Use of Glucagon-Like Peptide 1 Receptor Agonists and Risk of Serious Renal Events: Scandinavian Cohort Study

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Diabetes Care 2020;43:1326–1335 | https://doi.org/10.2337/dc19-2088

OBJECTIVE

To assess the association between use of glucagon-like peptide 1 (GLP-1) receptor agonists and risk of serious renal events in routine clinical practice.

RESEARCH DESIGN AND METHODS

This was a cohort study using an active-comparator, new-user design and nationwide register data from Sweden, Denmark, and Norway during 2010–2016. The cohort included 38,731 new users of GLP-1 receptor agonists (liraglutide 92.5%, exenatide 6.2%, lixisenatide 0.7%, and dulaglutide 0.6%), matched 1:1 on age, sex, and propensity score to a new user of the active comparator, dipeptidyl peptidase 4 (DPP-4) inhibitors. The main outcome was serious renal events, a composite including renal replacement therapy, death from renal causes, and hospitalization for renal events. Secondary outcomes were the individual components of the main outcome. Hazard ratios (HRs) were estimated using Cox models and an intention-to-treat exposure definition. Mean (SD) follow-up time was 3.0 (1.7) years.

RESULTS

Mean (SD) age of the study population was 59 (10) years, and 18% had cardiovascular disease. A serious renal event occurred in 570 users of GLP-1 receptor agonists (incidence rate 4.8 events per 1,000 person-years) and in 722 users of DPP-4 inhibitors (6.3 events per 1,000 person-years, HR 0.76 [95% CI 0.68–0.85], absolute difference −1.5 events per 1,000 person-years [−2.1 to −0.9]). Use of GLP-1 receptor agonists was associated with a significantly lower risk of renal replacement therapy (HR 0.73 [0.62–0.87]) and hospitalization for renal events (HR 0.73 [0.65–0.83]) but not death from renal causes (HR 0.72 [0.48–1.10]). When we used an as-treated exposure definition in which patients were censored at treatment cessation or switch to the other study drug, the HR for the primary outcome was 0.60 (0.49–0.74).

CONCLUSIONS

In this large cohort of patients seen in routine clinical practice in three countries, use of GLP-1 receptor agonists, as compared with DPP-4 inhibitors, was associated with a reduced risk of serious renal events.

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Received 18 October 2019 and accepted 20 March 2020

This article contains Supplementary Data online at https://doi.org/10.2337/dc20-1234/suppl.12016407.

Patients with type 2 diabetes are at high risk of chronic kidney disease and end-stage renal disease (1). Improved glucose control has been shown to reduce surrogate markers of renal complications (2–4), although evidence regarding advanced renal complications is limited (5).

Glucagon-like peptide 1 (GLP-1) receptor agonists are a class of drugs for treatment of type 2 diabetes that have shown beneficial effects on renal outcomes. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, patients at high cardiovascular risk randomized to liraglutide versus placebo experienced lower rates of a composite renal outcome including new-onset persistent macroalbuminuria, persistent doubling of creatinine, renal-replacement therapy, and death due to renal disease (15.0 vs. 19.0 events per 1,000 person-years, hazard ratio [HR] 0.78 [95% CI 0.67–0.92]) (6). Similar findings were observed for composite renal outcomes in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) of semaglutide (HR 0.64 [0.46–0.88]) (7) and the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial of dulaglutide (HR 0.85 [0.77–0.93]) (8). In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), renal events were not analyzed as efficacy outcomes but 9.4% of the exenatide group vs. 10.3% of the placebo group experienced micro- or macroalbuminuria (9). Similarly, in the Evaluation of LIXisenatide in Acute coronary syndrome (ELIXA) trial, lixisenatide was associated with lower risk of new-onset, as well as progression of, macroalbuminuria (10).

While GLP-1 receptor agonists constitute valuable therapeutic options for patients with type 2 diabetes, much uncertainty remains regarding their impact on renal outcomes in routine clinical practice. In the clinical trials in which renal outcomes have been assessed, results were driven by macroalbuminuria, whereas analyses of hard end points, including renal replacement therapy, were inconclusive due to limited number of events (6–8). In addition, the cardiovascular outcome trials of GLP-1 receptor agonists included patients who had established cardiovascular disease or were at high cardiovascular risk. Whether the findings of the trials are generalizable to broader unselected groups of patients is unknown.

In this register-based cohort study of patients from routine clinical practice, we used nationwide data from Sweden, Denmark, and Norway to assess whether use of GLP-1 receptor agonists, as compared with an active comparator (dipeptidyl peptidase 4 [DPP-4] inhibitors), is associated with a reduced risk of serious renal events.

RESEARCH DESIGN AND METHODS

Study Design

We conducted a cohort study, from January 2010 through December 2016, using data from nationwide health and administrative registers in Sweden, Denmark, and Norway. We used population registers (vital status, demographics, socioeconomic variables), patient registers (comorbidities, outcomes), prescription registers (study drugs, comedications), cause of death registers (outcomes), and the Swedish National Diabetes Register (glycated hemoglobin level, blood pressure, albuminuria, estimated glomerular filtration rate [eGFR], BMI, and smoking) as previously described (11,12) and as described in Supplementary Data.

To minimize the influence of confounding by indication and disease severity, we used an active-comparator, new-user study design (13) and controlled for a wide range of potential confounders through propensity score matching.

Active Comparator

The active-comparator design was used to mitigate the risk of confounding by indication, disease severity, and unmeasured clinical characteristics in the assessment of the clinical effectiveness of GLP-1 receptor agonists. The ideal active comparator would be a drug that is used in similar clinical situations and has no expected effects on the investigated renal outcomes. We used DPP-4 inhibitors as the active comparator drug class, as clinical guidelines used during the study period (14) recommended both GLP-1 receptor agonists and DPP-4 inhibitors as second- or third-line glucose-lowering therapies, and they were thus used at a similar stage of disease. Moreover, data from clinical trials in patients at high cardiovascular risk indicate that DPP-4 inhibitors have no or limited effects on renal outcomes (15).

Study Population

We included all patients in the three countries, aged 35–84 years, who filled their first prescription for either a GLP-1 receptor agonist or a DPP-4 inhibitor during the study period (Anatomic Therapeutic Chemical [ATC] codes for study drugs shown in Supplementary Table 1). Patients entered the cohort at the date of filling the first prescription. We excluded patients who had ever filled prescriptions for any of the study drugs and patients who had no specialist care contact or prescription drug in the past year. To reduce the risk of including events with onset occurring prior to cohort entry, and to reduce the influence of acute illness, patients who were hospitalized for any reason within 30 days before cohort entry were excluded. Other exclusion criteria were history of dialysis or renal transplantation, end-stage illness, drug misuse, and severe pancreatic disorders (Supplementary Table 2).

In each country separately, we estimated propensity scores using logistic regression for the probability of starting a GLP-1 receptor agonist in a model including sociodemographic characteristics, comorbidities, comedications, and health care utilization at cohort entry (Supplementary Table 3). Missing data on place of birth (<1%), civil status (<1%), and education (<3%) were handled with use of missing categories (16). Due to data availability, a few variables used for the propensity score in Norway differed slightly compared with those in Sweden and Denmark (Supplementary Table 3).

New users of GLP-1 receptor agonists and DPP-4 inhibitors were matched in a 1:1 ratio using the nearest neighbor algorithm (caliper width 0.2 of the SD for the logit propensity score) (17,18) with sex and age (5-year intervals) as additional matching criteria.

Covariates were considered well balanced if the standardized mean difference was <10%. The analyses were performed in a pooled data set of the matched cohorts of the three countries.

The study was approved by the Regional Ethics Committee in Stockholm, Sweden, and the Regional Committee for Medical and Health Research Ethics (REC Central), Norway. In Denmark, ethics approval is not required for register-based research.

Outcomes

The primary outcome was a composite of renal replacement therapy (dialysis or

renal transplantation), death from renal causes, and hospitalization for renal events as captured in the patient registers and the cause of death registers. Secondary outcomes were each component of the primary outcome. The outcome of hospitalization for renal events was based on events consistent with serious renal disease, including diabetic nephropathy, chronic kidney disease, and acute kidney injury, and was considered a renal analog to the outcome hospitalization for heart failure in cardiology; hence, it was regarded as an indicator of serious worsening of renal status. Supplementary Table 4 shows the ICD-10 codes and procedure codes used to define the outcomes.

Statistical Analyses

Patients were followed from cohort entry until outcome event, death, emigration, 5 years since cohort entry, or end of study (31 December 2016). In the analysis of the primary outcome, patients were followed until the time of the first outcome event; in the analyses of the secondary outcomes, patients were followed until the first occurrence of the outcome analyzed, independent of other outcomes. Patients were defined as exposed to the study drug from cohort entry throughout follow-up, analogous to an intention-to-treat design in a clinical trial. We used Cox proportional hazards regression with time since treatment initiation as the timescale to calculate HRs. The proportional hazards assumption was examined by a Wald test of the interaction between treatment status and time. HRs with 95% CIs that did not overlap 1 were considered statistically significant. The absolute rate difference was estimated by comparing incidence rates between the groups using Poisson regression.

We performed subgroup analyses for the primary outcome by sex, age-group, history of major cardiovascular disease (Supplementary Table 5), and history of chronic kidney disease (Supplementary Table 6). Effect modification by subgroup status was tested using an interaction term between treatment status and subgroup; a P value of <0.05 was considered statistically significant. To assess consistency across data sources, we also analyzed the primary outcome by country.

In an additional analysis of the primary and secondary outcomes, we used an as-treated exposure definition with treatment duration based on the estimated duration of the filled prescriptions (Supplementary Table 1) and a 30-day grace period to account for prescription overlap, irregular drug use, and events that occurred shortly after treatment cessation. In this analysis, patients were censored at treatment cessation and crossover to the other study drug (i.e., initiation of DPP-4 inhibitors among GLP-1 receptor agonist users and vice versa).

We performed two sensitivity analyses. *1*) In the propensity score–matched cohort in Sweden, we did additional confounding adjustment by including the following covariates in the Cox model: glycated hemoglobin level, blood pressure, albuminuria, eGFR, BMI, and smoking (Supplementary Table 7). Missing values in these variables (Supplementary Table 7) were imputed with multiple imputation (fully conditional specification imputation) using 10 imputed data sets (19). And *2*) we excluded patients with any renal disease, as defined in Supplementary Table 6.

We also performed analyses for liraglutide versus DPP-4 inhibitors. For these analyses, a separate study population was created in which new users of liraglutide and DPP-4 inhibitors were included, with separate estimation of the propensity score and 1:1 matching.

RESULTS

Study Population

We identified 45,880 new users of GLP-1 receptor agonists and 153,853 new users of DPP-4 inhibitors who fulfilled study eligibility criteria (Fig. 1). Baseline characteristics for the cohort before matching are shown in Supplementary Table 8. After 1:1 matching, the cohort included 38,731 pairs of new users of GLP-1 receptor agonists and DPP-4 inhibitors. The two groups were well balanced on all measured covariates (Table 1). Mean (SD) age was 59 (10) years, 57% were male, 18% had a history of major cardiovascular disease, and 5% had a history of chronic kidney disease. In the primary analysis, total follow-up time was 119,771 years (mean [SD] 3.1 [1.7] years) among GLP-1 receptor agonist users and 115,629 years (3.0 [1.7] years) among DPP-4 inhibitor users. Of the total follow-up time for GLP-1 receptor agonists, the proportion of follow-up time by drug initiated at cohort entry was 92.5% for liraglutide, 6.2% for exenatide, 0.7% for lixisenatide, and 0.6% for dulaglutide (Supplementary Table 9). The corresponding numbers for DPP-4 inhibitors were 71.8% for sitagliptin, 17.9% for vildagliptin, 6.6% for saxagliptin, 3.3% for linagliptin, and 0.4% for alogliptin (Supplementary Table 10).

Primary and Secondary Outcomes

The cumulative incidence of the primary composite outcome, serious renal events, is shown in Fig. 2. During follow-up, the primary composite outcome event occurred in 570 users of GLP-1 receptor agonists (incidence rate 4.8 events per 1,000 person-years) and 722 users of DPP-4 inhibitors (incidence rate 6.3 events per 1,000 person-years). Use of GLP-1 receptor agonists was associated with significantly lower risk of serious renal events compared with use of DPP-4 inhibitors (HR 0.76 [95% CI 0.68–0.85]) (Table 2). In the assessment of the proportional hazards assumption, there was a statistically significant interaction between years of follow-up and exposure to GLP-1 receptor agonists ($P = 0.0005$) (Schoenfeld residuals shown in Supplementary Fig. 1). The risk reduction associated with use of GLP-1 receptor agonists was driven by the first 2 years of follow-up, while HRs were not statistically significant between year 3 and 5 after cohort entry (HR for year 1 after cohort entry 0.56 [0.45–0.70], year 2 0.68 [0.54–0.85], year 3 0.95 [0.74–1.21], year 4 0.88 [0.67–1.16], and year 5 0.96 [0.72–1.30]).

For the secondary outcomes, use of GLP-1 receptor agonists versus DPP-4 inhibitors was associated with a significantly lower risk of renal replacement therapy (incidence rate 1.9 vs. 2.5 per 1,000 person-years, HR 0.73 [95% CI 0.62–0.87]) and hospitalization for renal events (incidence rate 3.7 vs. 5.1 per 1,000 person-years, HR 0.73 [95% CI 0.65–0.83]) but not death from renal causes (incidence rate 0.3 vs. 0.4 per 1,000 person-years, HR 0.72 [95% CI 0.48–1.10]) (Table 2).

In the additional analysis using an as-treated exposure definition, total follow-up time was 43,744 years (mean [SD] 1.1 [1.2] years) among GLP-1 receptor agonist users and 40,418 years (1.0 [1.0] years) among DPP-4 inhibitor users. The association between GLP-1 receptor agonists and the primary outcome tended to be stronger (incidence rate 3.6 vs. 5.9 events per 1,000 person-years, HR 0.60 [95% CI 0.49–0.74]) (Table 2, Fig. 2, and Supplementary Fig. 2) than in the main

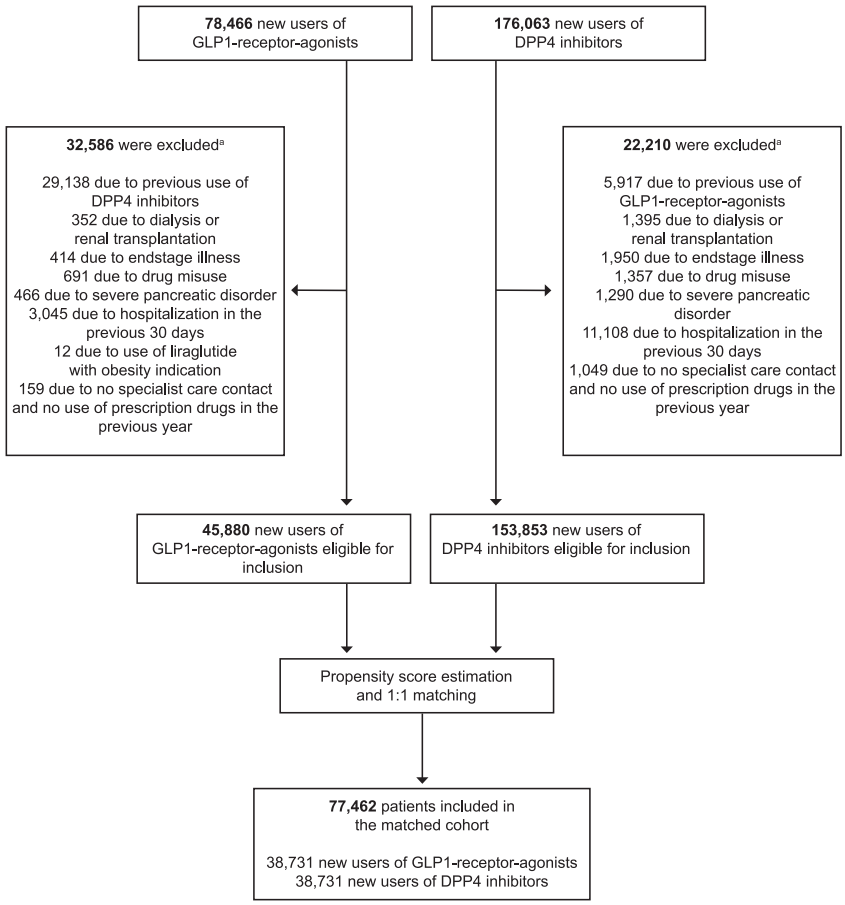

Figure 1—Flowchart of patient inclusion in the study cohort: Sweden, Denmark, and Norway, January 2010–December 2016. [a]One patient could be excluded due to more than one reason.

analysis. The proportional hazards assumption was met ($P = 0.12$) (Supplementary Fig. 2).

Subgroup Analyses

The results of subgroup analyses are shown in Fig. 3. In analyses by sex, age-group, and history of cardiovascular disease, there was no significant interaction between treatment status and subgroup. HRs of the primary outcome were lower for patients with a history of chronic kidney disease versus those without (HR 0.54 [95% CI 0.44–0.68] vs. 0.82 [0.72–0.93], respectively; $P_{interaction}$ 0.002). HRs were consistent across study countries (Supplementary Table 11).

Sensitivity Analysis

The distribution of glycated hemoglobin, blood pressure, albuminuria, eGFR, BMI, and smoking in the Swedish part of the cohort is shown in Supplementary Table 12. Additional adjustment for these variables did not materially affect the HR (0.72 [95% CI 0.60–0.86]) compared with the analyses of the Swedish part of the matched cohort without such adjustment (HR 0.75 [95% CI 0.63–0.89]). In analyses excluding patients with any renal disease, the association between use of GLP-1 receptor agonists and a reduced risk of serious renal events was weaker than in the total population and largely similar to that of patients without chronic kidney disease (HR 0.81 [95% CI 0.71–0.93]).

Analyses of Liraglutide

In the analyses of new users of liraglutide versus DPP-4 inhibitors, we included 70,162 matched patients (35,081 liraglutide users and 35,081 DPP-4 inhibitor users) in the study cohort (Supplementary Fig. 3 [baseline characteristics in Supplementary Table 13]). Use of liraglutide, as compared with DPP-4 inhibitors, was associated with a reduced risk of serious renal events (incidence rate 4.7 vs. 6.5 events per 1,000 person-years, HR 0.72 [95% CI 0.64–0.81]). Also, results of secondary outcome analyses (Supplementary Table 14) and subgroup analyses (Supplementary Table 15) were similar to the findings of the analyses including the whole drug class of GLP-1 receptor agonists.

CONCLUSIONS

In this cohort study, we used data from nationwide registers in Sweden, Denmark, and Norway to assess the clinical renal effectiveness of GLP-1 receptor agonists. Use of GLP-1 receptor agonists was associated with a significantly lower risk of the primary composite outcome of serious renal events (consisting of renal replacement therapy, renal death, and hospitalization for renal events) versus an active comparator (DPP-4 inhibitors). The protective association was significant for renal replacement therapy as well as hospitalization for renal events but not for death due to renal causes, although the point estimate was similar to those of other secondary outcomes.

While clinical trials of GLP-1 receptor agonists have shown beneficial effects on the risk of macroalbuminuria (6–8,10), the impact on hard clinical end points, including renal replacement therapy, has been uncertain due to limited number of events (6–8) or because such renal outcomes were not reported (9,10,20). In addition, the clinical trials of GLP-1 receptor agonists included patients at high cardiovascular risk, although a broader range of patients receive these drugs in routine clinical practice. With use of nationwide data from routine health care in three countries, our observational study suggests that the trial evidence of the renoprotective effects of GLP-1 receptor agonists may translate to clinical effectiveness with regard to serious renal complications, including initiation of renal replacement therapy and hospitalization due to renal events. Importantly, the association between GLP-1 receptor agonists and a reduced risk of serious renal events was observed in patients with and without major cardiovascular disease as well as those with and without chronic kidney disease at cohort entry. Our study complements data from clinical trials as well as our previous observational study using Scandinavian register data, which showed that use liraglutide was associated with a reduced risk of

Table 1—Baseline characteristics of propensity score–matched cohort of GLP-1 receptor agonist users and DPP-4 inhibitor users

	GLP-1 receptor agonists (n = 38,731)	DPP-4 inhibitors (n = 38,731)	Standardized mean difference (%)
Country[a]			
Sweden	19,214 (49.6)	19,214 (49.6)	—
Denmark	13,286 (34.3)	13,286 (34.3)	—
Norway	6,231 (16.1)	6,231 (16.1)	—
Male	22,043 (56.9)	22,043 (56.9)	0
Age, mean (SD)	59.3 (10.4)	59.4 (10.5)	—
Age, years			
35–39	1,441 (3.7)	1,441 (3.7)	0
40–44	2,544 (6.6)	2,544 (6.6)	0
45–49	4,036 (10.4)	4,036 (10.4)	0
50–54	5,241 (13.5)	5,241 (13.5)	0
55–59	6,092 (15.7)	6,092 (15.7)	0
60–64	6,735 (17.4)	6,735 (17.4)	0
65–69	6,403 (16.5)	6,403 (16.5)	0
70–74	3,984 (10.3)	3,984 (10.3)	0
75–79	1,793 (4.6)	1,793 (4.6)	0
80–84	462 (1.2)	462 (1.2)	0
Place of birth			
Scandinavia	34,049 (87.9)	34,211 (88.3)	1.3
Rest of Europe	2,082 (5.4)	2,018 (5.2)	0.7
Outside Europe	2,548 (6.6)	2,456 (6.3)	1.0
Missing	52 (0.1)	46 (0.1)	0.4
Civil status			
Married/living with partner	21,822 (56.3)	21,925 (56.6)	0.5
Single	16,808 (43.4)	16,696 (43.1)	0.6
Missing	101 (0.3)	110 (0.3)	0.4
Education[b]			
Primary/secondary school, vocational training	25,475 (78.4)	25,397 (78.1)	0.6
Short tertiary education	2,403 (7.4)	2,390 (7.4)	0.2
Medium or long tertiary education	3,982 (12.3)	4,082 (12.6)	0.9
Missing	640 (2.0)	631 (1.9)	0.2
Calendar year[c]			
2010–2011	11,340 (29.3)	10,565 (27.3)	—
2012–2014	15,077 (38.9)	15,621 (40.3)	—
2015–2016	12,314 (31.8)	12,545 (32.4)	—
Medical history			
Acute coronary syndrome	2,705 (7.0)	2,673 (6.9)	0.3
Other ischemic heart disease	5,998 (15.5)	5,952 (15.4)	0.3
Heart failure/cardiomyopathy	2,372 (6.1)	2,400 (6.2)	0.3
Valve disorders	726 (1.9)	774 (2.0)	0.9
Stroke	1,319 (3.4)	1,348 (3.5)	0.4
Other cerebrovascular disease	1,479 (3.8)	1,498 (3.9)	0.3
Atrial fibrillation	2,468 (6.4)	2,436 (6.3)	0.3
Other arrythmia	1,386 (3.6)	1,397 (3.6)	0.2
Coronary revascularization in the previous year	515 (1.3)	509 (1.3)	0.1
Other cardiac surgery/invasive procedure in the previous year	192 (0.5)	198 (0.5)	0.2
Arterial disease	2,246 (5.8)	2,275 (5.9)	0.3
Chronic kidney disease	1,799 (4.6)	1,855 (4.8)	0.7
Other renal disease	2,358 (6.1)	2,375 (6.1)	0.2
Diabetes complications	11,585 (29.9)	11,486 (29.7)	0.6
COPD	1,533 (4.0)	1,570 (4.1)	0.5
Other lung disease	2,860 (7.4)	2,927 (7.6)	0.7
Venous thromboembolism	981 (2.5)	958 (2.5)	0.4
Cancer	2,287 (5.9)	2,315 (6.0)	0.3
Liver disease	727 (1.9)	730 (1.9)	0.1
Rheumatic disease	1,100 (2.8)	1,091 (2.8)	0.1
Psychiatric disorder	3,856 (10.0)	3,849 (9.9)	0.1
Fracture in the previous year	657 (1.7)	677 (1.7)	0.4

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Table 1—Continued

	GLP-1 receptor agonists (n = 38,731)	DPP-4 inhibitors (n = 38,731)	Standardized mean difference (%)
Hospitalizations in previous year			
Cardiovascular causes	1,760 (4.5)	1,801 (4.7)	0.5
Type 2 diabetes–related causes	545 (1.4)	532 (1.4)	0.3
Non–cardiovascular/type 2 diabetes–related causes	5,250 (13.6)	5,188 (13.4)	0.5
Outpatient contacts in previous year			
Cardiovascular causes	3,719 (9.6)	3,649 (9.4)	0.6
Type 2 diabetes–related causes	9,374 (24.2)	9,239 (23.9)	0.8
Non–cardiovascular/type 2 diabetes–related causes	22,165 (57.2)	22,056 (56.9)	0.6
Diabetes drugs in previous 6 months			
None	3,190 (8.2)	3,130 (8.1)	0.6
Metformin	29,983 (77.4)	30,022 (77.5)	0.2
Sulphonylureas	9,436 (24.4)	9,780 (25.3)	2.1
SGLT2 inhibitors	636 (1.6)	638 (1.6)	0
Insulin	14,240 (36.8)	14,093 (36.4)	0.8
Other antidiabetics (glitazones, glinides, acarbose)	1,763 (4.6)	1,796 (4.6)	0.4
Prescription drugs in previous year			
ACEi/ARB	26,156 (67.5)	26,127 (67.5)	0.2
Calcium channel blocker	12,134 (31.3)	12,154 (31.4)	0.1
Loop diuretic[b]	5,837 (18.0)	5,881 (18.1)	0.4
Other diuretic[b]	6,645 (20.4)	6,598 (20.3)	0.4
β-Blocker	13,734 (35.5)	13,679 (35.3)	0.3
Digoxin	789 (2.0)	796 (2.1)	0.1
Nitrate	2,667 (6.9)	2,665 (6.9)	0
Platelet inhibitor	14,494 (37.4)	14,514 (37.5)	0.1
Anticoagulant	2,582 (6.7)	2,600 (6.7)	0.2
Lipid-lowering drug	26,345 (68.0)	26,297 (67.9)	0.3
Antidepressant	6,947 (17.9)	7,019 (18.1)	0.5
Antipsychotic	1,502 (3.9)	1,458 (3.8)	0.6
Anxiolytic hypnotic or sedative	6,947 (17.9)	6,828 (17.6)	0.8
β-2 agonist inhalant	4,096 (10.6)	4,127 (10.7)	0.3
Anticholinergic inhalant	1,290 (3.3)	1,307 (3.4)	0.2
Glucocorticoid inhalant	4,229 (10.9)	4,189 (10.8)	0.3
Oral glucocorticoid	2,948 (7.6)	2,907 (7.5)	0.4
NSAID	10,625 (27.4)	10,559 (27.3)	0.4
Opioid	7,974 (20.6)	7,941 (20.5)	0.2
No. of prescription drugs in previous year[b]			
0–5	5,850 (18.0)	5,820 (17.9)	0.2
6–10	12,667 (39.0)	12,728 (39.2)	0.4
11–15	8,312 (25.6)	8,315 (25.6)	0
>15	5,671 (17.4)	5,637 (17.3)	0.3

Data are n (%) unless otherwise indicated. Data are for Sweden, Denmark, and Norway from January 2010 through December 2016. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium–glucose cotransporter 2. [a]Propensity score matching was performed separately by country. [b]Not available in Norwegian data set; numbers are shown for patients in Sweden and Denmark. [c]Year of cohort entry was not included in the propensity score.

major adverse cardiovascular events (12).

The risk reduction observed in our study was driven by associations between GLP-1 receptor agonists and the primary outcome during the first 2 years since cohort entry; during years 3–5 after cohort entry, we observed no statistically significant associations. While our primary analyses aimed to estimate the overall effect of initiation of GLP-1 receptor agonists by using an intention-to-treat exposure definition, the findings of a differential association over time are likely explained by an on-treatment effect of GLP-1 receptor agonists and the relatively short duration of treatment for many of the patients. Previous studies have shown high rates of treatment discontinuation among patients receiving GLP-1 receptor agonists (21,22); in accordance with these findings, in our study, use of an as-treated exposure definition in which patients were censored at treatment cessation or switch to the other study drug led to a substantially shorter follow-up time for users of GLP-1 receptor agonists compared with the primary analyses (mean follow-up time 1.1 vs. 3.1 years). With use of this exposure definition, the association between GLP-1 receptor agonists and serious renal events was stronger than in the main analysis and the association did not differ significantly by year of follow-up.

To limit the risk of confounding, we used a propensity score that included a broad range of patient characteristics and a new-user design in which patients had no history of either study drug at cohort entry; this design eliminated the possibility of immortal time bias, which has been noted in other observational studies of new glucose-lowering drugs (23). In a sensitivity analysis in the

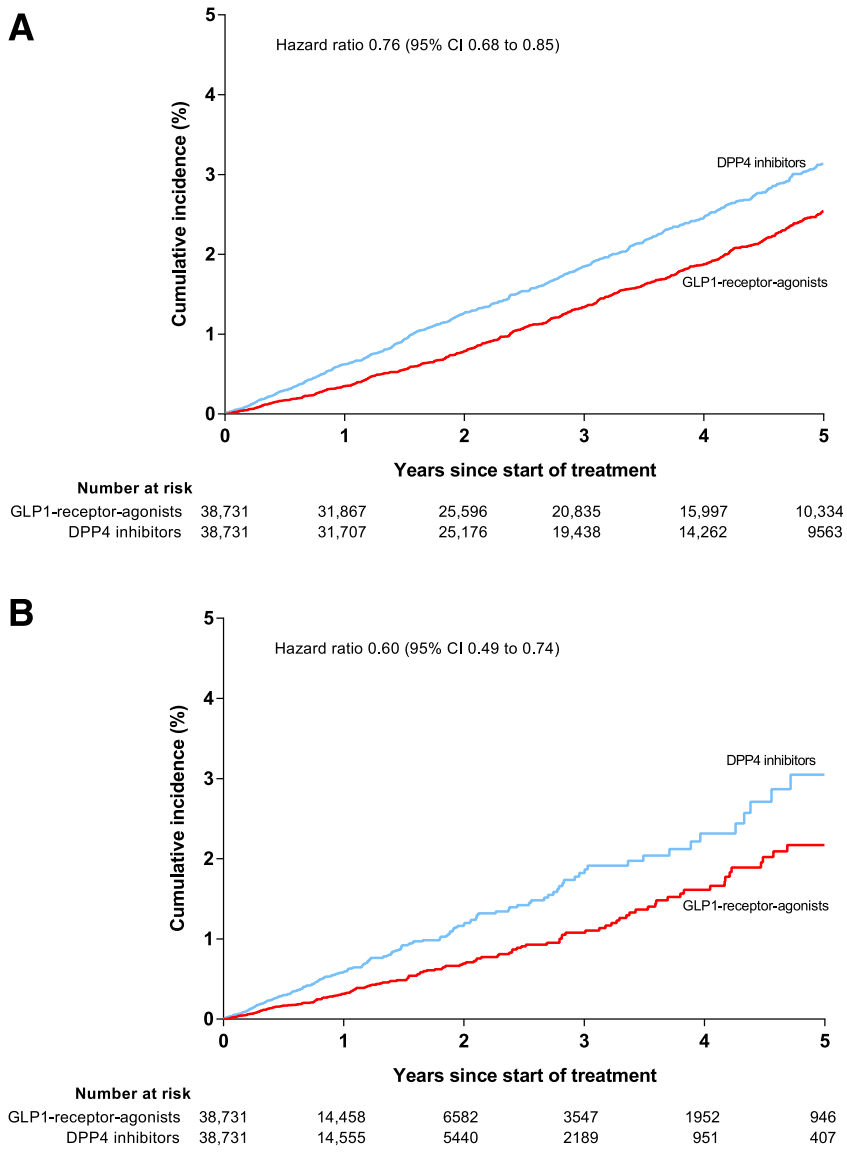

Figure 2—Cumulative incidence of serious renal events in users of GLP-1 receptor agonists and DPP-4 inhibitors in analyses using an intention-to-treat exposure definition (*A*) and an as-treated exposure definition (*B*).

Swedish part of the cohort, we made further adjustments by including glycated hemoglobin level, blood pressure, albuminuria, eGFR, BMI, and smoking in the outcome model. The adjustments did not materially affect the result, indicating that confounding due to these variables was minimal.

The active comparator drug class in our study, DPP-4 inhibitors, is used in similar clinical situations and at a similar stage of disease; this choice of comparator was intended to mitigate the risk of confounding by indication, disease severity, and unmeasured clinical characteristics. In parallel to its neutral impact on cardiovascular outcomes and mortality, data from clinical trials in patients at high cardiovascular risk indicate that DPP-4 inhibitors have no or limited effects on renal outcomes, although less data on renal outcomes are available for this drug class (15). In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), rates of a composite renal outcome, including doubling of serum creatinine, chronic dialysis, renal transplantation, and a serum creatinine >6.9 mg/dL, were similar among those receiving active treatment versus placebo (2.2% vs. 2.0%, respectively; HR 1.08 [95% CI 0.88–1.32]) (24), although secondary analyses indicated that saxagliptin led to reclassification of patients into a lower urine albumin-to-creatinine ratio category, irrespective of baseline urine albumin-to-creatinine ratio (25). In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, changes in eGFR and the rates of dialysis were similar in those receiving alogliptin versus placebo (26). In the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA), linagliptin versus placebo did not significantly affect the secondary renal composite outcome (sustained >40% decrease in eGFR from baseline, end-stage kidney disease, or renal death) (27), although in exploratory analyses, progression of the albuminuria category occurred less frequently in those receiving linagliptin (HR 0.86 [95% CI 0.78–0.95]) (27). In the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS), the follow-up time for which comprised 71.8% of the follow-up time of DPP-4 inhibitors in our study, the decline in eGFR was clinically similar in those receiving active treatment versus placebo (28). If DPP-4 inhibitors are not risk neutral, the HRs in our study might underestimate the reduction of serious renal events associated with GLP-1 receptor agonists, although this would not affect the overall interpretation of our findings and the analyses would still represent a head-to-head comparison of GLP-1 receptor agonists and DPP-4 inhibitors.

Our study has limitations. First, we analyzed GLP-1 receptor agonists as a drug class; liraglutide (92.5% of the total follow-up time among users of GLP-1 receptor agonists) and exenatide (6.2%) were the most common GLP-1 receptor agonists in our study population. Hence, our data are primarily applicable to liraglutide and, as expected, the results were similar in analyses of patients receiving liraglutide versus DPP-4 inhibitors. Assessment of serious renal events for other individual GLP-1 receptor agonists (as well as comparisons with other drug classes [15], such as sodium–glucose cotransporter 2 inhibitors) remains a topic for additional examination. Second, as drug exposure was defined based on filled prescriptions, low adherence may bias the results toward the null. Third, although procedure codes

Table 2—Primary and secondary outcome of association between use of GLP-1 receptor agonists versus DPP-4 inhibitors with risk of serious renal events

	GLP-1 receptor agonists (n = 38,731)		DPP-4 inhibitors (n = 38,731)			
	Events	Events per 1,000 person-years	Events	Events per 1,000 person-years	HR (95% CI)	Absolute difference, events (95% CI) per 1,000 person-years
ITT primary outcome[a]	570	4.8	722	6.3	0.76 (0.68–0.85)	−1.5 (−2.1 to −0.9)
ITT secondary outcomes						
Renal replacement therapy	223	1.9	291	2.5	0.73 (0.62–0.87)	−0.7 (−1.0 to −0.3)
Death from renal causes	39	0.3	51	0.4	0.72 (0.48–1.10)	−0.1 (−0.3 to 0.0)
Hospitalization for renal events	444	3.7	583	5.1	0.73 (0.65–0.83)	−1.4 (−1.9 to −0.8)
As-treated primary outcome[a]	159	3.6	239	5.9	0.60 (0.49–0.74)	−2.3 (−3.2 to −1.4)
As-treated secondary outcomes						
Renal replacement therapy	40	0.9	85	2.1	0.42 (0.29–0.62)	−1.2 (−1.7 to −0.7)
Death from renal causes	7	0.2	9	0.2	0.66 (0.24–1.79)	−0.1 (−0.3 to 0.1)
Hospitalization for renal events	133	3.0	193	4.8	0.63 (0.50–0.78)	−1.7 (−2.6 to −0.9)

Data are n unless otherwise indicated. ITT, intention to treat. [a]Serious renal events, a composite of renal replacement therapy, death from renal causes, and hospitalization for renal events.

and diagnoses recorded in Scandinavian health registers generally have high sensitivity and positive predictive value (29,30), validation studies of the specific codes used to define the outcome in our study have not been performed (29,30). While outcome misclassification may have introduced bias in our analyses, such misclassification is unlikely to be differential between exposure groups. Finally, although we used an active-comparator, new-user design and we accounted for a wide range of patient characteristics by using a propensity score, the observational nature of this study means that unmeasured and residual confounding cannot be ruled out. In particular, due to postmarketing reports of acute renal failure, GLP-1 receptor agonists are recommended to be used with caution in patients with renal impairment (31), and it is a possibility that DPP-4 inhibitors may be used more frequently in patients with worse renal prognosis. The risk reduction associated with use of GLP-1 receptor agonists in our study occurred soon after treatment

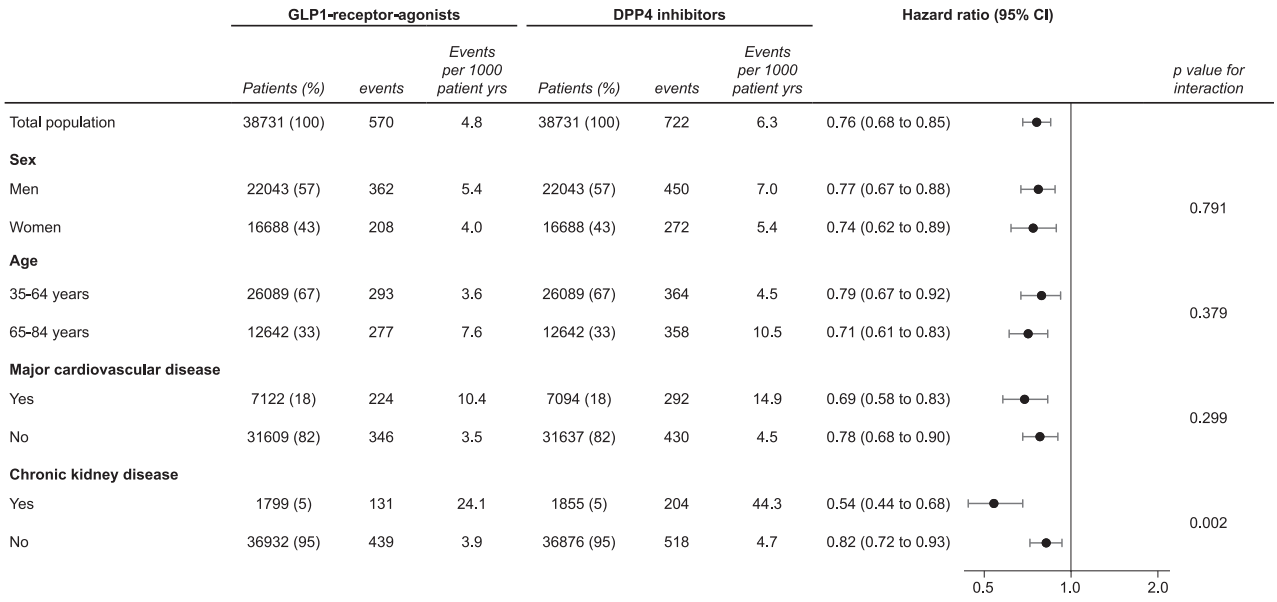

Figure 3—Subgroup analyses of serious renal events among GLP-1 receptor agonist users compared with DPP-4 inhibitor users. patient yrs, patient-years.

initiation and persisted during the first 2 years of follow-up in the primary analyses and throughout the study period in the as-treated analyses. The mechanisms by which GLP-1 receptor agonists may protect the kidney and their timing with respect to discernible effects on renal outcomes remain to be fully understood. It has been suggested that GLP-1 receptor agonists may affect renal outcomes through effects on body weight (32), blood pressure (33,34), postprandial lipid profiles (34), and inflammation or fibrosis (33). GLP-1 receptor agonists may also affect renal hemodynamics, although this has not been consistently demonstrated in mechanistic clinical trials (15).

In conclusion, in this analysis of nationwide registers from three countries, use of GLP-1 receptor agonists, as compared with DPP-4 inhibitors, was associated with a reduced risk of serious renal events.

Funding. B.P. was supported by an investigator grant from the Strategic Research Area Epidemiology program at Karolinska Institutet. P.U. was supported by grants from the Swedish Heart-Lung Foundation and the Swedish Society for Medical Research. The study was conducted with research grant support from the Swedish Cancer Society and the Novo Nordisk Foundation.

The funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Duality of Interest. All authors have completed the Unified Competing Interest form at icme.org/conflicts-of-interest (available on request from the corresponding author) and have the following declarations. B.E. reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Navamedic, Novo Nordisk, and RLS Global outside the submitted work and grants from Sanofi outside the submitted work. S.G. reports lecture fees and research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi outside of the submitted work. C.J. reports personal fees from Pfizer and Bayer outside the submitted work. H.S. reports consulting fees from Celgene and employment at IQVIA outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.P., V.W., H.S., and P.U. contributed to the study concept and design. All authors contributed to acquisition, analysis, or interpretation of data. B.P. and P.U. contributed to drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. V.W. performed statistical analysis. B.P. and P.U. obtained funding. B.P. and P.U. contributed to study supervision. B.P. and P.U. had full access to all the data in the study. P.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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