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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

1 | 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.[1,2] Currently, US and European guidelines recommend either of these two drug classes for patients with established cardiovascular disease or at high cardiovascular risk.[3-8]

While clinical guidelines place 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.[1] 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.[2] 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 heterogenous.[9,10]

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.

2 | 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%)[11]; 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.[12] 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,[13] 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,[14,15] 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.

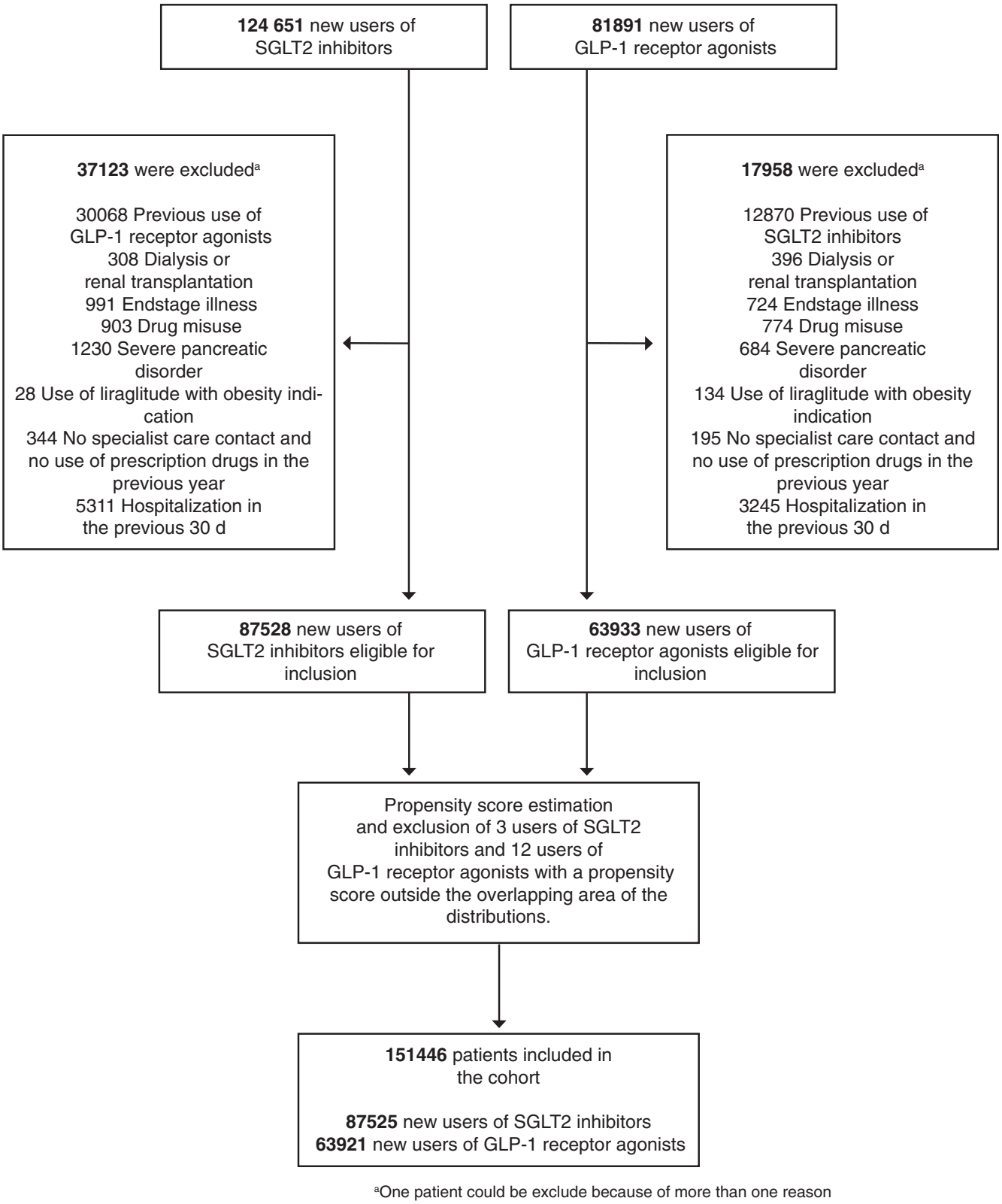


FIGURE 1 Flowchart of patient inclusion in the Scandinavian cohort study

TABLE 1 Patient characteristics at cohort entry for new users of SGLT2 inhibitors and GLP-1 receptor agonists before and after inverse probability of treatment weighting based on a propensity score

	Unweighted, n (%)			Propensity score-weighted, %		
	SGLT2 inhibitors (n = 87 525)	GLP-1 receptor agonists (n = 63 921)	Standardized difference (%)	SGLT2 inhibitors	GLP-1 receptor agonists	Standardized difference (%)
Country						
Sweden	37 099 (42.4)	35 291 (55.2)	25.9	47.9	47.8	0.2
Denmark	24 141 (27.6)	16 842 (26.3)	2.8	27.0	27.1	0.1
Norway	26 285 (30.0)	11 788 (18.4)	27.3	25.1	25.1	0.1
Male	55 661 (63.6)	36 599 (57.3)	13.0	60.9	61.0	0.1
Age, mean (SD)	62.3 (10.4)	60.3 (10.8)	-	61.4 (10.7)	61.4 (10.6)	-
Age group, 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
Place of birth						
Scandinavia	70 711 (80.8)	54 768 (85.7)	13.1	82.9	82.8	0.3
Rest of Europe	6426 (7.3)	3815 (6.0)	5.5	6.8	6.8	0.2
Outside Europe	10 299 (11.8)	5287 (8.3)	11.7	10.2	10.3	0.2
Missing	89 (0.1)	51 (0.1)	0.7	0.1	0.1	0
Civil status						
Married/living with partner	50 634 (57.9)	35 084 (54.9)	6.0	56.4	56.4	0
Single	36 528 (41.7)	28 602 (44.7)	6.1	43.2	43.2	0
Missing	363 (0.4)	235 (0.4)	0.8	0.4	0.4	0
Calendar year[a]						
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	-
Co-morbidities						
Acute coronary syndrome	7142 (8.2)	4575 (7.2)	3.8	7.8	7.7	0.1
Other ischaemic heart disease	15 491 (17.7)	10 174 (15.9)	4.8	17.0	17.0	0.1
Heart failure/cardiomyopathy	4801 (5.5)	4194 (6.6)	4.5	6.1	6.1	0
Valve disorders	2359 (2.7)	1599 (2.5)	1.2	2.6	2.6	0.1
Stroke	3246 (3.7)	2394 (3.7)	0.2	3.7	3.7	0
Other cerebrovascular disease	3739 (4.3)	2810 (4.4)	0.6	4.3	4.4	0.1
Atrial fibrillation	6303 (7.2)	4816 (7.5)	1.3	7.3	7.4	0.2
Other arrythmia	3787 (4.3)	2746 (4.3)	0.2	4.4	4.4	0.1

(Continues)

TABLE 1 (Continued)

	Unweighted, n (%)			Propensity score-weighted, %		
	SGLT2 inhibitors (n = 87 525)	GLP-1 receptor agonists (n = 63 921)	Standardized difference (%)	SGLT2 inhibitors	GLP-1 receptor agonists	Standardized difference (%)
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

TABLE 1 (Continued)

	Unweighted, n (%)			Propensity score-weighted, %		
	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	1592 (1.8)	1257 (2.0)	1.1	1.9	1.9	0.1
Nitrate	6400 (7.3)	4382 (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	6882 (7.9)	5262 (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	3172 (3.6)	2578 (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	7624 (8.7)	7164 (11.2)	8.3	9.9	9.8	0.1
Anticholinergic inhalant	2495 (2.9)	2168 (3.4)	3.1	3.1	3.1	0.1
Glucocorticoid inhalant	7896 (9.0)	7139 (11.2)	7.1	10.0	9.9	0.1
Oral glucocorticoid	6217 (7.1)	5215 (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						
≤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	8573 (9.8)	10 694 (16.7)	20.6	13.0	12.8	0.4
Time since first diabetes drug, y						
<1	9469 (10.8)	6913 (10.8)	0	10.6	10.8	0.5
1-2	11 072 (12.7)	7286 (11.4)	3.8	12.1	12.1	0.1
3-4	11 040 (12.6)	7631 (11.9)	2.1	12.4	12.4	0.1
5-6	5985 (6.8)	4046 (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.
[a]Not included in the propensity score.

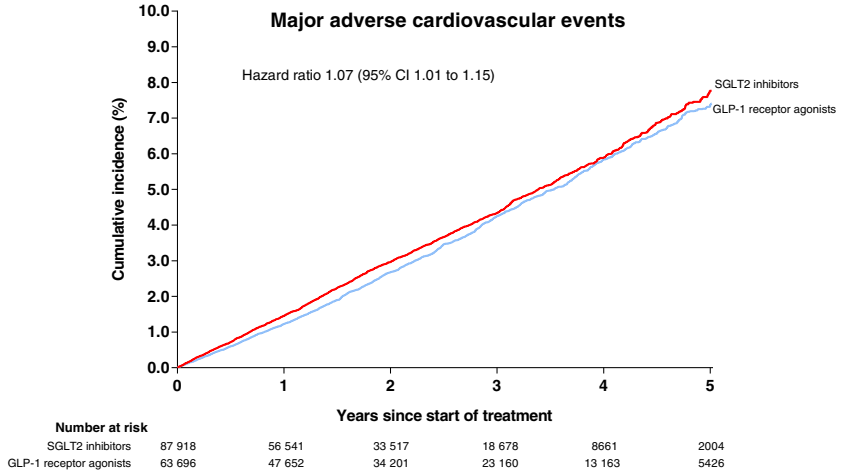
3 | RESULTS

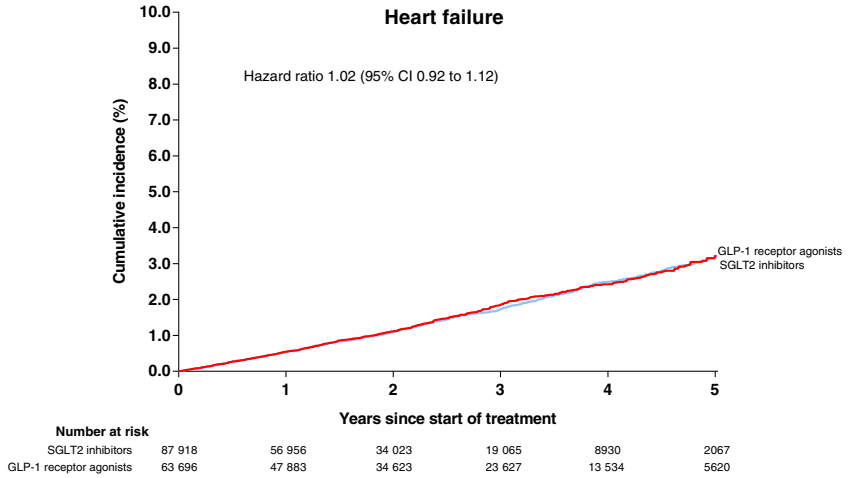
3.1 | Study population

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





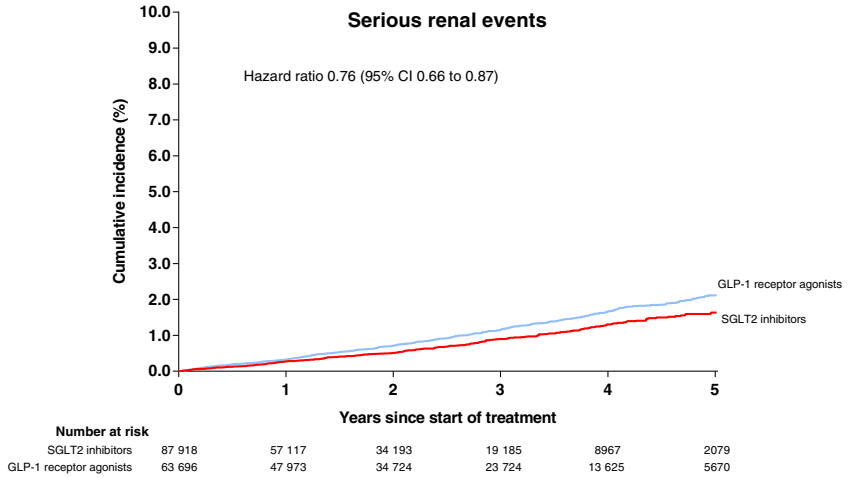


FIGURE 2 Adjusted cumulative incidence of co-primary outcomes among users of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. The cumulative incidences and numbers of patients at risk are propensity score-weighted

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% 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).

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			
	Events	Adjusted incidence rate (events per 1000 person-years)	Events	Adjusted incidence rate (events per 1000 person-years)	Adjusted HR (95% CI)	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	1.07 (1.01 to 1.15)	1.1 (0.1 to 2.1)
Heart failure	836	6.0	1028	6.0	1.02 (0.92 to 1.12)	0.1 (-0.5 to 0.7)
Serious renal event	418	2.9	679	4.0	0.76 (0.66 to 0.87)	-1.0 (-1.3 to -0.5)
Co-primary outcomes (as-treated)						
Major adverse cardiovascular event	945	13.5	754	12.2	1.11 (1.00 to 1.24)	1.4 (0.1 to 2.8)
Heart failure	277	4.5	343	5.1	0.88 (0.74 to 1.04)	-0.6 (-1.4 to 0.2)
Serious renal event	134	2.0	222	3.4	0.60 (0.47 to 0.77)	-1.3 (-1.8 to -0.8)
Secondary outcomes (ITT)						
Myocardial infarction	1263	8.0	1162	7.5	1.09 (1.00 to 1.19)	0.7 (0.0 to 1.4)
Stroke	930	5.9	825	5.3	1.14 (1.03 to 1.26)	0.7 (0.1 to 1.4)
Cardiovascular death	377	2.9	543	3.1	0.97 (0.84 to 1.12)	-0.1 (-0.5 to 0.4)
Any cause death	1632	11.0	1895	11.6	1.01 (0.94 to 1.09)	0.1 (-0.7 to 1.0)
Renal replacement therapy	107	0.8	196	1.1	0.74 (0.56 to 0.971)	-0.3 (-0.5 to 0.0)
Death from renal causes	21	0.2	40	0.2	0.75 (0.41 to 1.35)	-0.1 (-0.1 to 0.1)
Hospitalization for renal events	339	2.4	552	3.3	0.75 (0.65 to 0.88)	-0.8 (-1.2 to -0.4)
Secondary outcomes (as-treated)						
Myocardial infarction	529	7.4	392	6.3	1.19 (1.03 to 1.37)	1.2 (0.2 to 2.3)
Stroke	364	5.1	269	4.5	1.16 (0.97 to 1.37)	0.7 (-0.1 to 1.7)
Cardiovascular death	119	2.0	166	2.5	0.82 (0.63 to 1.07)	-0.4 (-0.9 to 0.2)
Any cause death	475	7.1	427	6.5	1.12 (0.97 to 1.29)	0.8 (-0.2 to 1.9)
Renal replacement therapy	29	0.38	62	0.91	0.44 (0.27 to 0.72)	-0.5 (-0.7 to -0.3)
Death from renal causes	4	0.05	10	0.13	0.37 (0.11 to 1.27)	-0.1 (-0.1 to 0.0)
Hospitalization for renal events	110	1.73	172	2.64	0.65 (0.49 to 0.85)	-0.9 (-1.3 to -0.4)

Abbreviations: GLP-1, glucagon-like peptide-1; ITT, intention-to-treat; SGLT2, sodium-glucose co-transporter-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

[95% CI 0.77-1.20] vs. 0.87 [95% CI 0.67-1.12]). In analyses using a propensity score including education in the Swedish and Danish parts of the cohort, the HR was 1.05 (95% CI 0.97-1.13) for MACE, 1.01 (95% CI 0.90-1.13) for heart failure, and 0.73 (95% CI 0.61-0.87) for serious renal events. In analyses in which weights above 5 were set to 5, the HR was 1.07 (95% CI 1.01-1.15) for MACE, 1.01 (95% CI 0.92-1.12) for heart failure, and 0.76 (95% CI 0.66-0.87) for serious renal events.

4 | DISCUSSION

We used nationwide register data from three countries to assess the comparative cardiovascular and renal effectiveness for SGLT2 inhibitors versus GLP-1 receptor agonists. In the primary analyses using an intention-to-treat exposure definition, the risk of serious renal events was lower with use of SGLT2 inhibitors, while the risk of MACE was slightly lower with use of GLP-1 receptor agonists, and the risk of heart failure was similar for the two drug classes. When using an as-treated exposure definition, the associations with MACE and serious renal events increased in magnitude, and the point estimate for the HR for heart failure tended towards a protective association for SGLT2 inhibitors.

Observational head-to-head analyses of SGLT2 inhibitors versus GLP-1 receptor agonists have been performed for cardiovascular outcomes using Medicare data in the United States from around 90 000 patients aged 66 years or older,[16] in an Italian study with around 8500 patients,[17] in a Danish register-based study including around 14 000 patients,[18] and in a study using Medicare and two US commercial claims databases that included more than 370 000 patients, although the median follow-up time was short (7 months) and data on mortality and cause of death were incomplete.[19] An analysis of canagliflozin versus GLP-1 receptor agonists, including 40 000 patients, has also been performed in a US healthcare database; this study lacked complete data on cardiovascular mortality.[20] For renal outcomes, an analysis has been presented using data from approximately 40 000 patients in the Veterans Affairs health system.[21] Comparisons of cardiorenal and other diabetes-related outcomes have also been performed in around 20 000 patients in the Swedish National Diabetes Register.[22] By using nationwide registers to include more than 150 000 patients (of whom >40 000 had a follow-up time of ≥3 years) across a wide age range with complete data on mortality and cause of death, and by assessing both cardiovascular and renal outcomes, our study expands on the data regarding the comparative effectiveness of SGLT2 inhibitors versus GLP-1 receptor agonists in routine clinical practice.

The slightly higher risk of MACE among users of SGLT2 inhibitors versus GLP-1 receptor agonists (HR 1.07 [95% CI 1.01-1.15]) in our analyses was driven by a nominal increase in myocardial infarction (HR 1.09 [95% CI 1.00-1.19]) and a statistically significant increase in stroke (HR 1.14 [95% CI 1.03-1.26]), while the risk of cardiovascular death was similar for the both drug classes (HR 0.97 [95% CI 0.84-1.12]). In meta-analyses of placebo-controlled clinical trials,[1,2] SGLT2 inhibitors and GLP-1 receptor agonists reduced MACE by a similar degree; both drug classes reduced the risk of myocardial infarction and cardiovascular death, while GLP-1 receptor agonists, but not SGLT2 inhibitors, reduced the risk of stroke. In the previous head-to-head study of SGLT2 inhibitors versus GLP-1 receptor agonists in Medicare patients aged 66 years or older,[16] the HRs in intention-to-treat analyses were similar to those observed in our study for MACE (HR 1.10 [95% CI 0.99-1.22]), myocardial infarction (HR 1.11 [95% CI 0.96-1.28]), and stroke (HR 1.11 [95% CI 0.94-1.32]), but not for cardiovascular mortality (HR 1.11 [95% CI 0.88-1.39]); the corresponding HR in the previous analysis of canagliflozin versus GLP-1 receptor agonists[20] was 0.97 (95% CI 0.75-1.24) for MACE. In the study based on Medicare and two US commercial claims databases,[19] the HR for a composite outcome of hospitalization for myocardial infarction or stroke was 0.99 (95% CI 0.93 to 1.06) in analyses, where the first exposure was carried forward 365 days to mimic an intention-to-treat exposure definition. In as-treated analyses where each component of the composite outcome was analysed separately, the risk of myocardial infarction and stroke did not differ in users of SGLT2 inhibitors versus GLP-1 receptor agonists.

In our primary analyses using an intention-to-treat exposure definition, we observed similar risks of heart failure among users of SGLT2 inhibitors versus GLP-1 receptor agonists (HR 1.02 [95% CI 0.92-1.12]). In placebo-controlled clinical trials, SGLT2 inhibitors have reliably reduced the risk of heart failure outcomes by approximately 30%, while effects of such magnitude and consistency have not been observed for GLP-1 receptor agonists.[1,2] When using an as-treated exposure definition, the HR of heart failure for use of SGLT2 inhibitors versus GLP-1 receptor agonists in our study decreased to 0.88 (95% CI 0.74-1.04); our findings may thus partly reflect a lower adherence to treatment among patients in routine clinical practice. Moreover, in the LEADER trial of liraglutide,[23] the HR for heart failure hospitalization was indicative of a protective effect versus placebo (0.87 [95% CI 0.73-1.05]). As liraglutide comprised 84.1% of the follow-up time for GLP-1 receptor agonist users, our analyses predominantly assessed the comparative effectiveness of SGLT2 inhibitors versus liraglutide. Further, the characteristics of patients included in clinical trials differ substantially from those treated in routine clinical practice.[9,10] Nonetheless, in the previous observational head-to-head analysis in Medicare patients aged 66 years or older,[16] use of SGLT2 inhibitors, compared with GLP-1 receptor agonists (58.7% liraglutide), was associated with a lower risk of heart failure (HR in intention-to-treat analyses 0.76 [95% CI 0.65-0.88]), and the HR in the analysis of canagliflozin versus GLP-1 receptor agonists[20] was 0.68 (95% CI 0.54-0.86). Similarly, in the US study based on Medicare and two US commercial claims databases,[19] use of SGLT2 inhibitors versus GLP-1 receptor agonists (50.6% liraglutide) was associated with a lower risk of hospitalization for heart failure (HR 0.74 [95% CI 0.67 to 0.81]) in analyses aiming to mimic an intention-to-treat exposure definition; in the as-treated analyses, the HR was 0.70 (95% CI 0.64 to 0.77).

In clinical trials, both SGLT2 inhibitors and GLP-1 receptor agonists have reduced the risk of composite renal outcomes. However,

	SGLT2 inhibitors			GLP-1 receptor agonists				
	n	Events	Adjusted incidence rate (events per 1000 person-years)	n	Events	Adjusted incidence rate (events per 1000 person-years)	Adjusted hazard ratio (95% CI)	*P* value for interaction
Major adverse cardiovascular event								
Total population	87 525	2328	15.2	63 921	2255	14.4	1.07 (1.01 to 1.15)	
Sex								
Men	55 661	1695	18.0	36 600	1538	16.8	1.10 (1.02 to 1.18)	
Women	31 861	633	11.1	27 327	716	10.7	1.06 (0.94 to 1.19)	.610
Age								
35-64 y	49 848	973	10.7	40 445	998	9.6	1.14 (1.03 to 1.25)	
65-84 y	37 673	1355	22.7	23 475	1255	22.7	1.03 (0.95 to 1.12)	.150
History of cardiovascular disease								
Yes	17 262	1003	5.8	12 419	892	31.4	1.13 (1.02 to 1.25)	
No	70 586	1419	10.8	51 299	1300	10.5	1.07 (0.98 to 1.16)	.398
History of heart failure								
Yes	4768	303	44.7	4187	387	40.2	1.11 (0.94 to 1.31)	
No	82 725	2024	13.7	59 729	1867	13.0	1.08 (1.01 to 1.16)	.794
History of chronic kidney disease								
Yes	2186	105	31.3	3647	215	26.1	1.19 (0.91 to 1.57)	
No	85 323	2223	14.6	60 228	2032	14.0	1.07 (1.00 to 1.14)	.436
Heart failure								
Total population	87 525	836	6.0	63 921	1028	6.0	1.02 (0.92 to 1.12)	
Sex								
Men	55 661	610	7.0	36 600	738	7.3	0.99 (0.88 to 1.11)	
Women	31 861	226	4.5	27 327	291	4.1	1.10 (0.90 to 1.34)	.361
Age								
35-64 y	49 848	258	3.1	40 445	341	3.0	1.09 (0.91 to 1.30)	
65-84 y	37 673	578	10.7	23 475	687	11.0	1.00 (0.88 to 1.13)	.425
History ofcardiovascular disease								
Yes	17 262	646	22.5	12 419	584	20.4	1.10 (0.97 to 1.25)	
No	70 586	310	2.3	51 299	341	2.7	0.94 (0.79 to 1.12)	.152
History of heart failure								
Yes	4768	398	59.1	4187	501	53.6	1.09 (0.94 to 1.26)	
No	82 725	437	3.1	59 729	526	3.4	0.97 (0.84 to 1.12)	.270
History of chronic kidney disease								
Yes	2186	87	25.6	3647	166	19.3	1.30 (0.97 to 1.73)	
No	85 323	748	5.2	60 228	860	5.6	0.97 (0.87 to 1.08)	.058
Seriousrenal event								
Total population	87 525	418	2.9	63 921	679	4.0	0.76 (0.66 to 0.87)	
Sex								
Men	55 661	264	3.1	36 600	424	4.2	0.76 (0.64 to 0.91)	
Women	31 861	154	2.7	27 327	256	3.7	0.76 (0.61 to 0.96)	.992
Age								
35-64 y	49 848	141	1.8	40 445	303	2.6	0.72 (0.58 to 0.90)	
65-84 y	37 673	277	5.0	23 475	376	6.3	0.81 (0.68 to 0.97)	.425
History of cardiovascular disease								
Yes	17 262	186	6.4	12 419	227	7.8	0.85 (0.68 to 1.06)	
No	70 586	291	2.2	51 299	387	3.1	0.74 (0.62 to 0.88)	.341
History of heart failure								
Yes	4768	71	10.6	4187	136	13.1	0.83 (0.59 to 1.15)	
No	82 725	347	2.5	59 729	543	3.5	0.76 (0.65 to 0.89)	.652
History of chronic kidney disease								
Yes	2186	73	19.7	3647	176	20.4	0.97 (0.71 to 1.32)	
No	85 323	344	2.3	60 228	499	3.4	0.72 (0.62 to 0.84)	.094

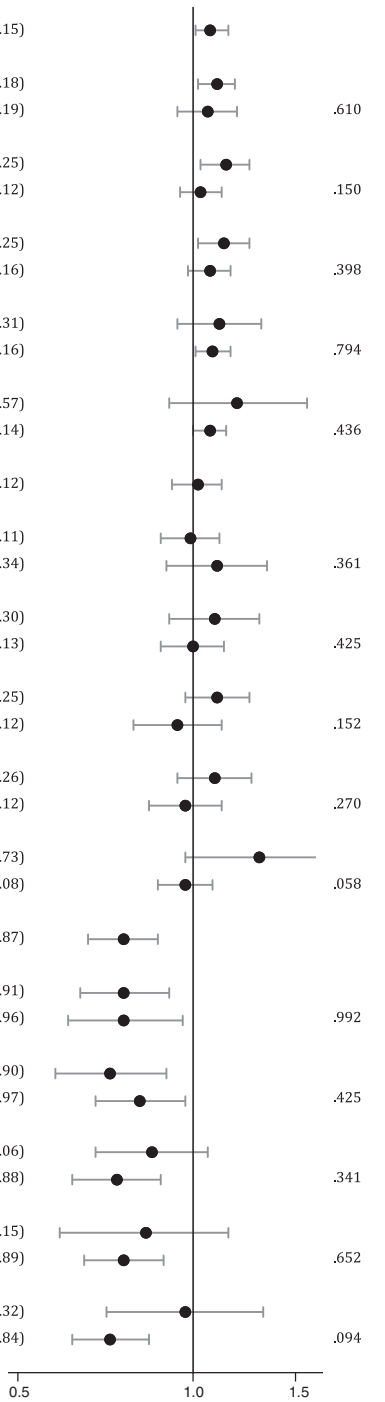


FIGURE 3 Subgroup analyses of co-primary outcomes for use of sodium-glucose co-transporter-2 (SGLT2) inhibitors versus glucagon-like peptide-1 (GLP-1) receptor agonists

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,[1] 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 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).[1] 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[21] 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[24-26] 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.[24,25] However, validation studies of the specific codes used for the renal outcomes in our study have not been conducted.[24,25] 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, Boerhringer 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, Boerhringer 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.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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