GLP-1 receptor agonist versus DPP-4 inhibitor and kidney and cardiovascular outcomes in clinical practice in type-2 diabetes

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Yang Xu[1,2,6], Edouard L. Fu[2,3,6], Catherine M. Clase[4], Faizan Mazhar[2], Meg J. Jardine[5] and Juan J. Carrero[2]

[1]Peking University Clinical Research Institute, Peking University First Hospital, Beijing, China; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [4]Department of Medicine and Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada; and [5]Kidney Health Research, NHMRC Clinical Trials Centre, University of Sydney, Sydney, New South Wales, Australia

Whether glucagon-like peptide-1 receptor agonists (GLP1-RA) reduce detrimental kidney outcomes is uncertain. In secondary analyses, trials have shown consistent reductions in macroalbuminuria, but inconclusive results about kidney function decline. To help clarify this, we conducted a cohort study to compare kidney and cardiovascular outcomes in individuals who started GLP1-RA or dipeptidyl peptidase-4 inhibitors (DPP4i) (reduces degradation of endogenous GLP1). The primary outcome was a composite of sustained doubling of creatinine, kidney failure or kidney death. The secondary outcomes were three-point major adverse cardiovascular events (MACE) and its individual components. Propensity score weighted Cox regression was used to balance 53 confounders. A total of 19,766 individuals were included, of whom 5,699 initiated GLP1-RA, and were followed for a median 2.9 years. Mean age was 63 years, 26.2% had atherosclerotic cardiovascular disease and 16.0% had an estimated glomerular filtration rate (eGFR) under 60 ml/min/1.73m^2. The adjusted hazard ratio for GLP1-RA vs. DPP4i was 0.72 (95% confidence interval 0.53-0.98) for the composite kidney outcome and 0.85 (0.73-0.99) for MACE, with absolute five-year risk reductions of 0.8% (0.1%-1.5%) and 1.6% (0.2%-2.9%), respectively. Hazard ratios were 0.79 (0.60-1.05) for cardiovascular death, 0.86 (0.68-1.09) for myocardial infarction and 0.74 (0.59-0.93) for stroke. Results were consistent within subgroups, including age, sex, eGFR and baseline metformin use. Thus, in our analysis of patients from routine clinical practice, the use of GLP1-RA was associated with a lower risk of kidney outcomes compared with DPP4i. Reductions in both kidney outcomes and MACE were similar in magnitude to those reported in large cardiovascular outcome trials.

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Correspondence: *Yang Xu, Peking University Clinical Research Institute, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, 100034 Beijing, China. E-mail: xuyang_pucri@bjmu.edu.cn*

[6]Shared first authorship.

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Diabetic kidney disease is a major public health concern,[1,2] being the leading cause of chronic kidney disease[3] and responsible for half of all end-stage kidney disease cases worldwide.[4] Potential treatment options to slow the loss of kidney function in type 2 diabetes mellitus include lifestyle interventions, risk factor management, and specific medications such as renin-angiotensin system inhibition, sodium-glucose cotransporter-2 inhibitors,[5,6] and nonsteroidal mineralocorticoid receptor antagonists.[7–9] Nevertheless, even with optimal current treatment strategies, substantial residual kidney risk remains.[5–7]

Multiple cardiovascular outcome trials have shown that glucagon-like peptide-1 receptor agonists (GLP1-RAs) reduce the risk of major adverse cardiovascular events (MACEs) in patients with type 2 diabetes mellitus and established cardiovascular disease or at high cardiovascular risk.[10–18] Whether GLP1-RA can also lower kidney disease risks is uncertain; although none of the trials have specifically targeted kidney outcomes, secondary analyses suggest nephroprotective effects.[19,20] A recent meta-analysis of these secondary outcome trials, including the recent Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial, showed that GLP1-RA significantly reduced a broad composite kidney outcome (hazard ratio 0.79; 95% confidence interval [CI], 0.73–0.87),[10,11,13,15,21–23] which was mainly driven by a reduction in macroalbuminuria, without consistent effects on the more clinically important kidney end point of *worsening of kidney function* (defined as doubling of serum creatinine or ≥40% decline in estimated glomerular filtration rate [eGFR]) (hazard ratio 0.86; 95% CI, 0.72–1.02).[10] Although the ongoing A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial (ClinicalTrials.gov identifier NCT03819153) will provide more definitive results on the effects of GLP1-RA on kidney

outcomes, results are not expected until 2024. Lastly, whether the effects observed in trials are generalizable to broader unselected patient groups has not been extensively investigated.[24,25]

In the absence of trial evidence, rigorously conducted observational studies can contribute valuable evidence on the effectiveness of medications in broad unselected patient groups. The aim of our study was to compare kidney and cardiovascular outcomes in individuals initiating GLP1-RA versus dipeptidyl peptidase-4 inhibitors (DPP4is) among individuals from routine clinical practice.

METHODS

Data source

The study population consisted of individuals included in the Stockholm Creatinine Measurements project, a health care utilization cohort including all adult residents from the region of Stockholm, Sweden, between 2006 and 2019.[26] The region of Stockholm had a population of 2.3 million citizens in 2019 and has universal health care access. Administrative databases with complete information on demographic data, health care use, diagnoses, and vital status were enriched with performed laboratory tests, dispensed prescriptions at Swedish pharmacies, and validated kidney replacement therapy end points. All linked registries are run by the Swedish National Board of Health and Welfare and are considered to have no or minimal loss to follow-up. The study used only de-identified data and thus was deemed not to require informed consent, being approved by the regional ethical review boards and the Swedish National Board of Health and Welfare.

Study population

We used an active comparator new user design to mitigate the risk of confounding by indication and time-related biases (i.e., immortal time bias and prevalent user selection bias).[27] The ideal active comparator would be a drug that is used in similar clinical situations as GLP1-RAs, but has no expected association with the outcomes under study. We chose DPP4is as an active comparator, because these drugs were also used as second- or third-line glucose-lowering therapies during the study period and therefore used in a similar stage of disease. Furthermore, meta-analyses of randomized controlled trials indicate that DPP4is have no or limited effects on kidney (doubling of serum creatinine or end-stage kidney disease) or cardiovascular outcomes.[28,29]

We included all adult (older than 18 years) community-dwelling individuals with type 2 diabetes mellitus who newly initiated GLP1-RAs or DPP4is between January 1, 2008, and December 31, 2018. *New initiation* was defined as a first dispensation for GLP1-RAs or DPP4is, with no dispensation of either drug in the previous year. Patients with a history of kidney failure (initiation of dialysis or kidney transplantation or a sustained eGFR of <15 ml/min per 1.73 m^2) or missing serum creatinine measurements were excluded (Figure 1). The *date of initiation* was defined as the cohort entry date and start of follow-up (T_0). Patients were followed from the index date to the first occurrence of a study outcome, death, migration, or end of follow-up (December 31, 2018). An overview of the longitudinal study design is presented in Supplementary Figure S1.

Exposure and covariates

The study exposure was initiation of GLP1-RAs (liraglutide, dulaglutide, semaglutide, exenatide, and lixisenatide) or DPP4is (sitagliptin, linagliptin, saxagliptin, and vildagliptin). Study covariates included age, sex, laboratory measurements (eGFR, glycated hemoglobin [HbA1c], and albumin-to-creatinine ratio), medical history (acute coronary syndrome, other ischemic heart disease, heart failure or cardiomyopathy, hypertension, diabetic complications, heart failure, valvular heart disease, stroke, other cerebrovascular disease, atrial fibrillation, other arrhythmia, peripheral arterial disease, diabetes complications, chronic obstructive pulmonary disease, other lung disease, venous thromboembolism, cancer, liver disease, rheumatic disease, psychiatric disorders ever, and coronary revascularization, other cardiac surgery, and fracture in previous year), diabetes drugs (metformin, sulfonylureas, sodium-glucose cotransporter-2 inhibitor, insulin, and other antidiabetics), other medications (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, loop diuretic, other diuretic, β-blocker, digoxin, nitrate, platelet inhibitor, anticoagulant, lipid-lowering drug, antidepressant, antipsychotic, anxiolytic hypnotic sedative, β_2 agonist inhalant, anticholinergic inhalant, glucocorticoid

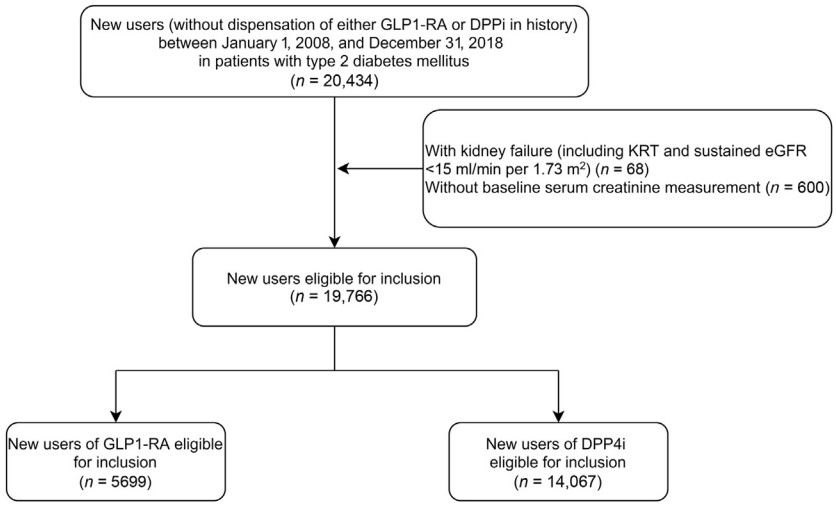

Figure 1 | Patient selection flowchart. DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonist; KRT, kidney replacement therapy.

inhalant, oral glucocorticoid, nonsteroidal anti-inflammatory drug, and opioid), health care utilization (outpatient and inpatient contacts in previous year), and calendar year. Definitions of each covariate are provided in Supplementary Table S1.

Outcomes

The *primary kidney outcome* was defined as the composite of kidney failure (initiation of dialysis or transplantation or a sustained eGFR of <15 ml/min per 1.73 m^2), a sustained doubling of serum creatinine, or death due to kidney disease (i.e., kidney disease reported as the main cause of death). eGFR was calculated from serum/plasma creatinine by using the Chronic Kidney Disease Epidemiology Collaboration equation.[30] To reduce outcome misclassification bias due to intrinsic eGFR variability and to confirm that reached eGFR/creatinine thresholds are sustained over time, we used a linear interpolation method to ascertain a sustained eGFR of <15 ml/min per 1.73 m^2 or sustained doubling of serum creatinine[31] as follows: For each individual, a linear regression line was fitted through all outpatient eGFR measurements. To be considered a sustained eGFR of <15 ml/min per 1.73 m^2, the linear regression slope needed to be negative and the 15 ml/min per 1.73 m^2 threshold needed to be crossed before the last measurement. The *time to event* was then defined as the moment in which the linear regression line crossed the 15 ml/min per 1.73 m^2 threshold. A sustained doubling of serum creatinine was defined in a similar manner.

Secondary outcomes included *MACEs*, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, and the individual components of MACEs (definitions provided in Supplementary Table S2).

Statistical analyses

Continuous variables are presented as mean ± SD or median with interquartile range, depending on the distribution, and categorical variables as number and percentage. The inverse probability of treatment weighting was used to adjust for confounding by indication.[32] We estimated the probability of initiating GLP1-RAs versus DPP4is as a function of all study covariates mentioned previously. Patients in the GLP1-RA group were weighted by 1/propensity score and in the DPP4i group by 1 / (1 − propensity score). Weights were stabilized by adding the marginal probability of the received treatment to the numerator of the weights. Standardized mean differences were calculated to evaluate the balance of covariates between treatment arms before and after weighting by using a standardized mean difference of >0.1 as the threshold for meaningful imbalance.[33] We also estimated crude incidence rates per 1000 person-years. Weighted Cox regression was used to estimate hazard ratios. Confidence intervals were obtained by robust variance estimation. In addition, weighted Kaplan-Meier curves were plotted to compare the cumulative incidences of the kidney and cardiovascular outcomes between treatment arms. Confidence intervals for the cumulative incidence curves were obtained by robust variance estimation. In our primary analysis, individuals were analyzed according to their initially assigned treatment group irrespective of discontinuation or treatment switch (intention-to-treat approach). Using all subsequent eGFR tests, we graphically represented the change in eGFR as a function of time between treatment groups by using a weighted mixed effects repeated measures model[34] that included treatment, date of the eGFR measurement (time), and their interaction term as fixed effects, with patient as a random effect. In our cohort, HbA1c and albuminuria were missing in 1.46% and 18.57%, respectively. We therefore used multiple imputation by chained equations by classification and regression trees to impute 5 complete data sets for each outcome separately. The imputation model included the treatment variable, all covariates, the event indicator for the outcome, and the Nelson-Aalen estimate of the baseline and each month's cumulative hazard. The propensity score and effect estimates were estimated separately in each imputed data set and then pooled using Rubin's rule.[35]

Subgroup and sensitivity analyses

Subgroup analyses were performed to test for potential effect modification of age (≥70 years vs. <70 years), sex, eGFR (≥60 ml/min per 1.73 m^2 vs. <60 ml/min per 1.73 m^2), *atherosclerotic cardiovascular disease* (defined as composite of acute coronary syndrome, ischemic heart disease, stroke, other cerebrovascular disease, and peripheral vascular disease), heart failure, and metformin use. In addition, we performed the following sensitivity analyses to test the robustness of our results. First, we performed a per-protocol analysis, in which individuals were censored when they discontinued or switched treatment during follow-up. *Treatment discontinuation* was defined as no refill within a period equal to the days of supply of the last filled dispensation plus a 60-day grace period. Days of supply for each dispensation of GLP1-RA or DPP4i were calculated by defined day doses (Supplementary Table S3). Because this censoring is likely to be informative, we used the inverse probability of censoring weighting to adjust for this. The analytical steps have been described previously.[36,37] Second, we calculated an *E* value to investigate the minimum strength of the association that an unmeasured confounder would need to have with both treatment and outcome, with all measured covariates adjusted, to fully explain the observed association.[38] Third, to investigate potential differential outcome ascertainment due to differences in the frequency of serum creatinine testing between the GLP1-RA and DPP4i arms, we calculated the number of serum creatinine tests during follow-up. All analyses were performed using R 3.4.3 software (The R Project for Statistical Computing).

RESULTS

Patient characteristics

We included a total of 19,776 individuals with type 2 diabetes mellitus who initiated GLP1-RAs or DPP4is between January 1, 2008, and December 31, 2018. Of these, 14,067 were new users of DPP4is (86.5% sitagliptin, 7.6% linagliptin, 3.0% saxagliptin, 1.9% unspecified, and 1% vildagliptin) and 5699 patients were new users of GLP1-RAs (84.7% liraglutide, 6.4% exenatide, 6.2% dulaglutide, 1.5% unspecified, 1.0% lixisenatide, and 0.2% semaglutide; Figure 1). Baseline characteristics before and after weighting are reported in Supplementary Table S4 and were all well-balanced after weighting (Figure 2). New users of GLP1-RAs were younger than new users of DPP4is (60 years vs. 65 years), had higher HbA1c (66 mmol/mol vs. 61 mmol/mol), and had a slightly higher eGFR (92 ml/min per 1.73 m^2 vs. 88 ml/min per 1.73 m^2). New users of GLP1-RAs had a higher prevalence of other lung disease (17% vs. 13%) and psychiatric disorder (31% vs. 24%) than did new users of DPP4is. New users of GLP1-RAs had a higher prevalence of the use of renin-angiotensin system inhibitors (72% vs. 67%), antidepressants (20% vs. 15%), β_2 agonist inhalers (12% vs. 9%) and a lower prevalence of the use of platelet

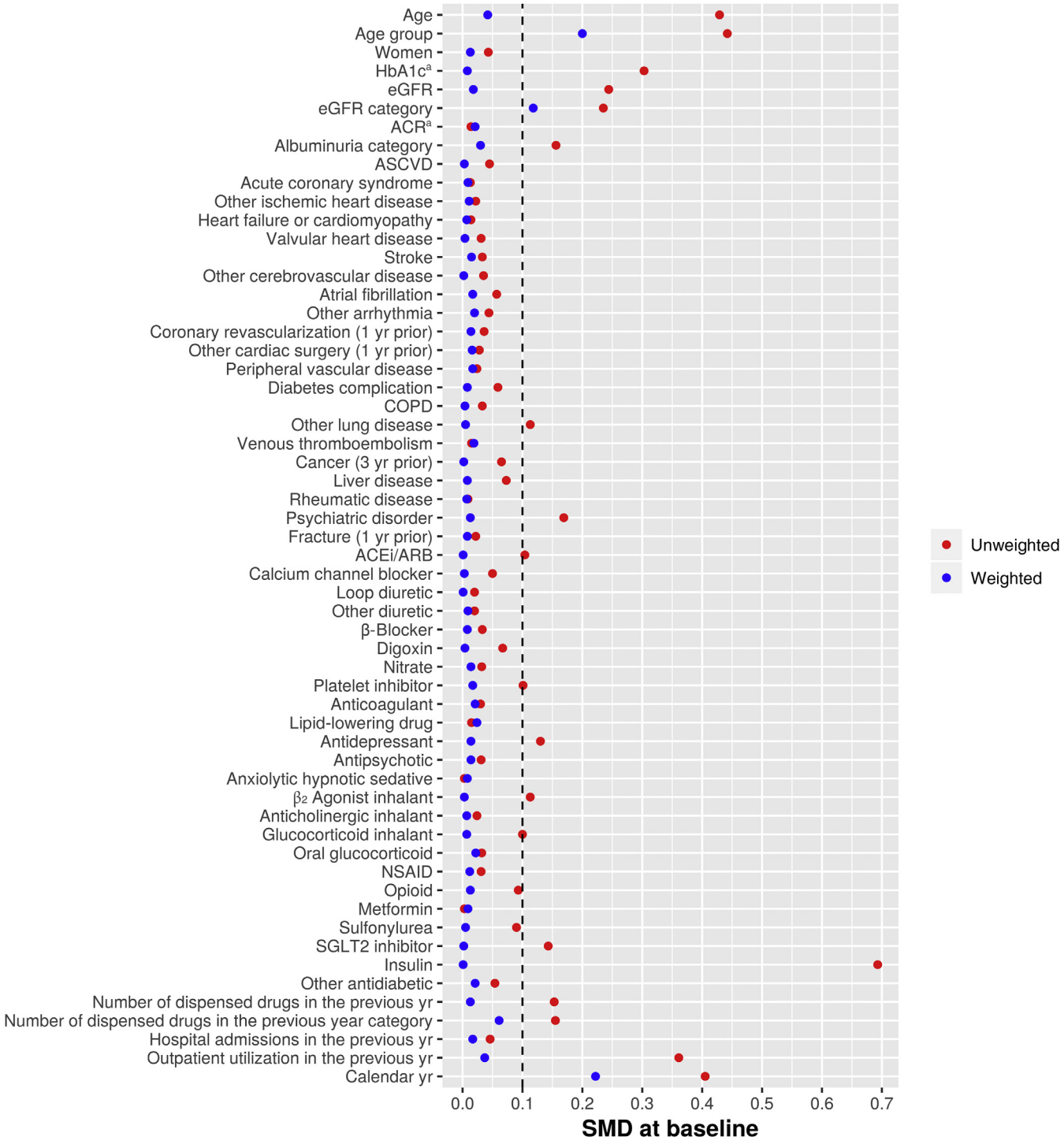

Figure 2 | Balance of baseline characteristics before and after weighting. ACEi, angiotensin-converting-enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference. [a]HbA1c was missing in 1.46% and ACR in 18.57%. Inverse probability weighting was performed after imputation. Baseline characteristics after imputation and weighting are shown. An SMD of >0.1 indicates meaningful imbalance between groups.

inhibitors (30% vs. 35%) than did new users of DPP4is. In addition, new users of GLP1-RAs received more sodium-glucose cotransporter-2 inhibitors (4% vs. 2%) and insulin (45% vs. 15%) than did new users of DPP4is. New users of GLP1-RAs used more drugs (median value 11 drugs vs. 10 drugs) and had twice more frequency of type 2 diabetes

mellitus–related outpatient visits (24% vs. 12%) than did new users of DPP4is.

Comparative effectiveness of GLP1-RAs and DPP4is on kidney and cardiovascular outcomes

During a median (interquartile range) follow-up time of 2.9 (1.2–5.8) years, 76 kidney composite outcomes (56 events of doubling of creatinine and 20 kidney failure events) occurred among 5699 new users of GLP1-RAs and 350 kidney composite events (213 events of doubling of serum creatinine, 129 kidney failure events, and 8 deaths attributed to kidney disease) among 14,067 new users of DPP4is, corresponding to incidence rates (95% CI) of 4.4 (3.5–5.4) and 6.3 (5.6–6.9) per 1000 person-years, respectively (Table 1). The adjusted hazard ratio for the kidney composite outcome was 0.72 (95% CI, 0.53–0.98). The weighted cumulative incidence curves are shown in Figure 3, which showed an early separation that was sustained throughout follow-up. The 5-year absolute risk of the composite kidney outcome was 2.18% (95% CI, 1.58%–2.79%) in the GLP1-RA arm and 3.00% (95% CI, 2.62%–3.38%) in the DPP4i arm, corresponding to a 5-year absolute risk difference of −0.82% (95% CI, −1.53% to −0.10%; Figure 3a). We used 208,192 subsequent routine outpatient measurements of eGFR to compute the slopes of eGFR decline in both treatment arms (median number of eGFR tests per patient was 6 [interquartile range 2–13]; Supplementary Figure S2). Graphically, the slope of eGFR decline was slightly flatter in the GLP1-RA arm than in the DPP4i arm, with a difference of mean eGFR decline of 0.65 (95% CI, 0.61–0.69) ml/min per 1.73 m^2 per year being lower ($P < 0.01$ for interaction).

For the secondary outcome MACEs, the adjusted hazard ratio was 0.85 (95% CI, 0.73–0.99; Table 1), and the weighted cumulative incidence curve similarly showed an early separation; the 5-year absolute risk of MACEs was 9.29% (95% CI, 8.09%–10.48%) in the GLP1-RA arm and 10.84% (95% CI, 10.16%–11.52%) in the DPP4i arm, corresponding to a 5-year absolute risk difference of −1.55% (95% CI, −2.93% to −0.17%; Figure 3b). The associations of GLP1-RA versus DPP4i with the individual components of MACE were similar in magnitude, with an adjusted hazard ratio (95% CI) of 0.79 (0.60–1.05) for cardiovascular death, 0.86 (0.68–1.09) for myocardial infarction, and 0.74 (0.59–0.93) for stroke (Table 1).

Subgroup and sensitivity analyses

The lower risks for GLP1-RAs on the kidney composite outcome were observed across subgroups of age (≥70 years vs. <70 years), sex, eGFR (≥60 ml/min per 1.73 m^2 vs. <60 ml/min per 1.73 m^2), atherosclerotic cardiovascular disease, and metformin use, with all P values > 0.05 for interaction, although a significant interaction was observed according to heart failure at baseline. In individuals with heart failure, the hazard ratio for the kidney composite outcome was lower than that in individuals without heart failure (0.25 [95% CI,

Table 1 | Number of events, incidence rates, and crude and adjusted hazard ratios for the association between GLP1-RA versus DPP4i and cardiovascular and kidney outcomes in intention-to-treat analyses

	GLP1-RAs				DPP4is					
Outcome	No. of persons	No. of events	Median follow-up time (IQR), yr	No. of events per 1000 person-years[a]	No. of persons	No. of events	Median follow-up time (IQR), yr	No. of events per 1000 person-years[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[b]
Primary outcome										
Kidney composite outcome[c]	5699	76	2.2 (1.0–4.3)	4.4 (3.5–5.4)	14,067	350	3.3 (1.5–6.2)	6.3 (5.6–6.9)	0.74 (0.58–0.95)	0.72 (0.53–0.98)
Secondary outcomes										
MACEs	5699	320	2.2 (0.9–4.2)	19.0 (17.0–21.1)	14,067	1307	3.1 (1.3–5.9)	24.2 (22.9–25.5)	0.78 (0.69–0.88)	0.85 (0.73–0.99)
CVD death	5699	97	2.3 (1.0–4.5)	5.5 (4.5–6.7)	14,067	456	3.3 (1.5–6.2)	8.1 (7.4–8.8)	0.70 (0.56–0.87)	0.79 (0.60–1.05)
MI	5699	127	2.2 (0.9–4.3)	7.4 (6.2–8.7)	14,067	474	3.2 (1.4–6.1)	8.6 (7.8–9.3)	0.86 (0.71–1.05)	0.86 (0.68–1.09)
Stroke	5699	131	2.2 (0.9–4.3)	7.6 (6.4–9.0)	14,067	585	3.2 (1.4–6.0)	10.6 (9.8–11.5)	0.71 (0.59–0.86)	0.74 (0.59–0.93)

ACEi, angiotensin-converting-enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular event (composite cardiovascular death, myocardial infarction, ischemic stroke); MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium-glucose cotransporter-2.

[a]Number of events, person-years, and incidence rates were calculated in the original unweighted population.

[b]Analyses were adjusted for the following 53 variables: age, sex, calendar year, acute coronary syndrome, other ischemic heart disease, heart failure or cardiomyopathy, valvular heart disease, stroke, other cerebrovascular disease, atrial fibrillation, other arrhythmia, coronary revascularization (1 yr prior), other cardiac surgery (1 yr prior), peripheral vascular disease, diabetes complication, COPD, other lung disease, venous thromboembolism, cancer (3 yr prior), liver disease, rheumatic disease, psychiatric disorder, fracture (1 yr prior), ACEi/ARB, calcium channel blocker, loop diuretic, other diuretic, β-blocker, digoxin, nitrate, platelet inhibitor, anticoagulant, lipid-lowering drug, antidepressant, antipsychotic, anxiolytic hypnotic sedative, β_2 agonist inhalant, anticholinergic inhalant, glucocorticoid inhalant, oral glucocorticoid, NSAID, opioid, metformin, sulfonylurea, SGLT2 inhibitor, insulin, other antidiabetic, HbA1c, eGFR, ACR, number of dispensed drugs (1 yr prior), hospital admissions (1 yr prior), and outpatient utilization (1 yr prior).

[c]The *primary kidney outcome* was defined as the composite of kidney failure (initiation of dialysis or transplantation or a sustained eGFR of <15 ml/min per 1.73 m^2), a sustained doubling of serum creatinine, or death due to kidney disease.

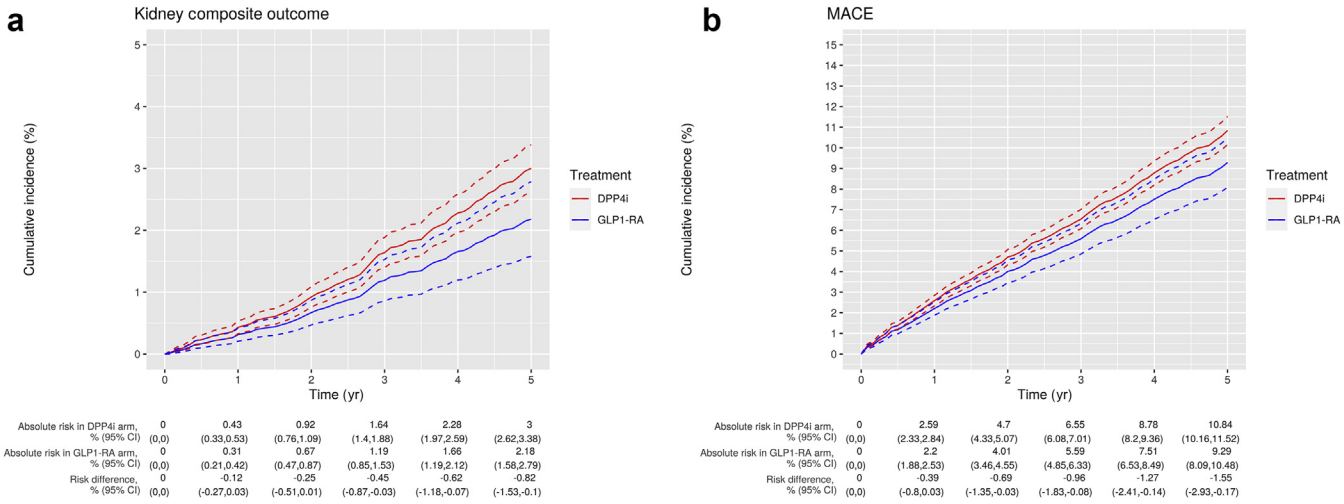

Figure 3 | Weighted cumulative incidence curves for (a) kidney composite outcome and (b) major adverse cardiovascular events (MACE; composite of myocardial infarction, ischemic stroke, and cardiovascular death) for glucagon-like peptide-1 receptor agonist (GLP1-RA) versus dipeptidyl peptidase-4 inhibitor (DPP4i) initiation. Dotted lines represent 95% confidence intervals (CIs).

0.10–0.62] vs. 0.81 [0.58–1.12]; $P = 0.03$ for interaction). No significant interactions were observed for the outcome MACEs across all subgroups (Supplementary Table S5). Results of the per-protocol analyses, which took into account treatment discontinuation or switch during follow-up, were consistent with our main analyses (Supplementary Table S6 and Supplementary Figure S3). *E* values for the kidney composite outcome and MACEs were 2.12 and 1.63, respectively, for the point estimates and 1.17 and 1.11, respectively, for the upper confidence limit (Supplementary Table S7). Lastly, no differences were observed in the frequency of creatinine measurements between both treatment arms during follow-up (Supplementary Table S8).

DISCUSSION

In this cohort study including 19,766 individuals from routine clinical practice, initiation of GLP1-RAs compared with DPP4is was associated with a significantly reduced risk of a composite kidney outcome as well as a significantly reduced risk of MACEs. These findings were observed across subgroups, including older adults, those with lower kidney function, and those using metformin. Findings consistent with our main results were also observed in per-protocol analyses, which took into account treatment discontinuations or switches during follow-up. In this predominantly primary prevention cohort, absolute risks were low (3.0% in the DPP4i arm and 2.2% in the GLP1-RA arm) and in agreement with previous trial[10] and observational data.[25]

Our observed relative reductions in kidney and cardiovascular outcomes are similar in magnitude to the findings of a recent meta-analysis of 8 GLP1-RA trials.[10] In that meta-analysis, the pooled hazard ratio was 0.86 (95% CI 0.80–0.93) for 3-point MACE and 0.86 (95% CI, 0.72–1.02) for worsening kidney function (defined as a composite of doubling creatinine or ≥40% eGFR decline). Although trials have shown a robust reduction in macroalbuminuria for GLP1-RA compared with placebo (pooled hazard ratio 0.68; 95% CI 0.58–0.80),[11,21–23,39–42] estimates on worsening kidney function from the individual trials have been inconsistent: the point estimates for worsening kidney function ranged from 0.35 (0.10–1.27) in AMPLITUDE-O to 1.28 (0.64–2.58) in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), with the I^2 statistic of 43%. This heterogeneity may be due to the limited number of events and low power in the trials, but also due to differences in the populations included and structural differences between the individual GLP1-RA. Our study expands these trial findings and provides novel evidence on the beneficial effects of GLP1-RA in individuals from routine clinical practice. In our study, the cardiovascular and kidney end points occurred soon, as shown by an early divergence of survival curves. This early separation is also consistent with the effect of GLP1-RA on MACE and its individual components reported in clinical trials.[13,14,17] Similarly, the recent AMPLITUDE-O trial showed an early separation of survival curves for the kidney outcome, already within 3 months of randomization.[11]

The beneficial effects of GLP1-RAs on the kidney and cardiovascular system are likely to be multifactorial[43] and may be mediated by reductions in body weight,[19,44] blood pressure,[45] and dyslipidemia.[46] GLP1-RAs may also reduce proteinuria and glomerular sclerosis by improving endothelial function and reducing oxidative stress and inflammation.[47,48] In addition, exogenous GLP1 has been shown to increase natriuresis and diuresis by acting on the proximal renal tubule.[49–51]

Our study findings also align with the 2 observational studies that have assessed the kidney benefits of GLP1-RAs to date[24,25]: A Scandinavian register-based cohort study found a lower risk of hospitalizations attributed to kidney disease and a lower risk of kidney replacement therapy in individuals

initiating GLP1-RAs compared with DPP4is.[25] Potential limitations of that study are a short follow-up for the evaluation of kidney replacement therapy risks, the lumping of hospitalizations attributed to both chronic kidney disease and acute kidney injury into a single composite outcome, and a lack of laboratory measurements (e.g., creatinine, albuminuria, and HbA1c) for the majority of individuals. An analysis of US veterans also found a lower risk for GLP1-RAs versus DPP4is for the composite outcome of 50% eGFR decline or end-stage kidney disease.[24] Potential limitations of that study are a low representation of women and (presumably) the use of a single eGFR to define >50% relative decline during follow-up, which may misclassify acute kidney injury events as chronic kidney disease progression events. Our analysis overcame some of those limitations as expanded below. Finally, our observed cardiovascular benefits with GLP1-RAs also align well with other observational analyses[52–55] and believe to offer reassurance on the plausibility of our findings.

We note that permanence rates in our study were lower than those reported by the US study.[24] We speculate that discontinuation of the drugs or treatment switch may have been more frequent in our cohort, rendering low power and lack of statistical significance in risk reduction of the outcomes in per-protocol analyses.

Strengths of this study include its active comparator new user design, which prevented time-related biases and reduced confounding. Indeed, most variables were balanced between the GLP1-RA and DPP4i groups before applying propensity score weighting. In addition, we adjusted for a wide and rich range of confounders, including laboratory measurements such as HbA1c, albuminuria, and eGFR that may determine the therapy but also strongly influence kidney risk. We used a linear interpolation method to ascertain chronic declines in kidney function, which is less susceptible to temporary acute declines that may misclassify the outcome when requiring only 1 measurement to pass the threshold. Because the frequency of creatinine testing was similar between both treatment arms, we believe that findings are unlikely to be explained by differential outcome ascertainment.

Our study also has limitations. First, our study predominantly included individuals initiating liraglutide or sitagliptin and therefore provides little information on other GLP1-RA drugs such as semaglutide or dulaglutide or other DPP4i drugs such as linagliptin or saxagliptin. Second, we were not able to look at macroalbuminuria outcomes, because these measurements are not systematically and regularly performed in clinical practice. Third, because of low power in this predominantly primary prevention population, we were unable to investigate the individual components of the composite kidney outcome. Fourth, although meta-analyses have shown that DPP4i have no effect on hard kidney end points (i.e., doubling of serum creatinine or end-stage kidney disease), a greater eGFR decline was observed for DPP4i than for placebo.[28] The beneficial effect of GLP1-RAs observed in our study could therefore be due to beneficial effects of GLP1-RAs on the kidney, harmful effects of DPP4is, or a combination of both. In the last 2 situations, the associations observed in our study would then be an overestimation of the true effect of GLP1-RAs compared with placebo. Lastly, our study remains observational in nature and residual confounding cannot be excluded. However, given our design and extensive confounding adjustment, the agreement with trial evidence, as well as the large *E* value, we find it unlikely that residual confounding fully explains the observed reduction in kidney outcomes. The reduction in kidney outcomes is also an "unintended" effect of GLP1-RAs, as these are not an indication for treatment, and unintended effects generally suffer less from confounding by indication than do intended effects.[56,57] Furthermore, the observed effect for MACEs was in line with findings from randomized trials, thereby offering reassurance and serving as a positive control outcome.[27]

In conclusion, this cohort study extends and complements evidence obtained in clinical trials and suggests that GLP1-RAs are associated with a reduction in both kidney and cardiovascular outcomes.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

YX, ELF, and JJC presented research idea and study design. JJC performed data acquisition. YX, ELF, CMC, MJJ, and JJC performed data analysis/interpretation. YX and ELF performed statistical analysis. ELF and YX drafted the manuscript. JJC performed supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision, approves the submitted version, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Definition and categorization of study covariates.

Table S2. Definition of study outcomes.

Table S3. Definition and estimated days of supply of exposure.
Table S4. Baseline characteristics of patients initiating glucagon-like peptide-1 (GLP1) or dipeptidyl peptidase-4 inhibitor (DPP4i) treatment between January 2008 and December 2018 in Stockholm before and after weighting.
Table S5. Adjusted hazard ratios for glucagon-like peptide-1 receptor agonists (GLP1-RA) vs. dipeptidyl peptidase-4 inhibitors (DPP4i) for the kidney composite outcome and major adverse cardiovascular events (MACE) across subgroups.
Table S6. Number of events, incidence rates, crude and adjusted hazard ratios for the association between glucagon-like peptide-1 receptor agonists (GLP1-RA) versus dipeptidyl peptidase-4 inhibitors (DPP4i) and kidney and cardiovascular outcomes in per-protocol analyses.
Table S7. E-values for the kidney composite outcome and major adverse cardiovascular events (MACE).
Table S8. Frequency of creatinine measurements during follow-up, overall and within yearly intervals.
Figure S1. Graphical depiction of longitudinal study design.
Figure S2. Changes in estimated glomerular filtration rate (eGFR) during follow up.
Figure S3. Weighted cumulative incidence curves for (**A**) the kidney composite outcome and (**B**) major adverse cardiovascular events (MACE) stratified by glucagon-like peptide-1 receptor agonists (GLP1-RA) or dipeptidyl peptidase-4 inhibitors (DPP4is) treatment.

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