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Comparative cardiovascular and renal outcomes of Liraglutide versus Dulaglutide in Asian type 2 diabetes patients

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Given the limited head-to-head comparison of cardiovascular and renal outcomes between liraglutide and dulaglutide, our study aimed to investigate the clinical outcomes between dulaglutide and liraglutide in a real-world setting. In this new-user design, comparative and retrospective cohort study, patients with type 2 diabetes mellitus with prescription for GLP-1RAs from January 1, 2016 to December 31, 2022 ($n = 8,278$) were included. Primary outcome was composite cardiovascular outcomes which was composed of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke. The composite renal outcome was also interested, including new macroalbuminuria, doubling of serum creatinine, worsening of estimated glomerular filtration rate (eGFR), and progression to dialysis. A total of 3,210 subjects receiving liraglutide and 5,068 subjects receiving dulaglutide were identified. In the adjusted cohort by applying inverse probability of treatment weighting, the incidence of composite cardiovascular outcomes was 18.4 and 18.7 events per 1000 person-years in the liraglutide and dulaglutide groups, respectively. The risk of cardiovascular outcomes did not significantly differ between groups (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.85–1.15). Moreover, the risk of composite renal outcomes was also comparable between groups (subdistribution HR 1.07, 95% CI 0.995–1.16). Liraglutide and dulaglutide demonstrated comparable cardiovascular and renal outcomes in a real-world setting.

Keywords Dulaglutide, Liraglutide, Cardiovascular outcomes, Renal outcomes

According to the International Diabetes Federation (IDF), as of 2021, there were an estimated 537 million adults (aged 20–79) living with diabetes worldwide. This represents a global prevalence of 8.5% among adults in this age range[1]. In patients with type 2 diabetes mellitus (DM) and high risks of cardiovascular disease, several trials and meta-analysis have shown that GLP-1 receptor agonists (GLP-1 RAs) have benefits in protecting against the occurrence of major adverse cardiovascular events (MACE) in addition to lowering serum glucose levels[2–4].

In pivotal trials, the LEADER study evaluated the effects of liraglutide on cardiovascular outcomes in a relatively high-risk population, becoming the first to demonstrate significant cardiovascular benefits[2]. After a median follow-up of 3.8 years, the study showed a reduction in major adverse cardiovascular events (MACE), primarily driven by a decrease in cardiovascular mortality. In contrast, the REWIND study assessed dulaglutide in a population with lower cardiovascular risk. With a median follow-up of 5.4 years, the study also demonstrated a reduction in MACE, largely due to a lower incidence of stroke[3]. The liraglutide and dulaglutide also revealed the lower composite renal outcome compared to placebo, primarily driven by the new onset of persistent macroalbuminuria[5,6]. Further meta-analysis also indicated that the GLP-1 RAs reduced MACE and composite renal outcome in patients with type 2 diabetes mellitus[7–10].

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Currently, the American Diabetes Association recommends GLP-1 RAs as monotherapy or add-on medication for patients with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease (ASCVD) or patients with chronic kidney disease (CKD) but not tolerate to sodium–glucose cotransporter 2 (SGLT2) inhibitor or contraindicated[11]. The European Society of Cardiology guidelines also recommend use of GLP-1 receptor agonists with proven CV benefit as first line therapy in type 2 diabetic patients with established ASCVD[12].

To date, no real-world studies have been published comparing the cardiovascular outcomes and renal protection of GLP-1 RAs. This study enrolled type 2 diabetes patients with prescription for liraglutide or dulaglutide. The primary outcomes were composite cardiovascular outcomes including cardiovascular death, myocardial infarction (MI) and ischemic stroke, and composite renal outcome included macroalbuminuria, worsening of estimated glomerular filtration rate (eGFR), progression to dialysis, and doubling of serum creatinine. The objective of our study is to assess the cardiovascular and renal outcome between liraglutide and dulaglutide in patients with type 2 diabetes.

Method

Study design and setting

We collected and analyzed the electronic medical records from the Chang Gung Research Database (CGRD). The CGRD compiles data from multiple centers within the Chang Gung Memorial Healthcare System.As one of the largest healthcare providers in Taiwan, Chang Gung Memorial Hospital annually handles an average of 8.6 million outpatient visits and around 370,000 admissions. The CGRD is the largest multi-institutional database in Taiwan, containing individual data from about 6% of the Taiwanese population. The CGRD includes comprehensive clinical data such as emergency service records, inpatient and outpatient history, laboratory tests, imaging, original surgical reports, and prescription medications including out-of-pocket expenses (self-paid). The details of CGRD have been described elsewhere[13,14].

The study was conducted in accordance with relevant guidelines and regulations, and in compliance with the Declaration of Helsinki. Approval was obtained from the Chang Gung Medical Foundation Institutional Review Board, which waived the requirement for informed consent due to the retrospective study design using anonymized data with minimal risk to the participants. This research, including tables and supplementary data, does not contain any personally identifiable information.

Patients and study design

This was designed as a new-user comparative study. Patients who received their first prescription of liraglutide or dulaglutide were included from January 1, 2016 to December 31, 2022. The date of first prescription of liraglutide or dulaglutide was considered as the index date. The inclusion criteria consisted of being over 20 years of age, receiving treatment with a GLP-1 receptor agonist, and having a diagnosis of type 2 diabetes mellitus. The exclusion criteria included patients with type 1 diabetes mellitus, gestational diabetes, missing demographic information (i.e., age and sex), use of other GLP-1 RAs or combination forms (e.g., insulin glargine and lixisenatide), and those without follow-up visits. The reason for not including semaglutide was that the health insurance coverage started later, and it was introduced to Chang Gung Memorial Hospital later, so semaglutide was not included. Patient followed up less than 30 days, experienced cardiovascular events or drug switch within 30 days were also excluded. Patients were followed until the occurrence of an outcome (e.g., MACE), death, drug switch, or the last visit in Chang-Gung Memorial Hospitals (the end of database: December 31, 2022), whichever came first. As the study was retrospective in design, no prior power calculation or sample size estimation was performed.

Covariates

The baseline characteristics included demographics, severity of diabetes, kidney function and stages, baseline comorbidities, vital signs, laboratory data, and concomitant medications. Demographic data including age, sex, body mass index (BMI) and smoking were recorded. The duration of DM, baseline glycated hemoglobin (HbA1c) level. Kidney function was assessed by calculating the eGFR using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Eq. 2021. Kidney function and stages were categorized as an eGFR between 15 and 30, < 15 mL/min/1.73m^2, and dialysis. The baseline comorbidities included hypertension, hyperlipidemia and seven others. Charlson's Comorbidity Index (CCI) score was also recorded. Comorbidities were registered using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes before 2016, and both ICD-9-CM and Tenth Revision (ICD-10-CM) codes thereafter (**Supplemental Table 1**). Vital signs included systolic and diastolic blood pressure and heart rate. The biochemistry data included serum creatinine, triglycerides, total cholesterol, high-density and low-density lipoprotein, urine albumin to creatinine ratio (UACR), alanine Aminotransferase (ALT) and hemoglobin. Concomitant medications were classified into glucose-lowering therapies (biguanide, sulfonylurea, insulin, and others) and cardiovascular agents (antihypertensive agents, lipid-lowering agents, and antiplatelet agents).

Study outcomes

The primary outcome was cardiovascular outcomes which was composed of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke. The composite renal outcome included new macroalbuminuria, doubling of serum creatinine, worsening of estimated glomerular filtration rate (eGFR), and progression to dialysis. The urine albumin-to-creatinine ratio (UACR) was calculated as the concentration of urine albumin divided by urine creatinine concentration (mg/g). The macroalbuminuria was defined as a UACR exceeding 300 mg/g. The worsening of estimated glomerular filtration rate (eGFR) was defined as an eGFR decline greater than 50%. Dialysis needs to meet three criteriae: (1) eGFR less than 10 mL/min/1.73m^2, (2)

imaging evidence of irreversible change and (3) two nephrologists confirmed necessary of permanent dialysis. The secondary outcomes were heart failure admission all-cause death, hypoglycemia. The date and cause of death were confirmed by linking to Taiwan Death Registry database. In additional to clinical events, vital signs (blood pressure and heart rate), body weight, glycated hemoglobin and renal function during follow up visits were also collected every six months up to 3 years of follow up.

Statistical analysis

The inverse probability of treatment weighting (IPTW) method, based on propensity scores, was used to balance the distribution of baseline characteristics between the liraglutide and dulaglutide study groups, resulting in an average treatment effect. Propensity scores were estimated using generalized boosted modeling with 10,000 trees, instead of traditional regression models like logistic regression[15]. Propensity scores were calculated based on all baseline characteristics listed in Table 1, with the follow-up duration substituted for the index date. The balance of baseline characteristics between the two study groups, before and after IPTW, was evaluated using the standardized difference (STD), with a value less than 0.1 considered to represent a negligible difference between groups. In addition, due to substantial missing data, missing data were imputed using the single Expectation-Maximization algorithm before IPTW and further analysis regarding outcome comparisons.

All outcome comparisons were made in the IPTW-adjusted cohort. We compared the risk of fatal outcomes (e.g., cardiovascular outcomes and all-cause death) between groups using the Cox proportional hazard model. We compared the incidence of non-fatal outcomes (e.g., composite renal outcomes and non-fatal ischemic stroke) between groups using the Fine and Gray subdistribution hazard model, treating all-cause death during follow-up as a competing risk. We compared the change in continuous measurements (e.g., body weight and glycated hemoglobin) from baseline to every six months up to a 3-year follow-up between the two groups using a linear mixed model. This model included main effects of time and study groups and an interaction effect between study groups and time. The baseline value (intercept) was set as a random effect in the linear mixed model. The study groups were the only one explanatory variable in the aforementioned regression models. A two-sided P values < 0.05 is considered to be statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

This study included 9,207 patients with using liraglutide or dulaglutide between January 1, 2016 and December 31, 2022 (Fig. 1). According to the exclusion criteria, a total 929 patients were excluded. We identified 3,210 and 5,068 patients prescribed with liraglutide and dulaglutide eligible for analysis. The clinical characteristics of the study patients were summarized in Table 1 before and after IPTW adjustment. Prior to adjustment, patients prescribed with liraglutide had an average age of 53.6 ± 15 years, while those prescribed with dulaglutide had an average age of 58.8 ± 14.3 years (Table 1, left side). The liraglutide group was characterized by a younger age (53.6 ± 15.0 vs. 58.8 ± 14.3 years old respectively), higher body mass index (BMI) (29.5 ± 6.0 vs. 28.5 ± 5.5 kg/m2 respectively), a shorter duration of diabetes (4.3 vs. 8.0 years respectively), and a lower established ASCVD (27.6% and 34.6% respectively and lower multiple risk factors for ASCVD (40.6% vs. 53.9 respectively). Notably, no significant differences in baseline characteristics between the two groups were observed after IPTW adjustment, as indicated by the small standardized difference.

Clinical events

The mean follow-up in the IPTW-adjusted cohort was 2.8 years (standard deviation = 1.8 years) without considering censoring and was 2.4 years with considering censoring for both groups (Table 1). The incidence of composite cardiovascular outcome was 18.4 and 18.7 events per 1000 person-years in the liraglutide and dulaglutide groups, respectively (Table 2). The risk of the composite cardiovascular outcome did not significantly differ between groups (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.85–1.15) (Fig. 2A). The risks of individual components of composite cardiovascular outcome, including cardiovascular death and non-fatal ischemic stroke, were also not significantly different between groups (cardiovascular death: HR 1.01, 95% CI 0.79–1.30; ischemic stroke: subdistribution HR 1.18, 95% CI 0.94–1.49). Notably, there was less risk of non-fatal myocardial infarction in the liraglutide group compared to the dulaglutide group (subdistribution HR 0.69, 95% CI 0.52–0.91) (Fig. 2B). Regarding renal outcomes, no significant difference between groups was observed, including macroalbuminuria, worsening of estimated glomerular filtration rate (eGFR), progression to dialysis, doubling of serum creatinine, and composite renal outcomes (subdistribution HR 1.07, 95% CI 0.995–1.16) (Fig. 2C).

Secondary outcomes

For the secondary outcomes, there was no statistical difference in the risks of all-cause death (HR 1.05, 95% CI 0.91–1.20) (Fig. 2D). The risk of admission due to heart failure was comparable between the liraglutide and dulaglutide groups (subdistribution HR 0.96, 95% CI 0.81–1.13). There was no statistical difference in the risk of adverse effects such as hypoglycemia between the liraglutide and dulaglutide groups (subdistribution HR 1.00, 95% CI 0.83–1.21). During the follow up measurements every six months until 36th month, the change of vital signs and renal function was comparable between the two groups (Fig. 3A, C and F). As the aspect of the reduction in body weight, the liraglutide contributed more weight reduction than dulaglutide (P for interaction < 0.001) (Fig. 3D) In contrast, the dulaglutide brought better hyperglycemic control than liraglutide (P for interaction < 0.001) (Fig. 3E).

Variables	Before imputation and IPTW[a]				After imputation and IPTW[b]		
	Available number	Liraglutide ($n=3,210$)	Dulaglutide ($n=5,068$)	STD	Liraglutide ($n=7,604.0$)	Dulaglutide ($n=7949.0$)	STD
Demographics							
Age, year	8,278	53.6 ± 15.0	58.8 ± 14.3	-0.36	55.9 ± 14.6	56.9 ± 14.7	-0.07
Male	8,278	1,471 (45.8)	2,536 (50.0)	-0.08	48.1	48.1	< 0.01
Smoker	8,278	473 (14.7)	873 (17.2)	-0.07	15.8	16.4	-0.02
Alcohol	8,278	239 (7.4)	429 (8.5)	-0.04	7.8	8.0	-0.01
Baseline body mass index, kg/m^2	7,593	29.5 ± 6.0	28.5 ± 5.5	0.18	29.0 ± 5.6	28.7 ± 5.5	0.05
Established ASCVD†	8,278	886 (27.6)	1,752 (34.6)	-0.15	32.0	31.6	0.01
Multiple risk factors for ASCVD‡	8,278	1,303 (40.6)	2,733 (53.9)	-0.27	46.9	48.5	-0.03
Severity of DM							
Duration of DM, year	8,278	4.3 [0.0, 11.7]	8.0 [2.4, 14.0]	-0.35	6.4 [0.7, 12.7]	6.9 [1.0, 13.2]	-0.06
Baseline HbA1c, %	7,229	8.7 ± 2.1	8.9 ± 1.8	-0.11	8.6 ± 1.9	8.6 ± 1.9	-0.01
DM nephropathy	8,278	900 (28.0)	1,873 (37.0)	-0.19	30.8	33.9	-0.07
DM retinopathy	8,278	539 (16.8)	917 (18.1)	-0.03	17.0	16.8	0.01
DM neuropathy	8,278	1,420 (44.2)	2,501 (49.3)	-0.10	48.3	46.9	0.03
No. of OPD for DM in the prior year	8,278	4.0 [0.0, 8.0]	5.0 [3.0, 9.0]	-0.14	5.0 [1.0, 9.0]	5.0 [1.0, 8.0]	0.01
CKD stage at baseline	8,278						
Without SCr		436 (13.6)	426 (8.4)	0.17	12.0	10.5	0.04
≥ 60 ml/min/1.73m^2		2,068 (64.4)	3,027 (59.7)	0.10	63.0	61.2	0.04
45–59 ml/min/1.73m^2		248 (7.7)	464 (9.2)	-0.05	7.7	8.3	-0.02
30–44 ml/min/1.73m^2		219 (6.8)	438 (8.6)	-0.07	7.3	7.9	-0.02
15–29 ml/min/1.73m^2		116 (3.6)	314 (6.2)	-0.12	4.7	5.4	-0.03
< 15 ml/min/1.73m^2		19 (0.6)	84 (1.7)	-0.10	0.9	1.4	-0.05
Dialysis		104 (3.2)	315 (6.2)	-0.14	4.6	5.3	-0.03
Comorbidity							
Hypertension	8,278	1,941 (60.5)	3,536 (69.8)	-0.20	65.3	65.9	-0.01
Hyperlipidemia	8,278	2,082 (64.9)	3,657 (72.2)	-0.16	69.5	68.5	0.02
Coronary artery disease	8,278	685 (21.3)	1,349 (26.6)	-0.12	24.6	24.5	< 0.01
Heart failure hospitalization	8,278	151 (4.7)	368 (7.3)	-0.11	5.7	6.4	-0.03
Coronary intervention	8,278	251 (7.8)	580 (11.4)	-0.12	9.7	10.1	-0.02
Ischemic stroke	8,278	166 (5.2)	367 (7.2)	-0.09	6.3	6.5	-0.01
Intracerebral hemorrhage	8,278	70 (2.2)	162 (3.2)	-0.06	3.0	2.7	0.02
Carotid artery stent	8,278	7 (0.2)	12 (0.2)	< 0.01	0.4	0.2	0.04
Myocardial infarction	8,278	161 (5.0)	324 (6.4)	-0.06	5.9	5.6	0.01
Atrial fibrillation	8,278	96 (3.0)	211 (4.2)	-0.06	3.6	3.7	-0.01
Major adverse limb events$	8,278	189 (5.9)	315 (6.2)	-0.01	6.6	5.7	0.04
Malignancy	8,278	268 (8.3)	532 (10.5)	-0.07	9.3	9.6	-0.01
Charlson's Comorbidity Index score	8,278	2.9 ± 2.5	3.6 ± 2.5	-0.29	3.2 ± 2.4	3.3 ± 2.4	-0.06
Vital signs at baseline							
Systolic blood pressure, mmHg	7,930	138.6 ± 21.0	138.6 ± 20.8	< 0.01	138.7 ± 20.4	138.2 ± 20.3	0.03
Diastolic blood pressure, mmHg	7,928	77.8 ± 12.6	77.3 ± 12.6	0.04	77.6 ± 12.3	77.6 ± 12.3	< 0.01
Heart rate, beat/min	7,913	86.6 ± 13.5	85.8 ± 13.7	0.06	86.3 ± 12.9	86.0 ± 13.3	0.02
LVEF at baseline	2,671	66.2 ± 11.9	64.8 ± 12.9	0.12	66.1 ± 7.1	65.9 ± 7.6	0.02
Biochemistry data							
Creatinine, mg/dL	6,997	1.0 ± 0.7	1.2 ± 0.9	-0.18	1.1 ± 0.7	1.1 ± 0.8	-0.05
Triglyceride, mg/dL	6,929	200.7 ± 174.8	196.0 ± 160.1	0.03	196.1 ± 155.9	193.0 ± 148.4	0.02
Total cholesterol, mg/dL	6,831	178.4 ± 45.0	171.0 ± 44.3	0.17	175.4 ± 40.9	174.1 ± 40.8	0.03
High-density Lipoprotein, mg/dL	6,558	43.6 ± 12.0	43.9 ± 12.3	-0.03	44.0 ± 10.9	44.4 ± 11.1	-0.04
Low-density lipoprotein, mg/dL	7,129	105.4 ± 51.5	98.4 ± 49.9	0.14	102.9 ± 46.3	101.7 ± 46.8	0.02
UACR, mg/g	4,478						
< 30		664 (39.4)	1,069 (38.3)	0.02	38.1	38.8	-0.01
30–300		568 (33.7)	1,004 (36.0)	-0.05	34.9	35.8	-0.02
> 300		455 (27.0)	718 (25.7)	0.03	27.0	25.4	0.04
ALT, U/L	7,006	34.2 ± 28.0	32.3 ± 26.2	0.07	33.3 ± 25.1	33.1 ± 25.0	0.01
Hemoglobin, g/dL	4,173	13.1 ± 2.1	12.6 ± 2.3	0.22	13.2 ± 1.7	13.1 ± 1.7	0.03
Continued							

Variables	Before imputation and IPTW[a]				After imputation and IPTW[b]		
	Available number	Liraglutide ($n=3,210$)	Dulaglutide ($n=5,068$)	STD	Liraglutide ($n=7,604.0$)	Dulaglutide ($n=7949.0$)	STD
Glucose lowering therapies	8,278						
Biguanide	8,278	1,761 (54.9)	3,398 (67.0)	-0.25	61.2	63.8	-0.05
Sulfonylurea	8,278	1,443 (45.0)	3,278 (64.7)	-0.40	55.4	58.1	-0.05
Thiazolinedione	8,278	455 (14.2)	1,406 (27.7)	-0.34	20.6	23.5	-0.07
Glinide	8,278	156 (4.9)	316 (6.2)	-0.06	5.8	5.2	0.02
Alpha glucosidase	8,278	391 (12.2)	941 (18.6)	-0.18	13.8	16.6	-0.08
SGLT2i	8,278	657 (20.5)	1,459 (28.8)	-0.19	24.7	25.9	-0.03
Dipeptidyl peptidase 4 inhibitors	8,278	1,133 (35.3)	2,443 (48.2)	-0.26	41.6	44.4	-0.06
Insulin	8,278	804 (25.0)	821 (16.2)	0.22	20.6	18.5	0.05
No. of oral hypoglycemic agents used	8,278	2.1 ± 1.6	2.8 ± 1.5	-0.43	2.4 ± 1.6	2.6 ± 1.6	-0.08
Cardiovascular agents							
RASi	8,278	1,512 (47.1)	2,868 (56.6)	-0.19	51.1	53.3	-0.04
Beta-blocker	8,278	701 (21.8)	1,435 (28.3)	-0.15	24.7	26.3	-0.04
DCCB	8,278	1,138 (35.5)	2,198 (43.4)	-0.16	38.3	41.1	-0.06
Oral anticoagulants	8,278	81 (2.5)	196 (3.9)	-0.08	3.1	3.4	-0.02
Digoxin	8,278	20 (0.6)	34 (0.7)	-0.01	0.9	0.6	0.03
Loop diuretics	8,278	280 (8.7)	642 (12.7)	-0.13	9.8	11.4	-0.05
Thiazide	8,278	103 (3.2)	161 (3.2)	<0.01	3.6	3.0	0.03
MRA	8,278	111 (3.5)	231 (4.6)	-0.06	3.9	4.2	-0.01
Nitrates	8,278	282 (8.8)	561 (11.1)	-0.08	10.1	10.2	<0.01
Vasodilator	8,278	48 (1.5)	132 (2.6)	-0.08	1.6	2.4	-0.06
Ivabradine	8,278	15 (0.5)	36 (0.7)	-0.03	0.6	0.6	<0.01
Statins	8,278	1,757 (54.7)	3,424 (67.6)	-0.27	61.1	63.3	-0.05
Fibrates	8,278	265 (8.3)	435 (8.6)	-0.01	8.6	8.5	0.01
Aspirin	8,278	706 (22.0)	1,361 (26.9)	-0.11	25.6	24.9	0.02
P2Y12 inhibitors	8,278	239 (7.4)	618 (12.2)	-0.16	9.2	10.9	-0.06
Follow-up year without considering censoring	8,278						
Mean ± SD		3.0 ± 2.0	2.6 ± 1.7	0.22	2.8 ± 1.8	2.8 ± 1.8	0.04
Median [Q1, Q3]		3.0 [1.2, 4.8]	2.4 [1.1, 3.9]	NA	2.7 [1.2, 4.3]	2.6 [1.1, 4.1]	NA
Follow-up year with considering censoring*	8,278						
Mean ± SD		2.6 ± 1.9	2.3 ± 1.6	0.13	2.4 ± 1.8	2.4 ± 1.7	-0.04
Median [Q1, Q3]		2.1 [0.8, 4.2]	2.0 [0.9, 3.5]	NA	2.0 [0.7, 3.8]	2.1 [0.9, 3.8]	NA

Table 1. Baseline characteristics of patients who received liraglutide versus dulaglutide. *IPTW* inverse probability of treatment weighting, *STD* standardized difference, *ASCVD* atherosclerotic cardiovascular disease, *DM* diabetes mellitus, *HbA1c* glycated hemoglobin, *OPD* outpatient department, *CKD* chronic kidney disease, *SCr* serum creatinine, *LVEF* left ventricular ejection fraction, *UACR* urine albumin to creatinine ratio, *ALT* alanine aminotransferase, *SGTL2i* sodium-glucose cotransporter 2 inhibitors, *RASi* renin-angiotensin-system inhibitor, *DCCB* dihydropyridine calcium channel blockers, *MRA* mineralocorticoid receptor antagonists, *P2Y12* purinergic receptor P2Y G-protein coupled, 12. [a]Data were presented as frequency (percentage), mean ± standard deviation or median [25th, 75th percentiles]; [b]Data were presented as percentage, mean ± standard deviation or median [25th, 75th percentiles]. [†]Any of coronary heart disease, coronary intervention, ischemic stroke, intracerebral hemorrhage, carotid artery stent, myocardial infarction, peripheral artery disease and lower limb endovascular therapy/bypass; [‡]Male over 55 years old and female over 60 years old with any of hyperlipidemia, hypertension and smoke; [$]Any of peripheral arterial disease, critical limb ischemia, claudication, lower limb endovascular therapy/bypass; *Patients were followed until death, drug switch, or the last visit in Chang-Gung Memorial Hospitals (the end of database: December 31, 2022).

Discussion

This cohort study presented a comprehensive real-world comparison of cardiovascular and renal outcomes between liraglutide and dulaglutide in a Taiwanese population with type 2 diabetes mellitus. The results revealed that both liraglutide and dulaglutide were associated with similar composite cardiovascular outcomes in patients with type 2 diabetes. Furthermore, there was no disparity observed in composite renal outcomes or their individual components between the liraglutide and dulaglutide groups. Additionally, our study indicated similar rates of all-cause mortality between the two groups. Taken together, liraglutide and dulaglutide have similar effects in preventing cardiovascular diseases, delaying kidney diseases and all-cause mortality.

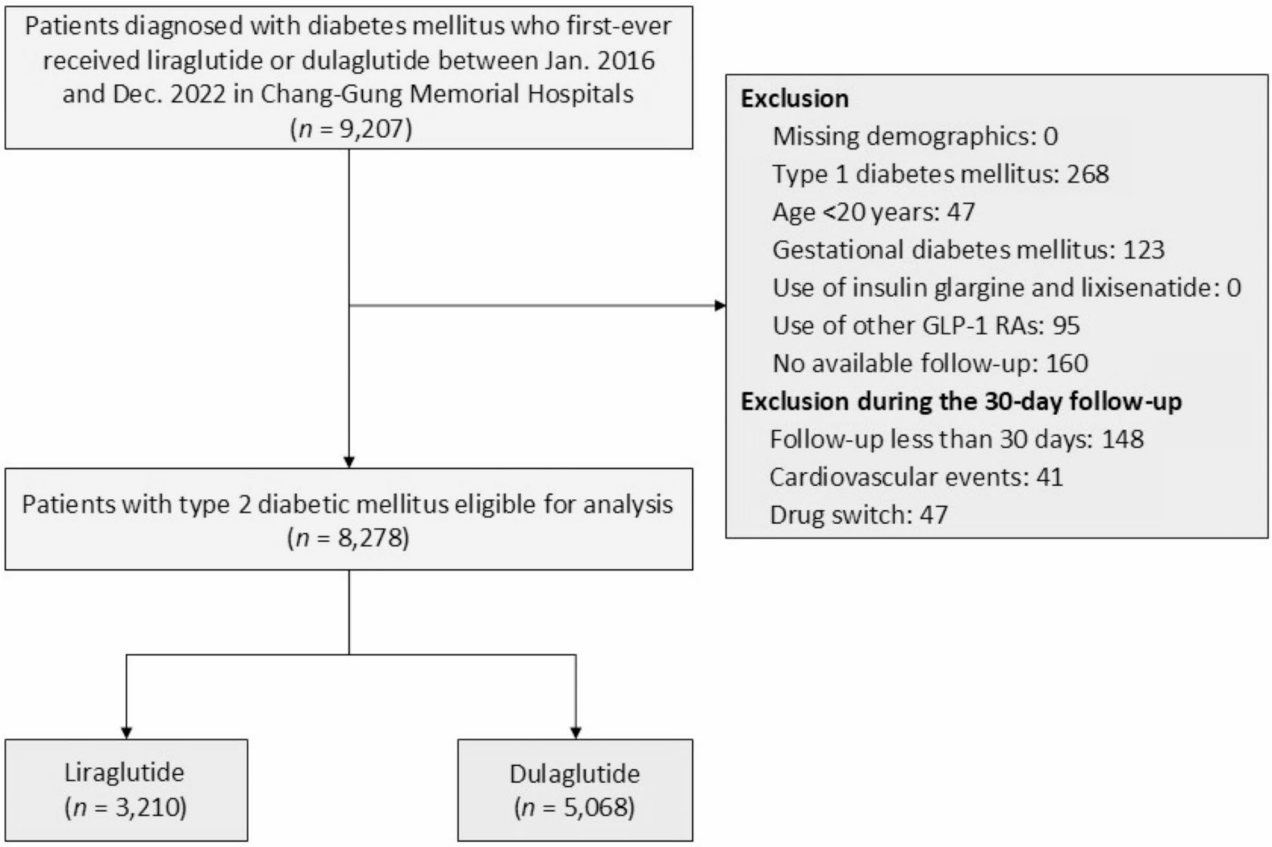

Fig. 1. The flowchart for the inclusion and exclusion of the study patients. GLP-1 RAs, glucagon-like peptide-1 receptor agonists.

	Liraglutide ($n = 7,604.0$)		Dulaglutide ($n = 7949.0$)		HR/SHR (95% CI)	*P*
Outcome	**Event rate (%)**	**Incidence (95% CI)***	**Event rate (%)**	**Incidence (95% CI)***	**For liraglutide**	**value**
Primary outcome: MACE#	4.3	18.4 (16.4–20.4)	4.4	18.7 (16.7–20.6)	0.99 (0.85–1.15)	0.856
Cardiovascular outcome						
Cardiovascular death	1.5	6.5 (5.3–7.7)	1.6	6.4 (5.3–7.6)	1.01 (0.79–1.30)	0.927
Non-fatal myocardial infarction	1.1	4.6 (3.6–5.6)	1.6	6.7 (5.5–7.9)	0.69 (0.52–0.91)	0.008
Non-fatal ischemic stroke	2.0	8.4 (7.1–9.8)	1.7	7.1 (5.9–8.3)	1.18 (0.94–1.49)	0.158
Kidney outcome						
Composite renal outcomes	17.7	87.1 (82.5–91.8)	17.3	81.5 (77.2–85.8)	1.07 (0.995–1.16)	0.069
eGFR decline > 50%	9.5	42.7 (39.6–45.9)	9.4	41.2 (38.3–44.2)	1.04 (0.94–1.15)	0.492
Doubling of SCr	7.6	33.7 (30.9–36.4)	7.6	32.5 (29.9–35.2)	1.03 (0.92–1.15)	0.624
Progression to dialysis	2.9	12.6 (10.9–14.3)	2.8	11.6 (10.1–13.2)	1.08 (0.90–1.30)	0.421
Newly UACR > 300, mg/g	9.6	44.3 (41.1–47.5)	9.5	42.4 (39.4–45.4)	1.05 (0.95–1.16)	0.381
Secondary outcomes						
All-cause death	5.4	22.7 (20.5–24.9)	5.3	21.8 (19.7–23.9)	1.05 (0.91–1.20)	0.528
Heart failure admission	3.4	14.8 (13.0–16.6)	3.7	15.5 (13.7–17.2)	0.96 (0.81–1.13)	0.627
Hypoglycemia (glucose < 54 mg/dL)	2.8	12.0 (10.4–13.6)	2.9	12.0 (10.5–13.6)	1.00 (0.83–1.21)	0.993

Table 2. Follow-up outcomes of patients who received liraglutide versus dulaglutide in the IPTW-adjusted cohort. *IPTW* inverse probability of treatment weighting, *HR* hazard ratio, *SHR* subdistribution hazard ratio, *CI* confidence interval, *MACE* major adverse cardiac events, *eGFR* estimated glomerular filtration rate, *SCr* serum creatinine, *UACR* urine albumin to creatinine ratio, *DKA* diabetic ketoacidosis, *HHS* hyperosmolar hyperglycemia state; *Number of events per 1,000 person-years; #Any of cardiovascular death, non-fatal myocardial infarction or non-fatal ischemic stroke; §Any of peripheral arterial disease, claudication, critical limb ischemia, endovascular thrombectomy or non-traumatic amputation.

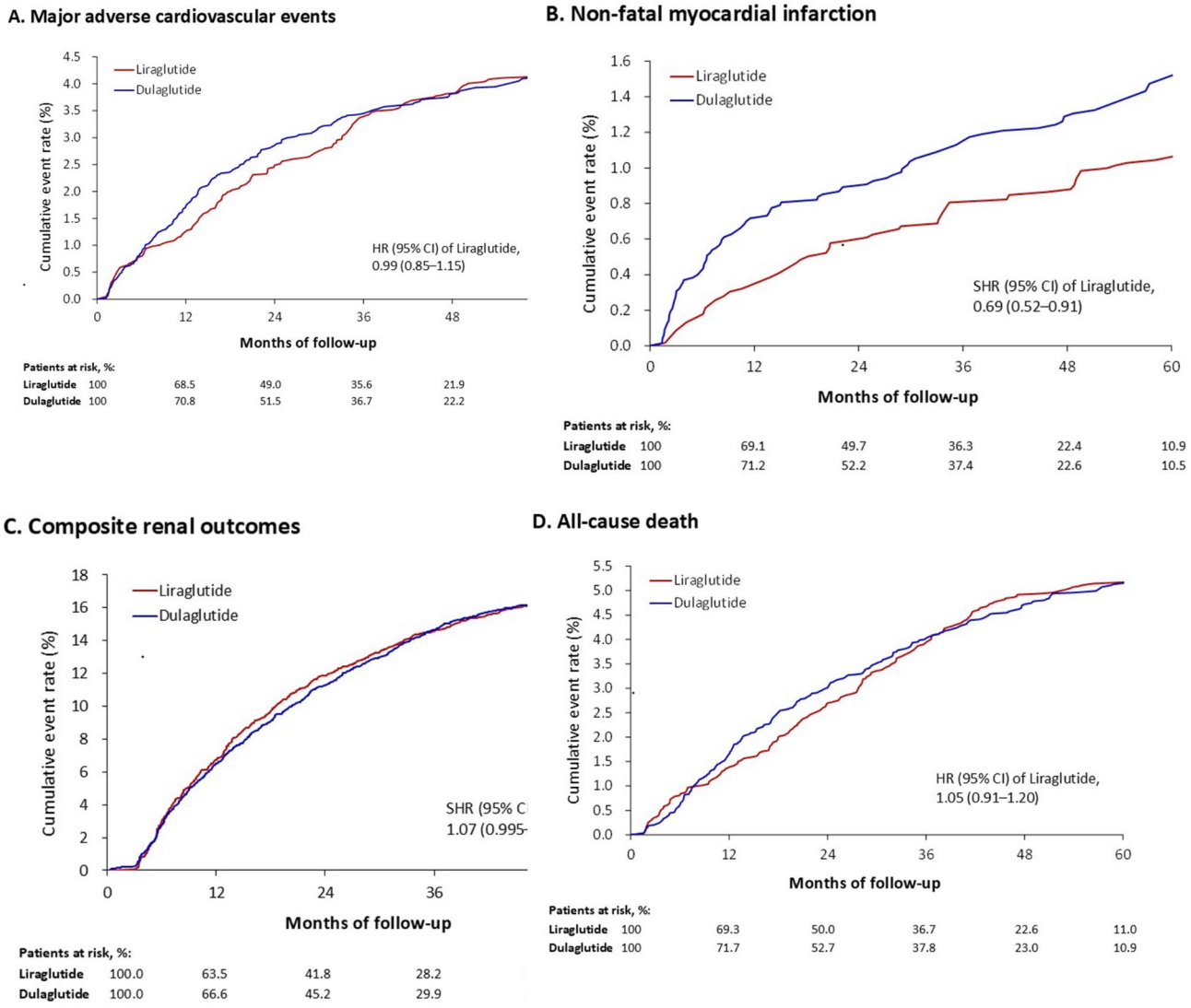

Fig. 2. The cumulative event rates of non-fatal myocardial infarction (**A**), major adverse cardiovascular events (**B**), composite renal outcomes (**C**), and all-cause death (**D**) among patients who received liraglutide versus dulaglutide in the IPTW-adjusted cohort. *IPTW* inverse probability of treatment weighting, *SHR* subdistributional hazard ratio, *CI* confidence interval, *HR* hazard ratio.

Cardiovascular outcomes

Our study indicated comparable composite cardiovascular outcomes between liraglutide and dulaglutide. The LEADER and REWIND trials provided evidence supporting the reduction of death from cardiovascular causes and non-fatal stroke, respectively. The potential mechanisms of GLP-1 RAs in mediating cardiovascular protection are not solely explained by lowering serum glucose levels. Other potential mechanisms, such as reducing inflammatory processes, improving vascular function to decrease blood pressure, and promoting more stabilized, less vulnerable plaques, have also been reported[16–19].

In Taiwan, most people used liraglutide and dulaglutide during our study period. The LEADER trial included a higher proportion of patients with very high cardiovascular risk (81%), whereas the REWIND trial included a lower proportion of high-risk patients (31%)[2,3]. This difference in patient populations suggests variation in the study groups. One meta-analysis discussed the cardiovascular protective effects between populations with and without established cardiovascular disease, finding no significant difference in the benefits of GLP-1 receptor agonists (GLP-1 RAs) on major adverse cardiovascular events (MACE) between these groups[20]. Despite this, direct comparisons of cardiovascular outcomes between dulaglutide and liraglutide remain limited. Our retrospective study examined type 2 diabetes mellitus (DM) patients receiving either liraglutide or dulaglutide treatment to assess the impact of these medications on cardiovascular outcomes. We found no significant differences in composite cardiovascular outcomes between the liraglutide and dulaglutide groups. GLP-1 RAs also exert multiple effects on cardiovascular risk factors, including reductions in systolic blood pressure and LDL cholesterol, improved glycemic control, and body weight reduction[21,22]. Our study found that dulaglutide contributed to better glycemic control, while liraglutide led to a larger reduction in body weight. Additionally, we

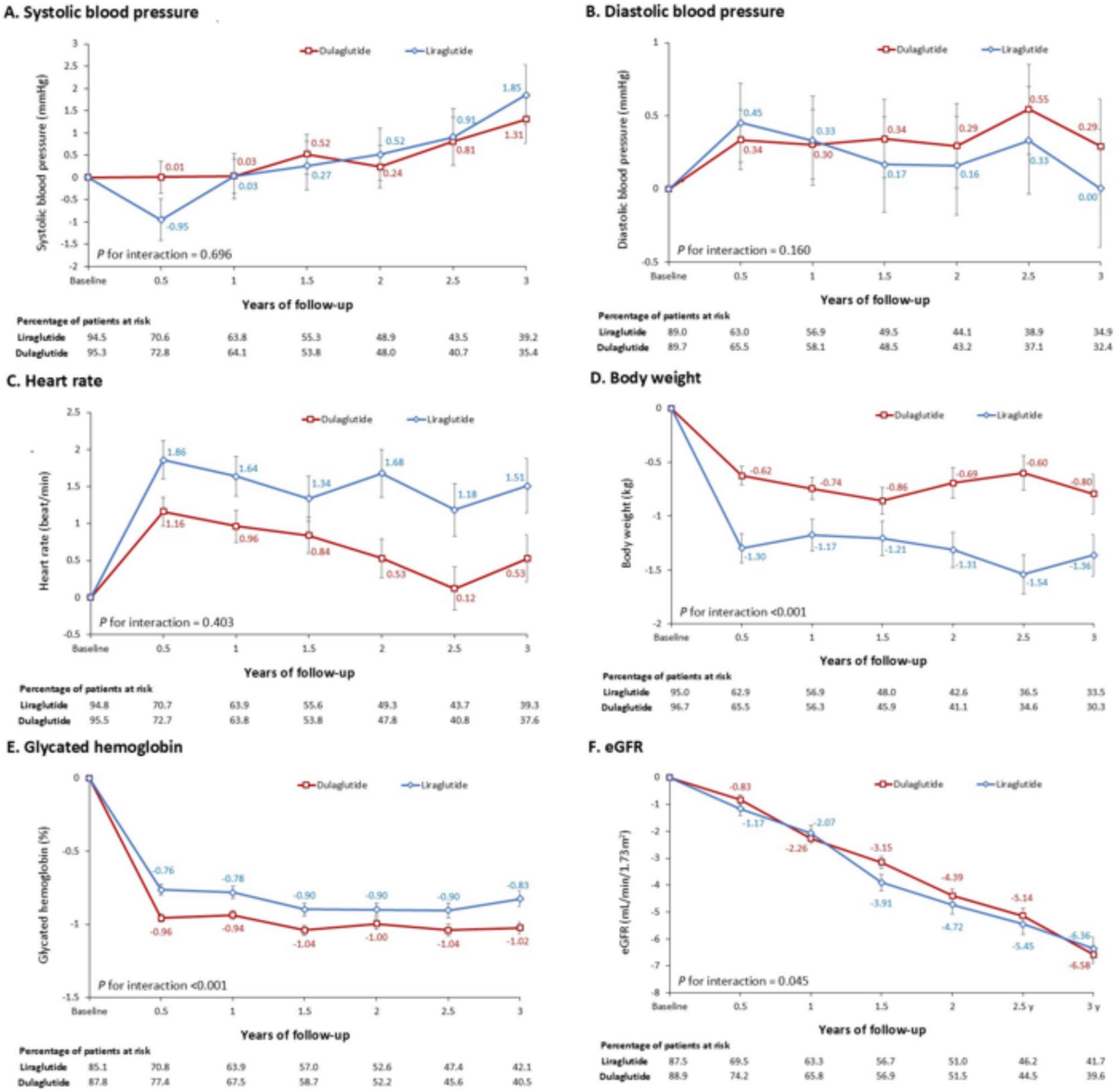

Fig. 3. The change of systolic blood pressure (**A**), diastolic blood pressure (**B**), heart rate (**C**), body weight (**D**), glycated hemoglobin (**E**) and eGFR (**F**) from baseline to follow up measurements among patients who received liraglutide versus dulaglutide in the IPTW-adjusted cohort. *IPTW* inverse probability of treatment weighting, *eGFR* estimated glomerular filtration rate.

observed no significant differences in systolic and diastolic blood pressure or heart rate between the liraglutide and dulaglutide groups. These findings may help explain the comparable composite cardiovascular outcomes observed over the three-year follow-up period. Our study provides real-world evidence on the cardiovascular outcomes of both liraglutide and dulaglutide.

Renal outcomes

Our study found no significant differences between the liraglutide group and the dulaglutide group regarding composite renal outcomes, reduction of estimated glomerular filtration rate, and the incidence of new macroalbuminuria. Currently, there is limited data available on the use of liraglutide and dulaglutide in patients with more advanced stages of chronic kidney disease (CKD)[23]. The LEADER and REWIND studies demonstrated benefits in composite renal outcomes, primarily due to a reduction in the incidence of new-onset macroalbuminuria. However, these trials excluded patients with more advanced CKD stages, defined as an estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2 and 15 ml/min/1.73m^2, respectively[5,6]. Only one Japanese cohort study reported a significant reduction in eGFR decline in stage 5 CKD patients[24].

Additionally, GLP-1 receptor agonists (GLP-1RAs) exert their effects on the kidneys by increasing renal plasma flow and glomerular filtration rate through GLP-1 receptors, and these effects may vary depending on the underlying renal pathology[25]. As a result, the renal protective effect of GLP-1RAs in patients with type 2 diabetes and advanced CKD remains inconclusive. Our study provided evidence of a comparable renal protective effect with liraglutide and dulaglutide treatment in patients with CKD and type 2 diabetes.

Secondary outcomes

We found no significant differences of all-cause death between two groups. Our liraglutide group exhibited comparable composite cardiovascular outcome, composite renal outcome, cardiovascular death, and heart failure admission compared to dulaglutide group. There finding may indirectly account for the comparable rates of all-cause death. Additionally, we demonstrated better weight control with liraglutide, consistent with the result of the AWARD-6 trial, which showed significantly larger body weight reduction associated with liraglutide compared to dulaglutide at 26 weeks[26]. The reason for the different effects on body weight is that dulaglutide is less transported across the blood–brain barrier or through fenestrated capillaries than liraglutide, thereby contributing less to satiety effects in the central nervous system[27] Moreover, dulaglutide resulted in a larger decrease in glycosylated hemoglobin. The AWARD-6 trial demonstrated the non-inferiority of reduction in HbA1c of dulaglutide versus liraglutide at 26 weeks[26]. Interestingly, a Japanese trial also showed the comparable effect on lowering HbA1c effect at 26 weeks[28]. However, with a longer follow-up period, the Japanese trial reported significant HbA1c reduction for dulaglutide versus liraglutide at 52 weeks[29]. Our real-world study is consistent with previous research and demonstrates greater benefits of glycemic control associated with the use of dulaglutide compared to liraglutide over a three-year follow-up period, with differences becoming apparent as early as six months into the study.

Limitations

Our study, based on real-world data, examines the outcomes of patients with type 2 diabetes receiving either liraglutide or dulaglutide. However, there are several limitations to consider. First, due to the retrospective observational design of our study, we can identify correlations but cannot establish causality between liraglutide or dulaglutide and cardiovascular or renal outcomes. Currently, there is a lack of direct head-to-head comparative trials of GLP-1RAs on long-term cardiovascular outcomes, highlighting the need for future studies with long-term follow-up periods. Second, potential selection bias may exist in our study, including possible coding errors. We attempted to mitigate these errors by cross-referencing diagnostic codes with drug registration data. For example, we defined hypertension as patients receiving antihypertensive agents and a diagnosis of hypertension, with similar definitions applied to other diseases. Third, as a retrospective design study, it is challenging to control for confounding factors that may influence outcome, such as medication compliance. Fourth, more frequent measurements could indeed result in more accurate endpoints. However, since this is a retrospective study, we are unable to conduct tests at precise time points as in a prospective study, nor can we conduct more frequent testing. Lastly, comparison of dulaglutide with semaglutide would be also important as both being once-weekly injections. Nevertheless, due to the small number of patients using semaglutide during our study period, we precluded them in this study. Recently, the FLOW trial (Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes) specifically focused on the impact of semaglutide on CKD progression[30]. The study demonstrated that semaglutide reduced the risk of major kidney disease events by 24% and slowed the annual decline in kidney function in patients with type 2 diabetes and CKD. Additionally, semaglutide lowered the risk of major cardiovascular events and death from any cause. It is worth exploring whether liraglutide and dulaglutide can also help slow the deterioration of kidney function in patients with type 2 diabetes and CKD. Future research evaluating the primary kidney outcomes of GLP-1 receptor agonist treatments and comparisons in real-world settings is warranted.

Conclusion

In conclusion, the real-world study comparing the treatment outcomes of liraglutide and dulaglutide in type 2 diabetic populations revealed similar cardiovascular and renal outcomes, cardiovascular death rates, all-cause mortality, and rates of heart failure admission. Liraglutide was found to result in greater body weight loss, while dulaglutide showed a more significant reduction in HbA1c levels.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to the policy and regulation of the Institutional Review Board of Chang Gung Memorial Hospital, but are available from the corresponding author on reasonable request.

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Author contributions

JWD, THC: study design; YL, XWL: data extraction; CJT, MLT: verification of extracted data; JWD, MJH: data analysis and execution of statistical analysis; JWD, THC: manuscript drafting; NIY, JWD: manuscript revision. All authors reviewed and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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