Empagliflozin reduces cardiorenal events, healthcare resource use and mortality in Sweden compared to dipeptidyl peptidase-4 inhibitors: Real world evidence from the Nordic EMPRISE study

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Abstract

Aims: To evaluate effectiveness and healthcare resource utilization (HCRU) of empagliflozin versus dipeptidyl peptidase-4 inhibitors (DPP-4i) in Swedish clinical practice, as part of the EMPRISE EU study (EUPAS27606, NCT03817463).

Materials and Methods: A non-interventional, cohort study using retrospectively collected data from Swedish national registries. Adults with type 2 diabetes newly initiated on empagliflozin or DPP-4i from May 2014 to December 2018 were matched 1:1 using propensity scores based on >180 covariates. Cardiovascular outcomes included hospitalization for heart failure (HHF), all-cause mortality (ACM), myocardial infarction (MI), stroke and cardiovascular mortality (CVM), as well as their composite outcomes. Renal outcomes included end-stage renal disease (ESRD), estimated glomerular filtration rate (eGFR) decline to <60 ml/min/1.73 m² and progression to micro/macroalbuminuria. HCRU outcomes were also assessed. Comparisons were done using Cox proportional hazards and Poisson regression models.

Results: Overall, 15,785 matched-pairs were identified, with a mean follow-up of 6.4 and 9.7 months for patients initiating empagliflozin versus DPP-4i, respectively. Empagliflozin was associated with significant reduction in rates of HHF (hazard ratio [HR] = 0.67; 95% confidence interval: 0.49-0.91), ACM (HR = 0.53; 0.41-0.68), HHF + ACM (HR = 0.59; 0.48-0.73), MI + stroke + ACM (HR = 0.68; 0.57-0.81), CVM (HR = 0.46; 0.29-0.73), HHF + CVM (HR = 0.61; 0.47-0.79) and MI + stroke + CVM (HR = 0.79; 0.63-0.98) versus DPP-4i. Empagliflozin also reduced the rates of ESRD (HR = 0.13; 0.03-0.57) and eGFR decline (HR = 0.83; 0.70-0.99). Regarding HCRU, empagliflozin was associated with lower risk of first inpatient stay (HR = 0.87; 0.81-0.93), and lower rate of inpatient and outpatient visits (rate ratio [RR] = 0.85; 0.80-0.89 and RR = 0.96; 0.94-0.98) than DPP-4i.
1 | INTRODUCTION

The number of patients with type 2 diabetes mellitus (T2DM) is rising worldwide. In Sweden, a total of 368,577 patients were registered in the National Quality Registry for Diabetes in 2014, increasing to 448,012 patients in 2019. If current trends continue, the number of people with diabetes in Sweden will be 940,000 inhabitants by year 2050.

Notwithstanding the impact of T2DM is characterized by decreased life expectancy and quality of life, this disease also represents a large economic burden due to high healthcare resource utilization (HCRU). In particular, T2DM is associated with high cardiovascular (CV) comorbidity and mortality, and renal failure, which lead to a substantial increase in the need for healthcare. In Sweden, the prevalence of CV disease (CVD) in patients with T2DM was estimated to be 28.3% in 2017 and Sweden was included among the top five countries with the highest health expenditure per person with diabetes worldwide in 2019. Among the population in the capital region, Stockholm, accessing healthcare between 2006 and 2011, diabetes was one of the factors most strongly associated with a higher relative risk of chronic kidney disease.

There are several options recommended as second-line treatments for T2DM in Sweden, including adding insulin to metformin, or repaglinide, sulphonylureas, pioglitazone, akarbos, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors as monotherapy or in addition to metformin. The GLP-1 analog liraglutide or the SGLT-2 inhibitor empagliflozin should be offered to persons with manifest CVD, as they have shown protective effects on CV events and all-cause mortality (ACM), in addition to glucose-lowering effects. The use of SGLT-2 inhibitors in T2DM tend to be cost-effective compared with older oral glucose-lowering drugs and with other new classes of antidiabetic treatments like DPP-4i in international studies, although further evidence is needed regarding the effectiveness of SGLT-2 inhibitors in clinical practice. In Sweden, initiation of dapagliflozin, a SGLT-2 inhibitor, was associated with significantly lower hospital healthcare need, mainly caused by lower CV and T2DM-related care, compared with another glucose-lowering drug in patients with T2DM similar to participants in the DECLARE-TIMI 58 trial.

For T2DM patients with manifest CVD, empagliflozin is part of the Swedish standard of care. The beneficial effects of empagliflozin on CV events and mortality, as well as on renal events, have been observed in both clinical trials and observational studies, suggesting the potential of empagliflozin to reduce HCRU. In the EMPAR-REG OUTCOME trial, empagliflozin reduced the risk of ACM, hospitalization for heart failure (HHF) and CV mortality (CVM) by 32%, 35% and 38% respectively compared with placebo. However, there is limited evidence regarding CV and renal events and mortality associated with empagliflozin use in Sweden and its impact on HCRU. In fact, only one recent 5-year retrospective cohort study including T2DM patients with established CVD in the region of Östergötland was identified, revealing that empagliflozin was associated with both survival gains and lower need for healthcare. Therefore, further studies are needed to confirm the cardiorenal effectiveness and benefits of empagliflozin in HCRU in Swedish patient populations with T2DM representing national routine care.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a non-interventional, retrospective cohort study that used data from Swedish national registries for comparing T2DM patients initiating treatment with empagliflozin with patients initiating any DPP-4i between May 2014 and December 2018. All data were obtained from electronically recorded longitudinal secondary data sources at the Swedish national level: The National Patient Register (NPR), The Prescribed Drug Register (PDR), The Cause of Death Register and The National Diabetes Register (NDR).

2.2 | Study population

Eligible patients had a T2DM diagnosis before the index date (i.e. the date of first filled prescription of the sub-cohort-defining drug), at least one filled prescription of empagliflozin or any DPP-4i during the study period (see all included study drugs in Supporting Information, Table S1) and no filled prescription of any other SGLT-2 inhibitor or DPP-4i during the preceding 12 months including at index date. Patients were excluded if they were aged <18 years old at first prescription of empagliflozin or DPP-4i, had a diagnosis of type 1 diabetes mellitus (T1DM) before index date, had a diagnosis of end-stage renal disease (ESRD), secondary diabetes or gestational diabetes 12 months before the index date or had missing or ambiguous data on age or gender.

Conclusions: Empagliflozin treatment compared to DPP-4i reduced cardiorenal events and overall mortality, which may explain lower HCRU among empagliflozin users in Sweden.
Cohorts of empagliflozin and DPP-4i initiators underwent 1:1 propensity score matching (PSM). Balance was assessed on >180 covariates, including sociodemographic, lifestyle, diabetes history and complications, other comorbidities, other antidiabetic drug use, prior drug use, HCRU, costs and laboratory covariates (imputed using multiple imputation by chained equations [MICE] in 7.6%-17.5% of patients with missing laboratory data). ICD-10 and ATC codes from the NPR and PDR were used to define drug and disease condition covariates, whereas categorical laboratory covariates were based on definitions from the NDR. Evaluation of the success of the matching procedure was based on a standardized difference (ST) of a covariate that was less than 0.1 between treatment groups.

2.3 Study outcomes

Primary effectiveness outcomes included HHF, ACM, composite outcome of HHF and ACM, and composite outcome of myocardial infarction (MI), stroke and ACM, as well as its individual components. Secondary CV outcomes included CVM, composite of HHF and CVM, 3-point major adverse CV events (MACE), defined as a composite outcome including MI, stroke and CVM, and the risk of coronary revascularization procedure. Renal outcomes included ESRD, estimated glomerular filtration rate (eGFR) decline to <60 ml/min/1.73 m², progression from normoalbuminuria to micro/macromicroalbuminuria and the composite outcome including eGFR decline to <60 ml/min/1.73 m² and progression from normoalbuminuria to micro/macromicroalbuminuria (Supporting Information, Table S2). HCRU outcomes comprised time to first hospitalization, hospital length of stay, and number of outpatient, inpatient and emergency room visits.

Follow-up for effectiveness and HCRU outcomes began on the index date and continued in an as-treated (AT) approach until the first occurrence of any of the following events: occurrence of an effectiveness outcome, death, discontinuation of the index drug use, switch to another study drug, initiation of concomitant use of empagliflozin/SGLT-2 inhibitor and a DPP-4i or two drugs within the same class, or end of data availability (i.e. 31st December 2018).

2.4 Statistical analysis

Descriptive analyses were provided for effectiveness and HCRU outcomes in the main study cohorts. Effectiveness outcomes and the risk of first hospitalization were analysed by reporting the number of events, patient-years (PY) at risk and incidence rates. Additionally, Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CIs). Sensitivity analyses of the main endpoints were performed using an intent-to-treat (ITT) methodology.

For visits, the total number of visits, PY at risk, incidence rates, and number of visits per member and month were calculated. Additionally, the total number of visits was compared across treatment groups using a Poisson regression model. The resulting rate ratios (RR) with 95% CI were reported. Hospital length of stay per cohort during follow-up was reported. The mean, standard deviation (SD), median, interquartile range, and minimum and maximum values were reported for the crude number of inpatient days per patient. The number of inpatient days was also calculated per PY.

To be included in the renal effectiveness outcomes analyses, patients needed to have an eGFR measurement during the 12 months before index, and then needed to be matched to another patient who had an eGFR test. Moreover, there were additional criteria for each specific outcome (see Supporting Information, Figure S1). Overall, these criteria led to smaller sub-cohorts for these outcomes compared with the main study cohorts. Within each sub-cohort for the renal effectiveness outcomes, PSM was not re-done, but any unbalanced variables were adjusted for using the multivariable models.

Statistical analyses were conducted using STATA version 16: StataCorp.

3 RESULTS

3.1 Participants

A total of 145,023 patients were prescribed/dispensed with empagliflozin, any SGLT-2 inhibitor or any DPP-4i in Sweden during the study period and were assessed for eligibility. After applying selection criteria and performing the PSM, the groups for the comparison between empagliflozin and any DPP-4i were reduced to 15,785 pairs (Figure 1 and Table 1).

Before matching, T2DM patients given empagliflozin were on average 4 years younger (62.72 years vs. 66.99 years), more often obese (55.47% vs. 41.84%, measured using body mass index of ≥30 kg/m²) and with more cardiac comorbidities (e.g. ischaemic heart disease [25.38% vs. 16.68%] or acute MI [13.33% vs 7.66%]), higher glycated haemoglobin (HbA1c) (66.48 mmol/mol vs. 63.11 mmol/mol) and GFR levels (89.00 ml/min/1.73 m² vs. 80.21 ml/min/1.73 m²), and lower total cholesterol (4.48 mmol/L vs. 4.63 mmol/L) and creatinine levels (73.37 μmol/L vs. 81.33 μmol/L), compared with patients starting treatment with any DPP-4i. Regarding baseline characteristics of the final matched cohorts, the majority of patients were male (65%) and the mean age was 63 years old. About 50% of patients were obese and the most common diabetes complication was retinopathy, in almost 11% of patients. Hypertension was the most common comorbidity, experienced by almost 28% of patients. Both cohorts revealed no remaining unbalance at covariate level after matching (all STD <0.1 between comparators) (Table 1).

In the empagliflozin cohort, empagliflozin in single-pill was administered in more than 91% of patients, while the remaining patients in this cohort received empagliflozin in combination with metformin. Regarding the DPP-4i cohort, the most common DPP-4i was sitagliptin (77.59%) followed by linagliptin (12.73%) and the combination of sitagliptin with metformin (8.41%). All other DPP-4i were administered in <1% of patients in this cohort (Supporting Information, Table S3). About 66% of patients received metformin, 24% insulin and 11% sulphonylureas as additional antidiabetic treatments during the study (Table 1).
The mean follow-up available for effectiveness outcomes was 6.44 and 9.77 months for the empagliflozin and DPP-4i cohorts, respectively. For HCRU outcomes (excluding first inpatient stay) the mean follow-up available was 6.96 and 12.01 months for the empagliflozin and DPP-4i cohorts, respectively. The follow-up was slightly shorter in the first inpatient stay analysis (5.93 months for the empagliflozin cohort and 8.68 months for the DPP-4i cohort).

3.2 Cardiovascular outcomes and all-cause mortality

Compared to DPP-4i, empagliflozin was significantly associated with a 33%, 47% and 41% risk reduction in HHF (HR = 0.67; 95% CI: 0.49-0.91), ACM (HR = 0.53; 0.41-0.68) and the composite of HHF + ACM (HR = 0.59; 0.48-0.73), respectively. For MI and stroke, although the incidence rates were numerically lower for empagliflozin compared with DPP-4i, there were no significant differences when analysed separately. However, there was a statistically lower risk (32%) of the composite of MI + stroke + ACM in the empagliflozin group compared to DPP-4i (HR = 0.68; 0.57-0.81). For CVM, the combination of HHF + CVM and MACES, empagliflozin was associated with a statistically lower risk of 54% (HR = 0.46; 0.29-0.73), 39% (HR = 0.61; 0.47-0.79) and 21% (HR = 0.79; 0.63-0.98), respectively, compared to DPP-4i. For coronary revascularization, no significant differences were observed (Figure 2).

3.3 Renal outcomes

Empagliflozin was associated with a significantly lower risk of ESRD (HR = 0.13; 0.03-0.57), eGFR decline to <60 ml/min/1.73 m² (HR = 0.83; 0.70-0.99) and the composite of eGFR decline plus microalbuminuria or macroalbuminuria (HR = 0.74; 0.63-0.87) compared to treatment with DPP-4i. The comparison for progression to microalbuminuria or macroalbuminuria alone was not statistically significant (Table 2).

3.4 Healthcare resource utilization

There was a small (4%) but significant lower number of outpatient visits in patients receiving empagliflozin compared with those receiving DPP-4i (RR = 0.96; 0.94-0.98). Inpatient visits were also lower in the empagliflozin group, as reflected by a 13% lower risk of first inpatient stay with empagliflozin compared to treatment with DPP-4i (RR = 0.87; 0.81-0.93) and a 15% lower risk of inpatient visits overall compared with DPP-4i (RR = 0.85; 0.80-0.89) (Table 3).

Among patients who had at least one hospital admission, the mean length of stay was shorter in the empagliflozin group compared to DPP-4i group (9.1 vs. 11.6 days) (Supporting Information, Table S4). Considering all admissions, the mean total number of inpatient days per PY was also shorter in the empagliflozin group compared with the DPP-4i group (1.5 vs. 2.0 days).

3.5 Sensitivity analyses

In the ITT analyses, the direction of HR of the effectiveness results was similar to the AT approach but HRs were larger, indicating a lower risk reductions compared to the AT approach. Empagliflozin was significantly associated with lower risk of HHF (HR = 0.73; 0.59-0.90), ACM (HR = 0.73; 0.63-0.85), and the composite of HHF + ACM (HR = 0.74; 0.65-0.84) and MI + stroke + ACM (HR = 0.82; 0.73-0.92) compared to DPP-4i (Supporting Information, Table S5).
| Variable | Before PSM | After PSM | STD |
|----------|------------|-----------|-----|
| Empagliflozin (n = 20,960) | DPP-4i (n = 59,054) | STD | Empagliflozin (n = 15,785) | DPP-4i (n = 15,785) | STD |
| **Baseline demographics** | | | | | |
| Age at index, mean ± SD | 62.72 ± 10.75 | 66.99 ± 12.27 | -0.37 | 63.49 ± 10.90 | 63.36 ± 11.49 | 0.01 |
| Male, n (%) | 13,861 (66.13) | 34,443 (58.32) | -0.16 | 10,202 (64.63) | 10,255 (64.97) | 0.01 |
| **Year of index date, n (%)** | | | | | |
| 2014 | 0 (0.00) | 0 (0.00) | 0.06 | 0 (0.00) | 0 (0.00) | 0.04 |
| 2015 | 893 (4.26) | 13,010 (22.03) | 0.06 | 816 (5.17) | 822 (5.21) | 0.01 |
| 2016 | 3065 (14.62) | 15,139 (25.64) | 0.09 | 2640 (16.72) | 2593 (16.43) | 0.01 |
| 2017 | 6668 (31.81) | 17,059 (28.89) | 0.11 | 5232 (33.15) | 5243 (33.22) | 0.01 |
| 2018 | 10,334 (49.30) | 13,846 (23.45) | 0.13 | 7097 (44.96) | 7127 (45.15) | 0.01 |
| **Lifestyle variables** | | | | | |
| Obesity (BMI of ≥30)\(a\), n (%) | 11,626 (55.47) | 24,708 (41.84) | 0.28 | 7961 (50.43) | 8022 (50.82) | -0.01 |
| Overweight (BMI of ≥25 and <30)\(a\), n (%) | 6093 (29.07) | 19,452 (32.94) | 0.00 | 4926 (31.21) | 4920 (31.17) | 0.00 |
| Smoking\(a\), n (%) | 2813 (13.42) | 6940 (11.75) | 0.05 | 2120 (13.43) | 2115 (13.40) | 0.00 |
| Alcohol abuse or dependence, n (%) | 542 (2.59) | 1418 (2.40) | 0.01 | 424 (2.69) | 398 (2.52) | 0.01 |
| Drug abuse or dependence, n (%) | 437 (2.08) | 1021 (1.73) | 0.03 | 335 (2.12) | 323 (2.05) | 0.01 |
| **Diabetes complications** | | | | | |
| Diabetic retinopathy, n (%) | 2589 (12.35) | 5899 (9.99) | 0.08 | 1679 (10.64) | 1602 (10.15) | 0.02 |
| Diabetic neuropathy, n (%) | 372 (1.77) | 673 (1.14) | 0.05 | 212 (1.34) | 212 (1.34) | 0.00 |
| Diabetic nephropathy, n (%) | 309 (1.47) | 698 (1.18) | 0.03 | 159 (1.01) | 159 (1.01) | 0.00 |
| **Other comorbidities\(b\)** | | | | | |
| Cardiovascular disease, n (%) | 11,820 (56.39) | 31,248 (52.91) | 0.07 | 8523 (53.99) | 8389 (53.15) | 0.02 |
| Hypertension, n (%) | 6024 (28.74) | 16,667 (28.22) | 0.01 | 4343 (27.51) | 4289 (27.17) | 0.01 |
| Hyperlipidaemia, n (%) | 4508 (21.51) | 10,663 (18.06) | 0.09 | 3109 (19.70) | 3134 (19.85) | 0.00 |
| Ischaemic heart disease, n (%) | 5320 (25.38) | 9853 (16.68) | 0.21 | 3478 (22.03) | 3446 (21.83) | 0.00 |
| Acute MI, n (%) | 2793 (13.33) | 4522 (7.66) | 0.19 | 1758 (11.14) | 1713 (10.85) | 0.01 |
| Acute coronary syndrome/unstable angina, n (%) | 4727 (22.55) | 8494 (14.38) | 0.21 | 3060 (19.39) | 3031 (19.20) | 0.00 |
| Old MI, n (%) | 2602 (12.41) | 4543 (7.69) | 0.16 | 1681 (10.65) | 1659 (10.51) | 0.00 |
| Stable angina, n (%) | 2492 (11.89) | 5019 (8.50) | 0.11 | 1659 (10.51) | 1677 (10.62) | 0.00 |
| Coronary atherosclerosis and other forms of chronic ischaemic heart disease, n (%) | 3068 (14.64) | 4973 (8.42) | 0.2 | 1883 (11.93) | 1869 (11.84) | 0.00 |
| Coronary revascularization procedure, n (%) | 3747 (17.88) | 5763 (9.76) | 0.24 | 2334 (14.79) | 2284 (14.47) | 0.01 |
| Osteoarthritis, n (%) | 3289 (15.69) | 9663 (16.36) | -0.02 | 2476 (15.69) | 2520 (15.96) | -0.01 |
| Other arthritis, arthropathies and musculoskeletal pain, n (%) | 6439 (30.72) | 16,454 (27.86) | 0.06 | 4699 (29.77) | 4757 (30.14) | -0.01 |
| Dorsopathies, n (%) | 3142 (14.99) | 8420 (14.26) | 0.02 | 2283 (14.46) | 2330 (14.76) | -0.01 |

(Continues)
| Variable | Before PSM | DPP-4i (n = 59 054) | STD | After PSM | DPP-4i (n = 59 054) | STD |
|----------|------------|---------------------|-----|-----------|---------------------|-----|
| Falls, n (%) | 4656 (22.21) | 13 854 (23.46) | -0.03 | 3521 (22.31) | 3525 (22.33) | 0.00 |
| Anxiety, n (%) | 7173 (34.22) | 22 189 (37.57) | -0.07 | 5447 (34.51) | 5454 (34.55) | 0.00 |
| **Laboratory values** | | | | | | |
| HbA1c (mmol/mol), mean ± SD | 66.48 ± 15.40 | 63.11 ± 14.38 | 0.23 | 65.25 ± 15.29 | 65.29 ± 15.82 | -0.01 |
| Total cholesterol (mmol/L), mean ± SD | 4.48 ± 1.13 | 4.63 ± 1.11 | -0.14 | 4.50 ± 1.17 | 4.49 ± 1.15 | 0.00 |
| Creatinine (μmol/L), mean ± SD | 7337 ± 18.56 | 81.33 ± 30.06 | -0.32 | 74.26 ± 18.56 | 74.26 ± 20.33 | 0.01 |
| GFR (ml/min/1.73 m²), mean ± SD | 89.00 ± 18.00 | 80.21 ± 23.45 | 0.42 | 87.27 ± 17.51 | 87.23 ± 19.33 | -0.02 |

**Prior concomitant use of other antidiabetic drugs**

| Number of antidiabetic substances at index date | | | | | | |
| Mean ± SD | 2.34 ± 0.83 | 1.99 ± 0.70 | 0.45 | 2.14 ± 0.72 | 2.16 ± 0.73 | -0.02 |
| Median (Q1-Q3) | 2.00 (2.00-3.00) | 2.00 (2.00-2.00) | -0.14 | 2.00 (2.00-3.00) | 2.00 (2.00-3.00) | 0.00 |
| Min-max | 1.00-700 | 1.00-7.00 | 1.00-600 | 1.00-7.00 | |
| Naïve new use of antidiabetic drugs, n (%) | 75 (0.36) | 862 (1.46) | -0.12 | 74 (0.47) | 68 (0.43) | 0.01 |

**Concomitant initiation or current use of other antidiabetic drugs**

| Metformin, n (%) | 13 978 (66.69) | 35 057 (59.36) | 0.15 | 10 464 (66.29) | 10 514 (66.61) | -0.01 |
| Sulphonylureas second generation, n (%) | 2273 (10.84) | 6680 (11.31) | -0.01 | 1760 (11.15) | 1792 (11.35) | -0.01 |
| GLP-1 receptor agonists, n (%) | 3021 (14.41) | 783 (1.33) | 0.50 | 523 (3.31) | 639 (4.05) | -0.04 |
| Thiazolidinediones, n (%) | 235 (1.12) | 370 (0.63) | 0.05 | 143 (0.91) | 159 (1.01) | -0.01 |
| Meglitinides, n (%) | 558 (2.66) | 1675 (2.84) | -0.01 | 432 (2.74) | 416 (2.64) | 0.01 |
| Insulin, n (%) | 6709 (32.01) | 10 233 (17.33) | 0.35 | 3817 (24.18) | 3911 (24.78) | -0.01 |
| Alpha-glucosidase inhibitors, n (%) | 29 (0.14) | 66 (0.11) | 0.01 | 16 (0.10) | 25 (0.16) | -0.02 |

**Prior use of other drugs**

| Angiotensin-converting-enzyme inhibitor, n (%) | 12 775 (60.95) | 34 140 (57.81) | 0.06 | 9269 (58.72) | 9153 (57.79) | 0.01 |
| Angiotensin II receptor blocker, n (%) | 9189 (43.84) | 24 450 (41.40) | 0.05 | 6681 (42.32) | 6698 (42.43) | 0.00 |
| Beta-blocker, n (%) | 11 973 (57.12) | 32 087 (54.34) | 0.06 | 8674 (54.95) | 8580 (54.36) | 0.01 |
| Calcium channel blocker, n (%) | 9955 (47.50) | 28 808 (48.78) | -0.03 | 7344 (46.53) | 7375 (46.72) | 0.00 |
| Thiazides, n (%) | 3739 (17.84) | 11 145 (18.87) | -0.03 | 2798 (17.73) | 2729 (17.29) | 0.01 |
| Loop diuretics, n (%) | 5258 (25.09) | 16 669 (28.23) | -0.07 | 3780 (23.95) | 3780 (23.95) | 0.00 |
| Other diuretics, n (%) | 2388 (11.39) | 6474 (10.96) | 0.01 | 1640 (10.39) | 1655 (10.48) | 0.00 |
| Nitrates, n (%) | 5824 (27.79) | 12 743 (21.58) | 0.14 | 3982 (25.23) | 3939 (24.95) | 0.01 |
| COPD or asthma medications, n (%) | 4469 (21.32) | 12 186 (20.64) | 0.02 | 3264 (20.68) | 3302 (20.92) | -0.01 |
| Statin, n (%) | 17 575 (83.85) | 45 540 (77.12) | 0.17 | 12 863 (81.49) | 12 876 (81.57) | 0.00 |
| Other lipid-lowering drugs, excluding statins, n (%) | 17 787 (84.86) | 46 582 (78.88) | 0.16 | 13 046 (82.65) | 13 081 (82.87) | -0.01 |
The beneficial effects of empagliflozin have been observed in clinical trials and observational studies, suggesting that SGLT-2 inhibitors have the potential to provide additional benefits (other than glucose-lowering) and to decrease HCRU in T2DM. Empagliflozin is recommended in both international and national guidelines for treatment of patients with T2DM and established CVD as well as for T2DM and congestive heart failure.

Given the high economic burden of this disease in Sweden, we assessed the cardiorenal effectiveness and HCRU of empagliflozin use in comparison to DPP-4i.

In Sweden, 15 785 PSM-matched patient pairs were identified. After PSM, both cohorts revealed no remaining unbalance at covariate level. The 24.7% of empagliflozin initiators (5175 of 20 960 patients) were excluded in the PSM. These excluded patients were on average younger, more often males with CVD and poorer diabetes control. The differences in baseline characteristics between empagliflozin and DPP-4i cohorts before matching reflects that, in the Swedish clinical practice from May 2014 until December 2018, these treatments were given to different patient profiles. Empagliflozin was given to younger patients with more obesity and cardiac comorbidities, but better renal function, which was in line with treatment recommendations as empagliflozin was not recommended for low levels of eGFR during the study period, in contrast to DPP-4i. Moreover, the dose adjustment required in patients with impaired renal function, could have made physicians more reluctant to prescribe empagliflozin in the subpopulation with renal impairment. On the contrary, empagliflozin was prescribed more often in patients with manifest CVD given its expected benefits in this subgroup, as per randomized clinical trials and according to Swedish guidelines.

In the present study, over 50% of the population had CVD. This figure is higher than in prior Swedish studies with 28%-34% of CVD among T2DM. Differences could be linked both to the fact that we included only T2DM patients receiving second or further line treatments (more advanced disease), where empagliflozin is specifically recommended in patients with manifest CVD, as well as to the wider definition of CVD used here (adding heart failure and transient ischaemic attack to the EMPA-REG OUTCOME trial definition).

The results obtained in Sweden are comparable with those from other countries included in the EMPRISE program. In the Swedish study, the event rate of HHF and ACM were 33% and 47% lower with empagliflozin compared to any DPP-4i. In an East Asian meta-analysis, the risk of HHF was 18% lower and ACM was 36% lower with empagliflozin compared to DPP-4i. The first interim analysis of the US EMPRISE also showed that the initiation of empagliflozin was associated with a lower risk of HHF. Overall, these findings support the EMPA-REG OUTCOME trial results, and consolidate the notion that empagliflozin prevents HHF and ACM in routine care patients with T2DM.

When focusing on renal effectiveness outcomes, results should be interpreted with caution. Empagliflozin was associated with

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**Table 1** (Continued)

| Variable | Before PSM | After PSM | Empagliflozin (n = 15 785) | DPP-4i (n = 59 054) | STD | Empagliflozin (n = 15 785) | DPP-4i (n = 59 054) | STD |
|----------|------------|-----------|---------------------------|-------------------|-----|---------------------------|-------------------|-----|
| Antithrombotic, n (%) | 29.2 (46.89) | 2914 (13.90) | 2914 (13.90) | 9295 (15.74) | 9295 (15.74) | 9295 (15.74) | 9295 (15.74) | 0.05 |
| Anticoagulants, n (%) | 3.26 (46.77) | 13.90 | 13.90 | 9295 (15.74) | 9295 (15.74) | 9295 (15.74) | 9295 (15.74) | 0.05 |
| Heparin and other low-molecular-weight heparins, n (%) | 0.95 (46.67) | 14.71 | 14.71 | 9338 (15.81) | 9338 (15.81) | 9338 (15.81) | 9338 (15.81) | 0.03 |
| Non-steroidal anti-inflammatory drugs, n (%) | 72.83 (46.67) | 72.83 | 72.83 | 41 143 (69.67) | 41 143 (69.67) | 41 143 (69.67) | 41 143 (69.67) | 0.07 |
| Oral corticosteroids, n (%) | 28.78 (46.67) | 28.78 | 28.78 | 17 419 (29.50) | 17 419 (29.50) | 17 419 (29.50) | 17 419 (29.50) | 0.02 |
| Opioids, n (%) | 58.00 (46.67) | 58.00 | 58.00 | 33 048 (55.96) | 33 048 (55.96) | 33 048 (55.96) | 33 048 (55.96) | 0.04 |
| Antidepressants, n (%) | 32.76 (46.67) | 32.76 | 32.76 | 18 550 (31.41) | 18 550 (31.41) | 18 550 (31.41) | 18 550 (31.41) | 0.03 |
| Anticonvulsants, n (%) | 12.17 (46.67) | 12.17 | 12.17 | 6746 (11.42) | 6746 (11.42) | 6746 (11.42) | 6746 (11.42) | 0.02 |
| Benzodiazepines, n (%) | 17.52 (46.67) | 17.52 | 17.52 | 11 873 (20.11) | 11 873 (20.11) | 11 873 (20.11) | 11 873 (20.11) | 0.07 |
| Other anxiolytics/hypnotics, n (%) | 26.17 (46.67) | 26.17 | 26.17 | 17 134 (29.01) | 17 134 (29.01) | 17 134 (29.01) | 17 134 (29.01) | 0.06 |

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; max, maximum; MI, myocardial infarction; min, minimum; PSM, propensity score matching; Q1, first quartile; Q3, third quartile; SD, standard deviation; STD, standardized difference.

**Data from the National Diabetes Registry (NDR).**

**Listed are covariates present in at least 10% of patients included in the study.**

**Excluding fixed-dose combinations with metformin and the study drugs or other marketed SGLT-2 or DPP-4i.**

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4 | **DISCUSSION**

T2DM is associated with high CV morbidity and mortality, which in turn contributes to increased healthcare costs. The beneficial effects of SGLT-2 inhibitors on CV events and mortality, as well as on renal events, have been observed in clinical trials and observational studies, suggesting that SGLT-2 inhibitors have the potential to provide additional benefits (other than glucose-lowering) and to decrease HCRU in T2DM. Empagliflozin is recommended in both international and national guidelines for treatment of patients with T2DM and established CVD as well as for T2DM and congestive heart failure. Given the high economic burden of this disease in Sweden, we assessed the cardiorenal effectiveness and HCRU of empagliflozin use in comparison to DPP-4i.

In Sweden, 15 785 PSM-matched patient pairs were identified. After PSM, both cohorts revealed no remaining unbalance at covariate level. The 24.7% of empagliflozin initiators (5175 of 20 960 patients) were excluded in the PSM. These excluded patients were on average younger, more often males with CVD and poorer diabetes control. The differences in baseline characteristics between empagliflozin and DPP-4i cohorts before matching reflects that, in the Swedish clinical practice from May 2014 until December 2018, these treatments were given to different patient profiles. Empagliflozin was given to younger patients with more obesity and cardiac comorbidities, but better renal function, which was in line with treatment recommendations as empagliflozin was not recommended for low levels of eGFR during the study period, in contrast to DPP-4i. Moreover, the dose adjustment required in patients with impaired renal function, could have made physicians more reluctant to prescribe empagliflozin in the subpopulation with renal impairment. On the contrary, empagliflozin was prescribed more often in patients with manifest CVD given its expected benefits in this subgroup, as per randomized clinical trials and according to Swedish guidelines.

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The results obtained in Sweden are comparable with those from other countries included in the EMPRISE program. In the Swedish study, the event rate of HHF and ACM were 33% and 47% lower with empagliflozin compared to any DPP-4i. In an East Asian meta-analysis, the risk of HHF was 18% lower and ACM was 36% lower with empagliflozin compared to DPP-4i. The first interim analysis of the US EMPRISE also showed that the initiation of empagliflozin was associated with a lower risk of HHF. Overall, these findings support the EMPA-REG OUTCOME trial results, and consolidate the notion that empagliflozin prevents HHF and ACM in routine care patients with T2DM.

When focusing on renal effectiveness outcomes, results should be interpreted with caution. Empagliflozin was associated with
FIGURE 2  Primary and secondary cardiovascular effectiveness outcomes in the empagliflozin versus DPP-4i matched sub cohorts (AT approach). The mean follow-up available was 6.44 months and 9.77 months for the empagliflozin and DPP-4i cohorts, respectively. ACM, all-cause mortality; AT, as-treated; CI, confidence interval; CVM, cardiovascular mortality; DPP-4i, dipeptidyl peptidase-4 inhibitor; H HF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PY, patient-years; SGLT-2, sodium-glucose cotransporter-2.

### TABLE 2  Renal effectiveness outcomes in the empagliflozin versus DPP-4i matched sub-cohorts (AT approach)

| Outcome                                      | Empagliflozin (n=15,785) | DPP-4i (n=15,785) | HR (95% CI) |
|----------------------------------------------|--------------------------|------------------|-------------|
|                                                                 | Events | PY  | Rate/1000 PY | Events | PY  | Rate/1000 PY |
| ESRD (n = 15 785)                             | 2      | 8520| 0.2         | 24     | 12 934| 1.9         | 0.13 (0.03-0.57) |
| eGFR decline to <60 ml/min/1.73 m² (n = 7844) | 195    | 4142| 47.1        | 319    | 6197 | 51.5       | 0.83 (0.70-0.99) |
| Progression to micro/macrosolmarninuria (n = 4926) | 149    | 2606| 57.2        | 257    | 3879 | 66.2       | 0.92 (0.75-1.13) |
| eGFR decline to <60 ml/min/1.73 m² + albuminaria (n = 4618) | 224    | 2429| 92.2        | 528    | 3416 | 154.6      | 0.74 (0.63-0.87) |

Abbreviations: AT, as-treated; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; PY, patient-years.

### TABLE 3  Healthcare resource utilization during follow-up (AT approach)

| Outcome                  | Empagliflozin (n = 15 785) | DPP-4i (n = 15 785) | Rate ratio (95% CI) |
|--------------------------|-----------------------------|---------------------|---------------------|
|                           | Count | PY  | Count/PY | Count | PY  | Count/PY |
| Outpatient visits         | 17 590 | 8486 | 2.07      | 27 888 | 12 875 | 2.17      | 0.96 (0.94-0.98) |
| Emergency room visits     | 1000  | 8486 | 0.12      | 1613  | 12 875 | 0.13      | 0.94 (0.87-1.01) |
| Inpatient visits          | 2413  | 8486 | 0.28      | 4310  | 12 875 | 0.33      | 0.85 (0.80-0.89) |
| First inpatient stay      | 1401  | 7823 | 0.18      | 2230  | 11 437 | 0.19      | 0.87 (0.81-0.93) |

Note: The mean follow-up available for visits was 6.96 months and 12.01 months for the empagliflozin and DPP-4i cohorts, respectively. The mean follow-up to first inpatient stay was 5.93 months and 8.68 months for the empagliflozin and DPP-4i cohorts, respectively.

Abbreviations: AT, as-treated; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; PY, patient-years.

aRate ratio based on Poisson model.

bSpecialist outpatient visits excluding primary care visits.
significantly lower risk of ESRD compared with DPP-4i in Sweden; however, only two and 24 ESRD events were identified in the empagliflozin and DPP-4i groups, respectively. We cannot dismiss the possibility that the low number of events is related to both empagliflozin’s indication, as this drug should not be used in patients with ESRD or on dialysis, and informative censoring of patients who discontinued empagliflozin once their renal function started to decline, but before reaching ESRD status. Of note, in the EMPRISE study, a low number of ESRD events were also identified. In the Swedish study, there was also a significantly slower eGFR decline with empagliflozin (17% less risk to decrease to <60 ml/min/1.73 m²) versus any DPP-4i, which could be also affected by informative censoring. In the composite of eGFR decline plus albuminuria there was a significant 26% risk reduction with empagliflozin compared to any DPP-4i. Despite these limitations, our results suggest that new empagliflozin users could have a reduced risk of worsening renal function when compared with DPP-4i initiators. This finding is in line with previous results from the EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58 trials. Our results are also supported by the CVD-REAL 3 study and a Scandinavian cohort study. Although baseline kidney-related comorbidities were well balanced between cohorts through PSM in this study, some remaining confounding could be still present. Moreover, in all renal analyses, patients without a renal laboratory measurement in the 12 months before index were excluded. This could be associated to a selection bias, given the fact that patients with poorer renal function are those more frequently monitored by the physician. Nevertheless, this bias should not necessarily impact relative results as it affected both arms.

Finally, for HCRU, results are in line with a prior health economic modeling study in Sweden, in which empagliflozin treatment was suggested to reduce mortality and the need for HCRU. In the present study, empagliflozin was statistically significant associated with a lower number of outpatient and inpatient visits. In the US EMPRISE study, empagliflozin was also associated with a significant lower HCRU compared to DPP-4i within the first two years of use, showing lower rates of emergency department visits, all hospital admissions and number of office visits as well as reduced length of stay and risk of first hospitalization. In the Swedish study, patients had approximately two outpatient visits per year, which excluded primary care visits. The low number of inpatient visits may reflect the lower share of CVD, HHF and mortality observed among empagliflozin patients versus DPP-4i. Therefore, results from the current study indicate that empagliflozin treatment could reduce HCRU.

This study has several strengths. The high coverage of the Swedish National Registries allows describing accurately the impact of empagliflozin and DPP-4i in routine clinical practice. The selection criteria ensured that only patients with T2DM, and not any other type of diabetes, were included. Despite being matched on >180 covariates, including sociodemographic, lifestyle, diabetes history and complications, other comorbidities, other antidiabetic drug use, prior drug use, HCRU, costs and laboratory covariates, the analyses were able to keep 75% of empagliflozin users. Additionally, patients were matched on eGFR (and other key laboratory covariates), which is important to mitigate potential confounding by indication. AT approaches may risk introducing informed censoring, and sensitivity analyses using an ITT methodology where therefore conducted for the primary endpoints. These analyses supported the main findings where the risk reductions were comparable with those observed using the AT approach.

Potential limitations of the study include the low number of renal events, which could be the result of well-managed diabetes for these patients and prevents drawing strong conclusions. Also, the fact that post-baseline renal laboratory data were only available for 25%-50% of the cohort (possibly patients at a higher risk or with better renal health) must be considered when extrapolating eGFR and albuminuria findings to the entire population of diabetic patients using the study drugs. We cannot fully dismiss overestimation of the benefits for empagliflozin in these outcomes. Moreover, the follow-up period was relatively short in the empagliflozin group and should be taken into consideration when interpreting study results. Finally, causality cannot be fully confirmed through a non-interventional study like the current study.

Overall, the results presented here suggest that the benefits of empagliflozin observed in clinical trials seem to translate to the broader patient population treated in clinical practice in Sweden, supporting current national and international guidelines. Empagliflozin was associated with significant reductions in the risk of HHF, ACM and CVM as well as with renal protective effects in routine care patients with T2DM compared with DPP-4i. Finally, evidence from this study show that empagliflozin treatment may reduce the need for healthcare.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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