

Safety and efficacy of Glucagon-Like Peptide 1 Receptor Agonist and Sodium Glucose Transporter 2 inhibitor on major limb adverse events and mortality in peripheral artery disease and diabetes

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Abstract

Background

Current guidelines recommend both Glucagon-Like-Peptide 1 receptor agonists (GLP1-RAs) and Sodium-glucose-transporter 2 inhibitors (SGLT2i) for patients with type 2 diabetes and atherosclerotic cardiovascular disease. Patients with peripheral artery disease (PAD) and diabetes are at particularly high risk of major adverse limb events (MALE), amputation, and mortality. While both drug classes have demonstrated cardiovascular benefits, real-world evidence regarding the safety and effectiveness of their combined use in PAD, particularly with respect to limb outcomes and mortality, remains limited.

Methods

We conducted a retrospective observational cohort study using the Clalit Health Services electronic medical record database. Patients with PAD and diabetes from 2015 to 2026 were classified into four groups: neither GLP1-RA nor SGLT2i, GLP1-RA alone, SGLT2i alone, and both GLP1-RA/SGLT2i therapy. Outcomes included MALE, limb revascularization, major and minor amputation, and all-cause mortality. Multinomial propensity scores and stabilized inverse probability of treatment weighting were used to balance baseline covariates, and weighted Cox models were used to estimate hazard ratios.

Results

The cohort included 13,471 patients. Median follow-up was 5.75 years for MALE and 4.42 years for mortality. Compared with neither treatment, combined therapy was associated with lower hazards of MALE (HR, 0.50; 95% CI, 0.33–0.75), major amputation (HR, 0.30; 95% CI, 0.17–0.53), and all-cause mortality (HR, 0.23; 95% CI, 0.19–0.28). SGLT2i monotherapy was also associated with reduced MALE, major amputation, and mortality, while GLP1RA monotherapy was associated with lower mortality; limb-specific estimates were limited by smaller subgroup size and event numbers.

Conclusions

Among patients with PAD and diabetes, treatment with GLP1-RA and SGLT2i was associated with lower MALE and mortality. SGLT2i showed the same trends. GLP1RA monotherapy showed a survival benefit, while its limb-specific associations should be interpreted with caution, given the limited subgroup size and event numbers.

Research Insights

What is currently known about this topic?

PAD with diabetes carries high limb-event and mortality risk.

GLP1-RAs and SGLT2is reduce cardiovascular risk in diabetes.

Combined limb-outcome data in PAD remain limited.

What is the key research question?

Are GLP1-RA/SGLT2i therapies linked to lower MALE and mortality in PAD and diabetes?

What is new?

This cohort included 13,471 patients with PAD and diabetes.

Combined therapy was linked to lower MALE, major amputation, and mortality.

SGLT2i showed favorable limb safety; GLP1-RA mainly showed survival benefit.

How might this study influence clinical practice?

Findings support considering dual therapy in eligible patients with PAD and diabetes.

Background

Peripheral artery disease (PAD) is a severe manifestation of systemic atherosclerosis that disproportionately affects individuals with diabetes (1). The coexistence of diabetes and PAD significantly amplifies the risk of major adverse limb events (MALE), including critical limb ischemia and major lower extremity amputation, alongside an increased risk of overall cardiovascular mortality (2).

The pharmacological management of diabetes has evolved with the introduction of glucagon-like peptide-1 receptor agonists (GLP1-RAs) and then sodium-glucose cotransporter-2 inhibitors (SGLT2i). Large cardiovascular outcome trials have demonstrated that these agents reduce major adverse cardiovascular events and mortality (3), (4), (5). However, the specific impact on limb-related outcomes in patients with PAD remains a subject of ongoing research. Early concerns regarding limb safety of SGLT2i were raised by the CANVAS program, which reported an increased risk of lower limb amputations associated with the SGLT2i canagliflozin (6), (7). This initial safety signal generated clinical hesitation in prescribing SGLT2is to patients with established PAD. Subsequent analyses by Alipour et al. (8) and Ueda et al. (9) suggested a potential increase in amputation risk, whereas Skeik et al. (10) reported a more neutral limb safety profile.

Furthermore, while contemporary guidelines increasingly recommend the concurrent use of both GLP1-RAs and SGLT2is for cardiovascular risk reduction in high-risk diabetic patients (11), (12), real-world data evaluating their comparative and combined effectiveness on MALE in a dedicated PAD cohort are limited. A critical knowledge gap persists regarding whether the combined administration of these agents is associated with additive limb salvage and survival benefits over standard monotherapy (11).

To address this gap, we conducted a large retrospective observational cohort study. Our primary objective was to evaluate the independent and combined associations of GLP1-RA and SGLT2i therapy with the incidence of MALE and all-cause mortality among patients with concurrent PAD and diabetes.

Method

Data Source and Study Design

This retrospective observational cohort study was conducted using the electronic medical record database of Clalit Health Services (CHS) in the Central District of Israel, the largest integrated healthcare organization in Israel, which provides longitudinal care for approximately half of the Israeli population. The database contains comprehensive patient-level information, including demographic characteristics, outpatient and inpatient diagnoses, laboratory measurements, medication dispensations, procedural records, vascular interventions, hospitalizations, and mortality data. Data were extracted using the Clalit Research Data Sharing Platform powered by MDCIone.

All cohort definitions, exposures, comorbidities, outcomes, and medications were identified using structured electronic health record data, including ICD-10 diagnosis codes, procedure codes, Anatomical Therapeutic Chemical medication codes, laboratory results, and medication dispensation records. Detailed definitions are provided in Supplementary eTables 1–4.

Study Population

The source cohort included 65,033 adults aged ≥ 18 years with PAD identified by ICD-10 codes between January 2000 and April 2026 (Supplementary eTable 1). GLP1-RA and SGLT2i therapies became clinically available in 2010 and 2015, respectively, we therefore excluded patients with a PVD diagnosed before 2015 to align cohort entry with medication availability and reduce potential immortal time bias. The cohort was then restricted to patients with documented diabetes mellitus, identified using ICD-10 diagnosis codes as detailed in Supplementary eTable 1. Patients with outcome events occurring before the index date were excluded. The final analytic cohort comprised 13,471 patients eligible for the GLP1-RA/SGLT2i exposure comparison. The cohort selection process is shown in Fig. 1.

Exposure Groups

Patients were classified into four mutually exclusive exposure groups according to GLP1-RA and SGLT2i use: neither GLP1-RA nor SGLT2i, GLP1-RA alone, SGLT2i alone, and both GLP1-RA plus SGLT2i therapy. Medication exposure was defined using recorded medication dispensations, and patients were considered exposed to a given drug class only if at least 2 dispensations were documented. When treatment initiation dates were available, exposure was defined based on treatment occurring on or after the PAD diagnosis/index date. Patients who received both drug classes during follow-up were classified in the combined therapy group, whereas patients without evidence of either treatment were classified as the reference group. To address treatment-timing concerns, we additionally performed sensitivity analyses excluding patients with GLP1-RA or SGLT2 inhibitor use before PAD diagnosis/index date and fitted time-varying Cox proportional hazards models in which exposure status was updated during follow-up according to the first recorded dispensing date of each medication. Patients without evidence of either treatment were classified as the reference group (Supplementary eTable 3).

Clinical Outcomes

The primary outcome was defined as MALE, a composite of incident lower-limb revascularization or lower-limb amputation during follow-up, identified using ICD-10 codes (Supplementary eTable 2). Major lower limb amputation was defined as an above-ankle amputation, while minor amputation was defined as below-ankle.

All-cause mortality was evaluated as an additional secondary outcome and was ascertained from CHS mortality records (10), (11), (12), (13). Follow-up time was calculated from the index date to the outcome event or censoring. For graphical time-to-event analyses, follow-up was administratively truncated at 11 years; events occurring after 11 years were censored at 11 years.

Statistical Analysis

Baseline characteristics were summarized across the four exposure groups. Continuous variables were reported as mean (SD), and categorical variables as number and percentage. Missing baseline continuous covariates were imputed using the cohort median, and missing binary covariates were imputed using the most frequent observed category. Clinical outcomes were not imputed.

A multinomial propensity score model was used to estimate the probability of membership in each exposure group. Stabilized IPTW were calculated as the marginal probability of the observed exposure group divided by the predicted probability of that group and were truncated at the 1st and 99th percentiles for the primary analysis. Covariate balance was assessed using maximum pairwise SMDs across the four exposure groups, with SMD < 0.10 considered adequate balance. Covariate balance before and after weighting is shown in Supplementary eFigure 1.

Clinical outcomes were compared using IPTW-weighted Cox proportional hazards models with robust standard errors, with the neither GLP1-RA/SGLT2i group as the reference category. HRs with 95% CIs were estimated for GLP1-RA alone, SGLT2i alone, and combined GLP1-RA plus SGLT2i therapy. Weighted incidence rates were calculated as IPTW-weighted events divided by IPTW-weighted person-years and reported per 100 person-years with 95% CIs. The primary outcome analyses are presented in Table 2.

IPTW-weighted cumulative incidence curves were generated for MALE, and IPTW-weighted Kaplan-Meier survival curves were generated for all-cause mortality. Number-at-risk tables were displayed below each curve. IPTW-weighted incidence-rate plots were also generated to compare absolute event burden across exposure groups. For graphical time-to-event and incidence-rate analyses, follow-up was administratively truncated at 11 years.

Sensitivity analyses included untruncated stabilized weights; weights truncated at the 1st and 99th percentiles; weights truncated at the 5th and 95th percentiles; IPTW plus covariate adjustment; exclusion of events within 90 days; and follow-up truncation at 5 and 10 years. These analyses are reported in Supplementary eTable 5. To further address treatment-timing concerns and potential immortal time bias, we performed 2 additional sensitivity analyses. First, we repeated the analysis after excluding patients with GLP1-RA or SGLT2 inhibitor use before PAD diagnosis/index date; this analysis is reported in Supplementary eTable 6. Second, we fitted time-varying Cox proportional hazards models in which GLP1-RA and SGLT2i exposure status was updated during follow-up according to the first recorded dispensing date of each medication, with patients contributing person-time to the combined exposure group only after both therapies had been initiated; this analysis is reported in Supplementary eTable 7.

Results

The analytic cohort consisted of 13,471 patients, with a mean age of 69.1 years, a mean body mass index (BMI) of 29.4 kg/m², and 62.8% were male. Of these, 6,616 patients (49.1%) received neither GLP1-RA nor SGLT2i therapy, 732 (5.4%) received GLP1-RA alone, 4,328 (32.1%) received SGLT2i alone, and 1,795 (13.3%) received both GLP1-RA and SGLT2i therapy. Median follow-up was 5.75 years (IQR, 2.78–8.53) for MALE and 4.42 years (IQR, 1.97–7.43) for all-cause mortality. Before weighting, several baseline characteristics showed marked imbalance, including age (maximum pairwise SMD, 0.723), BMI (SMD, 0.716), HbA1c (SMD, 0.654), insulin use (SMD, 0.651), and statin use (SMD, 0.632). After IPTW, covariate balance improved substantially; among the 44 covariates with calculable SMDs, 34 had SMDs < 0.10. The full baseline and weighted characteristics are shown in Table 1.

Table 1
Baseline Characteristics and Clinical Outcomes Before and After IPTW Weighting

Variable	Before weighting					After weighting				
	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD
No. of patients	6616	732	4328	1795		6603.5	660.5	4169.8	1531.2	
Demographic characteristics										
Age, mean (SD), years	71.59 (12.14)	63.20 (11.05)	69.13 (9.88)	64.88 (9.46)	0.723	69.25 (12.32)	67.93 (10.72)	69.48 (10.40)	67.72 (9.38)	0.176
Female sex, No. (%)	2823 (42.7)	387 (52.9)	1296 (29.9)	504 (28.1)	0.505	2503.8 (37.9)	235.5 (35.7)	1513.1 (36.3)	531.0 (34.7)	0.067
Low socioeconomic status, No. (%)	1091 (16.5)	112 (15.3)	635 (14.7)	259 (14.4)	0.057	1028.2 (15.6)	112.7 (17.1)	652.0 (15.6)	235.8 (15.4)	0.045
Body mass index, mean (SD)	28.93 (5.78)	33.23 (6.24)	29.24 (5.31)	30.99 (5.35)	0.716	29.68 (6.38)	30.50 (5.21)	29.62 (5.62)	30.25 (5.23)	0.163
Vital sign										
Systolic blood pressure, mean (SD), mm Hg	129.93 (16.35)	130.52 (15.61)	130.45 (16.33)	131.21 (15.06)	0.082	130.42 (16.08)	130.48 (15.99)	130.73 (16.37)	130.87 (14.55)	0.030
Diastolic blood pressure, mean (SD), mm Hg	73.15 (9.95)	75.50 (10.14)	73.08 (9.88)	75.02 (9.54)	0.242	73.63 (9.86)	73.29 (10.09)	73.63 (9.92)	73.99 (9.40)	0.072
Pulse, mean (SD), beats/min	75.08 (10.13)	76.04 (10.09)	75.18 (10.33)	75.28 (9.80)	0.094	75.39 (10.10)	75.58 (10.22)	75.37 (10.37)	75.34 (9.74)	0.022
Comorbidities and medication use										
Hypertension, No. (%)	5584 (84.4)	694 (94.8)	3912 (90.4)	1623 (90.4)	0.285	5753.2 (87.1)	581.3 (88.0)	3665.8 (87.9)	1328.6 (86.8)	0.041
Dyslipidemia, No. (%)	6166 (93.2)	698 (95.4)	4256 (98.3)	1775 (98.9)	0.291	6311.1 (95.6)	636.6 (96.4)	4013.0 (96.2)	1473.9 (96.3)	0.041
Hypertriglyceridemia, No. (%)	112 (1.7)	22 (3.0)	86 (2.0)	47 (2.6)	0.087	146.2 (2.2)	14.9 (2.3)	95.9 (2.3)	36.0 (2.4)	0.009
Coronary artery disease, No. (%)	2837 (42.9)	240 (32.8)	2655 (61.3)	1103 (61.4)	0.574	3282.0 (49.7)	330.4 (50.0)	2052.0 (49.2)	792.3 (51.7)	0.041
Myocardial infarction, No. (%)	1583 (23.9)	117 (16.0)	1615 (37.3)	627 (34.9)	0.482	1851.9 (28.0)	204.2 (30.9)	1237.0 (29.7)	433.9 (28.3)	0.063
Heart failure, No. (%)	2091 (31.6)	151 (20.6)	1818 (42.0)	625 (34.8)	0.461	2285.1 (34.6)	228.2 (34.5)	1482.2 (35.5)	543.9 (35.5)	0.021
Atrial fibrillation, No. (%)	1651 (25.0)	121 (16.5)	1099 (25.4)	367 (20.4)	0.218	1601.8 (24.3)	168.2 (25.5)	1022.0 (24.5)	358.3 (23.4)	0.048

Note. Values are presented as mean (SD) for continuous variables and No. (%) for categorical variables. Weighted values are shown after applying stabilized IPTW, truncated at the 1st and 99th percentiles, and may therefore be noninteger. The SMD columns represent the maximum pairwise standardized mean difference across the four exposure groups. Clinical outcomes are shown descriptively and were not included in the propensity score model or in covariate balance assessment. Empty SMD cells indicate outcomes or noncalculable SMDs. GLP1-RA indicates glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; MALE, major adverse limb events; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference. Balance Summary. A total of 45 baseline covariates were assessed, of which 44 had calculable SMDs. Before weighting, 9 covariates had SMD < 0.10; after weighting, 34 covariates had SMD < 0.10. The maximum pairwise SMD decreased from 0.723 to 0.239, and the median SMD decreased from 0.323 to 0.063. IPTW substantially reduced baseline imbalance across the GLP1/SGLT2 exposure groups, although residual imbalance remained for a limited number of covariates, including insulin use and statin use. These variables may be considered in secondary adjusted or sensitivity models if clinically appropriate.

Variable	Before weighting					After weighting				
	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD
No. of patients	6616	732	4328	1795		6603.5	660.5	4169.8	1531.2	
Stroke, No. (%)	1888 (28.5)	154 (21.0)	1147 (26.5)	459 (25.6)	0.173	1836.5 (27.8)	169.8 (25.7)	1118.0 (26.8)	417.7 (27.3)	0.048
Transient ischemic attack, No. (%)	1063 (16.1)	94 (12.8)	638 (14.7)	284 (15.8)	0.092	1033.3 (15.6)	105.9 (15.9)	637.9 (15.3)	215.6 (14.1)	0.051
Chronic kidney disease, No. (%)	2548 (38.5)	202 (27.6)	1770 (40.9)	725 (40.4)	0.280	2647.1 (40.1)	268.1 (40.6)	1669.4 (40.0)	612.0 (40.0)	0.013
Poly-vascular disease, No. (%)	496 (7.5)	61 (8.3)	456 (10.5)	274 (15.3)	0.245	607.9 (9.2)	72.9 (11.0)	402.3 (9.6)	164.1 (10.7)	0.061
Claudication PAD, No. (%)	1661 (25.1)	229 (31.3)	1311 (30.3)	638 (35.5)	0.227	1852.6 (28.1)	193.1 (29.2)	1215.1 (29.1)	442.2 (28.9)	0.026
Statin use, No. (%)	4847 (73.3)	641 (87.6)	3998 (92.4)	1724 (96.0)	0.632	5477.1 (82.9)	575.5 (87.1)	3541.9 (84.9)	1375.8 (89.9)	0.202
Antiplatelet use, No. (%)	4073 (61.6)	504 (68.9)	3391 (78.4)	1531 (85.3)	0.537	4584.0 (69.4)	480.1 (72.7)	2999.6 (71.9)	1131.9 (73.9)	0.100
Anticoagulant use, No. (%)	2022 (30.6)	219 (29.9)	1469 (33.9)	591 (32.9)	0.086	2105.9 (31.9)	230.2 (34.9)	1375.9 (33.0)	495.7 (32.4)	0.063
RAAS inhibitor use, No. (%)	4,206 (63.6)	519 (70.9)	3,658 (84.5)	1,574 (87.7)	0.562	4,822.8 (73.0)	498.4 (75.5)	3,297.8 (79.1)	1,227.4 (80.2)	0.168
Beta-blocker use, No. (%)	3391 (51.3)	388 (53.0)	2958 (68.3)	1235 (68.8)	0.358	3863.4 (58.5)	408.2 (61.8)	2517.3 (60.4)	946.0 (61.8)	0.067
Insulin use, No. (%)	1398 (21.1)	223 (31.7)	1824 (42.1)	943 (52.5)	0.651	2179.4 (33.0)	294.8 (44.6)	1420.0 (34.1)	599.4 (39.1)	0.239
Biguanide use, No. (%)	2889 (43.7)	525 (71.7)	2333 (53.9)	1331 (74.2)	0.620	3444.7 (52.2)	379.2 (57.4)	2296.2 (55.1)	894.8 (58.4)	0.126
laboratory										
Creatinine, mean (SD), mg/dL	1.27 (1.40)	0.95 (0.85)	0.98 (0.48)	0.94 (0.49)	0.314	1.13 (1.08)	1.10 (1.08)	1.06 (0.85)	1.05 (0.98)	0.077
Urea, mean (SD), mg/dL	48.09 (31.46)	39.49 (22.08)	43.08 (18.91)	39.76 (16.42)	0.332	45.25 (27.19)	43.93 (25.80)	44.68 (23.05)	43.64 (22.45)	0.065
Hemoglobin, mean (SD), g/dL	13.12 (1.81)	13.40 (1.81)	13.71 (1.74)	13.80 (1.71)	0.381	13.40 (1.79)	13.45 (1.67)	13.46 (1.77)	13.58 (1.80)	0.100
Hematocrit, mean (SD), %	40.35 (5.21)	41.11 (4.46)	42.16 (4.98)	42.29 (4.91)	0.383	41.17 (5.18)	41.29 (4.68)	41.32 (5.06)	41.72 (5.21)	0.104
HbA1c, mean (SD), %	6.73 (1.33)	8.97 (1.55)	7.43 (1.57)	7.71 (1.63)	0.654	7.19 (1.82)	7.28 (1.72)	7.17 (1.43)	7.32 (1.41)	0.108

Note. Values are presented as mean (SD) for continuous variables and No. (%) for categorical variables. Weighted values are shown after applying stabilized IPTW, truncated at the 1st and 99th percentiles, and may therefore be noninteger. The SMD columns represent the maximum pairwise standardized mean difference across the four exposure groups. Clinical outcomes are shown descriptively and were not included in the propensity score model or in covariate balance assessment. Empty SMD cells indicate outcomes or noncalculable SMDs. GLP1-RA indicates glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; MALE, major adverse limb events; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference. Balance Summary. A total of 45 baseline covariates were assessed, of which 44 had calculable SMDs. Before weighting, 9 covariates had SMD < 0.10; after weighting, 34 covariates had SMD < 0.10. The maximum pairwise SMD decreased from 0.723 to 0.239, and the median SMD decreased from 0.323 to 0.063. IPTW substantially reduced baseline imbalance across the GLP1/SGLT2 exposure groups, although residual imbalance remained for a limited number of covariates, including insulin use and statin use. These variables may be considered in secondary adjusted or sensitivity models if clinically appropriate.

Variable	Before weighting					After weighting				
	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD	No GLP1-RA/no SGLT2i	GLP1-RA alone	SGLT2i alone	GLP1-RA + SGLT2i	Max pairwise SMD
No. of patients	6616	732	4328	1795		6603.5	660.5	4169.8	1531.2	
LDL cholesterol, mean (SD), mg/dL	91.78 (33.51)	94.96 (33.95)	81.73 (32.79)	87.68 (33.58)	0.396	88.58 (33.00)	87.99 (32.65)	88.17 (34.41)	88.29 (32.80)	0.070
HDL cholesterol, mean (SD), mg/dL	45.34 (11.73)	44.51 (10.81)	42.78 (10.84)	41.47 (10.15)	0.353	44.02 (11.29)	43.53 (10.69)	43.95 (11.31)	43.30 (11.09)	0.064
Total cholesterol, mean (SD), mg/dL	188.30 (42.18)	172.76 (41.07)	158.90 (44.42)	164.90 (43.71)	0.371	164.24 (43.38)	164.98 (40.80)	164.08 (45.65)	162.16 (41.94)	0.068
Non-HDL cholesterol, mean (SD), mg/dL	120.81 (38.79)	127.92 (38.81)	114.09 (40.88)	123.48 (41.61)	0.347	120.09 (40.99)	121.75 (38.07)	119.82 (41.82)	118.55 (39.08)	0.083
AST, mean (SD)	22.70 (14.85)	23.39 (11.07)	22.71 (10.57)	23.09 (10.87)	0.062	22.75 (13.17)	22.42 (9.54)	22.69 (11.22)	22.38 (8.87)	0.035
Clinical outcomes during follow-up										
Major adverse limb events (MALE), No. (%)	357 (5.4)	23 (3.1)	182 (4.2)	79 (4.4)		410.9 (6.2)	26.5 (4.0)	147.3 (3.5)	53.4 (3.5)	
Limb revascularization, No. (%)	202 (3.1)	16 (2.2)	121 (2.8)	59 (3.3)		246.2 (3.7)	21.1 (3.2)	94.1 (2.3)	42.8 (2.8)	
Major amputation, No. (%)	179 (2.7)	9 (1.2)	74 (1.7)	25 (1.4)		192.8 (2.9)	8.7 (1.3)	61.9 (1.5)	13.1 (0.9)	
Minor amputation, No. (%)	46 (0.7)	4 (0.5)	45 (1.0)	29 (1.6)		59.0 (0.9)	10.1 (1.5)	42.7 (1.0)	21.4 (1.4)	
All-cause mortality, No. (%)	2551 (38.6)	104 (14.2)	708 (16.4)	201 (11.2)		2547.9 (38.6)	165.9 (25.1)	676.3 (16.2)	176.7 (11.5)	
Note. Values are presented as mean (SD) for continuous variables and No. (%) for categorical variables. Weighted values are shown after applying stabilized IPTW, truncated at the 1st and 99th percentiles, and may therefore be noninteger. The SMD columns represent the maximum pairwise standardized mean difference across the four exposure groups. Clinical outcomes are shown descriptively and were not included in the propensity score model or in covariate balance assessment. Empty SMD cells indicate outcomes or noncalculable SMDs. GLP1-RA indicates glucagon-like peptide-1 receptor agonist; IPTW, inverse probability of treatment weighting; MALE, major adverse limb events; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference. Balance Summary. A total of 45 baseline covariates were assessed, of which 44 had calculable SMDs. Before weighting, 9 covariates had SMD < 0.10; after weighting, 34 covariates had SMD < 0.10. The maximum pairwise SMD decreased from 0.723 to 0.239, and the median SMD decreased from 0.323 to 0.063. IPTW substantially reduced baseline imbalance across the GLP1/SGLT2 exposure groups, although residual imbalance remained for a limited number of covariates, including insulin use and statin use. These variables may be considered in secondary adjusted or sensitivity models if clinically appropriate.										

The IPTW-weighted clinical outcome analysis is summarized in Table 2. Compared with patients receiving neither GLP1-RA nor SGLT2i therapy, administration of both GLP1-RA/SGLT2i therapy was associated with significantly lower hazards of MALE (HR, 0.50; 95% CI, 0.33–0.75; $P < .001$) and major amputation (HR, 0.30; 95% CI, 0.17–0.53; $P < .001$). SGLT2 inhibitor monotherapy was also associated with lower hazards of MALE (HR, 0.67; 95% CI, 0.52–0.88; $P = .004$) and major amputation (HR, 0.61; 95% CI, 0.43–0.89; $P = .010$). GLP1-RA monotherapy showed numerically lower hazards of MALE and major amputation, but these estimates did not reach statistical significance. All active treatment groups were associated with lower all-cause mortality, with the greatest reduction observed in the among patients receiving both GLP1-RA and SGLT2i therapy.

The sensitivity analyses are presented in eTable 5. Overall, the direction of the associations was consistent across alternative weighting strategies, covariate-adjusted IPTW models, exclusion of early events, and follow-up truncation analyses. The most stable findings were the lower mortality associated with GLP1-RA alone, SGLT2i alone, and both GLP1-RA and SGLT2i therapy, as well as the lower major amputation risk observed for SGLT2i alone and among patients receiving both GLP1-RA and SGLT2i therapy.

Table 2
IPTW-Weighted Clinical Outcomes According to GLP1-RA/SGLT2i Exposure Group

Outcome	No GLP1-RA and no SGLT2i Incidence rate (95% CI)	GLP1-RA alone Incidence rate (95% CI)	GLP1-RA alone HR (95% CI); P value	SGLT2i alone Incidence rate (95% CI)	SGLT2i alone HR (95% CI); P value	GLP1-RA + SGLT2i Incidence rate (95% CI)	GLP1-RA + SGLT2i HR (95% CI); P value
Major adverse limb events (MALE)	0.7 (0.6–0.7)	0.4 (0.2–0.5)	0.55 (0.26–1.16); .116	0.5 (0.4–0.6)	0.67 (0.52–0.88); .004	0.3 (0.2–0.5)	0.50 (0.33–0.75); <.001
Limb revascularization	0.3 (0.3–0.4)	0.2 (0.1–0.4)	0.81 (0.30–2.22); .687	0.3 (0.2–0.3)	0.72 (0.50–1.03); .070	0.2 (0.1–0.3)	0.73 (0.43–1.24); .249
Major amputation	0.4 (0.4–0.5)	0.2 (0.1–0.3)	0.45 (0.18–1.15); .097	0.3 (0.2–0.4)	0.61 (0.43–0.89); .010	0.1 (0.1–0.2)	0.30 (0.17–0.53); <.001
Minor amputation	0.1 (0.1–0.2)	0.2 (0.1–0.3)	1.38 (0.32–5.95); .666	0.2 (0.1–0.2)	1.10 (0.62–1.97); .738	0.2 (0.1–0.3)	1.28 (0.67–2.45); .450
All-cause mortality	8.5 (8.2–8.9)	4.3 (3.6–4.9)	0.50 (0.39–0.63); <.001	3.6 (3.3–3.8)	0.42 (0.38–0.46); <.001	2.0 (1.7–2.2)	0.23 (0.19–0.28); <.001
Note. Incidence rates are weighted events per 100 person-years with 95% confidence intervals. Hazard ratios were estimated using IPTW-weighted Cox proportional hazards models with robust standard errors. The no GLP1-RA and no SGLT2i group served as the reference category. GLP1-RA indicates glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; MALE, major adverse limb events.							

IPTW-weighted time-to-event curves demonstrated clear separation between treatment groups for both MALE and all-cause mortality over 11 years of follow-up. For MALE, the cumulative incidence was highest among patients receiving neither GLP1-RA nor SGLT2i therapy, whereas patients receiving GLP1-RA alone, SGLT2i alone, or both GLP1-RA/SGLT2i therapy showed lower cumulative event burden throughout follow-up (Fig. 2A). Differences between treatment groups were statistically significant using IPTW-weighted Cox models with robust standard errors (global $P < .001$). For all-cause mortality, overall survival was substantially lower in the no-treatment group, while both GLP1-RA/SGLT2i group showed the most favorable survival trajectory across follow-up (Fig. 2B; global $P < .001$).

Consistent with the time-to-event analyses, IPTW-weighted incidence-rate plots demonstrated lower absolute event rates among treated groups compared with patients receiving neither therapy (Fig. 3). The largest absolute separation was observed for all-cause mortality, with the highest incidence rate in the neither GLP1-RA/ SGLT2i group and the lowest rate in both GLP1-RA/SGLT2i group. For limb-related outcomes, incidence rates of MALE, limb revascularization, and major amputation were generally lower among treated patients, particularly among those receiving combined therapy, whereas minor amputation rates were low across all groups. Together, these findings suggest that GLP1-RA and SGLT2i therapy, were associated with lower weighted incidence of adverse limb and mortality outcomes.

Discussion

In this large real-world retrospective cohort study comprising 13,471 patients with concurrent PAD and diabetes, we evaluated the comparative associations of GLP1-RAs and SGLT2is, with MALE and all-cause mortality outcomes. Compared with patients receiving neither therapy, administration of both GLP1-RA and SGLT2i therapy was associated with lower hazards of MALE (HR, 0.50; 95% CI, 0.33–0.75), major amputation (HR, 0.30; 95% CI, 0.17–0.53), and all-cause mortality (HR, 0.23; 95% CI, 0.19–0.28). SGLT2i monotherapy was associated with similarly reduced hazards of MALE and major amputation, supporting a favorable limb-specific association. GLP1-RA monotherapy was associated with lower overall mortality; however, its limb-specific estimates should be

interpreted cautiously because of the smaller GLP1-RA-alone subgroup and the limited number of MALE events within the primary weighted models.

This data is relevant given the limited randomized controlled trial data evaluating the combination of GLP-1RAs and SGLT2i in patients with PAD and diabetes and the scarcity of evidence regarding limb-specific outcomes in this population (14). Importantly, 35% of participants in the STRIDE trial, which evaluated semaglutide one mg in patients with PAD, were concomitantly using SGLT2i at baseline. In a subgroup analysis, semaglutide significantly improved maximum walking distance regardless of baseline diabetes medication use, including SGLT2i. However, the trial was not powered to assess MALE outcomes (14).

In our study, the observed associations across all treatment groups consistently favored reduced risks of adverse limb and mortality outcomes, with effect estimates generally pointing in the same beneficial direction, supporting the potential effectiveness of these therapies, particularly when both were used.

Further, these data provide a perspective on historical apprehensions regarding the safety of SGLT2is in patients with advanced PAD. Neal et al.(6) first reported the increased risk of lower extremity amputation in the CANVAS program, while Guthrie et al.(7) further discussed the clinical implications of this safety signal. However, our real-world findings align with several analyses (13), (15), (16), (17), which did not reproduce the severe amputation risk initially observed in the CANVAS program. The absence of an increased amputation risk among SGLT2i users in our cohort supports a favorable limb safety profile in patients with PAD (10). The discrepancy between our findings and early safety signals may relate to the observational nature of our data, differences in contemporary foot care protocols, or population-specific factors.

The observed benefits likely reflect complementary mechanisms of action. SGLT2i exert systemic and local hemodynamic effects, improving vascular compliance, microvascular perfusion, endothelial function, and inhibiting smooth muscle cell proliferation, which may help mitigate microvascular failure and restenosis in severe PAD (11), (12), (18). GLP1-RAs reduce systemic inflammation and atherosclerotic progression, promoting plaque stabilization and lowering the risk of major cardiovascular events and death (12).

Given that limb preservation in advanced PAD depends on both macrovascular and microvascular integrity, these distinct but complementary mechanisms may contribute to the favorable associations observed with both therapies (19), (20). This concept is consistent with the framework proposed by Sridhar et al. (11), suggesting that combined SGLT2i and GLP1-RA therapy may provide additive cardiovascular, renal, and vascular protection.

Prior evidence regarding limb and mortality outcomes in patients with PAD remains limited and somewhat heterogeneous, particularly for SGLT2i. A recent meta-analysis of randomized trial data in patients with PAD reported no significant reduction in all-cause mortality with SGLT2i, although cardiovascular death was reduced, and no significant increase in amputation risk was observed (21). Evidence for GLP1-RA therapy in PAD appears more consistent, with recent meta-analytic and real-world data suggesting lower mortality and fewer adverse limb outcomes among treated patients (22), (23). A 2025 meta-analysis of six RCTs including 7645 participants with type 2 diabetes and PAD found that GLP1RA significantly reduced all-cause mortality by 17% (RR 0.83; 95% CI 0.70–0.99, $p = 0.04$) (24), the American journal of cardiology 2025 Shuja SH). A large propensity scores matched study from TriNetX (55041 patients per group with moderate PAD found reduced mortality with GLP1RA (1.7% vs 4.4%, $p < 0.01$) and fewer MALE (0.8% vs 1.5%, $p < 0.01$) at one year (25).

In this context, our study adds real-world evidence specifically evaluating the administration of both GLP1-RA and SGLT2i therapy, supporting further prospective evaluation of combined cardiometabolic therapy as a strategy for cardiovascular and limb risk reduction in this high-risk population.

This study has several strengths. It utilizes a large population-level database, ensuring high external validity. We employed rigorous methodological approaches, including multinomial propensity score modeling and inverse probability of treatment weighting, to effectively balance 44 baseline covariates across the four exposure groups. Robust sensitivity analyses, including follow-up truncation and exclusion of early events, confirmed the stability of our primary findings.

Several limitations must be acknowledged. First, the retrospective observational design inherently limits our ability to definitively establish causality. Second, despite robust covariate balancing, the potential for residual or unmeasured confounding remains. Variables such as ankle-brachial index values, specific anatomical levels of vascular disease, and the severity of diabetic foot ulcers were not captured. Cohort and variable definitions were strictly reliant on diagnostic and procedural codes, which may be subject to misclassification bias. Additionally, diabetes type could not be reliably ascertained from ICD-based electronic health record coding.

Therefore, diabetes was analyzed as diabetes mellitus without further stratification. Finally, while weighting substantially improved baseline balance, residual imbalance remained for a limited number of covariates such as insulin use, which required consideration in secondary adjusted models.

Conclusion

In this large real-world cohort of patients with PAD and diabetes, the administration of GLP1-RA and SGLT2i therapy was associated with more favorable limb outcomes and reduced mortality compared with no exposure to either drug class. Prospective trials examining the combined effects of both therapies on PAD progression and mortality risk in diabetic patients are needed.

Abbreviations

ACE
Angiotensin-converting enzyme
AF
Atrial fibrillation
ARB
Angiotensin receptor blocker
ATC
Anatomical Therapeutic Chemical
BMI
Body mass index
CHS
Clalit Health Services
CI
Confidence interval
CKD
Chronic kidney disease
DM
Diabetes mellitus
DPP-4
Dipeptidyl peptidase-4
GLP-1 RA
Glucagon-like peptide-1 receptor agonist
HbA1c
Hemoglobin A1c
HDL
High-density lipoprotein
HR
Hazard ratio
ICD-10
International Classification of Diseases, 10th Revision
IHD
Ischemic heart disease
IPTW
Inverse probability of treatment weighting
IQR
Interquartile range
LDL
Low-density lipoprotein
MALE
Major adverse limb events

PAD
Peripheral artery disease
PCSK9
Proprotein convertase subtilisin/kexin type 9
PVD
Peripheral vascular disease
RAAS
Renin-angiotensin-aldosterone system
RCT
Randomized controlled trial
SD
Standard deviation
SES
Socioeconomic status
SGLT2i
Sodium-glucose cotransporter-2 inhibitor
SMD
Standardized mean difference
TIA
Transient ischemic attack
WBC
White blood cell

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of Kaplan Medical Center (approval no. 0143-22-KMC). All procedures were conducted in accordance with the Declaration of Helsinki and its later amendments. Given the retrospective design of the study and the use of anonymized registry-based data, the Institutional Ethics Committee waived the requirement for written informed consent.

Consent for publication

Not applicable.

Competing interests

E.Z. Fisman held the position of Editor-in-Chief of Cardiovascular Diabetology at the time of submission. He was not involved in the peer review or editorial decision-making process for this manuscript. The manuscript was handled independently by another editor.

Authors' information

Not applicable.

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Author Contribution

HAK, EH, MA, EZF, AK, and LS conceived and designed the study. HAK collected the data. HAK and MA performed the statistical analysis. HAK, MA, JK, KI, AQ, AD, AK, DN, MM, NAH, and YZF drafted the manuscript. AK, ER, EZF, NAH, KI, YAK, OH, and LS critically revised the manuscript for important intellectual content. All authors interpreted the data, read and approved the final manuscript, and agree to be accountable for all aspects of the work.

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Data Availability

The de-identified participant data generated and analyzed during the current study are not publicly available because of patient confidentiality and institutional ethical restrictions. Data may be made available from the corresponding author upon reasonable request after publication. Access may be granted to researchers who provide a methodologically sound proposal and agree to the terms of a data access agreement.

References

1. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(24):e1313–410. 10.1161/CIR.0000000000001251;SUBPAGE:STRING:FULL PubMed PMID: 38743805.
2. Fioretti V, Gerardi D, Giugliano G, Di Fazio A, Stabile E. Focus on Prevention: Peripheral Arterial Disease and the Central Role of the Cardiologist. *J Clin Med*. 2023;12(13):4338. 10.3390/JCM12134338 PubMed PMID: 37445373.
3. Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *Z fur Gefassmedizin*. 2016;13(1):17–8. doi:10.1056/NEJMOA1504720;CTYPE:STRING:JOURNAL PubMed PMID: 26378978.
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995–2008. doi:10.1056/NEJMOA1911303;REQUESTEDJOURNAL:JOURNAL:NEJM;PAGE:STRING:ARTICLE/CHAPTER PubMed PMID: 31535829.
5. Mann JFE, Fonseca V, Mosenzon O, Raz I, Goldman B, Idorn T, et al. Effects of Liraglutide Versus Placebo on Cardiovascular Events in Patients With Type 2 Diabetes Mellitus and Chronic Kidney Disease: Results From the LEADER Trial. *Circulation*. 2018;138(25):2908. 10.1161/CIRCULATIONAHA.118.036418 PubMed PMID: 30566006.
6. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondur N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644–57. 10.1056/NEJMOA1611925. ;WGROU:STRING:MMS PubMed PMID: 28605608.
7. Guthrie R. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *Postgrad Med*. 2018;130(2):149–53. 10.1080/00325481.2018.1423852 PubMed PMID: 29297732.
8. Alipour M, Rezaei J, Shahabi Rabori V, Arbuzia M, Norouzbeigi A, Rasta S, et al. Limb amputation following sodium-glucose cotransporter type 2 inhibitor therapy. *J Prev Epidemiol*. 2024;10(1):e38251–38251. 10.34172/JPE.2025.38251.
9. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363:k4365. 10.1136. /BMJ.K4365 PubMed PMID: 30429124.
10. Skeik N, Elejla SA, Sethi A, Manunga J, Mirza A. Effects of SGLT2 inhibitors and GLP1-receptor agonists on cardiovascular and limb events in peripheral artery disease: A review. *Vascular Med (United Kingdom)*. 2023;28(1):62–76. ;ISSUE:ISSUE:DOI PubMed PMID: 36593757.

11. Sridhar VS, Dubrofsky L, Boulet J, Cherney DZ. Making a case for the combined use of SGLT2 inhibitors and GLP1 receptor agonists for cardiorenal protection. *Brazilian J Nephrol.* 2020;42(4):467–77. 10.1590/2175-8239. -JBN-2020-0100 PubMed PMID: 32926067.
12. Rolek B, Haber M, Gajewska M, Rogula S, Pietrasik A, Gąsecka A. SGLT2 Inhibitors vs. GLP-1 Agonists to Treat the Heart, the Kidneys and the Brain. *J Cardiovasc Dev Disease* 2023. 2023;10(8):322. 10.3390/JCDD10080322.
13. Perkovic V, Jardine MJ, Neal B, Bompont S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380(24):2295–306. 10.1056/NEJMOA1811744. ;WGROU:STRING:MMS PubMed PMID: 30990260.
14. Bonaca MP, Catarig AM, Houliand K, Ludvik B, Nordanstig J, Ramesh CK, et al. Semaglutide and walking capacity in people with symptomatic peripheral artery disease and type 2 diabetes (STRIDE): a phase 3b, double-blind, randomised, placebo-controlled trial. *Lancet.* 2025;405(10489):1580–93. 10.1016/S0140-6736. (25)00509-4 PubMed PMID: 40169145.
15. Jardine MJ, Zhou Z, Mahaffey KW, Oshima M, Agarwal R, Bakris G, et al. Renal, cardiovascular, and safety outcomes of canagliflozin by baseline kidney function: A secondary analysis of the CREDENCE randomized trial. *J Am Soc Nephrol.* 2020;31(5):1128–39. 10. 1681/ASN.2019111168 PubMed PMID: 32354987.
16. Hanai K, Babazono T, CREDENCE. A silver lining in the dark cloud of diabetic nephropathy. *J Diabetes Investig.* 2019;11(3):527. 10. 1111/JDI.13175 PubMed PMID: 31705732.
17. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436–46. 10.1056/NEJMOA2024816. ;WGROU:STRING:MMS PubMed PMID: 32970396.
18. Zhang Q, Deng Z, Li T, Chen K, Zeng Z. SGLT2 inhibitor improves the prognosis of patients with coronary heart disease and prevents in-stent restenosis. *Front Cardiovasc Med.* 2024;10:1280547–1280547. 10.3389/. FCVM.2023.1280547 PubMed PMID: 38274313.
19. Panneflek J, Lauzea B, Barbarawi M, Greenaway A. The Microvascular–Immune Interface in Cardiovascular Disease: A Stage-Based Framework of Microvascular Failure. *Hearts.* 2026;7(2):17. 10.3390/HEARTS7020017.
20. Yang J, Zhang X, Zhong J. Cardiovascular remodeling: key mechanisms and clinical implications linking sarcopenia and heart failure. *Front Med (Lausanne).* 2026;13:1736824. 10.3389/. FMED.2026.1736824 PubMed PMID: 41767527.
21. Hu C, Ernst M, Snelling R, Ye Q, Paneni F, Zelniker TA et al. Cardiovascular, limb, and kidney effects of SGLT2 inhibitors in patients with peripheral artery disease: a systematic review and meta-analysis of randomized controlled trial data. *Cardiovascular Diabetology.* 2026. 2026 May 17. 10.1186/S12933-026-03207-Y
22. Shuja SH, Shuja MH, Shaukat A, Hannat R, Ahmed I, Adam S, et al. GLP-1 Receptor Agonists and Cardiovascular Outcomes in Adults With Diabetes and Peripheral Artery Disease: An Updated Systematic Review and Meta-Analysis. *Am J Cardiol.* 2026;258:268–75. 10.1016/j.amjcard.2025.09. .039 PubMed PMID: 41022246.
23. Go CC, Annie F, Drabish K, Eslami MH. Glucagon-like peptide-1 receptor agonists are associated with fewer major adverse cardiovascular and limb events in patients with moderate peripheral arterial disease. *J Vasc Surg.* 2025;82(3):1024–e10322. 10.1016/j.jvs.2025.05.037 . PubMed PMID: 40484062.
24. Shuja SH, Shuja MH, Shaukat A, Hannat R, Ahmed I, Adam S, et al. GLP-1 Receptor Agonists and Cardiovascular Outcomes in Adults With Diabetes and Peripheral Artery Disease: An Updated Systematic Review and Meta-Analysis. *Am J Cardiol.* 2026;258:268–75. 10.1016/j.amjcard.2025.09.039.
25. Go CC, Annie F, Drabish K, Eslami MH. Glucagon-like peptide-1 receptor agonists are associated with fewer major adverse cardiovascular and limb events in patients with moderate peripheral arterial disease. *J Vasc Surg.* 2025 Jun. 10.1016/j.jvs.2025.05.037.

Figures

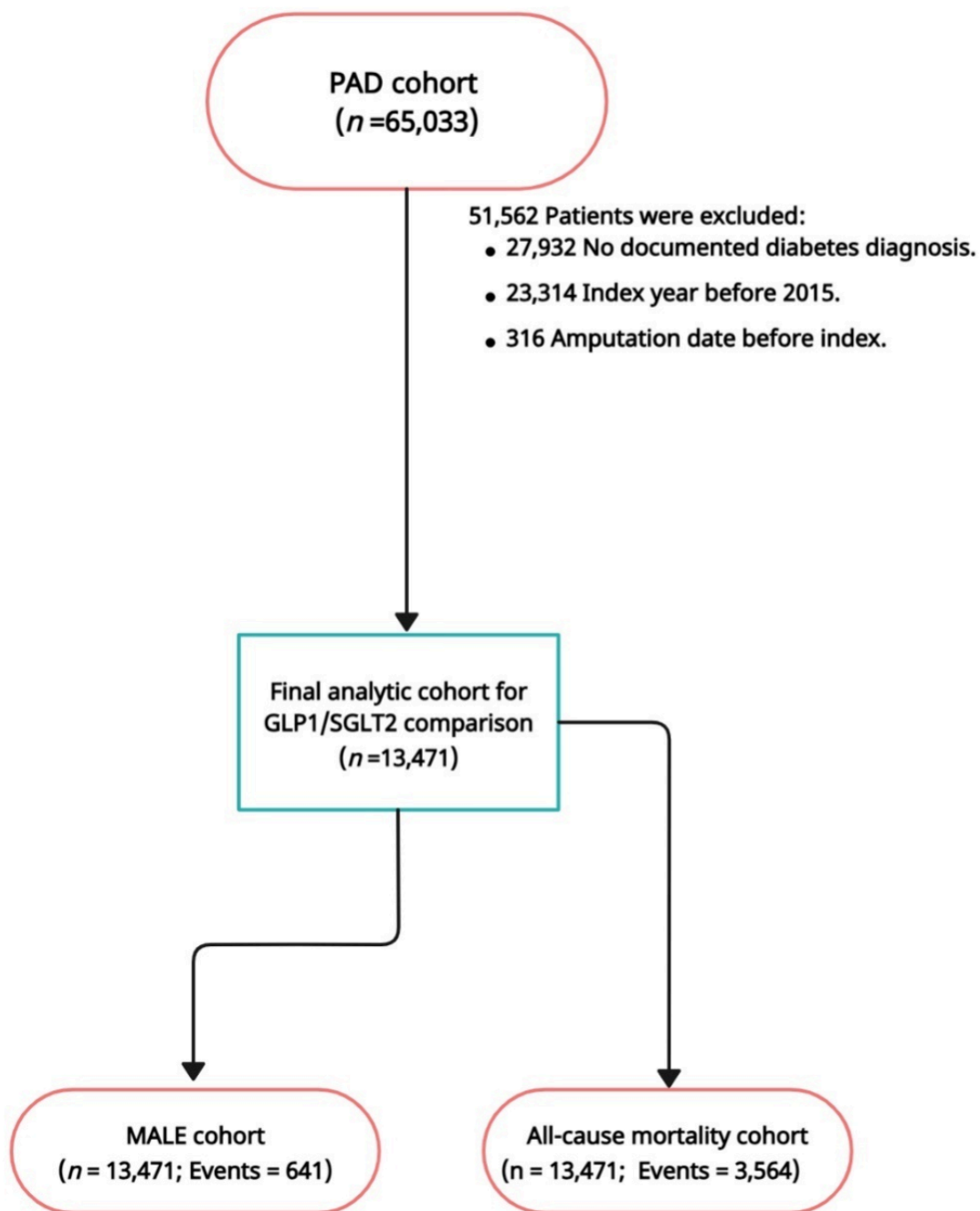


Figure 1

Flowchart of Cohort Selection for the GLP1-RA/SGLT2i Exposure Analysis

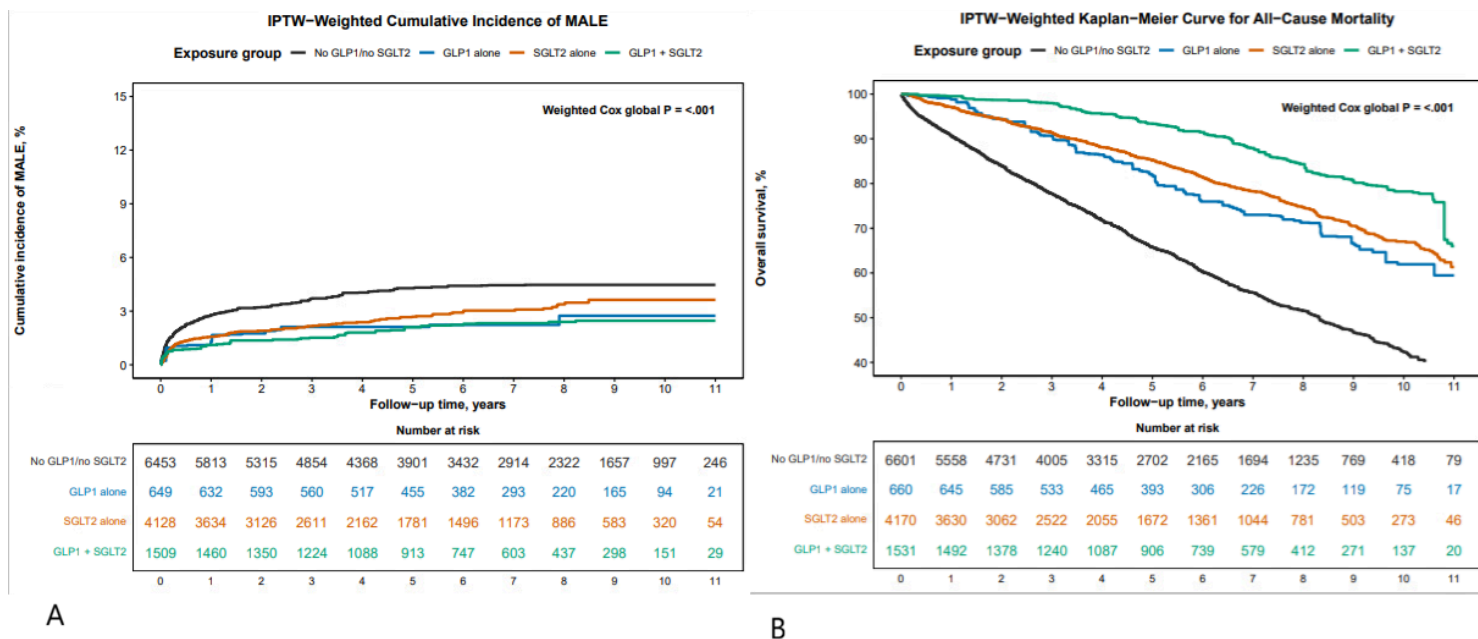


Figure 2

IPTW-Weighted Time-to-Event Curves for Major Adverse Limb Events and All-Cause Mortality According to GLP1-RA/SGLT2i Exposure Group

A. IPTW-Weighted Time-to-Event Curves for Major Adverse Limb Events According to GLP1-RA/SGLT2i Exposure Group

B. IPTW-Weighted Time-to-Event Curves for All-Cause Mortality According to GLP1-RA/SGLT2i Exposure Group

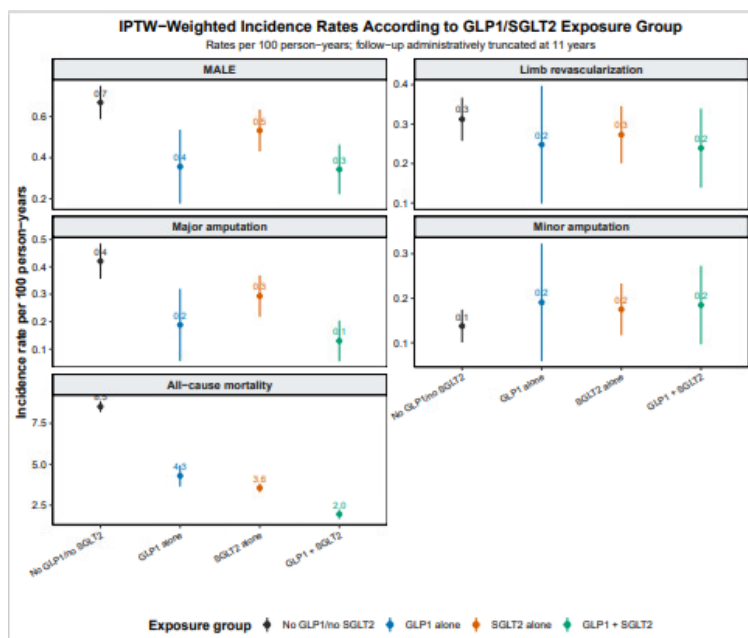


Figure 3

IPTW-Weighted Incidence Rates of Clinical Outcomes According to GLP1-RA/SGLT2i Exposure Group

Supplementary Files

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