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RESEARCH ARTICLE

Use of sodium–glucose co-transporter 2 inhibitors in patients with heart failure and type 2 diabetes mellitus: data from the Swedish Heart Failure Registry

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Aims Use of sodium–glucose co-transporter 2 inhibitors (SGLT2i) in real-world heart failure (HF) is poorly characterised. In contemporary patients with HF and type 2 diabetes mellitus (T2DM) we assessed over time SGLT2i use, clinical characteristics and outcomes associated with SGLT2i use.

Methods and results Type 2 diabetes patients enrolled in the Swedish HF Registry between 2016–2018 were considered. We performed multivariable logistic regression models to assess the independent predictors of SGLT2i use and Cox regression models in a 1:3 propensity score-matched cohort and relevant subgroups to investigate the association between SGLT2i use and outcomes. Of 6805 eligible HF patients with T2DM, 376 (5.5%) received SGLT2i, whose use increased over time with 12% of patients on treatment at the end of 2018. Independent predictors of SGLT2i use were younger age, HF specialty care, ischaemic heart disease, preserved kidney function, and absence of anaemia. Over a median follow-up of 256 days, SGLT2i use was associated with a 30% lower risk of cardiovascular (CV) death/first HF hospitalisation (hazard ratio 0.70, 95% confidence interval 0.52–0.95), which was consistent regardless of ejection fraction, background metformin treatment and kidney function. SGLT2i use was also associated with a lower risk of all-cause and CV death, HF and CV hospitalisation, and CV death/myocardial infarction/stroke.

Conclusion In a contemporary HF cohort with T2DM, SGLT2i use increased over time, was more common with specialist care, younger age, ischaemic heart disease, and preserved renal function, and was associated with lower mortality and morbidity.

Keywords SGLT2 inhibitors • Heart failure • HFmrEF • HFpEF • Outcomes • SwedeHF

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Introduction

Heart failure (HF) is the leading cause of hospitalisation in the Western world, with the risk of death raising after each HF hospitalisation.[1] Despite advances in treatment, prognosis in HF with reduced ejection fraction (HFrEF) remains poor, with no evidence-based treatment available in HF with preserved ejection fraction (HFpEF) and only limited evidence in HF with mid-range or mildly reduced ejection fraction (HFmrEF).[1]

Type 2 diabetes mellitus (T2DM) is an independent risk factor for the development of HF and both diseases closely influence each other.[2] Prevalence of T2DM is about 25% in patients with HF,[3] which increases to about 40% in hospitalised HF patients.[4] T2DM, however, is slightly less common in HFmrEF and HFrEF compared with HFpEF.[5]

Over the last 5 years, randomised placebo-controlled trials have demonstrated sodium–glucose co-transporter 2 inhibitors (SGLT2i) reducing the risk of hospitalisation for HF by 30–35% compared with standard of care (SOC) among T2DM patients at high risk for or with established cardiovascular (CV) disease.[6–10] This effect has been shown to be consistent across different levels of baseline HF risk.[11–13] Consequently, several trials have been initiated to test the hypothesis that SGLT2i may be as effective in HF regardless of the presence of T2DM. Of these, the DAPA-HF trial was the first to show a 26% reduction in the risk of CV death or worsening HF in patients receiving dapagliflozin vs. SOC. More recently, in the EMPEROR-Reduced trial, empagliflozin was also observed to reduce the risk of CV death or HF hospitalisation by 25% compared with SOC. Both trials enrolled patients with HFrEF, and both dapagliflozin and empagliflozin were effective regardless of the presence of T2DM.[9,14,15] Finally, the SOLOIST-WHF trial recently showed that sotagliflozin reduced the risk of CV death/HF hospitalisations/visits in T2DM patients who had recently been hospitalised for HF.[16]

Sodium–glucose co-transporter 2 inhibitors are a relatively new treatment, thus limitedly evaluated in real-world settings, particularly in HF populations.[17] Although treatment efficacy can only be demonstrated by randomised controlled trials, trial populations may be highly selected, and thus analyses in real-world populations are helpful to assess generalizability of trial findings and to rule out any signals of harm.[18]

Therefore, the aim of the current study was to investigate (i) the evolving use of SGLT2i; (ii) patient characteristics independently associated with SGLT2i use; and (iii) the association of SGLT2i use with outcomes, in an unselected cohort of T2DM patients with HF across the ejection fraction spectrum (HFpEF, HFmrEF, and HFrEF).

Methods

Study protocol and setting

Data from the Swedish HF registry (SwedeHF) were analysed. The SwedeHF has been described previously.[19] It is a voluntary HF quality registry founded in 2000. A majority of Swedish hospitals (approximately 60 of 75) enrol patients without financial compensation, and record approximately 80 variables from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion is clinician-judged HF, regardless of ejection fraction, thus including HFrEF, HFmrEF and HFpEF. Coverage of SwedeHF ranges between 10% for incident HF (i.e. most patients with new-onset HF are first seen in outpatient primary care or inpatient emergency departments, which do not report to SwedeHF) and 54% for prevalent HF.

For the current analysis, patients with HF and T2DM registered between 1 January 2016 and 31 December 2018 were considered, as this coincides with the availability of SGLT2i in Sweden. No further inclusion/exclusion criterion was considered. In SwedeHF, T2DM is diagnosed according to clinical judgement. Use of SGLT2i and other glucose-lowering agents was assessed through the Dispensed Drug Registry, which provides data on medications which are dispensed (and not only prescribed). A patient was considered as receiving SGLT2i/other glucose-lowering drugs at baseline if a dispensation was recorded in the Dispensed Drug Registry in the 5 months prior to or 14 days after the index date, i.e. the date of registration in SwedeHF. When a patient was registered more than once during the study period, i.e. 2016–2018, the last registration was selected since more representative of contemporary care.

Linkage to Statistics Sweden provided socioeconomic data such as income, level of education, living environment (cohabitating vs. living alone) and number of children. The National Patient Registry provided data on additional comorbidities and on the outcomes of HF hospitalisation, CV hospitalisation, hospitalisation for myocardial infarction (MI) and stroke. The Cause of Death Registry provided the outcomes of all-cause and CV death. The linkage of the aforementioned registries was enabled through a unique personal identification number that all Swedish residents have regardless of citizenship.

Establishment of the HF registry and this analysis with linking of the registries was approved by a multisite ethics committee. Individual patient consent was not required, but patients in Sweden are informed of entry into national registries and have the option not to participate.

Statistical analysis

Outcomes were a composite of CV death/first HF hospitalisation, time to all-cause death, CV death, first HF hospitalisation, first CV hospitalisation, and a composite of CV death/first hospitalisation for HF/MI/stroke. Data were censored at 31 December 2018 (end of study), death, or emigration.

In multivariable models, missing data were handled by multiple imputation using the mice package for 10 datasets and 10 interactions. Variables included in the models are specified in *Table 1*. The outcome of CV death/first HF hospitalisation was included as the Nelson–Aalen estimator, whereas SGLT2i use was not.

Baseline characteristics were compared in patients receiving vs. not receiving SGLT2i by Mann–Whitney test (if continuous) and by chi-squared test (if categorical).

Univariable and multivariable logistic regression models were fitted in order to investigate patient characteristics (demographics, organizational factors, clinical characteristics, comorbidities, concomitant treatments, socioeconomical characteristics) independently associated with SGLT2i use. Results were reported as odds ratio (OR) with 95% confidence intervals (CI). Outliers were investigated by Cook's distance and multicollinearity by the variance inflation factor. No action was deemed necessary.

Univariable Cox proportional hazard regression models were fitted to assess crude risk of outcomes in patients receiving vs. those not receiving SGLT2i. Incidence per 1000 patient-years was calculated with 95% CI by Poisson regression. Propensity scores (PS) for

Table 1 Baseline characteristics

Variables	Overall population					Matched population				
	Missing (%)	SGLT2i No	SGLT2i Yes	SMD	*P*-value	Missing (%)	SGLT2i No	SGLT2i Yes	SMD	*P*-value
n (%)		6429 (94.5)	376 (5.5)				1083 (75.0)	361 (25.0)		
Demographics/organizational										
Male sex, *n* (%)[a]	0.0	4324 (67.3)	297 (79.0)	0.267	<0.001	0.0	856 (79.0)	283 (78.4)	0.016	0.852
Age (years), median [IQR]	0.0	76.0 [69.0, 82.0]	69.0 [62.0, 75.0]	0.750	<0.001	0.0	70.0 [64.0, 74.0]	69.0 [62.0, 75.0]	0.128	0.073
Age ≥75 years, *n* (%)[a]	0.0	3645 (56.7)	98 (26.1)	0.654	<0.001	0.0	265 (24.5)	96 (26.6)	0.049	0.461
Location outpatient, *n* (%)[a]	0.0	4456 (69.3)	324 (86.2)	0.414	<0.001	0.0	934 (86.2)	310 (85.9)	0.011	0.930
Referral to nurse-led HF clinic, *n* (%)[a]	7.6	4058 (68.4)	296 (84.3)	0.382	<0.001	5.4	860 (83.5)	281 (83.6)	0.004	1.000
Referral to, *n* (%)[a]	4.6			0.377	<0.001	3.0			0.058	0.637
Hospital		3709 (60.5)	285 (77.7)				831 (79.2)	271 (77.0)		
Primary care		2298 (37.5)	78 (21.3)				205 (19.5)	77 (21.9)		
Other		119 (1.9)	4 (1.1)				13 (1.2)	4 (1.1)		
Clinical variables										
HF type, *n* (%)[a]	21.3			0.174	0.017	20.3			0.051	0.756
HFpEF		1430 (28.3)	64 (21.5)				170 (19.6)	61 (21.5)		
HFmrEF		1224 (24.2)	69 (23.2)				205 (23.6)	68 (23.9)		
HFrEF		2405 (47.5)	164 (55.2)				492 (56.7)	155 (54.6)		
HF duration ≥6 months, *n* (%)[a]	5.5	4208 (69.3)	242 (67.4)	0.041	0.487	4.8	683 (66.3)	231 (67.0)	0.014	0.878
NYHA class, *n* (%)	32.9			0.139	0.167	23.6			0.026	0.987
I		340 (7.9)	29 (10.5)				87 (10.4)	27 (10.2)		
II		1976 (46.1)	137 (49.5)				422 (50.4)	133 (50.0)		
III		1856 (43.3)	106 (38.3)				310 (37.0)	101 (38.0)		
IV		117 (2.7)	5 (1.8)				18 (2.2)	5 (1.9)		
NYHA class III–IV, *n* (%)[a]	32.9	1973 (46.0)	111 (40.1)	0.120	0.063	23.6	328 (39.2)	106 (39.8)	0.014	0.904
Body mass index (kg/m^2), median [IQR]	47.4	29.0 [25.6, 33.2]	30.3 [26.9, 34.9]	0.222	0.006	53.2	29.5 [26.2, 33.9]	30.3 [26.9, 34.6]	0.095	0.296
Body mass index ≥30 (kg/m^2), *n* (%)	47.4	1484 (43.3)	83 (53.5)	0.206	0.015	53.2	245 (46.6)	79 (52.7)	0.122	0.221
Systolic blood pressure (mmHg), median [IQR]	3.5	130.0 [115.0, 141.0]	120.0 [110.0, 137.5]	0.222	<0.001	4.6	125.0 [115.0, 140.0]	120.5 [110.0, 138.2]	0.072	0.113
Diastolic blood pressure (mmHg), median [IQR]	3.3	70.0 [65.0, 80.0]	70.0 [65.0, 80.0]	0.010	0.928	4.4	72.0 [65.0, 80.0]	70.0 [65.0, 80.0]	0.013	0.733
Mean arterial pressure (mmHg), median [IQR]	3.3	91.2 [83.3, 100.0]	90.0 [80.0, 98.3]	0.096	0.036	4.4	90.0 [83.3, 100.0]	90.0 [81.3, 99.3]	0.031	0.422
Mean arterial pressure ≥90 mmHg, *n* (%)[a]	3.3	3184 (51.2)	164 (45.6)	0.113	0.043	4.4	504 (48.6)	162 (47.0)	0.034	0.629
Heart rate (bpm), median [IQR]	5.1	72.0 [64.0, 83.0]	73.0 [64.0, 82.0]	0.010	0.815	6.8	72.0 [65.0, 82.0]	72.0 [64.0, 82.0]	0.030	0.984
Heart rate ≥70 bpm, *n* (%)[a]	5.1	3342 (54.7)	196 (56.5)	0.036	0.556	6.8	546 (53.9)	185 (55.6)	0.033	0.643
eGFR (CKD-EPI formula)	4.5	54.1 [38.6, 73.8]	69.3 [54.0, 86.7]	0.616	<0.001	5.0	71.2 [51.8, 86.5]	69.3 [53.9, 86.9]	0.031	0.807
eGFR (CKD-EPI formula – categorised), *n* (%)[a]	4.5			0.604	<0.001	5.0			0.042	0.794
30–60 mL/min/1.73 m^2		2848 (46.3)	107 (30.4)				329 (31.8)	104 (30.8)		
≥60 mL/min/1.73 m^2		2530 (41.2)	237 (67.3)				686 (66.3)	226 (66.9)		
<30 mL/min/1.73 m^2		770 (12.5)	8 (2.3)				19 (1.8)	8 (2.4)		
Potassium (mEq/L), median [IQR]	5.4	4.3 [4.0, 4.6]	4.3 [4.0, 4.6]	0.021	0.898	6.0	4.3 [4.0, 4.6]	4.3 [4.0, 4.6]	0.008	0.838
Potassium (categorised), *n* (%)[a]	5.4			0.137	0.075	6.0			0.045	0.785
Normokalaemia		5481 (90.0)	327 (93.7)				948 (92.7)	314 (93.7)		
Hypokalaemia		216 (3.5)	9 (2.6)				30 (2.9)	9 (2.7)		
Hyperkalaemia		390 (6.4)	13 (3.7)				45 (4.4)	12 (3.6)		
Haemoglobin (g/dL), median [IQR]	13.9	128.0 [115.0, 140.0]	142.0 [127.5, 154.0]	0.731	<0.001	15.4	136.0 [126.0, 146.0]	142.0 [127.0, 154.0]	0.311	<0.001
NT-proBNP (pg/mL), median [IQR]	28.3	2177.5 [916.8, 4854.0]	987.0 [347.0, 2294.0]	0.428	<0.001	25.7	1254.5 [501.2, 2793.5]	987.0 [354.0, 2330.5]	0.109	0.007
NT-proBNP ≥ median by EF, *n* (%)[a]	28.3	2357 (51.4)	86 (29.8)	0.451	<0.001	25.7	265 (33.4)	86 (30.8)	0.055	0.480
Treatment, *n* (%)										
RASi/ARNI[a]	1.0	5270 (82.8)	349 (93.1)	0.319	<0.001	0.6	1001 (93.0)	334 (92.8)	0.010	0.966
MRA[a]	0.9	2713 (42.6)	205 (54.7)	0.244	<0.001	0.4	618 (57.4)	197 (54.6)	0.057	0.384

Table 1 (Continued)

Variables	Overall population					Matched population				
	Missing (%)	SGLT2i No	SGLT2i Yes	SMD	*P*-value	Missing (%)	SGLT2i No	SGLT2i Yes	SMD	*P*-value
Digoxin[a]	0.6	650 (10.2)	47 (12.5)	0.074	0.170	0.5	142 (13.2)	43 (11.9)	0.037	0.605
Diuretic[a]	0.9	5369 (84.3)	288 (76.8)	0.190	<0.001	0.6	830 (77.1)	279 (77.5)	0.009	0.945
Nitrate[a]	0.7	1025 (16.1)	43 (11.5)	0.134	0.022	0.5	115 (10.7)	42 (11.7)	0.031	0.672
Antiplatelet[a]	0.8	2346 (36.8)	161 (43.0)	0.128	0.017	0.5	456 (42.3)	157 (43.7)	0.029	0.679
Oral anticoagulant[a]	0.6	3466 (54.2)	189 (50.5)	0.074	0.182	0.4	541 (50.1)	180 (50.1)	<0.001	1.000
Statin[a]	0.5	4352 (68.1)	308 (81.9)	0.324	<0.001	0.3	863 (80.1)	293 (81.2)	0.028	0.703
Beta-blocker[a]	0.4	5772 (90.2)	356 (94.7)	0.171	0.005	0.3	1035 (95.9)	342 (94.7)	0.056	0.421
CRT/ICD[a]	2.2	732 (11.6)	77 (20.8)	0.249	<0.001	1.2	210 (19.6)	70 (19.6)	0.001	1.000
Insulin[a]	0.0	2947 (45.8)	197 (52.4)	0.131	0.015	0.0	553 (51.1)	186 (51.5)	0.009	0.927
Metformin[a]	0.0	2771 (43.1)	245 (65.2)	0.454	<0.001	0.0	723 (66.8)	233 (64.5)	0.047	0.480
Sulfonylureas[a]	0.0	531 (8.3)	41 (10.9)	0.090	0.089	0.0	124 (11.4)	39 (10.8)	0.021	0.810
Alpha-glucosidase inhibitors	0.0	11 (0.2)	4 (1.1)	0.114	0.003	0.0	1 (0.1)	3 (0.8)	0.109	0.083
Thiazolidinediones	0.0	26 (0.4)	4 (1.1)	0.077	0.140	0.0	2 (0.2)	4 (1.1)	0.115	0.059
GLP1-RA[a]	0.0	315 (4.9)	63 (16.8)	0.389	<0.001	0.0	141 (13.0)	53 (14.7)	0.048	0.476
DPP4i[a]	0.0	950 (14.8)	69 (18.4)	0.096	0.070	0.0	189 (17.5)	64 (17.7)	0.007	0.968
Dapagliflozin	0.0	0 (0.0)	63 (16.8)	0.634	<0.001	0.0	0 (0.0)	58 (16.1)	0.619	<0.001
Canagliflozin	0.0	0 (0.0)	2 (0.5)	0.103	<0.001	0.0	0 (0.0)	2 (0.6)	0.106	0.102
Empagliflozin	0.0	0 (0.0)	313 (83.2)	3.152	<0.001	0.0	0 (0.0)	301 (83.4)	3.168	<0.001
Comorbidities, *n* (%)										
Smoking[a]	34.2			0.199	0.012	33.4			0.051	0.797
Current		429 (10.1)	33 (13.9)	0.117	0.078	33.4	103 (14.1)	31 (13.6)	0.013	0.949
Former		2032 (47.9)	126 (53.2)				377 (51.4)	123 (53.9)		
Never		1778 (41.9)	78 (32.9)				253 (34.5)	74 (32.5)		
Hypertension[a]	0.0	5618 (87.4)	323 (85.9)	0.044	0.448	0.0	924 (85.3)	310 (85.9)	0.016	0.863
Ischaemic heart disease[a]	0.0	4069 (63.3)	264 (70.2)	0.147	0.008	0.0	756 (69.8)	250 (69.3)	0.012	0.895
Peripheral artery disease[a]	0.0	791 (12.3)	47 (12.5)	0.006	0.975	0.0	132 (12.2)	47 (13.0)	0.025	0.747
Stroke[a]	0.0	1158 (18.0)	62 (16.5)	0.040	0.497	0.0	181 (16.7)	57 (15.8)	0.025	0.743
Atrial fibrillation[a]	0.0	3840 (59.7)	185 (49.2)	0.213	<0.001	0.0	525 (48.5)	176 (48.8)	0.006	0.976
Anaemia[a]	13.9	2471 (44.6)	68 (21.3)	0.511	<0.001	15.4	230 (25.2)	68 (22.1)	0.071	0.324
Valvular disease[a]	0.0	1208 (18.8)	47 (12.5)	0.174	0.003	0.0	145 (13.4)	46 (12.7)	0.019	0.823
Liver disease[a]	0.0	184 (2.9)	11 (2.9)	0.004	1.000	0.0	35 (3.2)	11 (3.0)	0.011	1.000
Malignancies (within 3 years)[a]	0.0	974 (15.2)	45 (12.0)	0.093	0.108	0.0	129 (11.9)	44 (12.2)	0.009	0.963
Chronic obstructive pulmonary disease[a]	0.0	1022 (15.9)	42 (11.2)	0.139	0.017	0.0	119 (11.0)	42 (11.6)	0.020	0.809
Socioeconomic characteristics, *n* (%)										
Living alone[a]	0.2	3127 (48.7)	177 (47.2)	0.031	0.597	0.5	491 (45.6)	170 (47.2)	0.033	0.633
Children ≥1[a]	0.0	5323 (82.8)	297 (79.0)	0.097	0.068	0.0	837 (77.3)	285 (78.9)	0.040	0.559
Education level[a]	2.4			0.110	0.125	2.1			0.044	0.767
Compulsory school		2791 (44.5)	145 (39.2)				396 (37.5)	141 (39.6)		
Secondary school		2561 (40.8)	163 (44.1)				482 (45.6)	156 (43.8)		
University		919 (14.7)	62 (16.8)				179 (16.9)	59 (16.6)		
Income above median[a,b]	0.2	3180 (49.6)	218 (58.1)	0.172	0.002	0.5	623 (57.8)	209 (58.1)	0.004	0.994

ARNI, angiotensin receptor–neprilysin inhibitor; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronisation therapy; DPP4i, dipeptidyl peptidase 4 inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose co-transporter 2 inhibitor; SMD, standardized mean difference.

[a]Variables included in the multiple imputation model and logistic/Cox proportional hazard regression models.

[b]Above median within each year.

the use of SGLT2i were calculated using a logistic regression model including the variables marked with * in *Table 1*. One-to-three matching with caliper = 0.01/sd(PS) without replacement was thereafter performed on the average of the PS from the 10 imputed datasets to match SGLT2i vs. non-SGLT2i-treated patients. The ability of PS matching to balance the baseline characteristics was assessed by standardized mean differences, where a value <0.10 was considered not significant. The independent association between SGLT2i and outcomes was assessed by Kaplan–Meier curves (with log-rank test) in the PS-matched cohort. Univariable Cox proportional hazard regression models in the PS-matched population were used to calculate hazard ratios (HR) with 95% CI where the matched pairs were modelled using a frailty term. The proportional hazard assumption was investigated through the scaled Schoenfeld residuals and found to be fulfilled.

As consistency analysis, in order to take into account potential cross-over/discontinuation in treatment use that might have impacted on the results of outcome analyses, we performed additional Cox regression models in the PS-matched cohort where SGLT2i use was included as a time-dependent variable. In patients treated with SGLT2i at baseline, a patient was assumed to be on SGLT2i until the last dispensation recorded +3 months or end of follow-up minus 5 months independent of time frame between dispensations. In untreated patients, crossover was defined as a new SGLT2i dispensation in the Dispensed Drug Registry and thereafter in the same manner as for patients treated with SGLT2i at baseline. Patients treated with SGLT2i at baseline were allowed to crossover no more than once (yes-no) and patients not receiving SGLT2i at baseline were allowed to crossover no more than twice (no-yes-no). The analyses were also performed using a sub-distributional hazard models where death was treated as a competing event.

Subgroup analyses based on ejection fraction strata, background use of metformin and kidney function [estimated glomerular filtration rate (eGFR) <60 vs. ≥60 mL/min/1.73 m^2] were individually performed in the PS-matched cohort by including an interaction term between these variables and SGLT2i in the Cox regression models.

All the analyses were performed on R version 3.6.2. The R code for all data handling and statistical analyses are found at https://github.com/KIHeartFailure/sglt2. Variable definitions are available at https://kiheartfailure.github.io/shfdb3/. A *P*-value<0.05 was considered statistically significant.

Results

Between 1 January 2016 and 31 December 2018 there were 6805 patients with HF and T2DM registered in SwedeHF. Median age was 76.0 [interquartile range (IQR) 69.0–82.0] years and 32.1% were female. In this study, 27.9% had HFpEF, 24.1% HFmrEF and 48.0% HFrEF.

Time trends in sodium–glucose co-transporter 2 inhibitor use

At baseline, 376 (5.5%) patients received a SGLT2i, with 16.8% of them treated with dapagliflozin, 0.5% with canagliflozin and 83.2% with empagliflozin. As many as 210 (55.9%) were new users of SGLT2i, i.e. had no dispensation of SGLT2i 5 months prior to the index date. *Figure 1* shows the time trends in SGLT2i use over time in the study population, with a gradual increase of ~12% of patients receiving an SGLT2i in 2018, and more specifically with 0.2% on ertugliflozin, 10.2% on dapagliflozin, 0.5% on canagliflozin and 89.2% on empagliflozin.

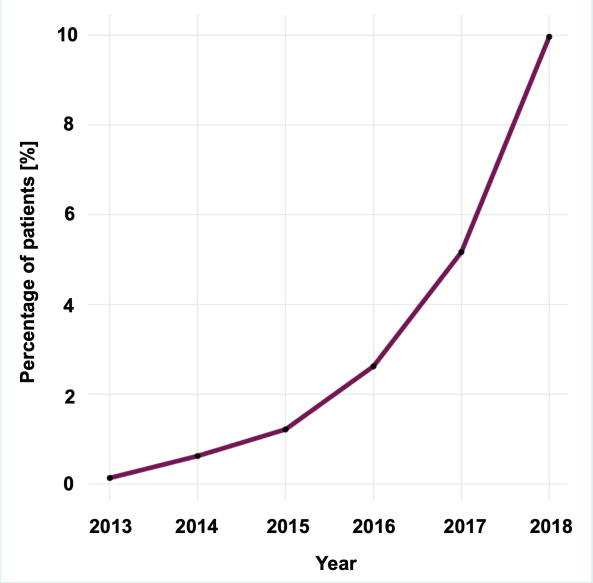

Figure 1 Use of sodium–glucose co-transporter 2 inhibitors over time in the study population.

Patient characteristics according to sodium–glucose co-transporter 2 inhibitor use

In the overall population, patients receiving vs. not receiving SGLT2i were more likely male and younger, had higher income, were more likely encountered in outpatient care and referred for follow-up to specialty care and nurse-led HF clinic. They were also more likely to have HFrEF, shorter duration of HF, lower New York Heart Association class and N-terminal pro-B-type natriuretic peptide levels. SGLT2i-treated patients were also more likely to have lower blood pressure. They were less likely to suffer from anaemia, atrial fibrillation, kidney disease, chronic obstructive pulmonary disease and valvular disease, but more likely to have ischaemic heart disease (IHD) and to be obese. There were no significant differences in use of HF and other CV treatments across the study groups (*Table 1*).

In the 1:3 PS-matched cohort of 1444 patients (25% on SGLT2i), patient characteristics were well matched. As many as 109 (10%) patients who were not receiving SGLT2i at baseline initiated treatment during follow-up, whereas 39 (11%) patients who were receiving SGLT2i at baseline discontinued treatment during follow-up (*Table 1*).

Independent predictors of sodium–glucose co-transporter 2 inhibitor use

Of all the variables tested in our multivariable model, independent predictors were younger age, outpatient setting, referral to

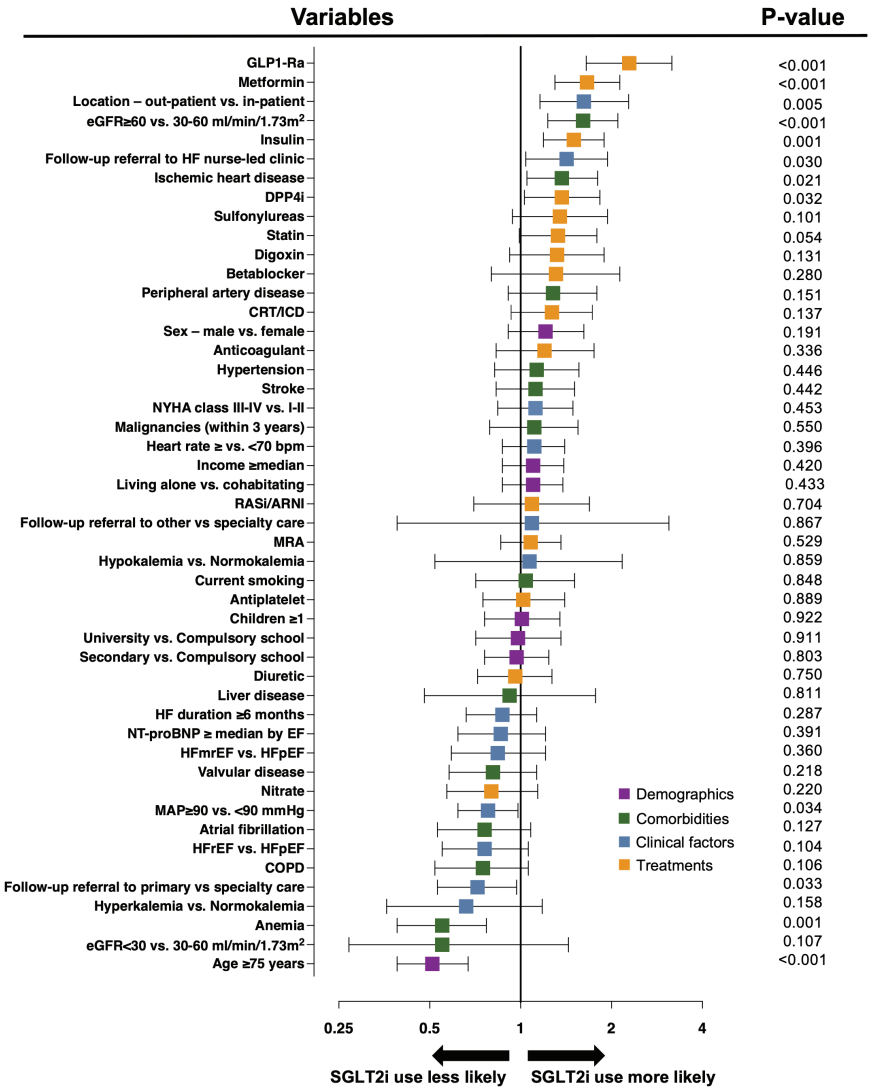

Figure 2 Independent predictors of sodium–glucose co-transporter 2 inhibitor (SGLT2i) use. ARNI, angiotensin receptor–neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; DPP4i, dipeptidyl peptidase 4 inhibitor; EF, ejection fraction; eGFR, estimated glomerular filtration rate; GLP1-Ra, glucagon-like receptor agonist; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor.

nurse-led HF clinic, referral to specialty care, lower blood pressure, use of other glucose-lowering drugs [insulin, metformin, glucagon-like peptide-1 receptor agonist (GLP1-RA), and dipeptidyl peptidase 4 inhibitor], IHD, preserved kidney function, and no history of anaemia (*Figure 2* and online supplementary *Table S1*).

Outcome analysis

Cardiovascular death or first heart failure hospitalisation

Over a median (IQR) follow-up of 256 (89–524) days, in the overall cohort event rates for CV death or first HF hospitalisation were 193 vs. 328 per 1000 patient-years in SGLT2i vs. no-SGLT2i study arm, respectively, corresponding to an unadjusted HR of 0.53 (95% CI 0.40–0.70).

In the PS-matched cohort, event rates were 195 vs. 247 per 1000 patient-years for SGLT2i vs. no-SGLT2i use. Therefore, SGLT2i was associated with a significant 30% lower risk of CV death/first HF hospitalisation (HR 0.70, 95% CI 0.52–0.95). The observed association of SGLT2i use with outcome was statistically significant at 60, 90 days and 1 year but not at 30 days. Consistency analyses with SGLT2i use as a time-dependent variable and with non-CV death as competing event confirmed the main analysis results (*Figures 3* and *4*; online supplementary *Table S2*).

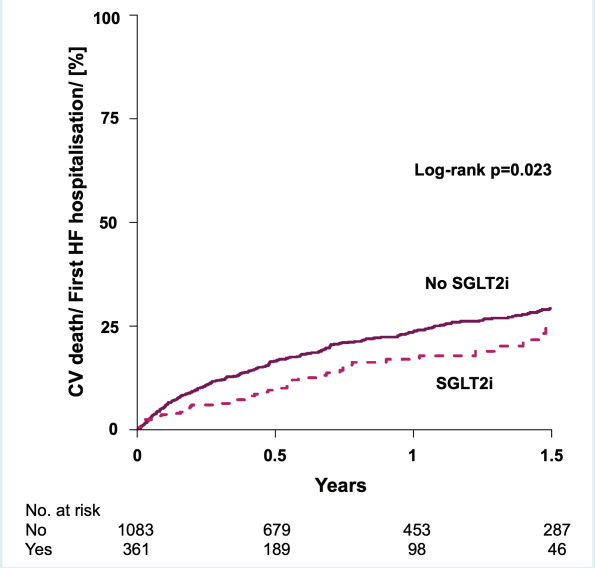

Figure 3 Kaplan–Meier curves for the risk of cardiovascular (CV) death or first heart failure (HF) hospitalisation in patients receiving vs. not receiving sodium–glucose co-transporter 2 inhibitors (SGLT2i) in the propensity score-matched population.

Other outcomes

In the overall (i.e. unadjusted analyses) and in the PS-matched (i.e. adjusted analyses) cohort, SGLT2i use was associated with a significant lower risk of all-cause death, CV death, first HF hospitalisation, first CV hospitalisation, CV death/first hospitalisation for HF/MI/stroke, which was confirmed at the consistency analyses (*Figure 4*, online supplementary *Tables S4–S7*).

Subgroup analysis

No significant interaction was observed between HF subtype (HFpEF vs. HFmrEF vs. HFrEF), concomitant treatment with metformin and eGFR <60 vs. ≥60 mL/min/1.73 m^2 and the association of SGLT2i use with risk of CV death/HF hospitalisation (*Figure 5*; online supplementary *Table S8*).

Discussion

In a nationwide, real-world cohort of patients with HF and T2DM, we found that (i) use of SGLT2i was relatively low but increased over time; (ii) key patient characteristics independently associated with SGLT2i use were younger age, HF specialty care, IHD and preserved kidney function; (iii) use of SGLT2i was associated with lower mortality (i.e. all-cause and CV death) and lower morbidity (i.e. CV and HF hospitalisations).

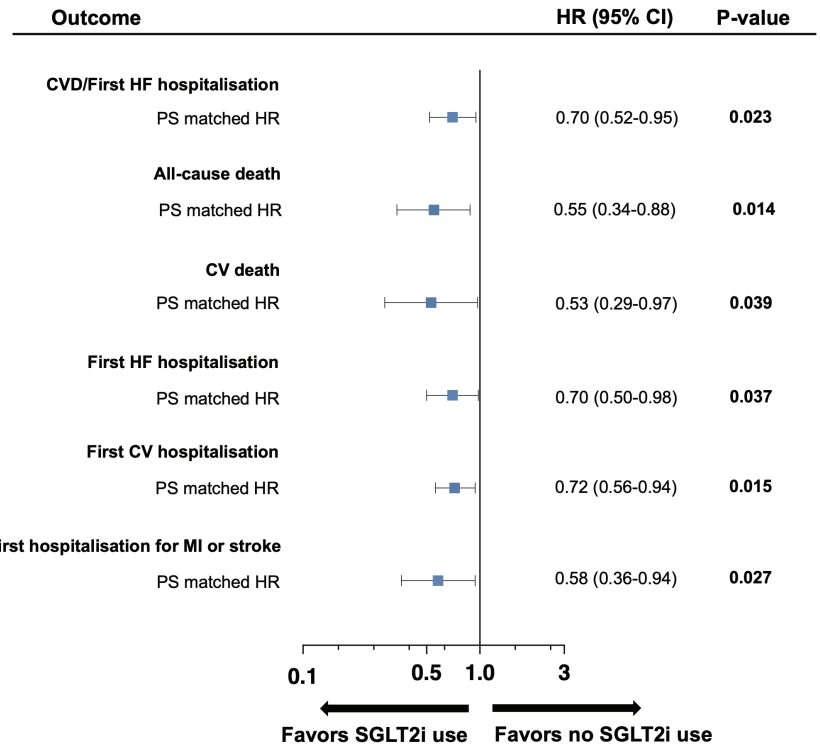

Figure 4 Outcome analysis in the propensity-matched cohort. X-axis is reported in logarithmic scale. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular death; HF, heart failure; HR, hazard ratio; PS, propensity score; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

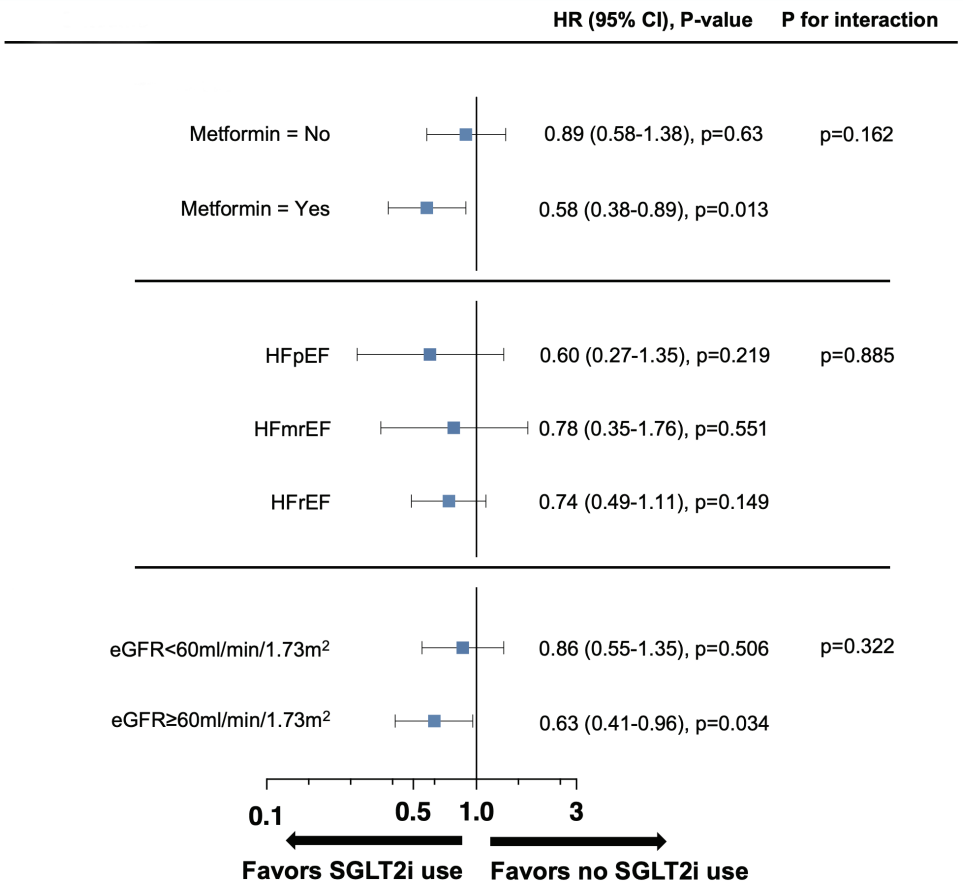

Figure 5 Subgroup analyses in the propensity-matched cohort. X-axis is reported in a logarithmic scale. CI, confidence interval; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Use of sodium–glucose co-transporter 2 inhibitor in real-world care

Sodium–glucose co-transporter 2 inhibitors are among the most recent oral anti-hyperglycaemic agents approved for the treatment of T2DM.[20] Although SGLT2i were developed for their glucose-lowering effect, large CV outcome trials showed striking, early beneficial effects in terms of mortality/HF risk reduction, which were consistent regardless of the presence and type of HF.[11–13] Based on this evidence, the European Society of Cardiology (ESC) guidelines on diabetes recommended the use of SGLT2i (and/or GLP1-RAs) as first-line therapy for T2DM in patients with established CV disease, such as those with HF (class IA).[21] Consistently, the American Diabetes Association and the European Association for the Study of Diabetes also recommended SGLT2i in patients with T2DM and HF.[22]

Although recommended by international guidelines on diabetes, SGLT2i are a relatively new treatment and the implementation of their use in clinical practice might require time. Previous data from the CHAMP-HF study in the US showed that only 2% of the HF population with T2DM enrolled in this registry received SGLT2i between December 2015 and October 2017.[17] Our analysis of this nationwide Swedish cohort, where the universal health care system might lead to a more unbiased assessment of treatment in clinical practice, showed a considerable increase of SGLT2i use in HF patients since 2016, i.e. the same year EMPA-REG OUTCOME was published. It might therefore not be surprising that in our study empagliflozin use was the highest, followed by dapagliflozin and canagliflozin. Based on these trajectories, a further increase in SGLT2i use might be expected in the near future.

In our analysis, key patient characteristics independently associated with SGLT2i use were younger age, IHD, preserved kidney function and better quality of care (i.e. referral to specialty care or to nurse-led HF clinics). Patients with IHD are considered to be at very high risk and are usually treated more intensively, which is consistent with our findings showing higher use of SGLT2i in patients with IHD. Preserved kidney function was an independent predictor of SGLT2i use, which is not surprising given that trials supporting SGLT2i use during our enrolment time excluded patients with chronic kidney disease, and consequently evidence for lower eGFR values was limited. However, the CREDENCE

and DAPA-CKD trials have recently shown efficacy/safety of canagliflozin and dapagliflozin, respectively, also in patients with chronic kidney disease.[23,24]

Increased use of SGLT2i with younger age and in absence of anaemia is consistent with the previously observed inverse relationship between risk and treatment rates, which might be explained by physicians' under appreciation of treatment benefits in older frail patients, with multi-comorbidities and therefore at higher risk of death.[5,25]

The strong and independent association between better quality of care and use of SGLT2i in our analysis is remarkable and supports the rationale and the need for (i) referring HF patients to a dedicated follow-up in specialty care or nurse-led HF clinics where specific HF patient characteristics (e.g. low blood pressure, impaired kidney function, etc.) might be less seen as an impediment to implement therapy and up-titrate dosage; (ii) educating primary care physicians to the use of these relatively new medications; (iii) bringing trial evidence from the academia and tertiary centres to less specialised care.

Association of sodium–glucose co-transporter 2 inhibitor use with outcomes in real-world heart failure patients with type 2 diabetes

DAPA-HF and EMPEROR-Reduced have recently demonstrated that dapagliflozin and empagliflozin improve major CV and renal outcomes in HFrEF regardless of the presence of T2DM.[14,15] Consequently, the US Food and Drug Administration has approved the use of the SGLT2i dapagliflozin for the treatment of HFrEF in adults with and without T2DM, and a label for empagliflozin is expected soon. Therefore, dapagliflozin and presumably empagliflozin are going to become part of the SOC for HFrEF patients, together with the triple cornerstone therapy including beta-blockers, mineralocorticoid receptor antagonists and angiotensin receptor–neprilysin inhibitors/renin–angiotensin system inhibitors.

Consistently, our analysis shows an association between SGLT2i use and mortality/morbidity in a real-world HF population where event rates are higher than in trials due to the more unselected characteristics of our study cohort. Nevertheless, the HRs for the association of SGLT2i use with CV death/HF hospitalisation in our analysis almost exactly replicates the estimates observed in DAPA-HF and EMPEROR-Reduced (HR 0.74 for HFrEF in our analysis vs. 0.75 in these trials).[14,15] Our analysis included also patients with HFpEF and HFmrEF, whereas available evidence from trials is mainly limited to HFrEF. Although the subgroup analysis had as major limitation the small sample size and number of outcome events, it is encouraging that we did not observe any interaction between ejection fraction and the association of SGLT2i with CV death/HF hospitalisation, which might mean similar association of SGLT2i use with outcome across the ejection fraction spectrum. Notably, the SOLOIST-WHF trial has recently shown sotagliflozin reducing CV death/HF hospitalisations/visits regardless of ejection fraction in T2DM patients recently hospitalised for HF.[16] The DELIVER and the EMPEROR-Preserved trials, which are currently investigating the use of dapagliflozin and empagliflozin, respectively, will provide evidence on the efficacy of SGLT2i in patients with HFmrEF and HFpEF (i.e. ejection fraction >40%).[26] The EMPERIAL-Preserved trial recently failed to show any effect of empagliflozin on the primary outcome consisting of 6-min walk test distance change to week 12.[27]

Finally, our subgroup analysis suggesting no interaction between eGFR and the association of SGLT2i with outcomes is also consistent with the findings from the EMPEROR-Reduced and DAPA-HF trials.[14,15] Our data also provide some further background for the current ESC guidelines on diabetes, recommending SGLT2i regardless of background metformin treatment in patients at high/very high CV risk (including HF).[21,28]

Limitations

Our study has several limitations that should be acknowledged. First, although SwedeHF collects many variables that allowed us to perform extensive adjustments using PS matching, we cannot rule out the presence of residual confounding or selection bias. Indeed, observational data allow to investigate the association between an exposure and outcome, but not to assess causality. The fact that HRs for mortality in our study were lower than in trials may indeed suggest that patients had unmeasured characteristics associated with lower risk. Second, the limited sample size might impact the interpretation of subgroup analyses, particularly as regards HF subtypes. Third, our analysis considered data until 2018, when evidence on SGLT2i in HF was still limited and use of SGLT2i was oriented to the risk reduction of atherosclerotic CV events in patients with T2DM. Fourth, a majority of patients received empagliflozin. However, large meta-analyses of randomized controlled trials in T2DM and HF regardless of T2DM suggest no heterogeneity for risk reduction of CV death and HF hospitalisation with SGLT2i in patients with HF.[29,30] Finally, SwedeHF coverage is around 54%, and previous studies show that patients enrolled in this registry are less sick, more likely male and younger, and better treated than the overall national HF population.[31] Therefore, generalizability of our results might be interpreted accordingly.

Conclusions

In a real-world population with HF and T2DM, use of SGLT2i is still low, though increasing over time. One of the key predictors of SGLT2i use was referral to advanced HF care. Consistently with evidence from clinical trials, SGLT2i use was associated with lower mortality and morbidity. These findings highlight the need for implementing the use of SGLT2i in T2DM patients with HF regardless of ejection fraction.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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