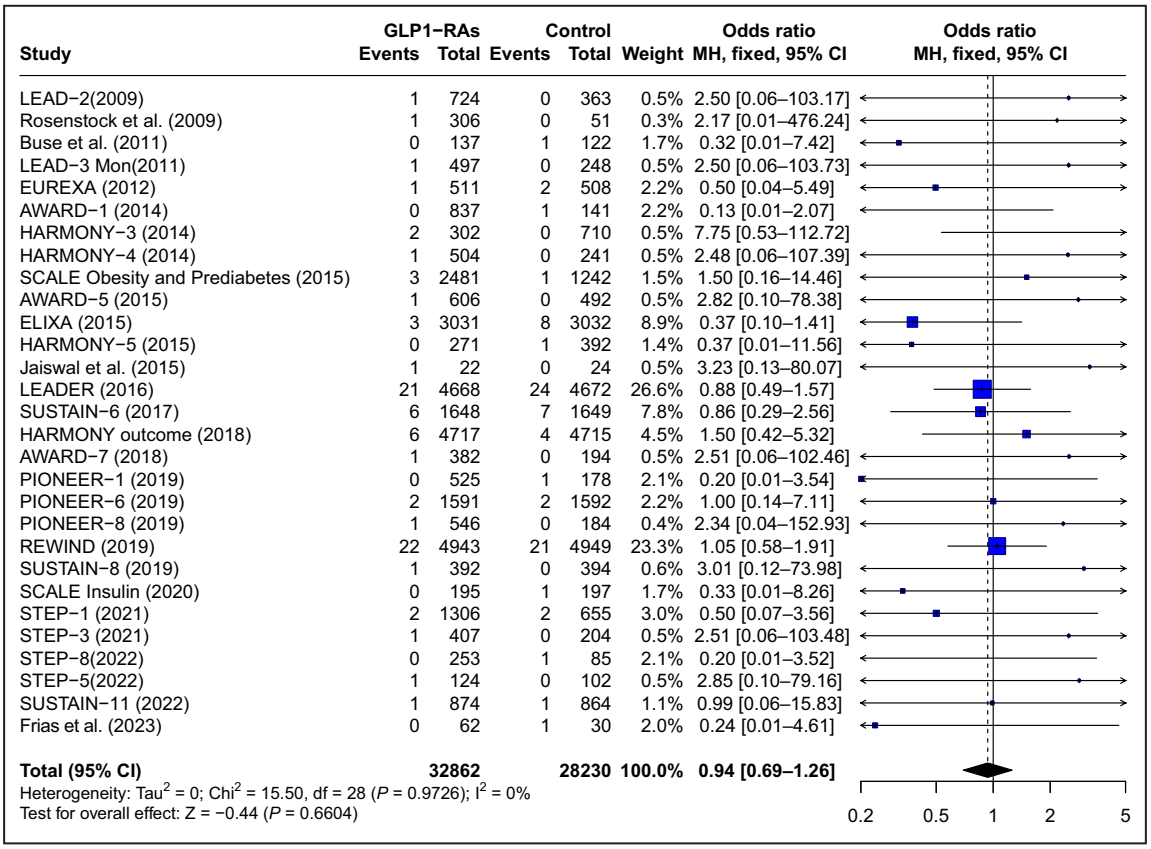

Figure 4. Association of GLP-1RAs with risk of PE compared with placebo or non-GLP-1RAs drugs.
AWARD indicates A Study in Participants With Type 2 Diabetes Mellitus; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EUREXA, European Exenatide Study;GLP-1RAs indicates glucagon-like peptide 1 receptor agonists; HARMONY, Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease; LEAD-2, Liraglutide Effect and Action in Diabetes-2; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MH, Mantel–Haenszel; PE, pulmonary embolism; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SCALE, Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes; and STEP, Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity.

GLP-1RAs and increased risk of DVT. Similarly, no significant association was identified between GLP-1RAs and risk of PE. It is universally acknowledged that PE is the life-threatening complication of DVT, and most PE was secondary to DVT. Previous investigations reported that among patients with confirmed PE, DVT was detected in 72% to 90% through autopsy and 71% to 93% by phlebography.[67–69] However, the results varied widely from 10% to 80% using proximal ultrasound. Approximately one third of DVT cases progress to PE, with the risk of PE varying significantly depending on the location and size of the clot. Proximal DVTs (eg, in the iliac or femoral veins) and larger clots have a higher likelihood of embolizing and causing PE, whereas distal DVTs (eg, in the calf veins) and smaller clots have a lower risk of causing PE. This might explain the discrepancy between DVT and PE in this meta-analysis. Regrettably, the RCTs included in our analysis did not provide detailed information on the location or size of DVTs. Future RCTs should report more specific details regarding the location and size of DVTs.

Specifically, we investigate the dose–response relationship between GLP-1RAs and the risk of DVT, highlighting a significant increase in DVT risk for those using GLP-1RAs for 1.5 years or longer. This dose–response relationship offers stronger evidence supporting the potential causal link between GLP-1RAs use and the increased risk of DVT and provides clearer guidance for clinicians when considering the use of GLP-1RAs in patients, enabling more informed, individualized treatment decisions. Interestingly, ORs>1 were not only observed in the pooled result of the 12 RCTs with treatment duration >1.5 years but also universally observed in every individual RCT with treatment duration >1.5 years. This finding deserves particular attention, indicating that the DVT risk attributed to long-term use of GLP-1RAs should be evaluated with more caution in clinical settings. A possible explanation is that the development of unprovoked DVT typically occurs over a longer period. Additionally, we found that GLP-1RAs were significantly associated with increased risk of DVT

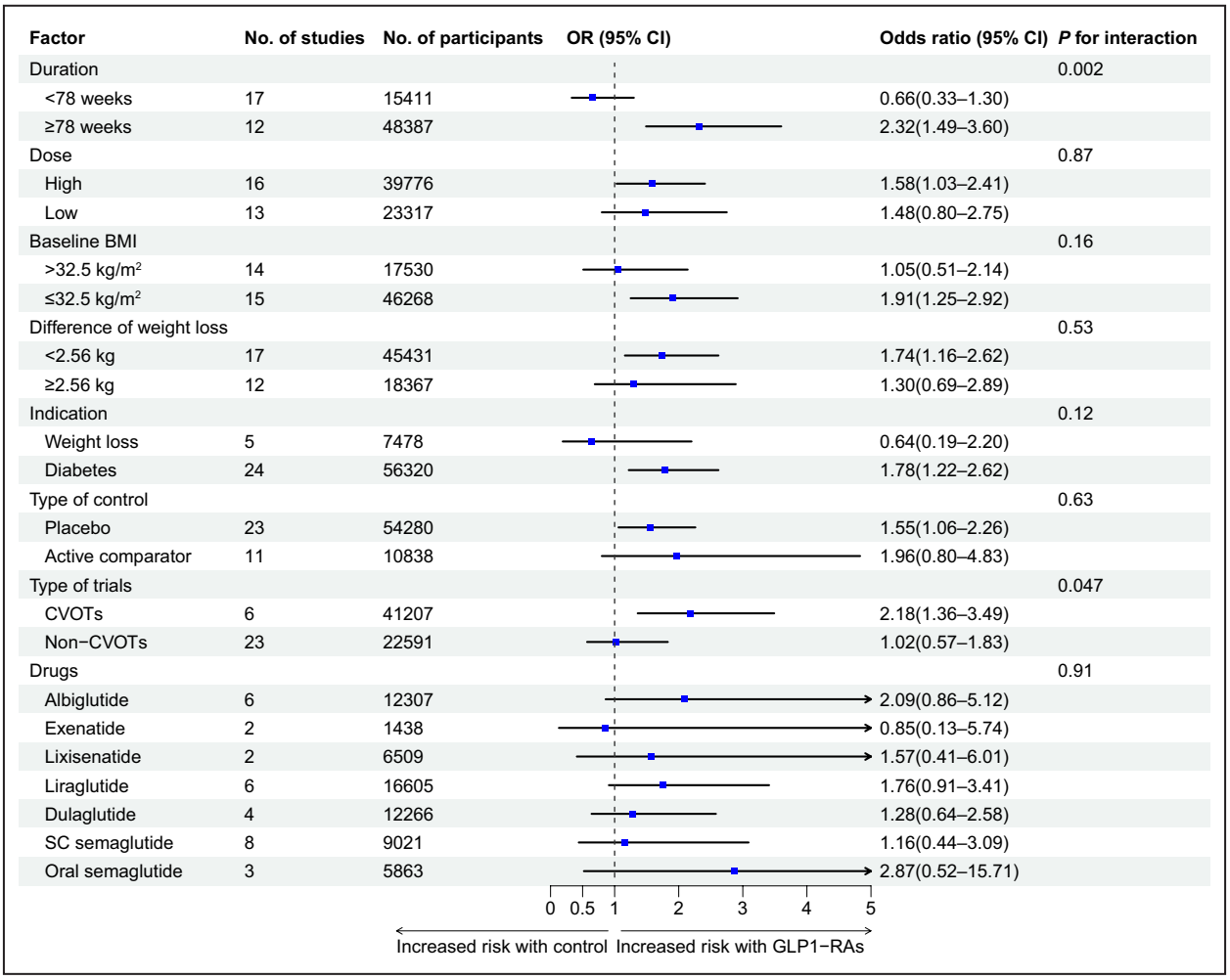

Figure 5. Summary of subgroup analyses of association between GLP-1RAs and risk of deep vein thrombosis.
The high and low dose was defined as follows: high-dose groups included liraglutide ≥1.8 mg once daily, subcutaneous semaglutide ≥1.0 mg once weekly, oral semaglutide ≥7 mg once daily, dulaglutide ≥1.5 mg once weekly, exenatide ≥10 μg twice daily, lixisenatide 20 μg (≥20 μg) once daily, and albiglutide ≥50 mg once weekly; low dose of GLP-1RAs included liraglutide 0.6 to 1.2 mg (<1.8 mg) daily, subcutaneous semaglutide 0.5 mg (<1.0 mg) once weekly, oral semglutide 3.0 mg (<7.0 mg) once daily, dulaglutide 0.75 mg (<1.5 mg) once weekly, exenatide <10 μg twice daily, lixisenatide 10 μg (<20 μg) once daily, and albiglutide 30 mg (<50 mg) once weekly. The cutoff point of the baseline BMI and weight loss was 32.5 kg/m^2 and 2.56 kg, which was the median of baseline BMI and weight loss. BMI indicates body mass index; CVOTs, cardiovascular outcomes trials; GLP-1RAs, glucagon-like peptide 1 receptor agonists; OR, odds ratio; and SC, subcutaneous.

both in the pooled analysis of the 6 CVOTs[30,31,54,56,58,63] and in the result of every individual CVOT. Compared with non-CVOTs, CVOTs were characterized with larger sample size, longer follow-up duration, and more comprehensive information regarding adverse events, which might partially explain the discrepancy between CVOTs and non-CVOTs. More importantly, this might indicate that some reporting bias could not be completely excluded in non-CVOTs, although the funnel plot and asymmetry tests did not identify publication bias. The possible reporting bias might underestimate the risk of DVT associated with GLP-1RAs, which alerts the researchers and clinicians to pay more attention to increased risk of DVT attributed to GLP-1RAs. Moreover, multiple sparse event correction methods including an exact method (exact inference for fixed effects meta-analysis) were applied in this meta-analysis to address the issue of rare events and yielded consistent results, which improves the accuracy of estimating treatment effects when events are infrequent, enhancing the statistical power of the analysis to provide more reliable and precise results.

Given that the common gastrointestinal symptoms such as nausea, vomiting, and diarrhea could result in dehydration, hemoconcentration and increased blood viscosity, important risk factors for DVT, might contribute to the association between GLP-1RAs and increased risk of DVT. However, to date, in the absence of further experimental studies, no pathophysiological hypothesis can explain this potentially specific

association between GLP-1RAs and increased risk of DVT. The underlying mechanism of how GLP-1RAs are involved in the development of DVT remains unclear. Further mechanistic studies are warranted to elucidate the potential effect of GLP-1RAs on the development of DVT and the underlying mechanism.

Several strengths deserve to be mentioned for this study. First, this is the first meta-analysis of RCTs systematically evaluating the association between GLP-1RAs and risk of VTE. A further strength is the ability to identify granular data on adverse events from all studies in ClinicalTrials.gov, providing confidence in event ascertainment. However, there are also some limitations for this study. First, DVT or PE events were not the predefined outcomes in these RCTs, so that the number of DVT or PE are likely underestimated. Second, given the low incidence of VTE in these RCTs, the study might be underpowered to detect that difference as significant. Third, considering that DVT or PE were not reported in quite a few trials, the potential publication bias cannot be fully excluded, although neither funnel plot nor statistical testing detected significant publication bias.

To date, the potential risk of VTE associated with GLP-1RAs use remains largely unexplored. Given the severity of VTE and the increasingly widespread use of GLP-1RAs,[4] the public health impact of the excess risk of DVT deserves careful scrutiny and requires further investigation. Researchers should pay more attention and fully report VTE events in clinical studies regarding GLP-1RAs and make them one of the predefined safety end points. More importantly, clinicians should carefully monitor patients who receive GLP-1RAs and present with predisposing factors of DVT, especially for those who are expected to use GLP-1RAs for a long period. Despite that GLP-1RAs increased relative risk of DVT, the low incidence and small increase in absolute risk of DVT (25 cases per 10 000 people per year) should be weighed against the benefits of GLP-1RAs in clinical practice.

CONCLUSIONS

Our findings suggest that GLP-1RAs might increase the risk of DVT, especially for the long-term use of GLP-1RAs. These findings deserve our concerns regarding the risk of DVT attributed to GLP-1RAs along with the increasingly widespread use of GLP-1RAs and provide a reference for clinicians in prescribing GLP-1RAs, which might aid in the continued development of clinical guidelines for the use of GLP-1RAs. VTE events deserve more attention, and sufficient report should be encouraged in the future investigations.

ARTICLE INFORMATION

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Author contributions: Huabing Zhang Yuxiu Li, Yiwen Liu, and Liyun He conceived and designed the study. Yiwen Liuand Liyun He performed the relevant literature searches. Yiwen Liu, Liyun He, Shumeng Han, Huabing Zhang, and Yuxiu Liscreened the articles for inclusion. Yiwen Liu, Liyun He, Fan Ping, and Lingling Xu extracted the data for analysis. Yiwen Liu, Huabing Zhang, and Yuxiu Liwere involved in the quality assessment of the eligible studies. Yiwen Liuand Huabing Zhang performed the meta-analysis and produced forest plots and summary results under the supervision of Huabing Zhang and Yuxiu Li. Yiwen Liu, Huabing Zhang, and Yuxiu Lidrafted the article. Shumeng Han, Fan Ping, Wei Li, Lingling Xu, Huabing Zhang, and Yuxiu Licritically revised the article for important intellectual content. All authors approved the final article. Huabing Zhang had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author (Huabing Zhang) attests that all listed authors meet the authorship criteria and that no others who meet the criteria have been omitted.

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Disclosures

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Supplemental Material

Tables S1–S4
Figures S1–S28

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