The comparative cardiovascular and renal effectiveness of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: A Scandinavian cohort study

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Abstract
Aim: To assess the comparative cardiovascular and renal effectiveness of sodium-glucose co-transporter-2 (SGLT2) inhibitors versus glucagon-like peptide-1 (GLP-1) receptor agonists in routine clinical practice.

Materials and Methods: A cohort study of nationwide registers from Sweden, Denmark, and Norway, including 87 525 new users of SGLT2 inhibitors and 63 921 new users of GLP-1 receptor agonists, was conducted using data from 2013-2018. Co-primary outcomes, analysed using an intention-to-treat exposure definition, were major adverse cardiovascular events (MACE; myocardial infarction, stroke, and cardiovascular death), heart failure (hospitalization or death because of heart failure), and serious renal events (renal replacement therapy, hospitalization for renal events, and death from renal causes).
Results: Use of SGLT2 inhibitors versus GLP-1 receptor agonists was associated with a higher risk of MACE (adjusted incidence rate: 15.2 vs. 14.4 events per 1000 person-years; HR 1.07 [95% CI 1.01-1.15]), a similar risk of heart failure (6.0 vs. 6.0 events per 1000 person-years; HR 1.02 [0.92-1.12]), and a lower risk of serious renal events (2.9 vs. 4.0 events per 1000 person-years; HR 0.76 [0.66-0.87]). In as-treated analyses, the HR (95% CI) was 1.11 (1.00-1.24) for MACE, 0.88 (0.74-1.04) for heart failure, and 0.60 (0.47-0.77) for serious renal events. In secondary outcome analyses, use of SGLT2 inhibitors versus GLP-1 receptor agonists was not associated with statistically significant differences for the risk of myocardial infarction (HR 1.09 [95% CI 1.00-1.19]), cardiovascular death (HR 0.97 [95% CI 0.84-1.12]), death from renal causes (HR 0.75 [95% CI 0.41-1.35]), or any cause death (HR 1.01 [95% CI 0.94-1.09]), while the risk of stroke was higher (HR 1.14 [95% CI 1.03-1.26]), and the risk of renal replacement therapy (HR 0.74 [95% CI 0.56-0.97]) and hospitalization for renal events (HR 0.75 [95% CI 0.65-0.88]) were lower among users of SGLT2 inhibitors.

Conclusions: Use of SGLT2 inhibitors versus GLP-1 receptor agonists was associated with a similar risk of heart failure and a lower risk of serious renal events, while use of GLP-1 receptor agonists versus SGLT2 inhibitors was associated with a slightly lower risk of MACE. In as-treated analyses, the associations with MACE and serious renal events increased in magnitude, and the HR for heart failure tended towards a protective association for SGLT2 inhibitors.

Keywords: antidiabetic drug, cohort study, cardiovascular disease, dapagliflozin, GLP-1 analogue, pharmaco-epidemiology

INTRODUCTION

Reducing the risk of cardiorenal complications constitutes a main objective for the treatment of type 2 diabetes. Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are two classes of glucose-lowering medications, for which large clinical trials have shown protective effects for cardiovascular and renal outcomes in patients at high cardiovascular risk. Currently, US and European guidelines recommend either of these two drug classes for patients with established cardiovascular disease or at high cardiovascular risk. When clinical guidelines placed similar importance on these two drug classes, data from clinical trials indicate that their effects may differ by type of clinical outcome. In a meta-analysis including eight placebo-controlled cardiovascular outcomes trials, SGLT2 inhibitors and GLP-1 receptor agonists reduced the risk of cardiovascular death, as well as major adverse cardiovascular events (MACE), by a similar degree. However, only SGLT2 inhibitors reduced hospitalization for heart failure, while GLP-1 receptor agonists did not have any statistically significant effect on this outcome. Moreover, while both drug classes reduced the risk of progression of kidney disease, including macroalbuminuria, only SGLT2 inhibitors reduced the risk of a composite of worsening estimated glomerular filtration rate (eGFR), end-stage kidney disease, or renal death. By contrast, GLP-1 receptor agonists reduced the risk of stroke, while this effect was not observed for SGLT2 inhibitors.

Comparative data on the effectiveness of SGLT2 inhibitors versus GLP-1 receptor agonists are necessary to inform treatment decisions in patients eligible for treatment with either of these drugs. However, the cardiovascular outcome trials were performed against placebo and head-to-head trials on hard outcomes have not been performed. Moreover, while the cardiovascular outcome trials were performed in patients with established cardiovascular disease or at high cardiovascular risk, patients receiving SGLT2 inhibitors and GLP-1 receptor agonists in clinical practice are more heterogeneous.

Using nationwide data from Sweden, Denmark, and Norway, we performed a register-based cohort study to assess the cardiovascular and renal comparative effectiveness of SGLT2 inhibitors versus GLP-1 receptor agonists among patients seen in routine clinical practice.

MATERIALS AND METHODS

2.1 Data sources

We used nationwide data sources in Sweden, Denmark, and Norway, including population registers and Statistics Denmark/Statistics...
Sweden (vital status, demographics, socioeconomic variables), patient registers (co-morbidities, outcomes), prescription registers (study drugs, co-medications), cause of death registers (outcomes), the Swedish National Diabetes Register (HbA1c level, blood pressure, albuminuria, eGFR, body mass index, and smoking), and the Danish Register of Laboratory Results for Research (HbA1c, albuminuria, and eGFR). The data sources are described in detail in the supporting information (Appendix).

2.2 Study population

All patients aged 35-84 years, who filled their first prescription for either a SGLT2 inhibitor or a GLP-1 receptor agonist during the study period (April 2013 through December 2018), were included. The anatomic therapeutic chemical codes for the study drugs are provided in Table S1. Cohort entry was defined as the date of filling the first study drug prescription. Exclusion criteria included previously filled prescriptions for any of the study drugs, no specialist care contact or prescription drug in the past year, a history of dialysis or renal transplantation, end-stage illness, drug misuse, severe pancreatic disorders, and hospitalization for any reason within 30 days before cohort entry (Table S2).

In the pooled dataset of patients from the three countries, we used logistic regression to estimate a propensity score representing the probability of starting a SGLT2 inhibitor versus a GLP-1 receptor agonist, conditional on the status of 59 covariates at cohort entry. Variables included sociodemographic characteristics, co-morbidities, co-medications, healthcare utilization, and two-way interaction terms between country and each covariate (Table S3). Missing categories were used to handle missing data on place of birth (<0.5%) and civil status (<0.5%)\(^1\); none of the other variables had missing data.

We used inverse probability of treatment weighting based on the propensity score (average treatment effect weighting) to control for confounding. For subgroup analyses, separate propensity scores were estimated for each subgroup level. Patients with a propensity score outside the overlapping area of the distribution for the two study drug groups were excluded.

2.3 Outcomes

The co-primary outcomes were a composite of myocardial infarction, stroke, and cardiovascular death (MACE), heart failure (hospital admission for or death because of heart failure), and serious renal events (a composite of renal replacement therapy [dialysis or renal transplantation], death from renal causes, and hospital admission for renal events). Hospitalization for renal events was based on events consistent with serious renal disease, including diabetic nephropathy, chronic kidney disease, and acute kidney injury; we considered this outcome as a renal analogue to the outcome of hospitalization for heart failure in cardiology, such that it was regarded as an indicator of serious worsening of renal status.\(^1\) Secondary outcomes were each component of the composite outcomes and any cause death. In a post hoc analysis, we also analysed hospital admission for heart failure as a secondary outcome. International Classification of Diseases (version 10) codes and procedure codes used to define the outcomes are shown in Tables S4 and S5.

2.4 Statistical analyses

Patients were followed from cohort entry until outcome event, death, emigration, 5 years of follow-up or end of the study period (31 December 2018). Each of the co-primary and secondary outcomes was analysed separately. We used an intention-to-treat exposure definition, such that patients were considered as exposed to the study drug with which they entered the cohort throughout follow-up. Cox proportional hazards regression with time since cohort entry as the time scale was used to estimate hazard ratios (HRs) for the use of SGLT2 inhibitors versus GLP-1 receptor agonists. HRs with 95% CI that did not overlap 1 were considered statistically significant. The absolute rate difference was calculated as HR-1 multiplied by the rate among users of GLP-1 receptor agonists. We described the cumulative incidence using Kaplan–Meier curves.

For the co-primary outcomes, we performed subgroup analyses by age group (35 to <65 and ≥65 years), history of major cardiovascular disease, history of heart failure, and history of chronic kidney disease (Table S6). Effect modification by subgroup status was examined with an interaction term between treatment status and subgroup; in these analyses, a P value of less than .05 was considered statistically significant. We also analysed the co-primary outcomes by country.

In an additional analysis, we used an as-treated exposure definition: patients were considered as exposed to the study drug as long as the prescriptions were refilled before the estimated end date of the most recent prescription (Table S1), including a 30-day grace period to account for prescription overlap, irregular drug use, and events that occurred shortly after treatment cessation. Patients were censored at treatment cessation or crossover to the other study drug (i.e. initiation of GLP-1 receptor agonists among users of SGLT2 inhibitors and vice versa).

We performed prespecified sensitivity analyses of the co-primary outcomes. First, in the Swedish and Danish parts of the cohort, we used a propensity score with additional variables, including HbA1c level, blood pressure, albuminuria, eGFR, body mass index, and smoking in Sweden, and HbA1c level, albuminuria, and eGFR in Denmark (Table S7). Given the proportion of patients with missing data for the additional variables (Table S7), we used multiple imputation (fully conditional specification imputation) to manage missing data.\(^1\) and 10 imputed datasets. Second, in the Swedish and Danish parts of the cohort, we also included education in the propensity score. Third, because the inverse probability of treatment weighting might generate large weights,\(^1\) we performed analyses in which weights above 5 were set to 5.

The study was approved by the Regional Ethics Committee in Stockholm, Sweden, and the Regional Committee for Medical and Health Research Ethics, Norway. In Denmark, ethics approval is not required for register-based research.
124651 new users of SGLT2 inhibitors

37123 were excluded

- 30068 Previous use of GLP-1 receptor agonists
- 308 Dialysis or renal transplantation
- 991 Endstage illness
- 903 Drug misuse
- 1230 Severe pancreatic disorder
- 28 Use of liraglutide with obesity indication
- 344 No specialist care contact and no use of prescription drugs in the previous year
- 5311 Hospitalization in the previous 30 d

81891 new users of GLP-1 receptor agonists

17958 were excluded

- 12870 Previous use of SGLT2 inhibitors
- 396 Dialysis or renal transplantation
- 724 Endstage illness
- 774 Drug misuse
- 684 Severe pancreatic disorder
- 134 Use of liraglutide with obesity indication
- 195 No specialist care contact and no use of prescription drugs in the previous year
- 3245 Hospitalization in the previous 30 d

87528 new users of SGLT2 inhibitors eligible for inclusion

63933 new users of GLP-1 receptor agonists eligible for inclusion

Propensity score estimation and exclusion of 3 users of SGLT2 inhibitors and 12 users of GLP-1 receptor agonists with a propensity score outside the overlapping area of the distributions.

151446 patients included in the cohort

- 87525 new users of SGLT2 inhibitors
- 63921 new users of GLP-1 receptor agonists

*One patient could be excluded because of more than one reason

**FIGURE 1** Flowchart of patient inclusion in the Scandinavian cohort study
| Country          | Unweighted, n (%) | Propensity score-weighted, % | Standardized difference (%) | Unweighted, n (%) | Propensity score-weighted, % | Standardized difference (%) |
|------------------|-------------------|-----------------------------|----------------------------|------------------|-----------------------------|----------------------------|
| **SGLT2 inhibitors** (n = 87 525) | **GLP-1 receptor agonists** (n = 63 921) | **SGLT2 inhibitors** | **GLP-1 receptor agonists** | **SGLT2 inhibitors** | **GLP-1 receptor agonists** | **Standardized difference (%)** |
| **辽宁** | 37 099 (42.4) | 35 291 (55.2) | 25.9 | 47.9 | 47.8 | 0.2 |
| **丹麦** | 24 141 (27.6) | 16 842 (26.3) | 2.8 | 27.0 | 27.1 | 0.1 |
| **挪威** | 26 285 (30.0) | 11 788 (18.4) | 27.3 | 25.1 | 25.1 | 0.1 |
| **男** | 55 661 (63.6) | 36 599 (57.3) | 13.0 | 60.9 | 61.0 | 0.1 |
| **年龄，均值（SD）** | 62.3 (10.4) | 60.3 (10.8) | - | 61.4 (10.7) | 61.4 (10.6) | - |
| **年龄组，y** | | | | | | |
| 35-39 | 1770 (2.0) | 2199 (3.4) | 8.7 | 2.7 | 2.6 | 0.1 |
| 40-44 | 3559 (4.1) | 3814 (6.0) | 8.7 | 4.9 | 4.9 | 0 |
| 45-49 | 6654 (7.6) | 6180 (9.7) | 7.4 | 8.6 | 8.5 | 0.4 |
| 50-54 | 10 463 (12.0) | 8515 (13.3) | 4.1 | 12.6 | 12.6 | 0.2 |
| 55-59 | 12 748 (14.6) | 9512 (14.9) | 0.9 | 14.7 | 14.8 | 0.1 |
| 60-64 | 14 655 (16.7) | 10 224 (16.0) | 2.0 | 16.4 | 16.6 | 0.4 |
| 65-69 | 15 304 (17.5) | 10 156 (15.9) | 4.3 | 16.7 | 16.7 | 0 |
| 70-74 | 13 011 (14.9) | 8020 (12.5) | 6.7 | 13.7 | 13.7 | 0 |
| 75-79 | 6660 (7.6) | 3936 (6.2) | 5.7 | 6.9 | 6.9 | 0.1 |
| 80-84 | 2701 (3.1) | 1365 (2.1) | 6.0 | 2.7 | 2.7 | 0.2 |
| **出生地** | | | | | | |
| **斯堪的那维亚** | 70 711 (80.8) | 54 768 (85.7) | 13.1 | 82.9 | 82.8 | 0.3 |
| **其他欧洲** | 6426 (7.3) | 3815 (6.0) | 5.5 | 6.8 | 6.8 | 0.2 |
| **欧洲以外** | 10 299 (11.8) | 5287 (8.3) | 11.7 | 10.2 | 10.3 | 0.2 |
| **缺失** | 89 (0.1) | 51 (0.1) | 0.7 | 0.1 | 0.1 | 0 |
| **民事状态** | | | | | | |
| **已婚/同居** | 50 634 (57.9) | 35 084 (54.9) | 6.0 | 56.4 | 56.4 | 0 |
| **单身** | 36 528 (41.7) | 28 602 (44.7) | 6.1 | 43.2 | 43.2 | 0 |
| **缺失** | 363 (0.4) | 235 (0.4) | 0.8 | 0.4 | 0.4 | 0 |
| **年份** | | | | | | |
| 2013 | 2173 (2.5) | 6235 (9.8) | - | 2.6 | 9.7 | - |
| 2014 | 7162 (8.2) | 8404 (13.1) | - | 8.3 | 13.1 | - |
| 2015 | 10 066 (11.5) | 10 508 (16.4) | - | 11.9 | 16.3 | - |
| 2016 | 14 843 (17.0) | 11 115 (17.4) | - | 17.2 | 17.1 | - |
| 2017 | 22 798 (26.0) | 12 792 (20.0) | - | 25.8 | 20.1 | - |
| 2018 | 30 483 (34.8) | 14 867 (23.3) | - | 34.2 | 23.8 | - |
| **合并症** | | | | | | |
| **急性冠状动脉综合症** | 7142 (8.2) | 4575 (7.2) | 3.8 | 7.8 | 7.7 | 0.1 |
| **其他心肌缺血** | 15 491 (17.7) | 10 174 (15.9) | 4.8 | 17.0 | 17.0 | 0.1 |
| **心力衰竭/心肌病** | 4801 (5.5) | 4194 (6.6) | 4.5 | 6.1 | 6.1 | 0 |
| **瓣膜疾病** | 2359 (2.7) | 1599 (2.5) | 1.2 | 2.6 | 2.6 | 0.1 |
| **中风** | 3246 (3.7) | 2394 (3.7) | 0.2 | 3.7 | 3.7 | 0 |
| **其他脑血管疾病** | 3739 (4.3) | 2810 (4.4) | 0.6 | 4.3 | 4.4 | 0.1 |
| **心房颤动** | 6303 (7.2) | 4816 (7.5) | 1.3 | 7.3 | 7.4 | 0.2 |
| **心律失常** | 3787 (4.3) | 2746 (4.3) | 0.2 | 4.4 | 4.4 | 0.1 |

(Continues)
| Complete | Unweighted, n (%) | GLP-1 receptor agonists | Standardized difference (%) | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) |
|----------|-------------------|-------------------------|------------------------------|------------------|-------------------------|------------------------------|
| **TABLE 1** (Continued) | | | | | | |
| | SGLT2 inhibitors (n = 87 525) | GLP-1 receptor agonists (n = 63 921) | | SGLT2 inhibitors | GLP-1 receptor agonists | |
| Coronary revascularization in the previous year | 1430 (1.6) | 852 (1.3) | 2.5 | 1.5 | 1.5 | 0 |
| Other cardiac surgery/invasive procedure in the previous year | 529 (0.6) | 365 (0.6) | 0.4 | 0.6 | 0.6 | 0.1 |
| Arterial disease | 4693 (5.4) | 3815 (6.0) | 2.6 | 5.7 | 5.7 | 0.1 |
| Chronic kidney disease | 2202 (2.5) | 3693 (5.8) | 16.4 | 4.0 | 3.9 | 0.3 |
| Other renal disease | 4905 (5.6) | 4986 (7.8) | 8.8 | 6.6 | 6.5 | 0.1 |
| Diabetic complications | 21 678 (24.8) | 20 011 (31.3) | 14.6 | 27.8 | 27.7 | 0.3 |
| COPD | 3001 (3.4) | 2702 (4.2) | 4.2 | 3.8 | 3.8 | 0 |
| Other lung disease | 5506 (6.3) | 5390 (8.4) | 8.2 | 7.3 | 7.3 | 0.3 |
| Venous thromboembolism | 1763 (2.0) | 1783 (2.8) | 5.1 | 2.4 | 2.4 | 0.1 |
| Cancer | 6047 (6.9) | 4505 (7.0) | 0.5 | 6.9 | 6.9 | 0.1 |
| Liver disease | 1708 (2.0) | 1518 (2.4) | 2.9 | 2.2 | 2.2 | 0.1 |
| Rheumatic disease | 2527 (2.9) | 2108 (3.3) | 2.4 | 3.1 | 3.1 | 0 |
| Psychiatric disorder | 7930 (9.1) | 7725 (12.1) | 9.8 | 10.5 | 10.5 | 0.2 |
| Fracture in the previous year | 1379 (1.6) | 1048 (1.6) | 0.5 | 1.6 | 1.6 | 0.1 |
| Healthcare utilization in previous year | | | | | | |
| Hospitalization because of cardiovascular causes | 4030 (4.6) | 2886 (4.5) | 0.4 | 4.6 | 4.7 | 0.1 |
| Hospitalization because of type 2 diabetes | 600 (0.7) | 804 (1.3) | 5.8 | 1.0 | 1.0 | 0.1 |
| Hospitalization not because of cardiovascular or type 2 diabetes causes | 9359 (10.7) | 8331 (13.0) | 7.2 | 11.9 | 11.8 | 0.3 |
| Outpatient contact because of cardiovascular causes | 9122 (10.4) | 6359 (9.9) | 1.6 | 10.3 | 10.3 | 0.1 |
| Outpatient contact because of type 2 diabetes | 17 603 (20.1) | 15 668 (24.5) | 10.6 | 22.2 | 22.0 | 0.6 |
| Outpatient contact not because of cardiovascular or type 2 diabetes causes | 44 425 (50.8) | 36 539 (57.2) | 12.9 | 53.6 | 53.4 | 0.4 |
| Diabetes drugs in previous 6 mo | | | | | | |
| No diabetes drug | 5399 (6.2) | 4446 (7.0) | 3.2 | 6.4 | 6.4 | 0.1 |
| Metformin | 72 242 (82.5) | 47 989 (75.1) | 18.3 | 79.4 | 79.4 | 0 |
| Sulphonylureas | 19 616 (22.4) | 12 614 (19.7) | 6.6 | 21.3 | 21.3 | 0.2 |
| DPP4 inhibitors | 34 486 (39.4) | 20 109 (31.5) | 16.7 | 36.2 | 36.5 | 0.6 |
| Insulin | 16 590 (19.0) | 25 827 (40.4) | 48.3 | 28.6 | 28.4 | 0.5 |
| Other antidiabetics (glitazones, glinides, acarbose) | 2804 (3.2) | 2067 (3.2) | 0.2 | 3.2 | 3.2 | 0.1 |
| Prescription drug use in previous year | | | | | | |
| ACEi/ARB | 56 702 (64.8) | 43 237 (67.6) | 6.0 | 66.1 | 66.2 | 0.2 |
| Calcium channel blocker | 25 457 (29.1) | 20 663 (32.3) | 7.0 | 30.4 | 30.4 | 0.1 |
| Loop diuretic | 8904 (10.2) | 10 550 (16.5) | 18.7 | 13.0 | 13.0 | 0.1 |
In total, 87,528 new users of SGLT2 inhibitors and 63,933 new users of GLP-1 receptor agonists were eligible for the analyses (Figure 1). After exclusion of those with a propensity score outside the overlapping area of the distributions, 87,525 users of SGLT2 inhibitors and 63,921 users of GLP-1 receptor agonists remained in the cohort. Population characteristics before and after weighting are shown in Table 1; covariates in the two groups were well balanced after weighting. Users of SGLT2 inhibitors tended to enter the cohort later in the study period compared with users of GLP-1 receptor agonists. Among the SGLT2 inhibitor users, median (IQR) follow-up time in the primary analyses was 1.6 (0.7, 2.8) years; the proportion of follow-up time by drug initiated at cohort entry was 58.3% for dapagliflozin, 40.8% for empagliflozin, 0.8% for canagliflozin, and less than 0.1% for ertugliflozin. Among the GLP-1 receptor agonist users, the median (IQR) follow-up time was 2.2 (1.0, 3.8) years; the proportion of follow-up time by drug initiated at cohort entry was 84.1% for liraglutide, 6.1% for exenatide, 7.1% for dulaglutide, 2.7% for lixisenatide, and 0.1% for semaglutide.

### Table 1 (Continued)

|                          | SGLT2 inhibitors (n = 87,525) | GLP-1 receptor agonists (n = 63,921) | Standardized difference (%) | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) |
|--------------------------|-----------------------------|------------------------------------|-------------------------------|------------------|------------------------|-------------------------------|
| Other diuretic           | 11,175 (12.8)               | 10,414 (16.3)                      | 10.0                          | 14.3             | 14.4                   | 0.1                           |
| Beta-blocker             | 30,668 (35.0)               | 23,483 (36.7)                      | 3.5                           | 35.7             | 35.8                   | 0.2                           |
| Digoxin                  | 1,592 (1.8)                 | 1,257 (2.0)                        | 1.1                           | 1.9              | 1.9                    | 0.1                           |
| Nitrate                  | 6,400 (7.3)                 | 4,382 (6.9)                        | 1.8                           | 7.1              | 7.2                    | 0.2                           |
| Platelet inhibitor       | 30,732 (35.1)               | 21,059 (32.9)                      | 4.6                           | 34.2             | 34.2                   | 0.2                           |
| Anticoagulant            | 6,882 (7.9)                 | 5,262 (8.2)                        | 1.4                           | 8.1              | 8.1                    | 0.1                           |
| Lipid-lowering drug      | 60,658 (69.3)               | 43,825 (68.6)                      | 1.6                           | 68.9             | 69.0                   | 0.1                           |
| Antidepressant           | 12,560 (14.4)               | 11,984 (18.7)                      | 11.9                          | 16.4             | 16.4                   | 0.1                           |
| Antipsychotic            | 3,172 (3.6)                 | 2,578 (4.0)                        | 2.1                           | 3.8              | 3.9                    | 0                             |
| Anxiolytic hypnotic or sedative | 14,149 (16.2) | 11,466 (17.9)                      | 4.7                           | 17.0             | 17.0                   | 0.2                           |
| Beta-2 agonist inhalant  | 7,624 (8.7)                 | 7,164 (11.2)                       | 8.3                           | 9.9              | 9.8                    | 0.1                           |
| Anticholinergic inhalant | 2,495 (2.9)                 | 2,168 (3.4)                        | 3.1                           | 3.1              | 3.1                    | 0.1                           |
| Glucocorticoid inhalant  | 7,894 (9.0)                 | 7,139 (11.2)                       | 7.1                           | 10.0             | 9.9                    | 0.1                           |
| Oral glucocorticoid      | 6,217 (7.1)                 | 5,215 (8.2)                        | 4.0                           | 7.5              | 7.5                    | 0                             |
| NSAID                    | 19,918 (22.8)               | 15,481 (24.2)                      | 3.4                           | 23.4             | 23.4                   | 0.1                           |
| Opioid                   | 15,077 (17.2)               | 13,077 (20.5)                      | 8.3                           | 18.8             | 18.7                   | 0.2                           |

No. of prescription drugs in previous year

| Time since first diabetes drug, y | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) |
|----------------------------------|------------------|------------------------|-------------------------------|------------------|------------------------|-------------------------------|
| ≤5                               | 22,064 (25.2)    | 11,387 (17.8)          | 18.1                          | 21.9             | 21.8                   | 0.3                           |
| 6-10                             | 38,287 (43.7)    | 25,150 (39.3)          | 8.9                           | 41.8             | 41.9                   | 0.3                           |
| 11-15                            | 18,475 (21.1)    | 16,586 (25.9)          | 11.4                          | 23.2             | 23.3                   | 0.1                           |
| >15                              | 8,573 (9.8)      | 10,694 (16.7)          | 20.6                          | 13.0             | 12.8                   | 0.4                           |

Time since first diabetes drug, y

| Time since first diabetes drug, y | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) | SGLT2 inhibitors | GLP-1 receptor agonists | Standardized difference (%) |
|----------------------------------|------------------|------------------------|-------------------------------|------------------|------------------------|-------------------------------|
| <1                               | 9,469 (10.8)     | 6,913 (10.8)           | 0                             | 10.6             | 10.8                   | 0.5                           |
| 1-2                              | 11,072 (12.7)    | 7,286 (11.4)           | 3.8                           | 12.1             | 12.1                   | 0.1                           |
| 3-4                              | 11,040 (12.6)    | 7,631 (11.9)           | 2.1                           | 12.4             | 12.4                   | 0.1                           |
| 5-6                              | 5,985 (6.8)      | 4,046 (6.3)            | 2.0                           | 6.6              | 6.6                    | 0.2                           |
| ≥7                               | 43,928 (50.2)    | 34,016 (53.2)          | 6.1                           | 51.6             | 51.6                   | 0                             |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NSAID, non-steroidal anti-inflammatory drug; SGLT2, sodium-glucose co-transporter-2.

*Not included in the propensity score.

### 3 | RESULTS

#### 3.1 | Study population

In total, 87,528 new users of SGLT2 inhibitors and 63,933 new users of GLP-1 receptor agonists were eligible for the analyses (Figure 1). After exclusion of those with a propensity score outside the overlapping area of the distributions, 87,525 users of SGLT2 inhibitors and 63,921 users of GLP-1 receptor agonists remained in the cohort. Population characteristics before and after weighting are shown in Table 1; covariates in the two groups were well balanced after weighting. Users of SGLT2 inhibitors tended to enter the cohort later in the study period compared with users of GLP-1 receptor agonists. Among the SGLT2 inhibitor users, median (IQR) follow-up time in the primary analyses was 1.6 (0.7, 2.8) years; the proportion of follow-up time by drug initiated at cohort entry was 58.3% for dapagliflozin, 40.8% for empagliflozin, 0.8% for canagliflozin, and less than 0.1% for ertugliflozin. Among the GLP-1 receptor agonist users, the median (IQR) follow-up time was 2.2 (1.0, 3.8) years; the proportion of follow-up time by drug initiated at cohort entry was 84.1% for liraglutide, 6.1% for exenatide, 7.1% for dulaglutide, 2.7% for lixisenatide, and 0.1% for semaglutide.

#### 3.2 | Primary outcomes

Figure 2 shows the adjusted cumulative incidence of the co-primary outcomes. Use of SGLT2 inhibitors versus GLP-1 receptor agonists was associated with a higher risk of MACE (adjusted incidence rate 15.2
vs. 14.4 events per 1000 person-years; HR 1.07 [95% CI 1.01-1.15]), a similar risk of heart failure (6.0 vs. 6.0 events per 1000 person-years; HR 1.02 [95% CI 0.92-1.12]), and a lower risk of serious renal events (2.9 vs. 4.0 events per 1000 person-years; HR 0.76 [95% CI 0.66-0.87]) (Table 2). Compared with the primary analyses using an intention-to-treat exposure definition, the point estimate of the HR comparing SGLT2 inhibitors with GLP-1 receptor agonists in the additional analyses using an as-treated exposure definition was lower for heart failure (HR 0.88 [95% CI 0.74-1.04]) and serious renal events (HR 0.60 [95% CI 0.47-0.77]), and slightly higher for MACE (1.11 [95% CI 1.00-1.24]) (Table 2).
3.3 Secondary outcomes and subgroup analyses

In the secondary outcome analyses, use of SGLT2 inhibitors versus GLP-1 receptor agonists was not associated with statistically significant differences in the risk of myocardial infarction (HR 1.09 [95% CI 1.00-1.19]), cardiovascular death (HR 0.97 [95% CI 0.84-1.12]), and any cause death (HR 1.01 [95% CI 0.94-1.09]), while the risk of stroke was higher among users of SGLT2 inhibitors (HR 1.14 [95% CI 1.03-1.26]).

The HR for the post hoc secondary outcome, hospital admission for heart failure, was 1.02 (95% CI 0.92-1.13).

In the secondary outcome analyses of renal outcomes, use of SGLT2 inhibitors versus GLP-1 receptor agonists was associated with a lower risk of renal replacement therapy (HR 0.74 [95% CI 0.56-0.97]) and hospitalization for renal events (HR 0.75 [95% CI 0.65-0.88]), but not for death from renal causes, although the point estimate was similar to those of the other secondary renal outcomes (HR 0.75 [95% CI 0.41-1.35]).

Subgroup analyses are shown in Figure 3 and analyses by country are shown in Table S8. While incidence rates differed substantially, there were no statistically significant interactions between treatment status and subgroup across the subgroups.

3.4 Sensitivity analysis

In the sensitivity analyses adjusted for additional variables in the Swedish part of the cohort (patient characteristics are shown in Table S9), the point estimates for the HR were largely similar to those of the country-specific analyses without such adjustment: 1.09 (95% CI 1.01-1.19) versus 1.08 (0.98-1.18) for MACE, 1.05 (95% CI 0.93-1.20) versus 1.03 (0.90-1.19) for heart failure, and 0.67 (95% CI 0.54-0.83) versus 0.63 (0.49-0.80) for serious renal events. Also, in the Danish part of the cohort (patient characteristics are shown in Table S10), the additionally adjusted HR was similar to the country-specific analyses, without such adjustment for MACE (1.00 [95% CI 0.88-1.13] vs. 0.99 [0.87-1.13]) and heart failure (0.98 [95% CI 0.82-1.18] vs. 0.99 [0.87-1.13]), while the protective association for SGLT2 inhibitors was attenuated for serious renal events (HR 0.96

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**Table 2** Association between the use of SGLT2 inhibitors versus GLP-1 receptor agonists for co-primary and secondary outcomes

|                          | SGLT2 inhibitors | GLP-1 receptor agonists | Adjusted absolute rate difference, events (95% CI) per 1000 person-years |
|--------------------------|------------------|-------------------------|--------------------------------------------------------------------------|
| **Co-primary outcomes (ITT)** |                  |                         |                                                                          |
| Major adverse cardiovascular event | 2328 15.2        | 2255 14.4               | 0.7 (0.0 to 1.4)                                                          |
| Heart failure            | 836 6.0          | 1028 6.0                | 0.1 (-0.5 to 0.7)                                                         |
| Serious renal event      | 418 2.9          | 679 4.0                 | -1.0 (-1.3 to -0.5)                                                       |
| **Co-primary outcomes (as-treated)** |                |                         |                                                                          |
| Major adverse cardiovascular event | 945 13.5        | 754 12.2                | 1.4 (0.1 to 2.8)                                                          |
| Heart failure            | 277 4.5          | 343 5.1                 | -0.6 (-1.4 to 0.2)                                                        |
| Serious renal event      | 134 2.0          | 222 3.4                 | -1.3 (-1.8 to -0.8)                                                       |
| **Secondary outcomes (ITT)** |                  |                         |                                                                          |
| Myocardial infarction    | 1263 8.0         | 1162 7.5                | 0.7 (0.0 to 1.4)                                                          |
| Stroke                   | 930 5.9          | 825 5.3                 | 0.7 (0.1 to 1.4)                                                          |
| Cardiovascular death     | 377 2.9          | 543 3.1                 | -0.1 (-0.5 to 0.4)                                                        |
| Any cause death          | 1632 11.0        | 1895 11.6               | 0.1 (-0.7 to 1.0)                                                         |
| Renal replacement therapy| 107 0.8          | 196 1.1                 | -0.3 (-0.5 to 0.0)                                                        |
| Death from renal causes  | 21 0.2           | 40 0.2                  | -0.1 (-0.1 to 0.1)                                                        |
| Hospitalization for renal events | 339 2.4     | 552 3.3                 | -0.8 (-1.2 to -0.4)                                                       |
| **Secondary outcomes (as-treated)** |             |                         |                                                                          |
| Myocardial infarction    | 529 7.4          | 392 6.3                 | 1.2 (0.2 to 2.3)                                                          |
| Stroke                   | 364 5.1          | 269 4.5                 | 0.7 (-0.1 to 1.7)                                                         |
| Cardiovascular death     | 119 2.0          | 166 2.5                 | -0.4 (-0.9 to 0.2)                                                        |
| Any cause death          | 475 7.1          | 427 6.5                 | 0.8 (-0.2 to 1.9)                                                         |
| Renal replacement therapy| 29 0.38          | 62 0.91                 | -0.5 (-0.7 to -0.3)                                                       |
| Death from renal causes  | 4 0.05           | 10 0.13                 | -0.1 (-0.1 to 0.0)                                                        |
| Hospitalization for renal events | 110 1.73   | 172 2.64                | -0.9 (-1.3 to -0.4)                                                       |

Abbreviations: GLP-1, glucagon-like peptide-1; ITT, intention-to-treat; SGLT2, sodium-glucose co-transporter-2.
patients aged 66 years or older,16 in an Italian study with around 8500 comes using Medicare data in the United States from around 90 000
GLP-1 receptor agonists have been performed for cardiovascular out-
the magnitude of effect has been substantially larger for SGLT2 inhibitors than for GLP-1 receptor agonists. For example, in a meta-analysis of cardiovascular outcome trials, the HR for a composite outcome of new-onset macroalbuminuria, sustained doubling of serum creatinine, a 40% decline in eGFR, end-stage kidney disease or renal death was 0.82 (95% CI 0.75-0.89) for GLP-1 receptor agonists.

**FIGURE 3** Subgroup analyses of co-primary outcomes for use of sodium-glucose co-transporter-2 (SGLT2) inhibitors versus glucagon-like peptide-1 (GLP-1) receptor agonists
agons and 0.62 (95% CI 0.58-0.67) for SGLT2 inhibitors. When excluding macroalbuminuria from the composite outcome, the effect of GLP-1 receptor agonists was no longer statistically significant, while the HR for SGLT2 inhibitors was 0.55 (95% CI 0.48-0.64). In line with these data, our analyses showed that use of SGLT2 inhibitors versus GLP-1 receptor agonists was associated with a lower risk of serious renal events (HR 0.76 [95% CI 0.66-0.87]; HR in as-treated analyses 0.60 [95% CI 0.47-0.77]), including renal replacement therapy, death from renal causes, and hospitalization for renal events. Our findings are also in line with the previous observational Veterans Affairs database analysis comparing use of SGLT2 inhibitors with GLP-1 receptor agonists, in which the HR for an eGFR decline of more than 50% or end-stage kidney disease was 0.87 (95% CI 0.78-0.98).

4.1 Limitations

Our study has some limitations. First, we analysed SGLT2 inhibitors and GLP-1 receptor agonists as drug classes. Most of the SGLT2 inhibitor users used dapagliflozin (58.3% of follow-up time) or empagliflozin (40.8%), and most of the GLP-1 receptor agonist users used liraglutide (84.1%). Head-to-head comparisons of individual SGLT2 inhibitors and GLP-1 receptor agonists are subjects for future studies. Second, we used filled prescriptions to determine exposure status; low adherence may bias the results towards the null. Third, Scandinavian validation studies have shown that register-based strategies for identification of cardiovascular outcomes have positive predictive values of 88%-100% for myocardial infarction, 69%-99% for stroke, and 76%-95% for heart failure, and that sensitivity and positive predictive values are also high for procedure codes and other diagnoses. However, validation studies of the specific codes used for the renal outcomes in our study have not been conducted. Although outcome misclassification is possible, such misclassification is unlikely to be different in patients receiving SGLT2 inhibitors versus GLP-1 receptor agonists. Fourth, although the definition of renal outcomes comprises patient-relevant events whose risk may be modified by SGLT2 inhibitors, the renal outcomes in our study did not directly correspond to those used in clinical trials; this may limit comparability with clinical trial data. Finally, although we used an active comparator new-user design and propensity score-weighting to control for many patient characteristics, the risk of unmeasured confounding cannot be ruled out.

In conclusion, in this cohort study using nationwide register data from three countries to compare outcomes associated with use of SGLT2 inhibitors versus GLP-1 receptor agonists, the risk of serious renal events was lower with SGLT2 inhibitors, while the risk of MACE was lower with GLP-1 receptor agonists, and the risk of heart failure was similar for both drug classes. In as-treated analyses, the associations with MACE and serious renal events increased in magnitude and the HR for heart failure tended towards a protective association for SGLT2 inhibitors versus GLP-1 receptor agonists.

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CONFLICT OF INTEREST

All authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author) and have the following declarations. CJ reports personal fees from Pfizer and Bayer outside the submitted work. BE 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. SG reports lecture fees and research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi outside the submitted work. HS reports consulting fees from Celgene and employment at IQVIA outside the submitted work. The other authors did not have any potential conflicts to report.

AUTHOR CONTRIBUTIONS

PU and BP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: PU, VW, ED, HS, and BP. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: PU and BP. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: VW and ED. Obtained funding: PU and BP. Study supervision: BP.

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Research data are not shared.

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