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ARTICLE

Major adverse cardiovascular and limb events in people with diabetes treated with GLP-1 receptor agonists vs SGLT2 inhibitors

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Abstract

Aims/hypothesis This study aimed to assess the real-world outcomes of people with diabetes mellitus treated with glucagon-like peptide-1 receptor agonists (GLP1RAs) compared with those treated with sodium–glucose cotransporter 2 inhibitors (SGLT2is) in terms of major adverse cardiovascular and limb events. Peripheral artery disease is a common cause of morbidity in people with diabetes. Previous cardiovascular outcome trials have demonstrated the benefits of GLP1RAs and SGLT2is for reducing various cardiovascular events, but the safety and efficacy of these drugs on limb outcomes remain subject to debate and ambiguity.

Methods A retrospective cohort study was conducted in which data were collected from the Taiwan National Health Insurance Research Database. In total, 379,256 individuals with diabetes receiving either GLP1RA or SGLT2i with treatment initiated between 1 May 2016 and 31 December 2019 were identified. The primary outcome was major adverse limb events (MALE), defined as the composite of newly diagnosed critical limb ischaemia, percutaneous transluminal angioplasty or peripheral bypass for peripheral artery disease, and non-traumatic amputation. The secondary outcome was major adverse cardiac events, which was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke. Other examined outcomes included death from any cause and hospitalisation for heart failure. Propensity score matching was performed at a 1:4 ratio between the GLP1RA and SGLT2i groups to mitigate possible selection bias.

Results A total of 287,091 patients were eligible for analysis, with 81,152 patients treated with SGLT2i and 20,288 patients treated with GLP1RA after matching. The incidence of MALE was significantly lower in the GLP1RA group than in the SGLT2i group (3.6 vs 4.5 events per 1000 person-years; subdistribution HR 0.80; 95% CI 0.67, 0.96), primarily due to a lower incidence of critical limb ischaemia. The reduced risks of MALE associated with GLP1RA use were particularly noticeable in people with diabetic peripheral neuropathy (subdistribution HR 0.66 vs 1.11; p for interaction 0.006).

Conclusions/interpretation In people with diabetes, GLP1RA use was associated with significantly reduced risks of MALE compared with SGLT2i within the first 2 years after initiation, especially among people with diabetic neuropathy.

Keywords Amputation · Diabetes · Glucagon-like peptide-1 receptor agonists · Major adverse cardiac events · Major adverse limb events · Sodium–glucose cotransporter 2 inhibitors

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Research in context

What is already known about this subject?

- Both sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP1RAs) have demonstrated efficacy in reducing major adverse cardiovascular events (MACE)
- Controversy surrounds the risk of amputation associated with SGLT2i use, while there is limited literature reporting beneficial effects of GLP1RAs on limb outcomes; the effects of both drugs on major adverse limb events (MALE) remain to be elucidated
- Although there is an abundance of data comparing SGLT2is and GLP1RAs against placebo or other control groups, direct comparisons between these two drug classes are scarce

What is the key question?

- How do the effects of SGLT2is and GLP1RAs differ in terms of preventing MALE and MACE?

What are the new findings?

- In people with diabetes, GLP1RA use was associated with significantly reduced risks of MALE compared with SGLT2is within the first 2 years after initiation, largely due to a reduction of incident critical limb ischaemia
- The limb-protective effects of GLP1RAs compared with SGLT2is were accentuated in people with pre-existing diabetic peripheral neuropathy

How might this impact on clinical practice in the foreseeable future?

- In people with diabetes, GLP1RA therapy offers greater limb protection and should be considered over SGLT2is, particularly in those at high risk of adverse limb events

Abbreviations

CAD	Coronary artery disease
CANVAS	CANagliflozin cardioVascular Assessment Study
CKD	Chronic kidney disease
CLI	Critical limb ischaemia
CVA	Cerebrovascular accident
CVOT	Cardiovascular outcome trial
DFU	Diabetic foot ulcer
ESRD	End-stage renal disease
GLP-1	Glucagon-like peptide-1
GLP1RA	Glucagon-like peptide-1 receptor agonist
HTN	Hypertension
LEAD	Lower extremity arterial disease
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	Major adverse cardiac events
MALE	Major adverse limb events
MI	Myocardial infarction
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
PAD	Peripheral artery disease
PSM	Propensity score matching
PTA	Percutaneous transluminal angioplasty
PY	Person-year
SGLT2i	Sodium–glucose cotransporter 2 inhibitor
SHR	Subdistribution HR
STD	Standardised difference
VTE	Venous thromboembolism

Introduction

Diabetes mellitus is a global pandemic, and CVD is the most common cause of morbidity and mortality among people with diabetes mellitus [1–3]. The presence of peripheral artery disease (PAD), in particular, is associated with worsened survival rate compared with disease limited to other vascular beds [4]. Diabetes not only promotes atherosclerosis but also worsens the prognosis of people with atherosclerotic disease. For example, people with diabetes and PAD have a fivefold increased risk of amputation and a threefold increased risk of death relative to their non-diabetic counterparts [5].

Over the past years, the introduction of several glucose-lowering agents has led to a paradigm shift in diabetes management from mere glycaemic control to the active reduction of adverse cardiovascular events. Namely, sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP1RAs) have demonstrated efficacy for reducing major adverse cardiac events (MACE) in several studies [6–10]. Although both SGLT2is and GLP1RAs have been shown to protect against MACE, effects

on the individual MACE components have varied between these two treatments. SGLT2is have been proposed to modulate the cardiovascular system through haemodynamic effects, whereas GLP1RAs are thought to decrease adverse events through anti-atherogenic activity [3]. The patient groups that benefit most from either drug may be different, and yet data directly comparing these two drug classes are currently scarce.

Furthermore, although SGLT2is exhibited remarkable efficacy for reducing cardiovascular events, concerns were raised regarding the safety of these drugs in terms of limb events due to the increased incidence of amputations observed in the CANagliflozin cardioVascular Assessment Study (CANVAS) [10], with an almost twofold increase in risk. However, this was not observed in other SGLT2i trials that followed [11–13], nor in a post hoc analysis of the EMPA-REG OUTCOME trial [14]. Meta-analyses [15, 16] reported neutral effects of SGLT2is on amputations, yet real-world data showed increase in risk [17, 18]. On the other hand, investigations on the effects of GLP1RA treatment on limb events have suggested positive results. A post hoc analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial [19] found that liraglutide was associated with reduced amputations compared with placebo. In prior randomised, controlled trials for SGLT2is and GLP1RAs, limb events were not examined as prespecified outcomes, and the effects of SGLT2i and GLP1RA treatments on limb events remain under debate.

The present study aimed to examine the real-world outcomes of people with diabetes treated with SGLT2is compared with those of people treated with GLP1RAs in terms of MACE and major adverse limb events (MALE). We enrolled participants from the largest cohort in Asia using a nationwide database that includes nearly 100% of adults with diabetes in Taiwan. Participants were subjected to propensity score matching (PSM) according to their clinical characteristics prior to analyses.

Methods

Data source This nationwide, population-based, retrospective cohort study utilised data collected from the Taiwan National Health Insurance (NHI) and the Taiwan Death Registry, following the de-identification of participants from their civil identification numbers. The NHI programme is a single-payer health insurance system that provides over 99.8% of medical expenditure coverage for the population of Taiwan. Enrolment in the NHI programme is obligatory in Taiwan. Established in March 1995, the NHI now insures approximately 23.5 million people, providing affordable and high-quality healthcare. Data from the NHI are managed by the Health and Welfare Data Science Center (HWDC), and data from 1995 up to 2019 are available for collection through the National Health Informatics Project (NHIP). Disease diagnoses were based on the ICD, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes before 31 December 2015; after 2015, diagnoses were based on ICD-10-CM. A full review by the Ethics Institutional Review Board of Taiwan University Hospital and informed consent were waived due to the de-identification of patient data. The NHI programme and the NHI databases were described in detail in previous publications [20–22].

Study cohort The payment for GLP1RAs by the Taiwan NHI started in 2011, whereas payment for SGLT2is began on 1 May 2016. Therefore, all people with diabetes who received either GLP1RA or SGLT2i between 1 May 2016 and 31 December 2019 were identified in the Taiwan NHI database. The index date was defined as the day on which GLP1RA or SGLT2i was first prescribed after 1 May 2016. Exclusion criteria included: (1) missing demographical data (n=1095); (2) age younger than 18 years (n=343); (3) prior exposure to GLP1RA before the index date (n=3871); (4) history of prior minor or major amputations (n=1634); (5) number of prescriptions of the drugs of interest <2 during the first 3 months of follow-up (n=67,704); (6) <3 months of follow-up (n=15,930); or (7) incidence of MALE within 3 months after initial drug exposure (n=1588). History of prior revascularisation procedures for lower extremity arterial disease (LEAD) was not considered an exclusion criterion because revascularisation can be repeated several times and is not mutually exclusive of future revascularisation procedures. Patients were categorised into two groups according to drug use: the GLP1RA group and the SGLT2i group (Fig. 1). The information on GLP1RA and SGLT2i use was extracted from claims data for outpatient visits and pharmacy refills found in the NHI database. Participants were followed from the index date (date of the initial drug exposure) until the day of drug switching, death or 31 December 2019, whichever came first.

Covariates The covariates examined in this study were age, sex, duration of diabetes mellitus, number of outpatient visits for diabetes in the previous year (as an indicator of compliance or disease severity), presence of LEAD, comorbid conditions, diabetic complications and concomitantly used medications. Specified manifestations of LEAD included PAD, claudication and critical limb ischaemia (CLI). Comorbid conditions included CVD, coronary artery disease (CAD), atrial fibrillation, hypertension (HTN), dyslipidaemia, chronic kidney disease (CKD), end-stage renal disease (ESRD) under dialysis, chronic obstructive pulmonary disease and malignancy. Comorbidities were considered if they appeared in outpatient diagnoses at least twice or were included in any inpatient

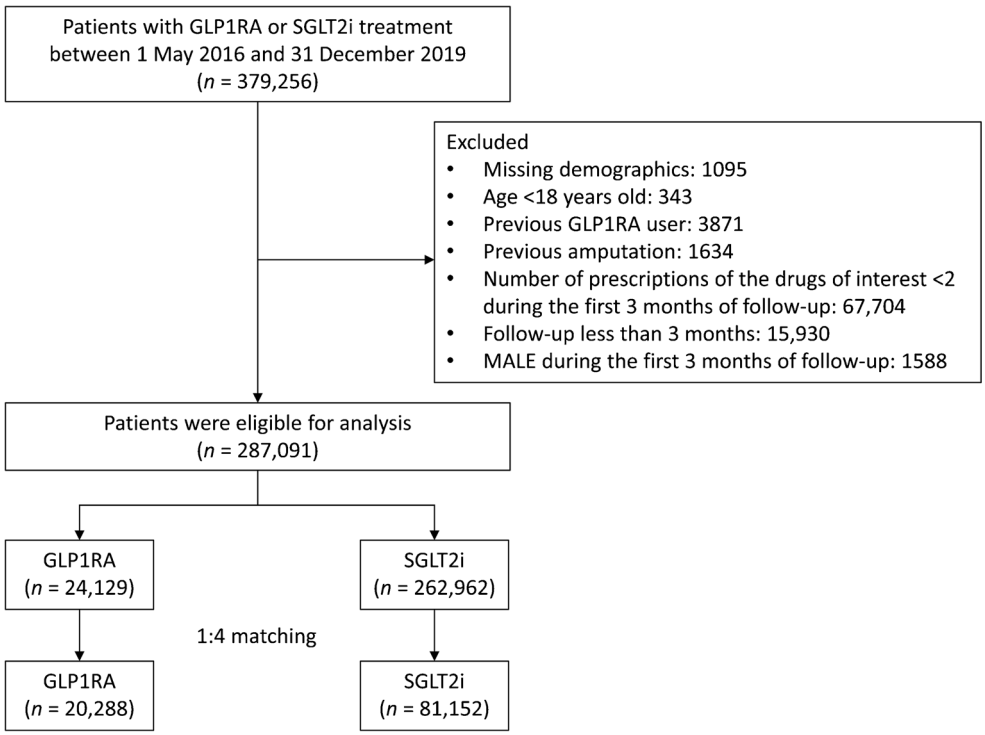

Fig. 1 Participant selection flowchart

diagnoses during the previous year. History of prior events was tracked as far back as 1995 and included any hospitalisation for myocardial infarction (MI), heart failure, cerebrovascular accidents (CVAs, including ischaemic stroke and intracranial haemorrhage), embolic events and venous thromboembolism (VTE). CVD was defined as a composite of PAD, CAD and history of admission for MI or CVA. Diabetic complications included retinopathy, autonomic neuropathy, peripheral neuropathy and nephropathy. Drug use was examined up to 6 months prior to the index date, and concomitant drugs were categorised into antiplatelet agents, anticoagulants, glucose-lowering agents and others.

Outcomes The primary outcome of this study was MALE, defined as the composite of newly diagnosed CLI, percutaneous transluminal angioplasty (PTA) or peripheral bypass surgery for PAD, and non-traumatic amputation. CLI was defined as persistent limb, foot or digit pain at rest or threatened tissue loss due to ischaemia (i.e., Fontaine classification III or IV ischaemia). Similar to the inclusion of covariates, diagnosis of CLI was recognised if it appeared at least twice in outpatient diagnoses or anytime in inpatient diagnoses. The occurrences of PTA, peripheral bypass and non-traumatic amputation were detected according to inpatient claims data based on the reimbursement codes for the Taiwan NHI. The secondary outcome was MACE, which was a composite of cardiovascular death, non-fatal MI and non-fatal ischaemic stroke. Other outcomes included death from any cause and hospitalisation for heart failure. Dates and causes of death were identified in the Taiwan Death Registry. Cardiovascular death was defined according to the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the United States Food and Drug Administration. Hospitalisation for MI, ischaemic stroke and heart failure was determined by the principal discharge diagnosis. Most of the diagnostic codes used in this study have been validated in previous National Health Insurance Research Database (NHIRD) studies [23–26].

Statistical analysis PSM was performed to minimise possible selection bias. The propensity score was defined as the conditional probability of the background covariates listed in Table 1 and was calculated using a multivariable logistic regression model in which the study groups (1: GLP1RA; and 0: SGLT2i) were regressed on the selected covariates (listed in Table 1, with the follow-up month replaced by the index date). Matching was conducted using a greedy nearest neighbour algorithm with a calliper of 0.2 times the standard deviation of the logit of the propensity score. Random matching order and replacement were not allowed. The anticipated incidence of the primary outcome (MALE) was low (e.g., less than 1%), and therefore participants in the GLP1RA and SGLT2i groups were matched at a 1:4 ratio to increase the statistical power. The quality of matching was assessed by the absolute value of the standardised difference (STD) between the groups after matching, where a value of less than 0.1 was considered negligible.

Table 1 Baseline characteristics of the diabetic patients who received GLP1RA vs SGLT2i therapy

Variable	Before PSM			After PSM		
	GLP1RA (*n*=24,129)	SGLT2i (*n*=262,962)	STD	GLP1RA (*n*=20,288)	SGLT2i (*n*=81,152)	STD
Age, years	56.5±13.7	58.7±12.1	−0.17	56.4±13.2	56.9±13.0	−0.04
Male	12,080 (50.1)	151,130 (57.5)	−0.15	10,471 (51.6)	41,763 (51.5)	<0.01
DM duration, years	7.1±2.9	6.6±3.1	0.17	6.9±3.0	7.0±2.9	−0.02
Number of outpatient visits for DM	9.3±6.2	7.6±5.0	0.29	8.5±5.2	8.4±5.3	<0.01
Prior LEAD						
PAD	1939 (8.0)	16,270 (6.2)	0.07	1408 (6.9)	5775 (7.1)	−0.01
Claudication	251 (1.04)	1356 (0.52)	0.06	165 (0.81)	648 (0.80)	<0.01
CLI	271 (1.12)	1574 (0.60)	0.06	150 (0.74)	605 (0.75)	<0.01
Any of above	2328 (9.6)	18,616 (7.1)	0.09	1644 (8.1)	6759 (8.3)	−0.01
Comorbid conditions						
CVD[a]	6236 (25.8)	73,954 (28.1)	−0.05	4893 (24.1)	19,826 (24.4)	−0.01
CAD	3815 (15.8)	52,792 (20.1)	−0.11	3061 (15.1)	12,454 (15.3)	−0.01
Atrial fibrillation	415 (1.7)	5500 (2.1)	−0.03	315 (1.6)	1365 (1.7)	−0.01
HTN	15,730 (65.2)	169,006 (64.3)	0.02	12,836 (63.3)	52,152 (64.3)	−0.02
Dyslipidaemia	17,600 (72.9)	187,248 (71.2)	0.04	14,947 (73.7)	59,868 (73.8)	<0.01
CKD (including dialysis)	10,263 (42.5)	72,408 (27.5)	0.32	7299 (36.0)	29,931 (36.9)	−0.02
COPD	871 (3.6)	9391 (3.6)	<0.01	688 (3.4)	2771 (3.4)	<0.01
Malignancy	1444 (6.0)	14,659 (5.6)	0.02	1176 (5.8)	4784 (5.9)	<0.01
History of events						
MI	811 (3.4)	12,097 (4.6)	−0.06	614 (3.0)	2596 (3.2)	−0.01
Heart failure	1197 (5.0)	10,043 (3.8)	0.06	688 (3.4)	3041 (3.7)	−0.02
CVA	1436 (6.0)	14,032 (5.3)	0.03	1056 (5.2)	4310 (5.3)	<0.01
Embolic event	187 (0.78)	1277 (0.49)	0.04	116 (0.57)	449 (0.55)	<0.01
VTE	112 (0.46)	798 (0.30)	0.03	62 (0.31)	271 (0.33)	<0.01
Diabetes complications						
Retinopathy	12,702 (52.6)	96,491 (36.7)	0.33	9811 (48.4)	39,528 (48.7)	−0.01
Autonomic neuropathy	3744 (15.5)	29,141 (11.1)	0.13	2807 (13.8)	11,162 (13.8)	<0.01
Peripheral neuropathy	12,736 (52.8)	99,233 (37.7)	0.31	9859 (48.6)	39,864 (49.1)	−0.01
Nephropathy	15,727 (65.2)	120,440 (45.8)	0.40	12,214 (60.2)	49,563 (61.1)	−0.02
Concomitant medications						
Antiplatelet agents						
Aspirin	7077 (29.3)	79,782 (30.3)	−0.02	5720 (28.2)	23,136 (28.5)	−0.01
Clopidogrel	1410 (5.8)	16,614 (6.3)	−0.02	1038 (5.1)	4226 (5.2)	<0.01
Ticagrelor	185 (0.77)	3881 (1.48)	−0.07	159 (0.78)	644 (0.79)	<0.01
Cilostazol	630 (2.6)	4200 (1.6)	0.07	392 (1.9)	1613 (2.0)	<0.01
Anticoagulants	494 (2.0)	6763 (2.6)	−0.03	379 (1.9)	1609 (2.0)	−0.01
Glucose-lowering medications						
Metformin	20,445 (84.7)	249,081 (94.7)	−0.33	18,872 (93.0)	75,058 (92.5)	0.02
SU	17,726 (73.5)	186,156 (70.8)	0.06	14,952 (73.7)	60,851 (75.0)	−0.03
Thiazolidinedione	5780 (24.0)	60,639 (23.1)	0.02	4932 (24.3)	19,870 (24.5)	<0.01
Alpha glucosidase inhibitors	5410 (22.4)	49,472 (18.8)	0.09	4396 (21.7)	17,440 (21.5)	<0.01
Non-SU insulin secretagogues (Glinide)	3302 (13.7)	15,811 (6.0)	0.26	1742 (8.6)	7497 (9.2)	−0.02
Insulin	6645 (27.5)	29,511 (11.2)	0.42	4018 (19.8)	15,091 (18.6)	0.03
Other medications						
ACEi or ARB	15,032 (62.3)	158,609 (60.3)	0.04	12,326 (60.8)	49,943 (61.5)	−0.02
ß-blockers	6948 (28.8)	78,974 (30.0)	−0.03	5567 (27.4)	22,698 (28.0)	−0.01

Table 1 (continued)

Variable	Before PSM			After PSM		
	GLP1RA (*n*=24,129)	SGLT2i (*n*=262,962)	STD	GLP1RA (*n*=20,288)	SGLT2i (*n*=81,152)	STD
DCCBs	7589 (31.5)	79,398 (30.2)	0.03	5878 (29.0)	24,256 (29.9)	−0.02
Statins	17,890 (74.1)	190,929 (72.6)	0.03	14,981 (73.8)	60,061 (74.0)	<0.01
NSAIDs/Cox-2 inhibitors	2250 (9.3)	21,967 (8.4)	0.03	1804 (8.9)	7276 (9.0)	<0.01
Diuretics	3074 (12.7)	19,920 (7.6)	0.17	1763 (8.7)	7497 (9.2)	−0.02
Spironolactone	1241 (5.1)	12,373 (4.7)	0.02	909 (4.5)	3806 (4.7)	−0.01
Propensity score	0.152±0.147	0.078±0.063	0.66	0.103±0.053	0.102±0.053	<0.01
Follow-up years	1.94±0.99	1.80±1.01	0.14	1.96±1.00	1.93±0.99	0.03

Data are mean±SD or *n* (%)

[a] Any one of PAD, CAD, MI or stroke

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; DCCB, dihydropyridine calcium channel blocker; DM, diabetes mellitus; NSAID, non-steroidal anti-inflammatory drugs; SU, sulfonylurea

The incidence of outcomes was expressed as the total number of events per 1000 person-years (PYs). The risks of fatal outcomes (i.e., MACE, cardiovascular death or all-cause mortality) were compared between the two groups using the Cox proportional hazards model. The incidence of non-fatal outcomes (e.g., MALE or amputation) was compared between groups using the Fine and Gray subdistribution hazard model, which considers all-cause mortality as a competing risk. For the analysis of MACE, death due to other causes was considered a competing risk. In addition to the subdistribution hazard method, we also performed analyses using the cause-specific hazard model as the sensitivity analysis. The study groups (GLP1RA vs SGLT2i) were the only explanatory variables included in survival analyses. The within-pair clustering of outcomes after matching was accounted for by using a robust standard error.

Subgroup analyses were further performed to examine whether the effects of treatment on the primary composite MALE outcome were consistent across different levels of prespecified subgroup variables. The prespecified subgroup variables of interest included age (dichotomised by 65 years); sex; diabetes duration (dichotomised by 5 years); any history of LEAD, CVD or CKD; the presence of microvascular complications of diabetes (i.e., retinopathy, neuropathy, nephropathy); and the use of statins. A two-sided p value <0.05 was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

The inclusion of study participants A total of 287,091 participants who met the previously detailed inclusion criteria were identified between 1 May 2016 and 31 December 2019. Of these, 262,962 were first treated with an SGLT2i and 24,129 were first treated with a GLP1RA during the study period. The mean length of follow-up was 1.80±1.01 years in the SGLT2i group and 1.94±0.99 years in the GLP1RA group before PSM. After PSM, 81,152 participants remained in the SGLT2i group, and 20,288 participants remained in the GLP1RA group (Fig. 1).

Baseline characteristics of the GLP1RA and SGLT2i groups The baseline characteristics for both the complete, unmatched and the PSM cohorts are listed in Table 1. Before matching, people who received GLP1RA were slightly younger (56.5 vs 58.7 years; STD −0.17), with a slightly longer diabetes duration (7.1 vs 6.6 years, STD 0.17), and attended clinic visits for diabetes-related reasons with slightly higher frequency (9.3 vs 7.6 times, STD 0.29). LEAD and all of its manifestations (i.e., PAD, claudication, CLI) were more prevalent in the GLP1RA group (9.6% vs 7.1% for LEAD, STD 0.09), as were all specified diabetic complications (retinopathy, neuropathy and nephropathy). In the GLP1RA group, higher prevalence rates of heart failure, dyslipidaemia, CKD and ESRD under dialysis were observed, in addition to higher prescription rates for antihypertensive drugs, cilostazol, statins, diuretics, glucose-lowering agents (except for metformin) and insulin (27.5% vs 11.2%, STD 0.42) at baseline. Metformin was prescribed less frequently in the GLP1RA group than in the SGLT2i group (84.7% vs 94.7%, STD −0.33). Before matching, the composite for cardiovascular disease was more prevalent in the SGLT2i group, largely due to a higher proportion of people with CAD. Antiplatelet agents, including aspirin, clopidogrel and ticagrelor, were more commonly used in the SGLT2i group than in the

GLP1RA group. After PSM, most baseline characteristics were well balanced between groups, as demonstrated by absolute STD values <0.1.

Limbs events for GLP1RA vs SGLT2i treatments The incidence of MALE was significantly lower in the GLP1RA group than in the SGLT2i group during follow-up (3.6 vs 4.5 events per 1000 PYs; subdistribution HR [SHR] 0.80; 95% CI 0.67, 0.96; Fig. 2a). The risk of newly diagnosed CLI was numerically lower in the GLP1RA group than in the SGLT2i group but did not reach significance (2.9 vs 3.4 events per 1000 PYs; SHR 0.83; 95% CI 0.68, 1.02; p=0.080; Fig. 2b). None of the other individual MALE components was significantly different between the two groups (Table 2). The results derived from cause-specific hazard models demonstrated consistent findings with the primary analysis by Fine and Gray subdistribution hazard models (the rightmost panel in Table 2).

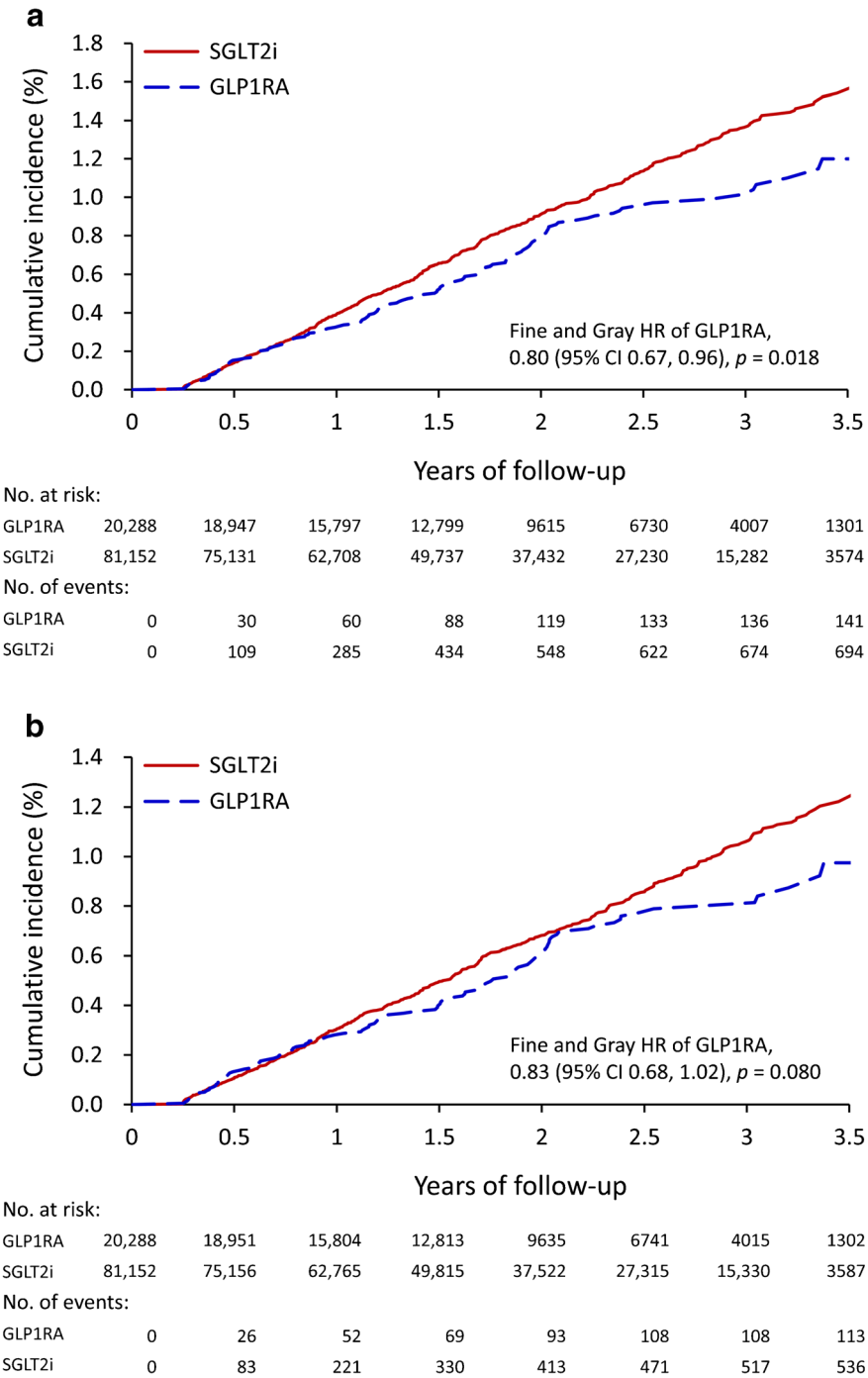

Fig. 2 The cumulative incidence functions for MALE (**a**) and newly diagnosed CLI (**b**) among people with diabetes treated with GLP1RAs vs SGLT2is in the propensity score-matched cohort

Table 2 Clinical events of the diabetic patients who received GLP1RA vs SGLT2i therapy in the propensity score-matched cohort

Outcome	GLP1RA (*n*=20,288) ID (95% CI)[a]	SGLT2i (*n*=81,152) ID (95% CI)[a]	Subdistribution hazard model		Cause-specific hazard model	
			SHR (95% CI)	*p* value	HR (95% CI)	*p* value
Primary outcome: MALE						
Newly diagnosed CLI	2.9 (2.3, 3.4)	3.4 (3.1, 3.7)	0.83 (0.68, 1.02)	0.080	0.83 (0.68, 1.02)	0.077
PTA or peripheral bypass	1.03 (0.72, 1.35)	1.22 (1.05, 1.39)	0.85 (0.61, 1.19)	0.343	0.85 (0.61, 1.19)	0.338
Amputation	0.65 (0.40, 0.91)	0.84 (0.70, 0.99)	0.78 (0.51, 1.19)	0.249	0.78 (0.51, 1.19)	0.245
Composite outcome	3.6 (3.0, 4.2)	4.5 (4.1, 4.8)	0.80 (0.67, 0.96)	0.018	0.80 (0.67, 0.96)	0.017
Secondary outcome: MACE						
Cardiovascular death	4.7 (4.1, 5.4)	5.2 (4.9, 5.6)	0.91 (0.78, 1.07)	0.238	0.91 (0.78, 1.06)	0.232
Ischaemic stroke	6.0 (5.3, 6.8)	6.5 (6.1, 6.9)	0.93 (0.81, 1.07)	0.316	0.93 (0.81, 1.07)	0.303
Acute MI	2.2 (1.8, 2.7)	2.7 (2.4, 2.9)	0.83 (0.66, 1.04)	0.108	0.83 (0.66, 1.04)	0.104
Composite outcome	12.5 (11.4, 13.6)	13.5 (12.9, 14.1)	0.93 (0.84, 1.02)	0.128	0.93 (0.84, 1.02)	0.122
Other outcomes						
All-cause death	9.7 (8.7, 10.7)	10.8 (10.3, 11.4)	NA	NA	0.90 (0.80, 1.00)	0.048
Heart failure hospitalisation	1.4 (1.0, 1.8)	1.7 (1.5, 1.9)	0.82 (0.61, 1.09)	0.166	0.81 (0.61, 1.09)	0.161

[a] Number of events per 100 PYs

ID, incidence density; NA, not applicable

Cardiovascular events and other outcomes for GLP1RA vs SGLT2i treatments The incidence of MACE occurred at similar frequencies in the GLP1RA and SGLT2i groups (12.5 vs 13.5 events per 1000 PYs; SHR 0.93; 95% CI 0.84, 1.02; *p*=0.128; Table 2). The incidences of all MACE components were also not significantly different between the two groups. The results derived from cause-specific hazard models demonstrated consistent findings with the primary analysis by Fine and Gray subdistribution hazard models (the rightmost panel in Table 2). The mortality rate was modestly but significantly lower in the GLP1RA group than in the SGLT2i group (9.7 vs 10.8 events per 1000 PYs; HR 0.90; 95% CI 0.80, 1.00; *p*=0.048).

Subgroup analysis of MALE The observed reduction in MALE associated with GLP1RA use remained consistent across various levels of subgroup variables, except for the presence of diabetic peripheral neuropathy (SHR 0.66 vs 1.11; *p* for interaction = 0.006), which revealed that the beneficial effects from GLP1RA use were more pronounced among people with diabetic peripheral neuropathy (Fig. 3).

Discussion

In this nationwide, retrospective cohort study, GLP1RA use reduced the risk of the primary composite outcome of MALE (consisting of newly diagnosed CLI, peripheral revascularisation interventions or amputations) compared with SGLT2i use after a mean follow-up of approximately 2 years, largely due to a lower incidence of new-onset CLI in the GLP1RA group. The incidences of MACE and its components, including cardiovascular death, MI and ischaemic stroke, were similar between the two treatment groups. All-cause mortality was significantly but modestly lower in people taking GLP1RAs. Subgroup analyses found that GLP1RA use was associated with significantly greater protective effects against MALE than in the SGLT2i group among people with diabetic peripheral neuropathy. These results suggest that GLP1RA use may be more favourable than SGLT2i use in people with diabetes who are at high risk of adverse limb events. The choice between these two drugs should be tailored according to each patient's underlying comorbidities.

Although significantly increased risk of amputation associated with SGLT2i use was not reported in any of the SGLT2i trials following the CANVAS study [10], controversy surrounding the potentially adverse association between SGLT2i and limb outcomes persisted as several meta-analyses [15, 27, 28] suggested a non-significant trend toward increased risk. Contrarily, data on the effects of GLP1RAs on limb outcomes, although scarce, point to beneficial results. A post hoc analysis of the LEADER trial [19] reported the benefits of liraglutide in reducing amputations due to diabetic foot ulcers (DFUs). Prior studies from the NHIRD reported superiority of GLP1RAs compared with dipeptidyl peptidase-4 inhibitors in terms of limb protection [29]. Ueda et al investigated the risks of serious adverse events with SGLT2i therapy in the real-world setting with GLP1RA as an active comparator and found increased risk of lower-limb amputation with SGLT2i use [17]; other limb outcomes, such as CLI or revascularisation procedures, were not reported. In our study,

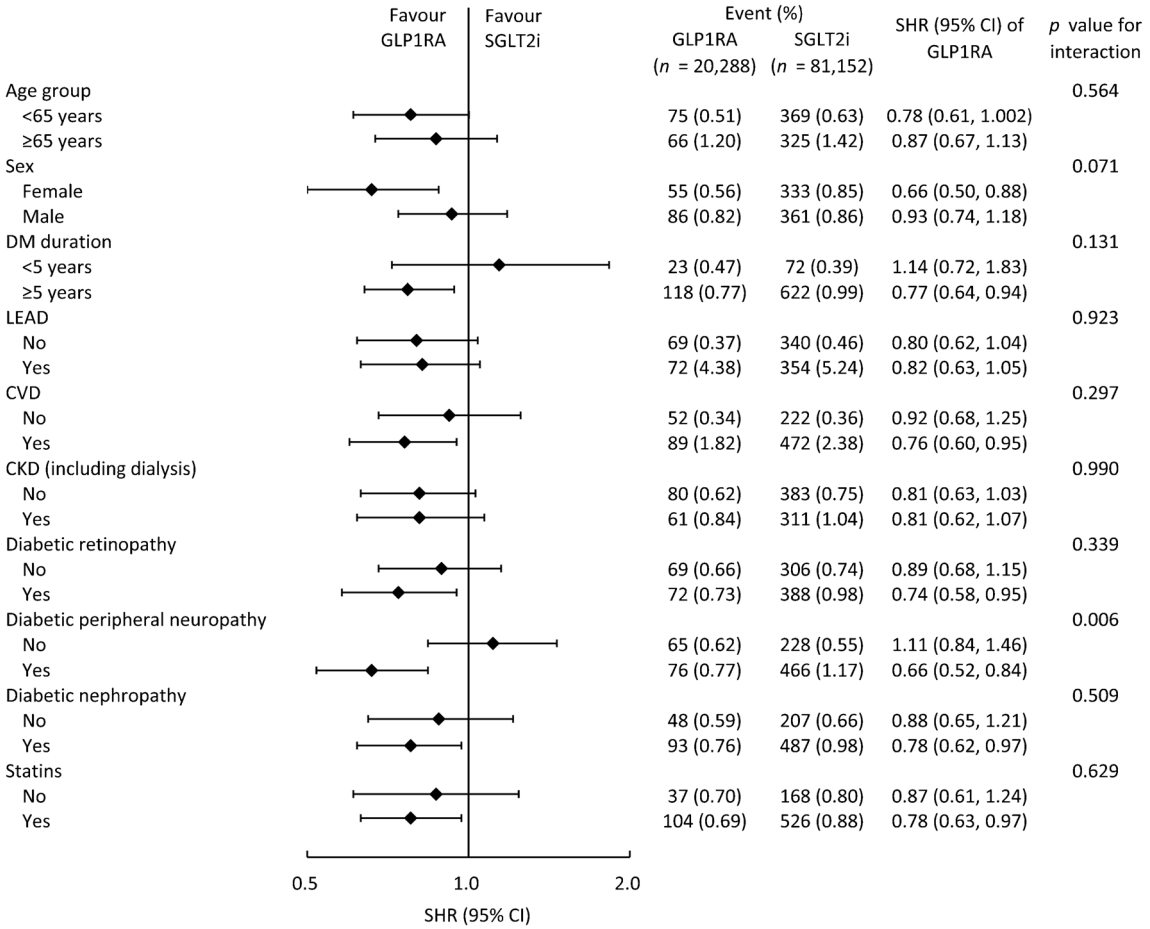

Fig. 3 The subgroup analysis comparing the effects of GLP1RA vs SGLT2i therapy on the risks of MALE in the propensity score-matched cohort. DM, diabetes mellitus

the use of GLP1RAs significantly reduced MALE occurrence compared with SGLT2i use. Although this was likely largely due to a reduction in newly diagnosed CLI, the hazards for all MALE components were numerically smaller for the GLP1RA group, despite the lack of statistically significant differences. The lack of significance observed for outcomes such as PTA, or surgical bypass and amputation, may have been limited by the small number of these events in the GLP1RA group. We look forward to more robust data that may be available with longer periods of follow-up.

Ever since SGLT2is and GLP1RAs demonstrated cardiovascular benefits in cardiovascular outcome trials (CVOTs), studies have attempted to elucidate the mechanisms of these drugs in reducing cardiovascular events. Currently, it is believed that SGLT2is exert more haemodynamic effects, while GLP1RAs have stronger anti-atherogenic actions [3]. In vitro studies have reported inhibition of several markers of endothelial dysfunction after exposure of human vascular endothelial cells to liraglutide [30, 31]. In apolipoprotein E-deficient mice, liraglutide prevented atherosclerotic plaque progression and promoted plaque stability [32]. Similar findings have also been reported in human in vivo investigations. Intravenous infusion of human recombinant glucagon-like peptide 1 (GLP-1) enhanced flow-mediated vasodilation (a hallmark of normal endothelial function) in people with type 2 diabetes and CAD [33], while exposure to exenatide improved endothelium-dependent vasorelaxation [34]. Treatment with liraglutide has also been reported to reduce carotid intima–media thickness in people living with diabetes and the metabolic syndrome [35]. Patients with LEAD are at extremely high risk of atherosclerotic cardiovascular events, with limb events being a manifestation of advanced disease. Other recent database studies that examined the effects of GLP1RAs and SGLT2is on limb events also found lower risks associated with GLP1RA use [18, 36]. Although direct causality between the aforementioned mechanistic findings and limb outcomes has not been established, the effects of GLP1RAs on atherosclerosis and endothelial function possibly play a role in the protection against MALE observed in our study.

In the present study, all-cause mortality was modestly but significantly reduced in the GLP1RA group compared with

the SGLT2i group (SHR 0.90; 95% CI 0.80, 1.00; p=0.048). At present, there are no large, randomised studies that directly compare the effects of these two drugs on overall survival rate. Previous network meta-analyses based on CVOTs showed no difference between GLP1RAs and SGLT2is in terms of all-cause mortality [37, 38]. In the present study, the risks of MACE and its components were, although numerically smaller in the GLP1RA group, not statistically different between the two groups. It is unknown how this may be related to the findings on all-cause mortality. In a recent database study comparing GLP1RAs against SGLT2is by Hsiao et al, the adjusted HR of all-cause death associated with GLP1RA use was 0.56 (95% CI 0.31, 1.01; p=0.054), albeit not significant [36]. Of note, in this study the risks of MI and stroke were significantly lower with GLP1RA use. Because non-cardiovascular deaths were considered in the results of our study, we extracted the causes of death from the NHIRD. We found that the causes of death included cancers, infections, liver failure, renal failure and diabetic complications. These results should be interpreted with caution as they might be due to confounding bias, which is often inevitable in observational database studies. Despite our limitations, we present data from a large database with up to 287,091 participants included in our analysis. As the use of GLP1RAs and SGLT2is continues to grow, this issue certainly warrants further investigation.

The results of our subgroup analyses showed that the reduction in MALE observed with GLP1RA use was more prominent in people with diabetic neuropathy. The association between peripheral neuropathy and adverse limb events is well known. In the observational Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) follow-up study, which followed participants from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial for up to 3 years after its conclusion, peripheral neuropathy (assessed by an abnormal 10 g filament test) was strongly predictive of lower-limb amputations during follow-up [39]. DFUs are the leading risk factor for non-traumatic lower-limb amputations in people with diabetes [40], and both neuropathy and PAD independently increase the risks of DFUs. The presence of both neuropathic and ischaemic aetiologies in DFUs, coined ‘neuro-ischaemic ulcers’, is reported to constitute up to 30% of all DFUs [41]. People with diabetic neuropathy are at particularly high risk of lower-limb complications, and concomitant atherosclerotic disease further heightens this risk. This likely explains why the benefits of GLP1RAs in reducing MALE are accentuated in these patients. Besides these clinical relationships between diabetic neuropathy and adverse limb outcomes, mechanistic investigations have also suggested therapeutic and neuroprotective actions of GLP1RAs in diabetic neuropathy [42]. Preclinical studies have demonstrated enhanced nerve regeneration and repair with incretin-based therapy in diabetic animal models [42]. Whether these actions contributed to the observed benefits of GLP1RA treatment in our study is unknown. Further prospective studies focusing on people with neuropathy with both quantifiable outcomes of nerve function and hard outcomes of limb events are needed to shed light on this subject.

Limitations This study has several limitations. First, the study population was identified in the NHIRD via ICD-9-CM and ICD-10-CM codes. However, the NHIRD does not include haemodynamic data, laboratory tests and imaging studies, which may contain substantial information regarding disease severity. Prognosis may be associated with the levels of serum creatinine, glycosylated haemoglobin, low-density lipoprotein or blood pressure. Although our study lacks these data, the prevalence of microvascular complications and insulin use may serve as surrogates for diabetes severity. In the present study, the two study groups were matched in terms of underlying diseases and drug use, aiming to minimise the confounding effects of disease severity.

Second, observational database studies are prone to influence by unmeasured confounders. For example, clinician and patient behaviours and socioeconomic status could not be assessed from the data included in the NHIRD. Socioeconomic status is strongly associated with cardiovascular outcomes, and the ‘healthy user’ effect may influence the choice of glucose-lowering drugs [43]. In the present study, GLP1RA was administered subcutaneously, whereas SLGT2i was administered orally. People who received GLP1RA are, therefore, more likely to be compliant with treatment and more capable of self-care. The aim of the present study was to assess and report the associations between GLP1RA or SGLT2i use and cardiovascular and limb events in real-world settings. Unmeasured confounders should be considered but, unfortunately, are impossible to eliminate completely in the real world.

Finally, as with many database studies, the length of follow-up was relatively short in our study; cardiovascular risk modification likely takes time to affect outcomes. In addition, the studied outcomes have a reportedly low incidence in the literature, even among high-risk individuals. The effects of the studied drugs might, therefore, be underestimated. Further investigations with longer study periods should be considered to better address these issues.

Conclusion In people with diabetes mellitus, GLP1RA use was associated with significantly lower risks of adverse limb events compared with the use of SGLT2is within the first 2 years after initiation. The reduction of risk was likely driven by the decreased incidence of CLI. The limb-protective effects of GLP1RAs were more pronounced in people with diabetic neuropathy.

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