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ARTICLE

Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors

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Abstract

Aims/hypothesis The safety and efficacy of glucagon-like peptide-1 receptor agonists (GLP1RAs) and dipeptidyl peptidase-4 inhibitors (DPP4is) in major cardiovascular adverse events were previously examined in cardiovascular outcome trials. However, the effects of these drugs on adverse limb outcomes were poorly examined. This study aimed to determine the real-world outcomes of patients with diabetes mellitus receiving GLP1RAs as compared with those receiving DPP4is in terms of major adverse cardiovascular and limb events.

Methods A retrospective cohort study was conducted with data collected by the Taiwan National Health Insurance database between 1 May 2011 and 31 December 2017. Patients who were treated for type 2 diabetes with a GLP1RA or DDP4i during this period ($n = 1{,}080{,}993$), were identified. The primary outcome was a composite of major adverse limb events, defined as peripheral artery disease (PAD), critical limb ischaemia, percutaneous transluminal angioplasty or peripheral bypass for PAD, and amputation. The secondary cardiovascular outcome was the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke. Propensity-score matching (PSM) at a 1:3 ratio between GLP1RA and DPP4i groups was done to minimise possible selection bias.

Results A total of 948,342 individuals treated between 1 May 2011 and 31 December 2017, were identified, with 4460 in the GLP1RA group and 13,380 in the DPP4i group after PSM. The incidence of primary composite outcome events was significantly lower in those treated with GLP1RAs compared with those treated with DPP4is (2.59 vs 4.22 events per 1000 person-years; subdistribution HR [SHR] 0.63 [95% CI 0.41, 0.96]), primarily due to lower rates of amputation (1.29 events per 1000 person-years for GLP1RAs vs 2.4 events per 1000 person-years for DPP4is; SHR 0.55 [95% CI 0.30, 0.99]). Treatment with GLP1RAs was also associated with significantly lower risks of secondary composite outcome events (11.02 vs 17.95 events per 1000 person-years; HR 0.62 [95% CI 0.51, 0.76]). Moreover, the observed beneficial effects of GLP1RAs on reducing composite adverse limb outcomes were particularly noticeable in the non-cardiovascular patients and statin users (p for interaction <0.05).

Conclusions/interpretation In individuals with diabetes, the use of GLP1RAs was associated with significantly lower risks of major adverse limb events when compared with the use of DPP4is. The reduction in risk was driven largely by reduced rate of amputations. Moreover, treatment with GLP1RAs was also associated with lower risks of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction and death from any cause. However, some unexplored confounding factors may exist in this observation study and future large-scale randomised controlled trials are needed.

Keywords Diabetes · Dipeptidyl peptidase-4 inhibitors · Glucagon-like peptide-1 receptor agonist · Major adverse cardiovascular events · Major adverse limb events

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Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CANVAS	Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
CLI	Critical limb ischaemia
CVOT	Cardiovascular outcome trial

Research in context

What is already known about this subject?

- Glucagon-like peptide-1 receptor agonists (GLP1RAs) have been shown to reduce major adverse cardiovascular events (MACE) compared with placebo, and dipeptidyl peptidase-4 inhibitors (DPP4is) have also demonstrated cardiovascular safety
- The impact of GLP1RAs and DPP4is on major adverse limb outcomes (MALE) is poorly investigated in the literature
- Prior studies have mainly compared GLP1RAs and DPP4is against placebo; how they compare with each other in prevention of MACE and MALE is largely unknown

What is the key question?

- How do GLP1RAs and DPP4is compare in terms of preventing MALE and MACE?

What are the new findings?

- In individuals with diabetes, the use of GLP1RAs was associated with significantly lower risks of MALE than the use of DPP4is, the reduction in risk being driven largely by a reduced rate of amputations
- Treatment with GLP1RAs was also associated with reduced MACE compared with DPP4i

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

- In individuals with diabetes, the use of GLP1RAs should be considered over DPP4is, especially in those at high risk for MALE and MACE

DFU	Diabetic foot ulcers
DPP4i	Dipeptidyl peptidase-4 inhibitor
GLP1RA	Glucagon-like peptide-1 receptor agonist
HFH	Hospitalisation for heart failure
LEAD	Lower-extremity arterial disease
LEADER	Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
PAD	Peripheral artery disease
PSM	Propensity-score matching
PTA	Percutaneous transluminal angioplasty
RWD	Real-world data
SHR	Subdistribution HR
SGLT2i	Sodium–glucose cotransporter 2 inhibitor
STD	Standardised difference
TDR	Taiwan Death Registry

Introduction

Diabetes mellitus is a global pandemic, affecting over 400 million people worldwide in 2014 according to WHO statistics [1], with a prevalence of 8.5% in the adult population. Cardiovascular disease is the most common cause of morbidity and mortality in individuals with diabetes [2–4]. Diabetes is a strong risk factor for systemic atherosclerosis, with peripheral artery disease (PAD) subsequently being a major source of morbidity [5–7]. In addition, diabetes per se leads to worse prognosis in individuals with atherosclerotic disease (e.g. the combination of diabetes and PAD is associated with a fivefold increased risk of amputation and a threefold increased risk of death as compared with PAD alone [8]).

It is well known that adequate glycaemic control improves microvascular outcomes in individuals with diabetes but has little effect on macrovascular events [9–11]. In recent years, there has been a paradigm shift in the treatment of diabetes, from historically aiming for euglycaemia to now targeting the prevention of cardiovascular events. Since 2008, it has been mandatory that all novel glucose-lowering agents be evaluated for cardiovascular safety in cardiovascular outcome trials (CVOTs). CVOTs have demonstrated the safety of dipeptidyl peptidase-4 inhibitors (DPP4is) [12–16]. On the other hand, sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP1RAs) have exhibited excellent effects in reducing major adverse cardiovascular events (MACE) [17–27]. These unique effects have been validated through numerous studies involving real-world data (RWD). Current guidelines also advocate these drugs as first-line therapies for patients with high cardiovascular risk in order to reduce future MACE.

Notably, however, the outcomes of interest in CVOTs have primarily been cardiovascular mortality, myocardial infarction, stroke, heart failure and all-cause mortality, whereas the effects of glucose-lowering agents on PAD have been poorly examined. A potential safety issue was observed in the

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) Program, in which canagliflozin was found to be associated with a higher risk of amputation [27]. However, real-world evidence regarding the association between amputations and the use of SGLT2is has been inconsistent. Similarly, there have been only limited investigations of the effects of GLP1RAs on amputation. Liraglutide was found to have superior efficacy in reducing limb events in comparison with a control group in the Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) programme [28] but this has not been demonstrated by other GLP1RAs. Furthermore, in previous CVOTs, the safety and efficacy of GLP1RAs and DPP4is have been investigated mostly in comparison with a placebo. Direct comparisons between GLP1RAs and DPP4is, meanwhile, are lacking in the literature, and the performance of either drug in preventing adverse limb events is largely unknown.

The present study thus aimed to determine the real-world outcomes of individuals with diabetes receiving GLP1RAs vs DPP4is in terms of major adverse cardiovascular and limb events. We enrolled individuals from the largest cohort in Asia using a nationwide database including nearly 100% of the adult patients with diabetes in Taiwan, with the enrolled patients being subjected to propensity-score matching (PSM) according to their clinical characteristics.

Methods

Data source This retrospective cohort study linked patient data from the Taiwan National Health Insurance (NHI) database to data from the Taiwan Death Registry (TDR) via unique and de-identified civil identification numbers. Taiwan's NHI programme is a single-payer system that was established in March 1995 and currently provides coverage to more than 99.8% of the population in Taiwan (currently approximately 23.7 million people). The NHI data were collected by the National Health Informatics Project (NHIP) and managed by the Health and Welfare Data Science Center (HWDC). Data on patients covered by the NHI programme from 1995 through 2017 is available in the National Health Insurance Research Database (NHIRD). Enrolment in the NHI programme is mandatory and affordable in Taiwan, and offers appropriate acute and long-term care that is in line with global standards. This study was exempted from a full review by the Ethics Institutional Review Board of Taiwan University Hospital as all personal information in the NHIRD are de-identified and anonymised, such that informed consent was not needed. Further information regarding the NHI programme and the NHI database has been reported in previous publications [29–31].

Study cohort Patients who were first treated for type 2 diabetes (ICD, Ninth Revision, Clinical Modification [ICD-9-CM] Code 250 [http://www.icd9data.com/2007/Volume1/default.htm] between 1 May 2011 and 31 December 2015 or ICD-10-CM codes E10.0, E10.1, E10.9, E11.0, E11.1 and E11.9 [http://apps.who.int/classifications/icd10/browse/2016/en] between 1 January 2016 and 31 December 2017) with either GLP1RAs or DDP4is between 1 May 2011 and 31 December 2017 ($n = 1{,}080{,}993$), were identified. Individuals who met the following criteria were excluded: (1) those who had missing demographical data (<1%); (2) those who were aged <18 years (3); those who were previously exposed to a DPP4i or SGLT2i within 3 months before the index date; or (4) those who had undergone a prior amputation. The individuals who were ultimately included were separated into two groups according to drug exposure: the GLP1RA group and the DPP4i group (Fig. 1). The index date for each study group was defined as the day on which a GLP1RA or DPP4i was first prescribed after 1 May 2011. Individuals were followed until the occurrence of any study outcomes or 31 December 2017, whichever came first.

Covariates The covariates were age, sex, diabetes duration, number of outpatient visits for diabetes in the previous year (as a proxy of compliance or disease severity), history of lower-extremity arterial disease (LEAD), comorbidities, history of events, diabetes complications and concomitant medications. The history of LEAD included any incidence of claudication, PAD or critical limb ischaemia (CLI). Comorbidities included CVD, coronary artery disease (CAD), atrial fibrillation, hypertension, dyslipidaemia, chronic kidney disease, dialysis, chronic obstructive pulmonary disease and malignancy. CVD consisted of PAD, CAD, myocardial infarction or stroke. The history of events included any prior hospitalisation for myocardial infarction, heart failure, stroke, embolic event or venous thromboembolism that could be tracked back to 1995. Diabetes complications consisted of retinopathy, autonomic neuropathy, peripheral neuropathy and nephropathy. Instances of LEAD and its components, comorbidities and diabetes complications were detected with at least two outpatient diagnoses or any single inpatient diagnosis in the previous year. According to the prescription records for the previous 6 months, the medications were classified into three categories: anti-thrombotic, glucose-lowering and other. Details of the ICD diagnostic codes used in this study are provided in the supplement (electronic supplementary material [ESM] Table 1).

Outcomes The primary outcome of this study was the composite of major adverse limb events (MALE), defined as the first event of newly diagnosed PAD, newly diagnosed CLI, percutaneous transluminal angioplasty (PTA) or peripheral bypass for PAD, and amputation. Amputations included major, minor, below-the-knee and above-the-knee

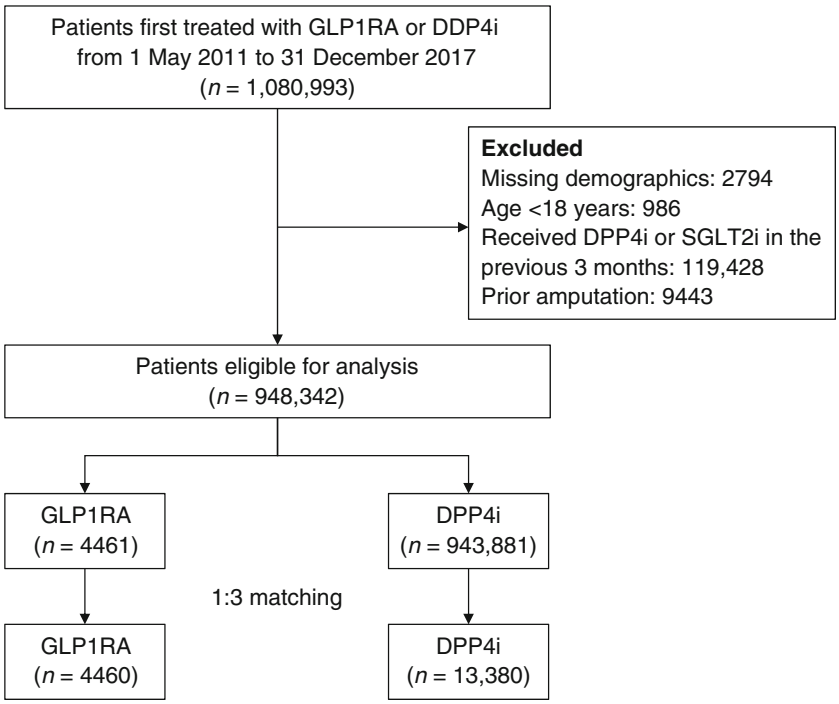


Fig. 1 Flowchart showing patient selection

amputations. The ICD-9-CM clinical diagnosis codes 440.22 (rest pain), 440.23 (ulceration) and 440.24 (gangrene) were applied in accordance with previous CLI studies [32, 33]. 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). The occurrence of PAD and CLI required at least two outpatient diagnoses or any single inpatient diagnosis. PTA, peripheral bypass and amputation were identified using Taiwan's NHI reimbursement codes contained in the inpatient claims data. The secondary cardiovascular outcomes were MACE (the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke). Other outcomes examined included all-cause death and hospitalisation for heart failure (HFH). The date and cause of death were determined using the TDR. The definition of cardiovascular death was based on the criteria of the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials published by the USA Food and Drug Administration. Myocardial infarction, ischaemic stroke and HFH were detected using the principal discharge diagnosis. Most of the above diagnostic codes have been validated in previous NHIRD studies [34–39].

Statistical analysis To mitigate possible selection bias, PSM was utilised in this study. The propensity score, defined as the conditional probability of the background covariates listed in Table 1, was calculated using a multivariable logistic regression model in which the study groups (1, GLP1RAs; 0, DPP4is) were regressed on the selected covariates (listed in Table 1), without considering interaction effects among covariates. The matching was processed using a greedy nearest neighbour algorithm with a calliper of 0.2 times the SD of the logit of the propensity score. A random matching order and replacement were not allowed. Individuals in the GLP1RA and DPP4i groups were matched at a 1:3 ratio. The quality of matching was assessed by the absolute value of standardised difference (STD) between the groups after PSM, where a value of less than 0.1 was considered negligible.

The incidence of each outcome was expressed as the total number of events per 1000 person-years at risk. The risk of fatal outcomes (i.e. all-cause death or MACE) was compared between the two groups using the Cox proportional hazard model. The incidence of non-fatal outcomes (e.g. MALE or amputation) was compared between the groups using the Fine and Gray subdistribution hazard model, which considered all-cause mortality a competing risk. The study group (GLP1RA vs DPP4i) was the only explanatory variable in the aforementioned survival analyses. The within-pair clustering of outcomes after PSM was accounted for by using a robust SE.

Further subgroup analyses were conducted to evaluate the consistency of the observed treatment effects on specified outcomes across different levels of subgroup variables. The outcomes of interest included MALE and MACE. The pre-specified subgroup variables of interest included age (dichotomised by 65 years), sex, duration of diabetes (dichotomised by 10 years), the presence of LEAD, the presence of CVD (a composite of PAD, CHD, history of prior myocardial infarction, and cerebrovascular accidents), the presence of chronic kidney disease, the presence of

Table 1 Baseline characteristics of the diabetic patients who received GLP1RA vs DPP4i therapy before and after matching

Variable	Before matching			After matching		
	GLP1RA (n=4461)	DPP4i (n=943,881)	STD	GLP1RA (n=4460)	DPP4i (n=13,380)	STD
Age, years	50.3±13.2	62.2±13.2	−0.90	50.3±13.2	50.2±13.0	0.01
Male sex	2110 (47.3)	506,169 (53.6)	−0.13	2110 (47.3)	6279 (46.9)	0.01
Diabetes duration, years	8.4±5.7	7.7±5.1	0.12	8.4±5.7	8.3±5.6	0.02
No. of outpatient visits for diabetes in the previous year	7.7±5.3	7.1±5.6	0.10	7.7±5.3	7.7±6.0	<0.01
History of LEAD						
Claudication	42 (0.9)	5442 (0.6)	0.04	42 (0.9)	102 (0.8)	0.02
PAD	324 (7.3)	83,802 (8.9)	−0.06	324 (7.3)	972 (7.3)	<0.01
CLI	4 (0.1)	964 (0.1)	<0.01	4 (0.1)	13 (0.1)	<0.01
Any of the above	382 (8.6)	96,053 (10.2)	−0.06	382 (8.6)	1154 (8.6)	<0.01
Comorbidity						
CVD[a]	902 (20.2)	294,606 (31.2)	−0.25	902 (20.2)	2707 (20.2)	<0.01
CAD	501 (11.2)	158,435 (16.8)	−0.16	501 (11.2)	1447 (10.8)	0.01
Atrial fibrillation	41 (0.9)	20,920 (2.2)	−0.10	41 (0.9)	132 (1.0)	−0.01
Hypertension	2519 (56.5)	594,792 (63.0)	−0.13	2518 (56.5)	7578 (56.6)	<0.01
Dyslipidaemia	2882 (64.6)	493,462 (52.3)	0.25	2881 (64.6)	8615 (64.4)	<0.01
Chronic kidney disease	1169 (26.2)	201,821 (21.4)	0.11	1168 (26.2)	3550 (26.5)	−0.01
Dialysis	35 (0.8)	16,527 (1.8)	−0.09	35 (0.8)	108 (0.8)	<0.01
Chronic obstructive pulmonary disease	121 (2.7)	44,200 (4.7)	−0.10	121 (2.7)	360 (2.7)	<0.01
Malignancy	158 (3.5)	63,350 (6.7)	−0.14	158 (3.5)	483 (3.6)	<0.01
History of event						
Myocardial infarction	102 (2.3)	35,955 (3.8)	−0.09	102 (2.3)	290 (2.2)	0.01
Heart failure	145 (3.3)	48,880 (5.2)	−0.10	145 (3.3)	424 (3.2)	<0.01
Stroke	215 (4.8)	103,853 (11.0)	−0.23	215 (4.8)	628 (4.7)	0.01
Embolic event	35 (0.8)	7095 (0.8)	<0.01	35 (0.8)	99 (0.7)	<0.01
Osteomyelitis	32 (0.7)	5943 (0.6)	0.01	32 (0.7)	93 (0.7)	<0.01
Venous thromboembolism	15 (0.3)	3571 (0.4)	−0.01	15 (0.3)	49 (0.4)	−0.01
Diabetes complications						
Retinopathy	1554 (34.8)	163,477 (17.3)	0.41	1553 (34.8)	4658 (34.8)	<0.01
Autonomic neuropathy	806 (18.1)	166,010 (17.6)	0.01	806 (18.1)	2382 (17.8)	0.01
Peripheral neuropathy	1671 (37.5)	246,676 (26.1)	0.25	1671 (37.5)	4965 (37.1)	0.01
Nephropathy	1979 (44.4)	269,551 (28.6)	0.33	1978 (44.4)	5958 (44.5)	<0.01
Anti-thrombotic medications						
Aspirin	977 (21.9)	283,572 (30.0)	−0.19	976 (21.9)	2917 (21.8)	<0.01
Clopidogrel	73 (1.6)	43,098 (4.6)	−0.17	73 (1.6)	230 (1.7)	−0.01
Ticagrelor	12 (0.3)	4808 (0.5)	−0.04	12 (0.3)	45 (0.3)	−0.01
Cilostazol	80 (1.8)	20,718 (2.2)	−0.03	80 (1.8)	227 (1.7)	0.01
Anticoagulants	33 (0.7)	14,628 (1.6)	−0.08	33 (0.7)	110 (0.8)	−0.01
Glucose-lowering medications						
Metformin	3930 (88.1)	816,420 (86.5)	0.05	3929 (88.1)	11,856 (88.6)	−0.02
Sulfonylurea	2572 (57.7)	633,434 (67.1)	−0.20	2572 (57.7)	7789 (58.2)	−0.01
Thiazolidinedione	1003 (22.5)	156,492 (16.6)	0.15	1002 (22.5)	3044 (22.8)	−0.01
α-Glucosidase inhibitors	404 (9.1)	127,273 (13.5)	−0.14	404 (9.1)	1209 (9.0)	<0.01
Non-sulfonylurea insulin secretagogues (glinide)	129 (2.9)	68,979 (7.3)	−0.20	129 (2.9)	369 (2.8)	0.01
Insulin	2383 (53.4)	140,478 (14.9)	0.89	2382 (53.4)	7044 (52.7)	0.02
Other medications						
ACEi or ARBs	2561 (57.4)	546,098 (57.9)	−0.01	2560 (57.4)	7675 (57.4)	<0.01

Table 1 (continued)

Variable	Before matching			After matching		
	GLP1RA ($n = 4461$)	DPP4i ($n = 943,881$)	STD	GLP1RA ($n = 4460$)	DPP4i ($n = 13,380$)	STD
β-Blockers	1353 (30.3)	318,840 (33.8)	−0.07	1352 (30.3)	4047 (30.3)	<0.01
DCCBs	1186 (26.6)	349,619 (37.0)	−0.23	1186 (26.6)	3522 (26.3)	0.01
Digoxin	39 (0.9)	19,863 (2.1)	−0.10	39 (0.9)	121 (0.9)	<0.01
Statins	2779 (62.3)	494,358 (52.4)	0.20	2778 (62.3)	8294 (62.0)	0.01
NSAIDs/COX-2 inhibitors	337 (7.6)	88,710 (9.4)	−0.07	337 (7.6)	1007 (7.5)	<0.01
Diuretics	392 (8.8)	118,896 (12.6)	−0.12	392 (8.8)	1250 (9.3)	−0.02
Spironolactone	144 (3.2)	39,787 (4.2)	−0.05	143 (3.2)	439 (3.3)	<0.01
Follow-up period, years	2.3±1.9	3.2±1.9	−0.51	2.3±1.9	2.2±1.9	0.04

Data are shown as mean ± SD or *n* (%)

[a] Any one of PAD, CAD, myocardial infarction or stroke

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COX-2, cyclooxygenase-2; DCCBs, dihydropyridine calcium channel blockers; NSAID, nonsteroidal anti-inflammatory drug

microvascular complications of diabetes (i.e. retinopathy, neuropathy, nephropathy) and the use of certain drugs (i.e. antiplatelet agents, metformin, sulfonylureas, insulin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, dihydropyridine calcium channel blockers, statins). A two-sided p value <0.05 was considered to be statistically significant. However, the clinical significance criterion of the subgroup analyses was loosened to $p < 0.1$ because the interaction test was conservative. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), including the procedures of 'psmatch' for PSM, 'phreg' for survival analysis, and the macro of '%cif' for generating cumulative incidence functions under the Fine and Gray subdistribution hazard method.

Results

The inclusion of study patients A total of 948,342 patients treated between 1 May 2011 and 31 December 2017 were identified in accordance with the aforementioned inclusion criteria. During the study period, individuals who were first treated with either a GLP1RA ($n = 4461$) or a DPP4i ($n = 943,881$) were included. Before matching, the GLP1RA group was followed for a mean of 2.3 years (SD 1.9 years) and the DPP4i group was followed for a mean of 3.2 years (SD 1.9 years). After matching, there remained 4460 individuals in the GLP1RA group and 13,380 individuals in the DPP4i group (Fig. 1).

Baseline characteristics of GLP1RA and DDP4i groups The baseline characteristics of the entire unmatched and propensity-score matched cohorts are listed in Table 1. Before matching, the GLP1RA group had the following features in relation to the DPP4i group: they were much younger (50.3 vs 62.2 years, STD −0.90); had a longer diabetes duration (8.4 vs 7.7 years, STD 0.12); had greater prevalence rates of retinopathy, peripheral neuropathy and nephropathy; had a higher rate of insulin use (53.4% vs 14.9%; STD 0.89); had higher prevalence rates of dyslipidaemia and statin use; had lower rates of CAD and CVD; and had lower rates of prescriptions for aspirin, clopidogrel and dihydropyridine calcium channel blockers at baseline. Notably, PAD and its related comorbidities, including claudication, lower limb ulcers and CLI, were present at similar proportions in both groups prior to matching. After matching, all of the baseline characteristics were well-balanced between the groups, as demonstrated by all the STD values being <0.1.

Limb events in GLP1RA vs DDP4i groups During a mean follow-up of 2.2 years, the incidence of MALE was significantly lower in individuals treated with GLP1RAs compared with those treated with DPP4is (2.59 vs 4.22 events per 1000 person-years; Subdistribution HR [SHR] 0.63 [95% CI 0.41, 0.96]) (Fig. 2a). Noticeably, this was largely driven by a lower risk of amputation (1.29 for GLP1RA vs 2.4 for DPP4i events per 1000 person-years; SHR 0.55 [95% CI 0.30, 0.99]) (Fig. 2b). The risks of newly diagnosed PAD and peripheral revascularisation procedures were not significantly different between the matched GLP1RA and DPP4i groups. There were no newly diagnosed cases of CLI in individuals receiving GLP1RAs (Table 2).

Cardiovascular events in GLP1RA vs DDP4i groups There was a significantly lower frequency of secondary composite outcome events in the GLP1RA group compared with the DPP4i group (11.02 vs 17.95 events per 1000 person-years;

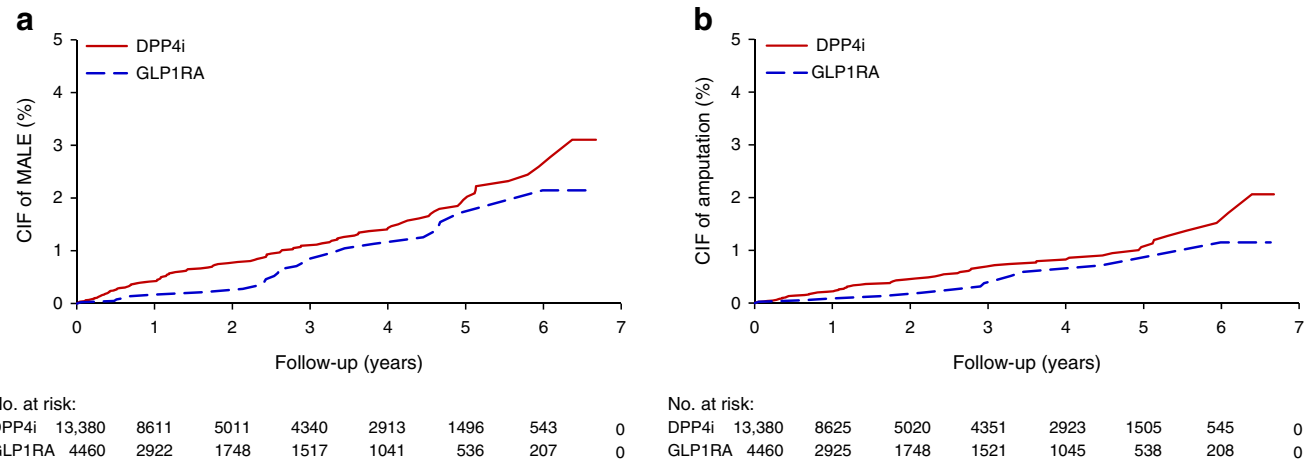


Fig. 2 The cumulative incidence functions of MALE (**a**) and amputation (**b**) for the diabetic patients who received GLP1RA vs DPP4i therapy in the propensity-score matched cohort. The SHR (95% CI) for GLP1RAs vs DPP4is was 0.63 (0.41, 0.96) ($p = 0.030$) for MALE and 0.55 (0.30, 0.99) ($p = 0.046$) for amputation. CIF, cumulative incidence function

HR 0.62 [95% CI 0.51, 0.76]) (Fig. 3a). Treatment with GLP1RAs was also associated with significantly lower risks of cardiovascular death (4.46 vs 8.42 events per 1000 person-years; HR 0.53 [95% CI 0.39, 0.73]), non-fatal ischaemic stroke (5.2 vs 7.51 events per 1000 person-years; HR 0.71 [95% CI 0.52, 0.96]) and non-fatal myocardial infarction (2.39 vs 3.8 events per 1000 person-years; HR 0.63 [95% CI 0.40, 0.97]). Death from any cause occurred at a lower rate in individuals receiving GLP1RAs compared with those receiving DPP4i (7.73 vs 18.14 events per 1000 person-years; HR 0.43 [95% CI 0.34, 0.54]) (Fig. 3b). The risk of HFH was not significantly different between the two groups (Table 2).

Subgroup analysis of MALE and MACE The decreased risk of MALE associated with the use of GLP1RAs remained consistent across different levels of subgroup variables, except for CVD history and statin use. The beneficial effects of GLP1RAs were particularly noticeable in non-CVD patients and statin users (p for interaction <0.05) (Fig. 4). In terms of MACE, the improved outcomes associated with GLP1RA treatment remained consistent across different levels of subgroup variables, except for statin use. The beneficial effects of GLP1RAs were more apparent in the statin users (p for interaction <0.1) (Fig. 5).

Table 2 Clinical events of the diabetic patients who received GLP1RA vs DPP4i therapy after matching

Outcome	GLP1RA (n=4460)		DPP4i (n=13,380)		GLP1RA vs DPP4i	
	Events, n (%)	ID (95% CI)[a]	Events, n (%)	ID (95% CI)[a]	HR or SHR (95% CI)	p value
Primary outcome: MALE	26 (0.58)	2.59 (1.59, 3.58)	123 (0.92)	4.22 (3.47, 4.96)	0.63 (0.41, 0.96)	0.030
Individual component of MALE						
Newly diagnosed PAD	8 (0.18)	0.79 (0.24, 1.34)	38 (0.28)	1.30 (0.89, 1.71)	0.63 (0.29, 1.35)	0.233
Newly diagnosed CLI	0 (0.00)	0.00 (0.00, 0.00)	5 (0.04)	0.17 (0.02, 0.32)	NA	NA
PTA or peripheral bypass	12 (0.27)	1.19 (0.52, 1.87)	57 (0.43)	1.95 (1.44, 2.45)	0.63 (0.34, 1.17)	0.142
Amputation	13 (0.29)	1.29 (0.59, 1.99)	70 (0.52)	2.40 (1.83, 2.96)	0.55 (0.30, 0.99)	0.046
Secondary outcome: MACE	110 (2.47)	11.02 (8.96, 13.08)	516 (3.86)	17.95 (16.40, 19.50)	0.62 (0.51, 0.76)	<0.001
Individual component of MACE						
Cardiovascular death	45 (1.01)	4.46 (3.16, 5.76)	247 (1.85)	8.42 (7.37, 9.47)	0.53 (0.39, 0.73)	<0.001
Non-fatal ischaemic stroke	52 (1.17)	5.20 (3.78, 6.61)	217 (1.62)	7.51 (6.51, 8.51)	0.71 (0.52, 0.96)	0.024
Non-fatal myocardial infarction	24 (0.54)	2.39 (1.43, 3.34)	113 (0.84)	3.87 (3.16, 4.59)	0.63 (0.40, 0.97)	0.038
Other outcomes						
All-cause death	78 (1.75)	7.73 (6.02, 9.45)	532 (3.98)	18.14 (16.59, 19.68)	0.43 (0.34, 0.54)	<0.001
HFH	39 (0.87)	3.90 (2.67, 5.12)	145 (1.08)	4.98 (4.17, 5.80)	0.80 (0.56, 1.13)	0.206

[a] Expressed as no. of events per 1000 person-years

ID, incidence density

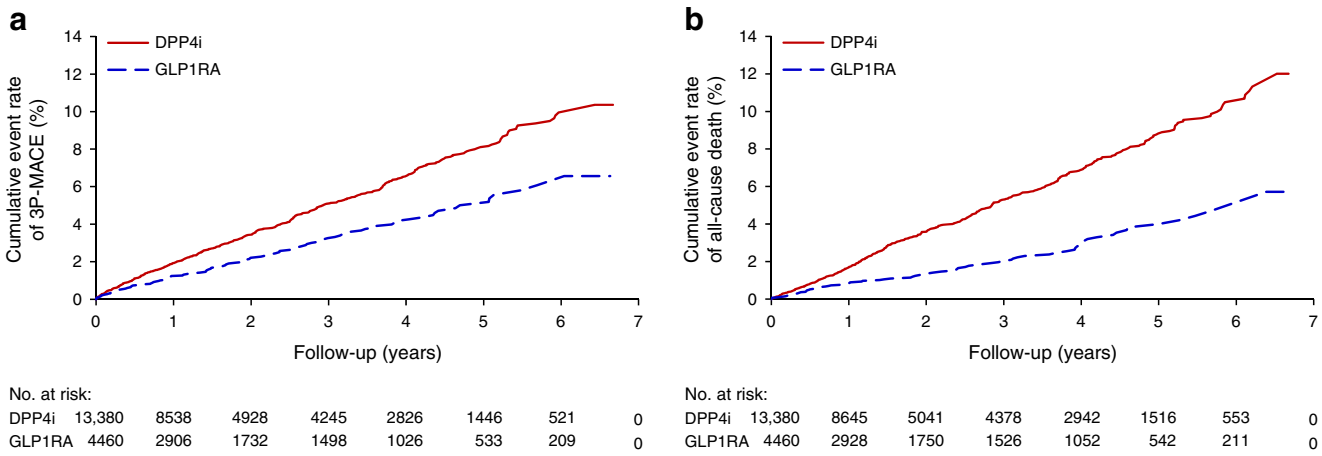


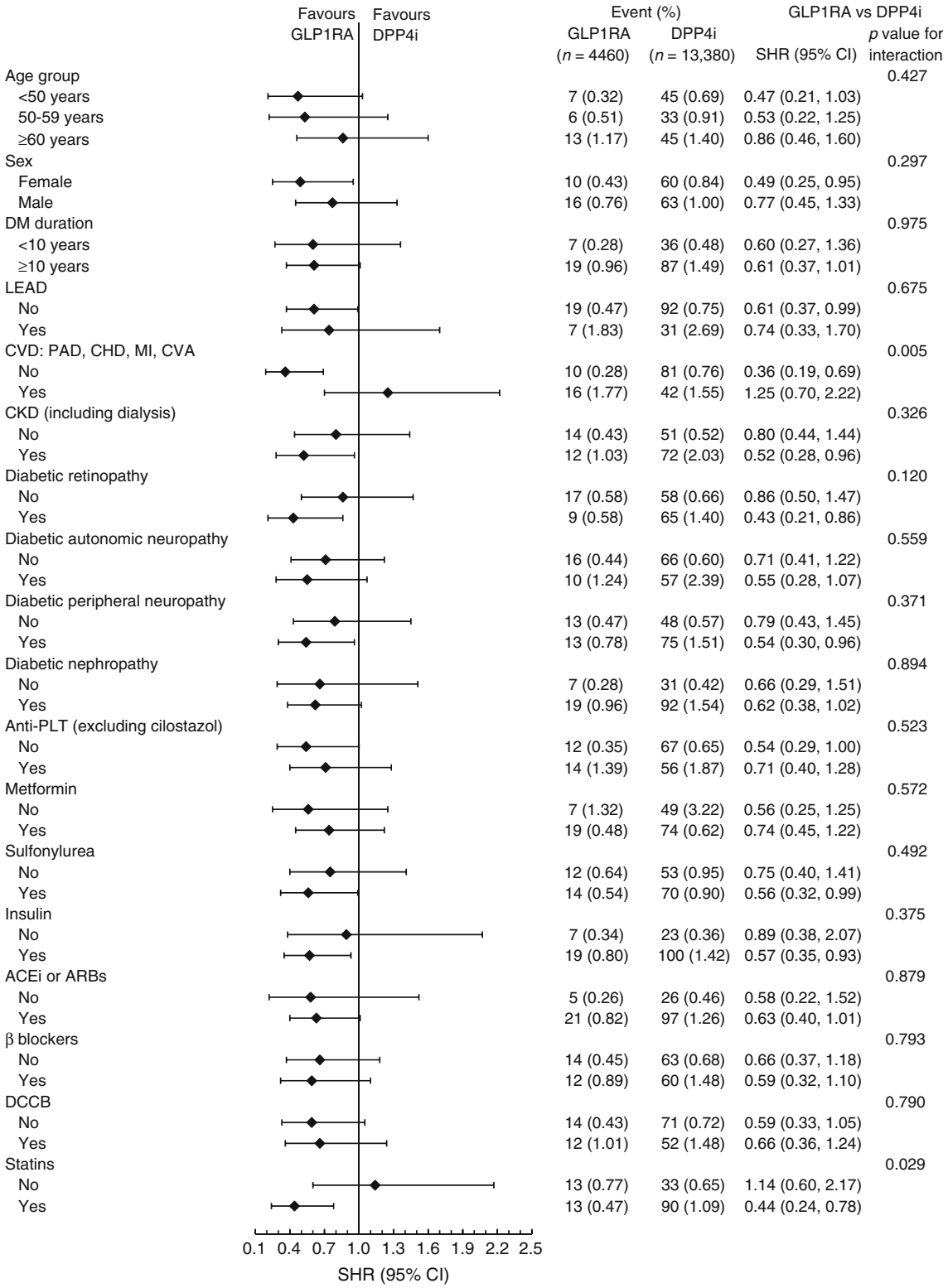
Fig. 3 The cumulative event rates of three-point MACE (**a**) and all-cause death (**b**) for the diabetic patients who received GLP1RA vs DPP4i therapy in the propensity-score matched cohort. The HR (95% CI) for GLP1RAs vs DPP4is was 0.62 (0.51, 0.76) ($p < 0.001$) for MACE and 0.43 (0.34, 0.54) ($p < 0.001$) for all-cause death. 3P, three-point

Discussion

To our knowledge, this is the first study to directly compare the safety and efficacy of GLP1RAs and DPP4is in terms of adverse limb and cardiovascular events in a real-world setting. In this nationwide, retrospective cohort study, we demonstrated that the use of GLP1RAs compared with DPP4is in individuals with type 2 diabetes reduced the risks of amputation and the primary composite outcome (first occurrence of new PAD diagnosis, peripheral revascularisation intervention or amputation). GLP1RAs also reduced the risks of non-fatal stroke, non-fatal myocardial infarction, death from cardiovascular causes and death from any cause. Our results suggest that the use of GLP1RAs in individuals with type 2 diabetes, who are at high risks of adverse limb and cardiovascular events, is beneficial in improving both limb and cardiovascular outcomes.

PAD is a complex condition that portends worsened prognosis. Lower limb outcomes, namely, lower-extremity amputations, are 'sentinel outcomes' that are debilitating and the occurrence of which reflects the summation of multiple risk factors [40]. The 5 year mortality rate of patients who have had an amputation related to diabetic foot ulcers (DFUs) may be as high as 70% [41]. This endpoint was, however, insufficiently evaluated in CVOTs of GLP1RAs and DPP4is. A post hoc analysis of the LEADER trial reported a lower risk of amputation resulting from DFUs in individuals treated with liraglutide vs placebo [28]. This conforms with the main results of our study, in which use of GLP1RAs led to a reduced composite of MALE, with the reduction largely driven by lower risks of amputation. Chang et al found that patients using DPP4i had decreased risks of lower-extremity amputations compared with non-users in an observational cohort study [42]. Our investigation directly compared the effects of GLP1RAs and DPP4is in a real-world setting, and our results suggest that GLP1RAs outperforms DPP4is in the prevention of adverse limb events, particularly amputations. Of note, SGLT2is exhibited remarkable effects in reducing cardiovascular events but concerns were raised over the safety of these drugs in the light of increased amputations observed in the CANVAS Program. RWD have shown that the use of SGLT2is, as compared with GLP1RAs, was associated with higher risk of lower limb amputation [43]. Both GLP1RAs and SGLT2is are recognised as glucose-lowering medication that improve MACE outcomes but only GLP1RAs are associated with better MALE outcomes.

In our study, the incidence rates of other limb outcomes, namely, new diagnoses of PAD and peripheral revascularisation, were not significantly different between the GLP1RA and DPP4i groups. Interestingly, in the aforesaid post hoc analysis of the LEADER cohort, the occurrence of DFU events (defined as new DFU or the worsening of pre-existing DFU during follow-up) favoured liraglutide use but the difference did not reach statistical significance [28]. Time to first infection complicating DFUs were similar between the liraglutide and placebo arms but the HR for this event was significantly lower in liraglutide-treated individuals if only events that occurred more than 1 year from randomisation were analysed. The median follow-up was 3.8 years in the LEADER trial [18]. In the present study, the mean follow-up durations were 2.3 ± 1.9 and 2.2 ± 1.9 years in the matched GLP1RA and DPP4i group, respectively. In vitro studies have described how GLP1RAs may reduce cardiovascular events through anti-inflammatory and pro-angiogenic effects and by stabilising atherosclerotic plaques [44, 45]; these actions likely take time to translate into clinical outcomes. Our observations on how GLP1RAs and DPP4is affect the incidence rates of PAD, CLI and peripheral revascularisation may thus have been limited by the relatively short follow-up time and low number of events.



	Event (%)		GLP1RA vs DPP4i	
	GLP1RA (n = 4460)	DPP4i (n = 13,380)	SHR (95% CI)	p value for interaction
Age group				0.427
<50 years	7 (0.32)	45 (0.69)	0.47 (0.21, 1.03)	
50-59 years	6 (0.51)	33 (0.91)	0.53 (0.22, 1.25)	
≥60 years	13 (1.17)	45 (1.40)	0.86 (0.46, 1.60)	
Sex				0.297
Female	10 (0.43)	60 (0.84)	0.49 (0.25, 0.95)	
Male	16 (0.76)	63 (1.00)	0.77 (0.45, 1.33)	
DM duration				0.975
<10 years	7 (0.28)	36 (0.48)	0.60 (0.27, 1.36)	
≥10 years	19 (0.96)	87 (1.49)	0.61 (0.37, 1.01)	
LEAD				0.675
No	19 (0.47)	92 (0.75)	0.61 (0.37, 0.99)	
Yes	7 (1.83)	31 (2.69)	0.74 (0.33, 1.70)	
CVD: PAD, CHD, MI, CVA				0.005
No	10 (0.28)	81 (0.76)	0.36 (0.19, 0.69)	
Yes	16 (1.77)	42 (1.55)	1.25 (0.70, 2.22)	
CKD (including dialysis)				0.326
No	14 (0.43)	51 (0.52)	0.80 (0.44, 1.44)	
Yes	12 (1.03)	72 (2.03)	0.52 (0.28, 0.96)	
Diabetic retinopathy				0.120
No	17 (0.58)	58 (0.66)	0.86 (0.50, 1.47)	
Yes	9 (0.58)	65 (1.40)	0.43 (0.21, 0.86)	
Diabetic autonomic neuropathy				0.559
No	16 (0.44)	66 (0.60)	0.71 (0.41, 1.22)	
Yes	10 (1.24)	57 (2.39)	0.55 (0.28, 1.07)	
Diabetic peripheral neuropathy				0.371
No	13 (0.47)	48 (0.57)	0.79 (0.43, 1.45)	
Yes	13 (0.78)	75 (1.51)	0.54 (0.30, 0.96)	
Diabetic nephropathy				0.894
No	7 (0.28)	31 (0.42)	0.66 (0.29, 1.51)	
Yes	19 (0.96)	92 (1.54)	0.62 (0.38, 1.02)	
Anti-PLT (excluding cilostazol)				0.523
No	12 (0.35)	67 (0.65)	0.54 (0.29, 1.00)	
Yes	14 (1.39)	56 (1.87)	0.71 (0.40, 1.28)	
Metformin				0.572
No	7 (1.32)	49 (3.22)	0.56 (0.25, 1.25)	
Yes	19 (0.48)	74 (0.62)	0.74 (0.45, 1.22)	
Sulfonylurea				0.492
No	12 (0.64)	53 (0.95)	0.75 (0.40, 1.41)	
Yes	14 (0.54)	70 (0.90)	0.56 (0.32, 0.99)	
Insulin				0.375
No	7 (0.34)	23 (0.36)	0.89 (0.38, 2.07)	
Yes	19 (0.80)	100 (1.42)	0.57 (0.35, 0.93)	
ACEi or ARBs				0.879
No	5 (0.26)	26 (0.46)	0.58 (0.22, 1.52)	
Yes	21 (0.82)	97 (1.26)	0.63 (0.40, 1.01)	
β blockers				0.793
No	14 (0.45)	63 (0.68)	0.66 (0.37, 1.18)	
Yes	12 (0.89)	60 (1.48)	0.59 (0.32, 1.10)	
DCCB				0.790
No	14 (0.43)	71 (0.72)	0.59 (0.33, 1.05)	
Yes	12 (1.01)	52 (1.48)	0.66 (0.36, 1.24)	
Statins				0.029
No	13 (0.77)	33 (0.65)	1.14 (0.60, 2.17)	
Yes	13 (0.47)	90 (1.09)	0.44 (0.24, 0.78)	

Fig. 4 The subgroup analysis comparing the effects of GLP1RA vs DPP4i therapy on the risks of MALE. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DCCB, dihydropyridine calcium channel blocker; DM, diabetes mellitus; MI, myocardial infarction; PLT, platelet

In the present study, treatment with GLP1RAs was associated with significantly decreased risks of MACE when compared with treatment with DPP4is. Although antiplatelet therapy is fundamental for patients with established

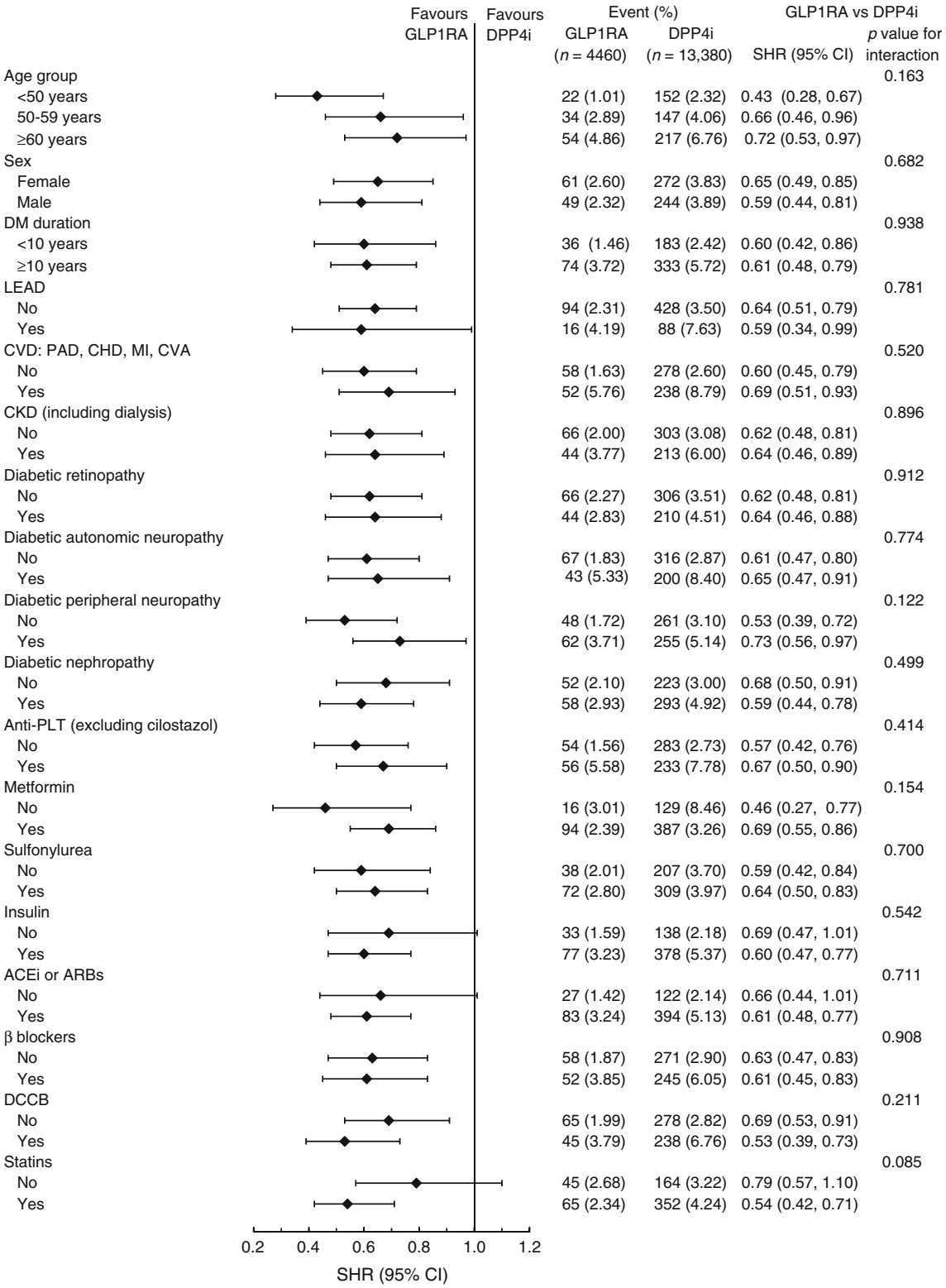


Fig. 5 The subgroup analysis comparing the effects of GLP1RA vs DPP4i therapy on the risks of MACE. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DCCB, dihydropyridine calcium channel blocker; DM, diabetes mellitus; MI, myocardial infarction; PLT, platelet

atherosclerotic cardiovascular disease (ASCVD) to prevent MACE, its efficacy in diabetic patients (who are regarded to be at high cardiovascular risk) is controversial. The ASCEND trial found that primary aspirin use in diabetes patients

prevented serious vascular events but led to increased major bleeding [46]. On the other hand, GLP1RA and SGLT2i use in diabetes patients with high cardiovascular risk and established ASCVD as a means of MACE and cardiovascular mortality prevention is relatively safe and is advocated by current guidelines. Around 20% of the individuals in our cohort were using aspirin, similar to the proportion of individuals with CVD. The superiority of GLP1RAs was evident in all components of the secondary composite outcome, including death from cardiovascular causes, non-fatal stroke and non-fatal myocardial infarction. The risk of death from any cause was also significantly lower in the GLP1RA group. Cardiovascular events are a major cause of morbidity and death in individuals with diabetes, and CVOTs of GLP1RAs and DPP4is have examined their safety and efficacy in terms of cardiovascular outcomes. In general, CVOTs of DPP4i have found no difference in cardiovascular outcomes between DPP4is and placebo [12, 13, 15, 16]. Meanwhile, several, albeit not all, GLP1RA CVOTs demonstrated reduced risks of three-point MACE compared with placebo [18, 19, 22, 23], while the remaining studies reported noninferiority [17, 20, 21]. Our results are consistent with those of prior randomised controlled trials, adding RWD to the growing body of evidence regarding the efficacy of GLP1RAs in preventing cardiovascular events.

The results from this study showed that the absence of documented CVD was associated with significantly fewer MALE events in individuals treated with GLP1RAs, whereas an age <65 years was associated with more favourable outcomes in terms of both MALE and MACE. Interestingly, the effects of GLP1RAs on MALE outcomes remained consistent whether there was underlying LEAD or not. This phenomenon was also seen in the analyses of MACE, in which neither the presence nor absence of underlying CVD interacted with the effects of GLP1RA use. These findings suggest that the protective effects of GLP1RAs are most prominent in the early stages of disease when there is established atherosclerosis but before the occurrence of cardiovascular events. In a post hoc analysis of the LEADER trial [47], the cardiovascular benefits of liraglutide were most significant in individuals with documented CVD but without a history of prior myocardial infarction or stroke. In vivo studies have demonstrated that liraglutide inhibited the progression of early-onset, low-burden atherosclerosis but had little effect on late-onset, high-burden disease [42]. It has been suggested that GLP1RAs exert anti-inflammatory effects, enhance endothelial function and stabilise atherosclerotic plaques through actions not entirely dependent on the incretin system [48, 49]. In the present study, although better MALE and MACE outcomes were not noted in individuals who were taking statins at baseline in the GLP1RA group ($p = 0.06$ and $p = 0.085$, respectively), it is still worthy of further discussion. Recently, Pastori et al found that statins reduced the incidence of MALE, all-cause and cardiovascular mortality in patients with PAD from their meta-analysis [50]. Another study demonstrated that GLP1RAs reduced serum LDL-cholesterol in individuals with type 2 diabetes treated with statins and the percentage of reduction was associated with reduction in HbA_{1c} [51]. The combination of GLP1RAs and statins may be a reasonable therapeutic option in type 2 diabetes with dyslipidaemia. This suggests possible synergistic anti-inflammatory and plaque-stabilising effects between the two types of drug, although further studies are necessary to shed light on this subject.

Limitations This study has several limitations. First, diseases in the NHIRD were identified using ICD-9-CM and ICD-10-CM codes, and haemodynamic data, laboratory tests and imaging studies are not available from the database. Serum HbA_{1c} levels, LDL levels, creatinine levels, BP, etc., are among a few markers of diabetic control that may influence prognosis. This is a great limitation of the current work. In our study, the severity of diabetes was represented by the presence of microvascular complications, which is known to closely correlate with glycaemic control. The use of insulin also reflects, in part, the severity of the disease. In addition, ICD clinical diagnosis codes were used to search for the diagnosis of CLI in administrative claims databases. While administrative diagnosis codes are highly specific in identifying individuals with the disease, there may be people with CLI who were not coded, thus resulting in reduced sensitivity. The ICD-9-CM clinical diagnosis codes we used, namely 440.22 (rest pain), 440.23 (ulceration) and 440.24 (gangrene), conform with prior CLI studies [32]. Subsequent validation analyses have indicated that the true prevalence of CLI may be underestimated by 25% if only administrative codes were used [33].

Second, the behaviour of clinicians and patients could not be assessed using the data from the NHIRD database. This may be of significance as most GLP1RAs are administered subcutaneously, as opposed to the oral administration of DPP4is. It is thus possible that GLP1RAs are more likely to be prescribed to individuals who are more compliant and capable of self-care. The goal of this study was to compare real-world outcomes of GLP1RAs vs DPP4is in the prevention of limb and cardiovascular adverse events. At the same time, clinician and patient behaviours likely reflect clinical choices in reality.

Last, this was a retrospective observational database study and confounding factors were possibly present that may have influenced the results of our analysis. PSM was conducted to minimise the effects of potential confounders but further contributions from prospective, randomised studies would be valuable.

Conclusion In individuals with type 2 diabetes, the use of GLP1Ras, compared with the use of DPP4is, led to

significantly lower risks of MALE. The reduction in risk was driven largely by reduced incidence of amputations. Compared with treatment with DPP4is, treatment with GLP1RAs was also associated with reduced risks of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction and death from any cause. The benefits of GLP1RAs in reducing MALE were most prominent in individuals with prior CVD. However, some unexplored confounding factors may exist in this observational study and future large-scale randomised controlled trials are needed to validate these results.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05497-1.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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