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Impact of glucagon-like peptide-1 receptor agonism-based therapies on limb outcomes in peripheral artery disease and type 2 diabetes: An updated systematic review and meta-analysis

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Abstract

Aims: Glucagon-like peptide-1 receptor agonism (GLP1RA)-based therapies (GLP1RA-BTs) form the cornerstone for managing type 2 diabetes (T2D) and obesity. However, their impact on limb-specific outcomes in peripheral artery disease (PAD) remains unclear. This systematic-review and meta-analysis evaluated the safety and efficacy of GLP1RA-BTs on limb outcomes in PAD and T2D.

Materials and methods: Electronic databases were searched for studies involving GLP1RA-BTs in PAD and/or T2D. Primary outcome was the major adverse limb events (MALEs). Secondary outcomes were all-cause mortality, revascularization, amputation, major adverse cardiovascular events (MACE), cardiovascular mortality, myocardial infarction (MI), stroke, hospitalization for heart-failure (HHF), and amputations. Analyses were performed separately for studies exclusively enrolling patients with PAD (PAD cohort) and for those in broader T2D populations reporting limb outcomes but not limited to PAD, in which PAD comprised <15% of participants (T2D cohort).

Results: Data from 10 studies for PAD cohort (352 743 patients) and 7 studies for T2D cohort (1 759 799 patients) were analysed. In PAD cohort, MALE [OR 0.66 (0.44, 1.00); $p = 0.05$; $I^2 = 94\%$], all-cause mortality [OR 0.55 (0.38, 0.78); $p = 0.0008$; $I^2 = 97\%$], MACE [OR 0.68 (0.52, 0.88); $p = 0.004$; $I^2 = 85\%$], and MI [OR 0.68 (0.51, 0.91); $p = 0.009$; $I^2 = 42\%$] were lower in patients on GLP1RA-BTs compared to controls. In the PAD cohort, need for revascularization was significantly lower in GLP1RA-BTs than in controls [OR 0.85 (0.80, 0.90); $p < 0.001$; $I^2 = 0\%$]. In

Deep Dutta and Kunal Mahajan contributed equally to this study and should be considered as joint first authors.

the T2D cohort, MALE [OR 0.70 (0.57, 0.85); $p = 0.0005$; $I^2 = 0\%$], amputations [OR 0.58 (0.48, 0.69); $p < 0.001$; $I^2 = 0\%$], and all-cause mortality [OR 0.55 (0.43, 0.69); $p < 0.001$; $I^2 = 85\%$] were significantly lower in GLP1RA-BT compared to controls.

Conclusions: GLP1RA-BTs are beneficial in PAD, especially in reducing the need for revascularization.

KEYWORDS

cardiovascular outcomes, liraglutide, peripheral artery disease, semaglutide, tirzepatide

1 | INTRODUCTION

Glucagon-like peptide-1 receptor (GLP1R) agonism-based therapies (GLP1RA-BTs) include the GLP1R agonists (GLP1RAs) (exenatide, liraglutide, dulaglutide, semaglutide, albiglutide, lixisenatide, among others) and twincretins [GLP1R and glucose-dependent insulinotropic polypeptide (GIP) dual agonists; tirzepatide] have established themselves for their anti-hyperglycaemic, weight loss, cardiovascular, and nephron-protective properties.[1,2] Peripheral artery disease (PAD) is a common but often unrecognised and untreated condition in people living with type 2 diabetes (T2D) and obesity.[3] Sodium–glucose co-transporter-2 inhibitors (SGLT2Is) are another class of medicine with proven anti-diabetes, mild weight-loss, cardiovascular, heart failure, and nephroprotective properties. However, SGLT2Is, specifically canagliflozin, have potential safety issues when used in patients with PAD.[4] The impact of GLP1R-BTs on limb-specific outcomes in PAD remains unclear.

A few randomized controlled trials (RCTs) have been published evaluating the role of GLP1R-BTs in PAD.[5,6] A recently published systematic review and meta-analysis (SR/MA) by Shuja et al. evaluating the use of GLP1RAs on cardiovascular outcomes in people with PAD noted a significant reduction in all-cause mortality and major adverse cardiovascular events (MACE), without any impact on major adverse limb events (MALEs).[7] Shuju et al. analysed MALEs outcome data from only two studies on people living with PAD.[7] Also, this SR/MA analysed data limited to GLP1RAs and did not look into the impact of tirzepatide on PAD.[7] Since this SR/MA was conducted,[7] many studies have been published examining the effects of GLP1R-BTs on PAD.[5,8,9] Garagoli et al. recently published an SR/MA examining MALEs treated with GLP1RAs in T2D.[10] This was not an exhaustive meta-analysis of all RCTs on the use of GLP1RAs in T2D, as only six RCTs were included in this SR/MA, and the authors noted that GLP1RAs were associated with fewer PAD-related clinical events.[10] A few more SR/MAs have been published on this topic, but it is hard to interpret their results because limb-related outcomes were studied in a cohort where only a tiny fraction had PAD.[11–13] The key outcomes and limitations of previously published SR/MAs are summarized in Table 1.

We need to recognize that we have two main questions to answer. First, do GLP1RA-BTs improve limb outcomes in people with established PAD (tertiary prevention)? Second, are GLP1RA-BTs helpful in improving limb outcomes for people with T2D and atherosclerotic cardiovascular disease (ASCVD) who are at very high risk of developing PAD (secondary prevention)? No SR/MA has been published, primarily looking into the limb-specific outcomes (MALEs, amputation, and walking distance) of GLP1RA-BTs in people with established PAD (PAD cohort), and separately in people with T2D with ASCVD (high risk of having PAD) (T2D cohort), without mixing of the studies. Hence, the goal of this SRMA was to evaluate the safety and efficacy of GLP1RA-BTs on limb-specific outcomes in PAD and T2D.

2 | METHODS

The recommendations of the Cochrane Handbook for Systematic Reviews of Interventions were followed in this SR/MA, which was registered with a predefined protocol in PROSPERO (CRD420251168219).[17] This meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17] Since ethical approval already exists for the individual studies, no separate approval was required for this SRMA.

2.1 | Search strategy

We conducted an extensive literature search across databases, including PubMed, Ovid Embase, Ovid Medline, Cochrane Library, ClinicalTrials.gov, CNKI, and Google Scholar. All studies published up to 1 November 2025 were examined. The search strategy utilized combinations of key terms such as "exenatide," "liraglutide," "dulaglutide," "semaglutide," "albiglutide," "lixisenatide," "efpeglenatide," "glucagon-like peptide-1 receptor agonist," "glp1 agonist," "twincretin," "tirzepatide" along with "peripheral artery disease," "peripheral vascular disease," "amputation," "walking distance," "diabetes," "type-2 diabetes" using appropriate Boolean search operators "AND" and "OR." Additionally, reference lists of relevant studies were reviewed to identify further publications.

TABLE 1 Summary of previous systematic reviews and meta-analyses assessing GLP-1RA-BT and PAD-related outcomes.

Study (year)	Design/data sources	Population and inclusion	Drugs/ comparators	Primary outcomes	Key findings	Limitations/gaps
Shuja et al.[7]	Meta-analysis of 4 RCTs	PAD + T2D subgroups ($n \approx 6800$)	GLP-1RA vs. placebo	MACE, CV death, MI, stroke	↓ MACE (RR 0.86 [0.76–0.98]); no effect on mortality or stroke	Included only CVOTs; no MALE or limb outcomes
Lin, 2025[14]	Large network meta-analysis (26 RCTs; 151 789 pts)	ASCVD phenotypes (CAD, PAD, HF, CKD)	GLP-1RA vs. SGLT2i vs. placebo	MACE by phenotype	GLP-1RA ↓ MACE in PAD (RR 0.86 [0.76–0.98])	No limb/MALE data; PAD subgroup under-powered
Cimellaro, 2024[15]	Systematic review (narrative; all agents)	T2D + PAD any stage	GLP-1RA, SGLT2i, DPP-4i, metformin	MACE, MALE	GLP-1RA and SGLT2i best for CV risk reduction	Narrative only; no quantitative pooling
Ashraf et al.[12]	Meta-analysis of RCTs and RWE on MALE	PAD + T2D (subgroup analyses)	GLP-1RA vs. placebo/others	MALE, LEA risk	GLP-1RA ↓ MALE (OR 0.78); neutral on major LEA	Limited studies; variable MALE definitions
Gargoli, 2025[10]	Network meta-analysis of ≥10 CVOTs	T2D with ASCVD ± PAD (~12% PAD)	GLP-1RA vs. SGLT2i vs. DPP-4i	MACE, HF hospitalization, renal outcomes	GLP-1RA >DPP-4i for MACE; neutral vs. SGLT2i	Did not isolate PAD subgroup; mixed ASCVD cohorts
Caruso, 2022[16]	Systematic review ± meta-analysis of limb outcomes	T2D with/ without PAD	GLP-1RA, SGLT2i, DPP-4i	LEA, revascularization events	GLP-1RA ↓ amputation vs. DPP-4i; trend vs. SGLT2i	Combined RWE + RCT; PAD trials not separated
Lu, 2023[11]	Meta-analysis of antidiabetic classes and LEA	General T2D (~6% PAD)	GLP-1RA vs. SGLT2i vs. others	Amputation risk	Neutral for GLP-1RA vs. control; SGLT2i ↑ LEA risk	PAD under-represented; crude outcomes
Du et al.[13]	Pairwise + network meta-analysis (RWE + RCTs)	General T2D (3–8% PAD)	GLP-1RA vs. SGLT2i vs. DPP-4i vs. others	Amputation risk	No increased amputation with GLP-1RA; signal with canagliflozin only	Not PAD-focused; RWE heterogeneity; no MALE definition

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA-BT, glucagon-like peptide-1 receptor agonism-based therapies; HF, heart failure; LEA, lower-extremity amputation; MALE, major adverse limb event; MACE, major adverse cardiovascular event; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; pts, patients; RCT, randomized controlled trial; RR, risk ratio; RWE, real-world evidence; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; GLP1RA, glucagon-like peptide-1 receptor agonist.

2.2 | Eligibility criteria

The PICOTT criteria were utilized to screen and select the studies. The population (P) included patients with PAD and/or T2D. The intervention (I) consisted of the use of GLP1RA-BTs in addition to the background standard therapy for managing PAD and/or T2D. The control (C) group consisted of patients receiving standard therapy with or without a placebo in place of GLP1RA-BTs for PAD and/or T2D. The outcomes (O) focused on changes in major adverse limb events (MALEs), all-cause mortality, need for revascularization, amputation, major adverse cardiovascular events (MACE), cardiovascular mortality, myocardial infarction (MI), stroke, hospitalization for heart failure, and occurrence of gangrene. The type of question (T) referred to the interventional (treatment outcome) meta-analysis conducted. The type of studies (T) referred to RCTs and/or observational studies (OS) (cohort and case–control). Cross-sectional studies, case reports, case series, reviews, expert opinions, editorials, letters to the editor, and duplicate reports were excluded from the analysis. Duplicates were removed before screening articles by title and abstract, followed by full-text screening to confirm eligibility.

2.3 | Study outcomes

The primary outcome was the impact on MALEs. Secondary outcomes were impacts on all-cause mortality, need for revascularization, amputation, MACE, cardiovascular mortality, MI, stroke, hospitalization for heart failure, and occurrence of gangrene. Analyses were conducted separately for studies exclusively enrolling patients with established peripheral artery disease (defined as the "PAD cohort" or tertiary-prevention cohort) and for studies performed in broader type 2 diabetes populations that reported limb outcomes but were not limited to PAD, in which individuals with PAD comprised less than 15% of participants (defined as the "T2D cohort" or secondary-prevention cohort).

2.4 | Study selection

Two authors independently screened the titles and abstracts of the studies identified. The full text was reviewed for eligibility if a study could not be excluded solely based on the title and abstract. Any

disagreements about the study's eligibility were settled by consulting a third author. Only studies that fulfilled the above PICOTT criteria and had at least one of the three outcomes (MALE, amputation, or walking distance) were analysed.

2.5 | Data synthesis

The data analysis focused on prespecified outcomes in two groups: patients on GLP1RA-BTs (intervention group) and patients not on GLP1RA-BTs (control group). The Review Manager online software (RevMan Web) version 9.14.0 (Cochrane Collaboration UK, 2025) was used for statistical analysis and the creation of forest plots. Pooled effect estimates of the primary and secondary outcomes, expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs), were calculated. Random-effects models were selected to address expected heterogeneity arising from variations in population characteristics and study duration. The inverse-variance statistical method was used in all instances. CI calculated by the Wald-type method. Tau^2 was estimated by the Restricted Maximum-Likelihood method. Heterogeneity was assessed using the prediction interval and Higgin's I^2 test. Thresholds for I^2 values were defined as follows: 25% for low heterogeneity, 50% for moderate heterogeneity, and 75% for high heterogeneity.[18] When a meta-analysis showed significant heterogeneity among studies, the prediction interval was used to estimate the potential variation in effect sizes across future studies. A prediction interval analysis helps us understand the extent of variability across different study populations, potentially highlighting limitations of the current analysis.[19] A p-value <0.05 was considered statistically significant.

2.6 | Methodological quality and certainty of evidence

Two independent reviewers carefully evaluated the risk of bias in the included studies. The Cochrane Risk of Bias Tool, version 2 (ROB2) was used to assess potential biases in RCTs, concentrating on key areas such as randomization procedures, deviations from intended interventions, incomplete outcome data, measurement of outcomes, and selective reporting.[20] For non-randomized studies, the Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) tool was employed to assess risk of bias.[21]

3 | RESULTS

An initial search revealed 215 articles. Eleven duplicates were removed. After reviewing the title and abstract, the search was down to 22 articles. Finally, 17 articles that met our inclusion and exclusion criteria were included in our analysis (Figure 1). These included 10 studies (five RCTs and five OS; 352 743 patients) which evaluated limb outcomes in people with PAD (tertiary prevention cohort), and data from these studies have been analysed and presented separately.[5–9,22–27] The limb outcomes analysed specifically in patients with PAD from the two major cardiovascular outcomes trials on liraglutide [LEADER (NCT01179048)] and semaglutide [SUSTAIN 6 (NCT01720446)] were published separately by Verma et al., which was used in our analysis.[28] In the retrospective cohort study by Hong et al., the lower extremity complications with GLP1RA-BT was compared separately with SGLT2Is and dipeptidyl peptidase-4 inhibitors (DPP4i).[27] In our analysis with have used the data comparing limb outcomes of GLP1RA-BT to SGLT2Is.[27]

Also, data from eight different cohorts of patients from seven observational studies (1 759 799 patients), which evaluated the limb outcomes in people with T2D having <15% people with PAD (T2D cohort/secondary prevention cohort), have been analysed separately.[29–35] The study by Baviera et al. presented data from two different cohorts of patients from Italy; hence, their results have been analysed separately as Baviera 2021 (OS Italy Apulia) and Baviera 2021 (OS Italy Lombardy), respectively.[35] The profiles of the patients in the studies analysed under the PAD cohort and T2D cohort have been elaborated in Table 2 and Table S1, Supporting Information, respectively. The studies that were excluded because they did not fulfil the inclusion criteria of our study—specifically, they did not evaluate limb-specific outcomes—have been elaborated in Table S2 (five studies). These included the studies by Perkovic et al. (FLOW trial),[36] Gerstein et al. (AMPLITUDE-O trial),[37] Zinman et al. (SUSTAIN-9),[38] Hernandez et al. (HARMONY trial),[39] and Pfeffer et al. (ELIXA trial).[40]

3.1 | Risk of bias in the included studies

The summaries of risk of bias for the five RCTs analysed in this SR/MA have been elaborated in Figure S1 using the ROB2 tool. The risk of bias was low in all the RCTs analysed (Figure S1). The risk of bias was low in the non-RCTs (observational studies) included in this SRM, as assessed using the ROBINS-I tool (Figure S2).

3.2 | Peripheral artery disease cohort (tertiary prevention cohort)

3.2.1 | Primary outcomes

Data from six studies (268 973 patients) were analysed to find the impact of GLP1RA-BTs on MALE in PAD. MALE was significantly lower in patients who received GLP1RA-BTs as compared to controls in people with PAD [OR 0.66 (95%CI: 0.44, 1.00); $p = 0.05$; $I^2 = 94\%$; Figure 2A]. However, the significance was lost in the prediction interval analysis due to substantial data heterogeneity, leading to a wider CI [0.25, 1.75].

3.2.2 | Secondary outcomes

Data from eight studies (274 763 patients) were analysed to find the impact of GLP1RA-BTs on all-cause mortality in PAD. All-cause

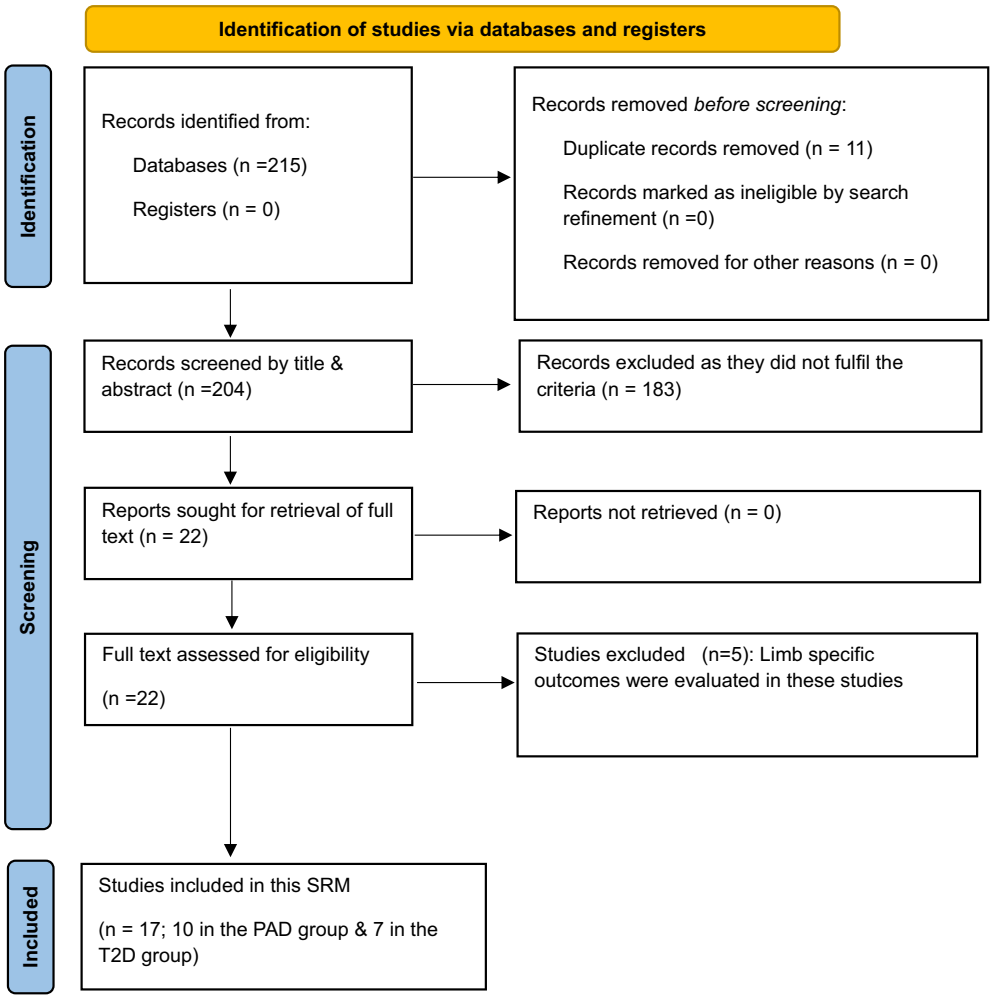

FIGURE 1 Flowchart elaborating on study retrieval and inclusion in this systematic review and meta-analysis. SRM, systematic review and meta-analysis; PAD, peripheral artery disease; T2D, type 2 diabetes.

mortality was significantly lower in patients who received GLP1RA-BTs as compared to controls in people with PAD [OR 0.55 (95%CI: 0.38, 0.78); $p = 0.0008$; $I^2 = 97\%$; Figure 2B]. However, the significance was lost in the prediction interval analysis due to significant data heterogeneity, leading to a wider CI [0.22, 1.35].

Data from six studies involving 262 220 patients were analysed to assess the impact of GLP1RA-BTs on the need for revascularization in PAD. Need for revascularization was significantly lower in patients who received GLP1RA-BTs compared with controls in people with PAD [OR 0.85 (95%CI: 0.80, 0.90); $p < 0.001$; $I^2 = 0\%$; Figure 2C], and this effect persisted in the prediction interval analysis due to low heterogeneity [0.80, 0.90].

Data from five studies (262 330 patients) were analysed to find the impact of GLP1RA-BTs on the need for amputation in PAD. Need for amputation was not significantly different in patients who received GLP1RA-BTs as compared to controls, in people with PAD [OR 0.74 (95%CI: 0.54, 1.02); $p = 0.07$; $I^2 = 90\%$; Figure 2D].

Data from six studies (122 899 patients) were analysed to find the impact of GLP1RA-BTs on MACE in PAD. MACE was significantly lower in patients who received GLP1RA-BTs compared with controls, in people with PAD [OR 0.68 (95%CI: 0.52, 0.88); $p = 0.004$; $I^2 = 85\%$; Figure 2E]. However, the significance was lost on prediction interval analysis due to the presence of significant data heterogeneity, leading to a further spread of the CI [0.38, 1.21].

Data from four studies (4771 patients) were analysed to find the impact of GLP1RA-BTs on cardiovascular deaths in PAD. GLP1RA-BTs had no additional impact on cardiovascular death as compared to controls, in people with PAD [OR 0.87 (95%CI: 0.69, 1.11); $p = 0.26$; $I^2 = 0\%$; Figure 2F].

Data from five studies (12 817 patients) were analysed to find the impact of GLP1RA-BTs on MI and stroke in PAD. MI was significantly lower in patients who received GLP1RA-BTs as compared to controls, in people with PAD [OR 0.68 (95%CI: 0.51, 0.91); $p = 0.009$; $I^2 = 42\%$; Figure 3A]. However, the significance was lost on prediction interval analysis due to the presence of moderate data heterogeneity, leading to a further spread of the CI [0.42, 1.11]. GLP1RA-BTs had no additional impact on stroke as compared to controls, in people with PAD [OR 0.67 (95%CI: 0.39, 1.17); $p = 0.16$; $I^2 = 72\%$; Figure 3B]. Data from three studies (4447 patients) were analysed to find the impact of GLP1RA-BTs on hospitalization for heart failure in PAD. Patients on GLP1RA-BTs tended to have a lower need for hospitalization for heart failure, which was however, statistically not significant [OR 0.77 (95%CI: 0.58, 1.03); $p = 0.08$; $I^2 = 2\%$; Figure 3C]. Data from three studies (147 201 patients) were analysed

TABLE 2 Included studies with peripheral artery disease and type 2 diabetes reporting limb-related outcomes.

Study (year)	Study type	Design and population	Intervention/ comparator	Sample size	Duration	Primary endpoint	Main findings	Remarks/comments
Caruso et al. (STARDUST)[22]	Prospective, open-label RCT	T2D + PAD ($TcPO_2$ 30–49 mmHg)	Liraglutide ≤1.8 mg/ day vs. standard care	55 (≈27 per arm)	18 months	$TcPO_2$, angiogenic and inflammatory markers	↑ $TcPO_2$ by +10.9 mmHg; ↓ CRP and IL-6; ↑ VEGF and EPCs	Demonstrated microvascular and anti-inflammatory benefits
Bonaca et al. (STRIDE)[6]	Double-blind RCT	T2D + symptomatic PAD	Semaglutide 1 mg weekly vs. placebo	792 (396 per arm)	52 weeks	Treadmill walking distance	↑ Walking distance by 13% ($p = 0.0004$) vs. placebo	Demonstrated functional improvement with GLP-1RA
Caruso et al. (Sema OS) (SMILE)[9]	Retrospective real-world cohort	T2D + PAD or foot ulcers	Semaglutide (oral or SC) vs. other agents	334 (167 + 167 matched)	≈30 months	Major limb events (PTA/CLI)	HR 0.77 (95%CI: 0.61–0.97); LEA ↓ by 50%	Real-world support for limb protection with semaglutide
Go et al. (TriNetX OS)[8]	Multicentre observational, propensity-matched study	PAD (ABI 0.4–0.9) ± T2D	Any GLP1RA vs. no GL1RA	110 082 (55 041 + 55 041)	1 year	MACE and MALE	↓ Mortality (1.7 vs. 4.4%); ↓ MACE HR 0.87; ↓ MALE HR 0.57	Large database confirming CV and limb benefits class-wide
Wu et al.[5]	Real-world, propensity-matched cohort	T2D + PAD from TriNetX database	Tirzepatide vs. non-users	8046 (4023 + 4023)	12 months	MALE, mortality, MACE	HR 0.44 (95%CI: 0.33–0.59); ↓ mortality, stroke, MACEs	First dual GIP/GLP-1 agent reducing limb events
Yehualashet et al.[26]	Multicentre retrospective registry	PAD post-revascularization (surgical or endovascular)	GLP1RA users (semaglutide, liraglutide, dulaglutide) vs. non-users	1226 (613 + 613 matched)	2 years	Composite of re-intervention, MALE, or mortality	HR 0.68 (95%CI: 0.50–0.92); amputation ↓ by 45%	Extends GLP-1RA limb benefit to post-surgical PAD population
Verma et al.[28] (LEADER and SUSTAIN-6) (Marso et al.[24] and Marso et al.[25])	Post hoc analysis of two CVOTs	T2D ± PAD subgroups	Liraglutide ≤1.8 mg/ day or Semaglutide 0.5–1 mg/week vs. placebo	1644 (1184 + 460)	2.1–3.8 years	MACE	Liraglutide HR 0.77; Semaglutide HR 0.61; consistent across PAD status	GLP1RA reduce MACE in PAD subgroups. In SUSTAIN 6, expanded MACE included peripheral revascularization
Badjatiya et al. (EXSCEL)[23]	Post hoc analysis of RCT	T2D ± PAD from EXSCEL CV outcomes trial	Exenatide 2 mg weekly vs. placebo	14 752 (2800 with PAD)	3.2 years	MACE and LEA	No difference in MACE or LEA with exenatide vs. placebo	Early GLP-1RA neutral for CV and limb outcomes; PAD linked with higher mortality and amputation
Hong et al. (OS USA)[27]	Real-world, propensity-matched retrospective cohort study	U.S. Network within TriNetX Analytics platform (May 2013–January 2025)	GLP1RA vs. SGLT2i; GLP-1RA vs. DPP4i	GLP1RA ($n = 99\,056$) SGLT2i ($n = 116\,756$) DPP4i ($n = 45\,333$)	3 years follow-up	Major amputation (MA), lower extremity revascularization and mortality	GLP1RA lower risks of MA and mortality wrt SGLT2i	Similar reductions WITH GLP1RA was seen versus DPP4i

Abbreviations: ABI, ankle–brachial index; CI, confidence interval; CLI, critical limb ischemia; CRP, C-reactive protein; CV, cardiovascular; CVOT, cardiovascular outcomes trial; T2D, type 2 diabetes; EPC, endothelial progenitor cell; GLP1RA, glucagon-like peptide-1 receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor; DPP4i, dipeptidyl peptidase 4 inhibitor; HR, hazard ratio; IL-6, Interleukin-6; LEA, lower extremity amputation; MACE, major adverse cardiovascular event; MALE, major adverse limb event; PAD, peripheral artery disease; PTA, percutaneous transluminal angioplasty; RCT, randomized controlled trial; SC, subcutaneous; $TcPO_2$, transcutaneous oxygen pressure; VEGF, vascular endothelial growth factor; wrt, with regards to.

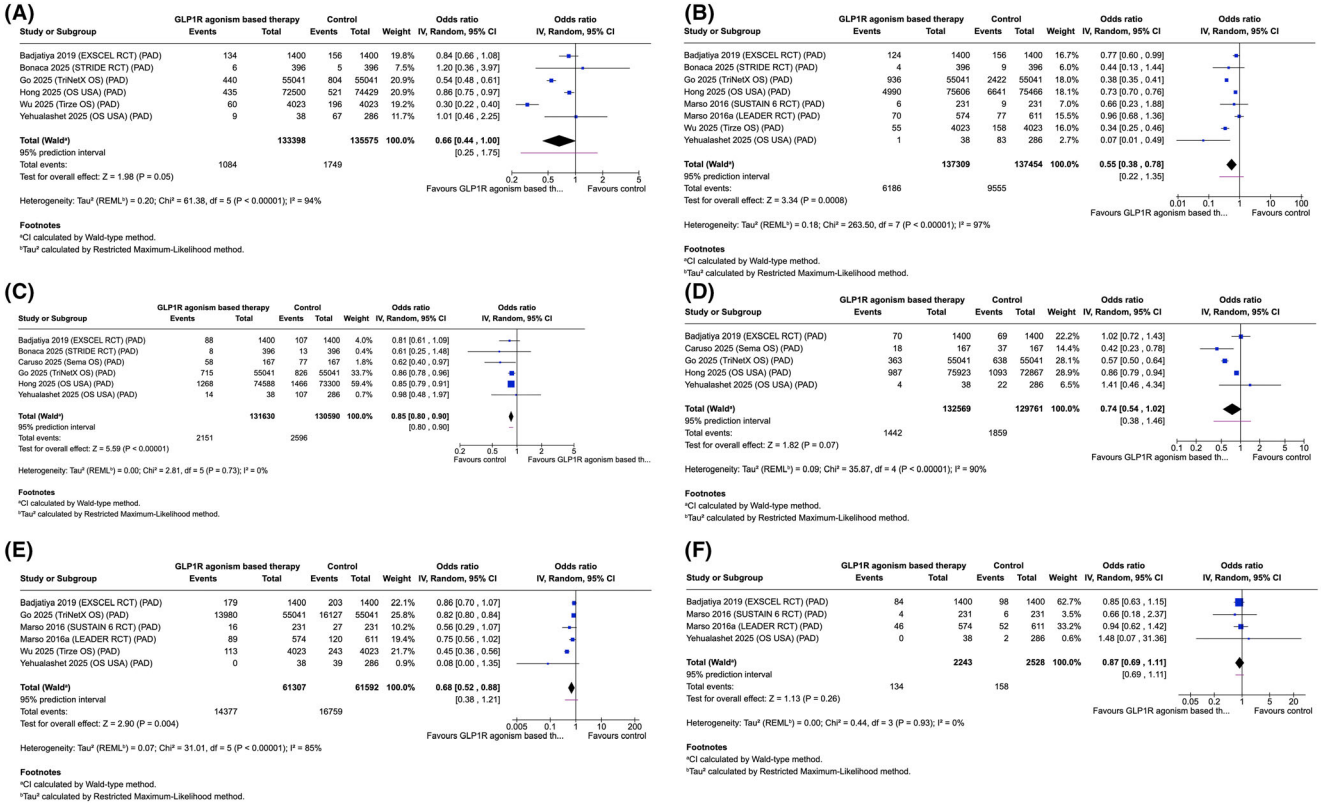

FIGURE 2 Impact of glucagon-like peptide-1 receptor agonism-based therapies in peripheral artery disease (PAD) on (A) major adverse limb events, (B) all-cause mortality, (C) need for revascularization, (D) need for amputation, (E) major adverse cardiovascular events (MACE), and (F) cardiovascular mortality.

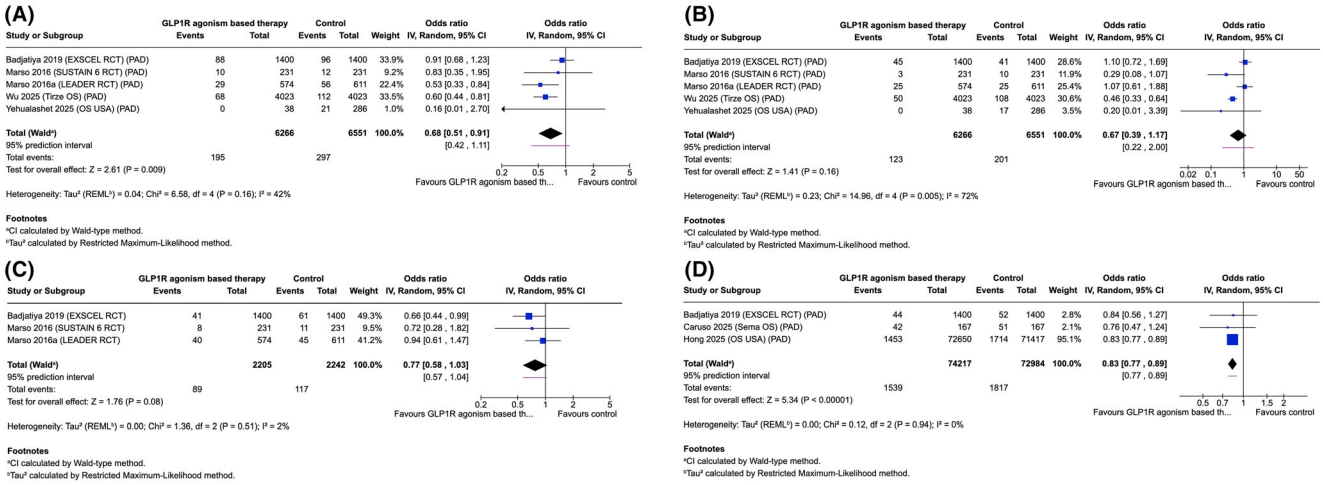

FIGURE 3 Impact of glucagon-like peptide-1 receptor agonism-based therapies in peripheral artery disease (PAD) on (A) myocardial infarction (MI), (B) stroke, (C) hospitalization for heart failure, and (D) gangrene.

to find the impact of GLP1RA-BTs on gangrene in PAD. The occurrence of gangrene was significantly lower in patients on GLP1RA-BTs compared to controls [OR 0.83 (95%CI: 0.77, 0.89); $p < 0.0001$; $I^2 = 0\%$; Figure 3D], which persisted on prediction interval analysis due to low data heterogeneity.

3.3 | Type 2 diabetes cohort (high risk of PAD cohort/secondary prevention cohort)

In people with T2D, MALE [OR 0.70 (95%CI: 0.57, 0.85); $p = 0.0005$; $I^2 = 0\%$; Figure 4A], amputations [OR 0.58 (95%CI: 0.48, 0.69);

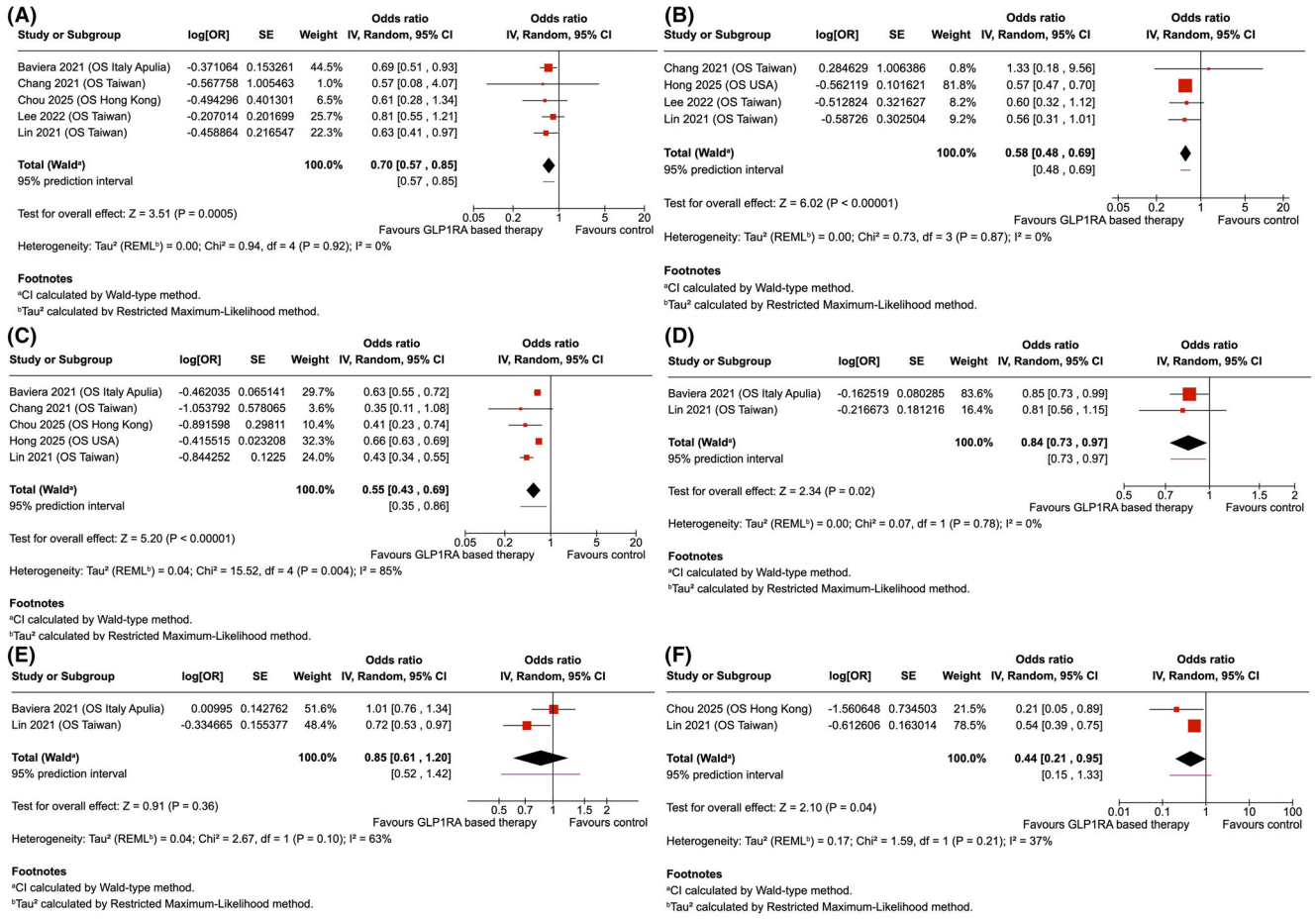

FIGURE 4 Impact of glucagon-like peptide-1 receptor agonism-based therapies in people with type-2 diabetes on (A) major adverse limb events, (B) amputations, (C) all-cause mortality, (D) hospitalization for heart failure, (E) stroke, and (F) cardiovascular mortality.

$p < 0.001$; $I^2 = 0\%$; Figure 4B], all-cause mortality [OR 0.55 (95%CI: 0.43, 0.69); $p < 0.001$; $I^2 = 85\%$; Figure 4C], and hospitalization for heart failure [OR 0.84 (95%CI: 0.73, 0.97); $p = 0.02$; $I^2 = 0\%$; Figure 4D] were significantly lower in patients who received GLP1RA-BTs compared to controls. In people with T2D, the occurrence of stroke was comparable between patients who received GLP1RA-BTs and controls [OR 0.85 (95%CI: 0.61, 1.20); $p = 0.36$; $I^2 = 63\%$; Figure 4E]. In people with T2D, cardiovascular mortality [OR 0.44 (95%CI: 0.21, 0.95); $p = 0.04$; $I^2 = 37\%$; Figure 4F] was lower in patients who received GLP1RA-BTs compared to controls. The significance was lost in the prediction interval analysis due to moderate data heterogeneity, leading to a wider CI [0.15, 1.33].

4 | DISCUSSION

The potential mechanism of the vasculo-protective effects of GLP1RA-BTs is multifactorial and includes reduction in endothelial dysfunction through enhanced endothelial nitric oxide (NO) production, through activation of endothelial NO synthase, leading to reduced vascular stiffness and increased vascular relaxation.[41] GLP1RA-BTs reduce systemic inflammation through reduced circulating levels of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein, which contribute to plaque stabilization and reduced risks of plaque rupture.[42] This class of medicines, through their beneficial impact on blood pressure, lipid parameters, downregulating plasminogen activator inhibitor type 1 (PAI-1) and vascular adhesion molecule, downregulation of the NLRP3 inflammasome complex, and peroxisome proliferator-activated receptor gamma (PPARγ) also exert their anti-atherosclerotic properties.[3]

Our analysis of data from patients with established PAD (tertiary prevention cohort) showed that GLP1RA-BTs may reduce MALE, all-cause mortality, MACE, and myocardial infarction. However, the statistical significance of the benefit was lost due to heterogeneity in the data. There was a trend towards the benefit of use of GLP1RA-BTs in PAD on amputation and reducing hospitalization for heart failure. GLP1RA-BTs significantly reduced the need for revascularization therapy in PAD, a benefit that persisted in prediction-interval analysis, highlighting the therapeutic benefit of this class of therapy in PAD. In people with T2D, use of GLP1RA-BTs was associated with a significant reduction in MALE, amputations, all-cause mortality, and hospitalization for heart failure. Our analysis suggests that GLP1RA-BTs confer greater relative benefit on limb outcomes when used in patients with T2D than in those with established PAD. This pattern may reflect the enhanced vasculo-protective and anti-inflammatory effects of GLP1RA-BTs when initiated earlier in the atherosclerotic

process, before fixed structural and microvascular damage has occurred. In advanced PAD, where arterial remodelling and occlusive changes are largely irreversible, the capacity of GLP1RA-BTs to modify disease progression may be attenuated. Prior studies have shown that GLP1RA-BTs reduce the risk of stroke for both secondary and potentially primary prevention.[43] However, in our study, the GLP1RA-BTs did not achieve statistical significance for stroke reduction in either the PAD cohort or the T2D cohort. This difference can be explained because the analysed studies were not powered to look at the stroke outcomes. The total number of studies available for analysis and the actual number of stroke events were small.

The strength of our analysis in people with established PAD is that five of the eight analysed studies were RCTs, having a low risk of bias. In contrast, our analysis in the T2D cohort (secondary prevention cohort) came from seven OS, with none of the studies being RCTs. Observational studies have their limitations of their inherently associated bias. Limitations of this SRM include that data from different molecules in the class of GLP1RA-BTs were analysed together. Individual drug analysis was not possible due to the paucity of data. Pooling data from different drugs together may have contributed to the data heterogeneity.

5 | CONCLUSION

This systematic review and meta-analysis demonstrates that GLP1RA-BTs are associated with meaningful reductions in adverse limb events, revascularization, and all-cause mortality among patients with diabetes and peripheral artery disease. The benefit appears greater when therapy is initiated earlier in the disease course, suggesting a preventive vascular effect beyond glycaemic control. These findings support the incorporation of GLP1RA-BTs into comprehensive secondary and tertiary prevention strategies for patients with diabetes at risk for or living with PAD, and underscore the need for prospective outcome trials specifically designed for limb protection.

AUTHOR CONTRIBUTIONS

The study was conceptualized by DD and KM. Literature search was done by DD, KM, NM, MS, and SV. Data entry was done by DD, ABMKH, MS, and KM. Analysis was done by DD and ABMKH. NM, MS, and SV critically reviewed the manuscript for important intellectual content. All authors contributed equally to manuscript preparation. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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