ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 1648–1658
doi:10.1002/ejhf.2971

RESEARCH ARTICLE

Real-world use of sodium–glucose cotransporter 2 inhibitors in patients with heart failure and reduced ejection fraction: Data from the Swedish Heart Failure Registry

Davide Stolfo[1,2], Lars H. Lund[1,3], Lina Benson[1], Felix Lindberg[1], Giulia Ferrannini[1], Ulf Dahlström[4], Gianfranco Sinagra[2], Giuseppe M.C. Rosano[5], and Gianluigi Savarese[1,3]*

[1]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [2]Cardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI) and University Hospital of Trieste, Trieste, Italy; [3]Heart and Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linkoping University, Linkoping, Sweden; and [5]Department of Medical Sciences, IRCCS San Raffaele, Rome, Italy

Received 18 April 2023; revised 28 June 2023; accepted 4 July 2023; online publish-ahead-of-print 24 July 2023

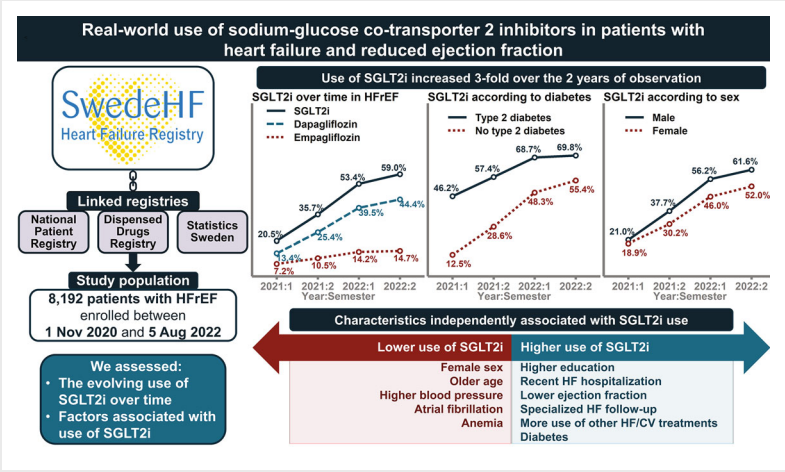
Aims Sodium–glucose cotransporter 2 inhibitors (SGLT2i) reduce mortality/morbidity in heart failure (HF). We explored the implementation of SGLT2i over time, and patient characteristics associated with their use, in a large, nationwide population with HF with reduced ejection fraction (HFrEF).

Methods and results Patients with HFrEF (ejection fraction <40%), no type 1 diabetes, estimated glomerular filtration rate (eGFR) <20 ml/min/1.73 m^2 and/or on dialysis, registered in the Swedish HF Registry between 1 November 2020 and 5 August 2022 were included. Independent predictors of use were investigated by multivariable logistic regressions. Of 8192 patients, 37% received SGLT2i. Use increased overall from 20.5% to 59.0% over time, from 46.2% and 12.5% to 69.8% and 55.4% in patients with and without type 2 diabetes, from 14.7% and 22.3% to 58.0% and 59.8% in eGFR <60 versus ≥60 ml/min/1.73 m^2, from 21.0% and 18.9% to 61.6% and 52.0% in males versus females, from 24.2% and 18.0% to 60.8% and 57.7% in patients with versus without recent HF hospitalization, from 26.1% and 19.8% to 54.7% and 59.6% in inpatients versus outpatients, and from 20.2% and 21.2% to 59.2% and 58.7% in those with HF duration <6 versus ≥6 months, respectively. Important characteristics associated with SGLT2i use were male sex, recent HF hospitalization, specialized HF follow-up, lower ejection fraction, type 2 diabetes, higher education level, use of other HF/cardiovascular interventions. Older age, higher blood pressure, atrial fibrillation and anaemia were associated with less use. Discontinuation rate at 6 and 12 months was 13.1% and 20.0%, respectively.

Conclusions Use of SGLT2i increased three-fold over 2 years. Although this indicates a more rapid translation of trial results and guidelines into clinical practice compared to previous HF drugs, further efforts are advocated to complete the implementation process while avoiding inequities across different patient subgroups and discontinuations.

*Corresponding author. Division of Cardiology, Department of Medicine, Karolinska Institutet, Norrbacka S3:00, 171 76 Stockholm, Sweden. Tel: +46 72 5968340, Email: gianluigi.savarese@ki.se

Graphical Abstract



In this real-world analysis from the SwedeHF registry including 8,192 patients with heart failure with reduced ejection fraction (HFrEF), 37% of patients were treated with SGLT2i. The use of SGLT2i increased 3-fold, from 20.5% to 59%, over the 2 years of observation (2021–2022). In patients without vs. with T2DM use was lowest at the start of the observation period but had a greater increase over time; in females vs males the increase in use was lower over time. Several characteristics were associated with higher or lower likelihood of SGLT2i use in the study population, which higlights targets for interventional strategies to promote better GDMT implementation. CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Keywords Heart failure with reduced ejection fraction • Implementation • Guideline-directed medical therapy • Sodium–glucose cotransporter 2 inhibitors

Introduction

Heart failure (HF) is a global pandemic and its prevalence is steadily increasing.[1,2] Despite the advances in pharmacological and non-pharmacological treatments, the prognosis remains poor and the rate of HF-related hospitalizations high.[3,4] The impact of HF on worldwide healthcare systems is dramatic, both in terms of human and financial resources. In Europe the estimated costs for HF amount to ~€29 billion and are predominantly driven by the frequent, prolonged and recurrent hospitalizations.[5]

Over the last few years the pharmacological treatment of HF with reduced ejection fraction (HFrEF) has benefited from the availability of novel drugs which have been shown to reduce mortality and/or morbidity, and therefore have been incorporated in the guidelines.[4,6] Among these, sodium–glucose cotransporter 2 inhibitors (SGLT2i) significantly reduced the risk of all-cause and cardiovascular death and/or of HF hospitalizations in chronic HFrEF in two landmark randomized controlled trials (RCTs), while showing also a safe profile and good tolerability leading to low discontinuation rates.[7,8]

One of the major unmet needs in HFrEF is the limited implementation of guideline-directed medical therapies (GDMT), i.e. underprescription, use of suboptimal doses, and frequent discontinuation of drugs.[9] Data on the current status of implementation of SGLT2i in HFrEF clinical practice are scarce, partly because of their recent introduction in routine care, but also due to the limited availability of updated real-world data sources where it is feasible to explore their use after the most recent HF guidelines and the eventual barriers to their implementation.[4,6]

Therefore, in the present study we sought to investigate the evolving use of SGLT2i, and to assess the patient characteristics associated with their use in a large, nationwide cohort of patients with HFrEF.

Methods

Data sources

The study population was selected from the Swedish HF Registry (SwedeHF). SwedeHF has been previously described.[10] Briefly, it is an ongoing voluntary health care quality registry founded in 2000 and implemented on a national basis in 2003. Written consent is not required, but patients are informed of registration and allowed to opt out. A majority of Swedish hospitals (69 out of 76 hospitals) and to a minor extent also primary care centres enrol patients without financial compensation, and collect approximately 80 variables, i.e. data on demographics, comorbidities, clinical parameters, biomarkers, treatments and organizational aspects, from adult inpatient wards and outpatient clinics (www.swedehf.se). The inclusion criterion was clinician-judged HF until April 2017, and after that a diagnosis of HF according to the following International Statistical Classification of

Diseases, 10th revision (ICD-10) codes: I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0 and I13.2. Coverage of SwedeHF in 2022 was 32% of the prevalent HF population in Sweden. Linkage between SwedeHF and Statistics Sweden allowed to consider socioeconomic data, whereas the National Patient Registry provided additional data on comorbidities (online supplementary *Table S1*), the Cause of Death Registry provided the date of death, and use of SGLT2i (empagliflozin and dapagliflozin – the only SGLT2i to have guideline recommendation for chronic HFrEF) was obtained through the National Prescribed Drug Registry. Linkage between these registries was allowed by the personal identification number, which all residents in Sweden have.

Index date was defined as the date of registration in SwedeHF, i.e. the date of the outpatient visit for outpatients and the date of discharge for inpatients. A patient was considered as receiving SGLT2i if a dispensation was recorded in the National Prescribed Drug Registry during the 5 months prior to or 14 days after the index date.

Establishment of the HF registry and this analysis including the linkage across several registries was approved by the Swedish Ethical Review Authority and complies with the Declaration of Helsinki.

Study population

Heart failure patients with ejection fraction <40%, without type 1 diabetes, with estimated glomerular filtration rate (eGFR) ≥20 ml/min/1.73 m^2 (as use of SGLT2i is contraindicated below 20 ml/min/1.73 m^2), not on dialysis and with follow-up ≥14 days (to avoid immortal time bias due to the 14-day post index definition used to capture SGLT2i from the National Prescribed Drug Registry) registered between 1 November 2020 and 5 August 2022, as this date coincided with the approval of SGLT2i for the treatment of HFrEF in Sweden, were considered. When a patient was registered more than once during the study period, i.e. 2020–2022, the first registration was selected. A flow chart summarizing the cohort selection process is reported in online supplementary *Figure S1*.

Statistical analysis

Temporal trends in use of SGLT2i were calculated by considering at each half calendar year the ratio between the number of patients with at least one SGLT2i dispensation (numerator) and the total population fulfilling the study inclusion/exclusion criteria (denominator). Patient characteristics were reported as median (interquartile range [IQR]) and compared by Mann–Whitney test according to SGLT2i use if continuous, and as counts (percentages) and compared by chi-square test if categorical. In order to evaluate the difference in likelihood of being prescribed SGLT2i at two randomly selected centres, the median odds ratio was calculated for a model including the intercept and centre as a random variable.

Multivariable logistic regression models were fitted to investigate patient characteristics independently associated with use/non-use of treatments (variables included in the logistic regression models are marked with [a] in *Table 1*). Subgroup analyses according to renal function (i.e. eGFR ≥60 vs. <60 ml/min/1.73 m^2), type 2 diabetes mellitus (T2DM), history of a recent HF hospitalization (i.e. <12 months), sex, inpatient versus outpatient setting and HF duration <6 versus ≥6 months were performed by including an interaction term between these variables and SGLT2i use in the logistic regression models. Results were reported as odds ratio with 95% confidence intervals. Discontinuation was considered to occur if there was >5 months gap between pill dispensations and set at 3 months after last dispensation. Rate of discontinuation was calculated at 6 and 12 months with the Kaplan–Meier method. Outliers were investigated by assessing Cook's distance and multicollinearity by analysing the variance inflation factor; no action was deemed necessary. No adjustment for multiple comparisons was performed. Multiple imputation models (10 imputed datasets generated) were used to handle missing values for the variables included in the multivariable models (marked by [a] in *Table 1*, missing rates are reported in online supplementary *Table S2*); SGLT2i use was not included in these models.

All the statistical analyses were performed using R version 4.2.1 (R Core Team 2019). The code for the data management and statistical analyses performed is found at https://github.com/KIHeartFailure/sglt2ihf. The level of significance was set to 5%, two-sided.

Results

A cohort of 8192 patients with HFrEF was analysed. Median age was 73 (IQR 64–79) years, 27.2% were female.

Temporal trends in use of sodium–glucose cotransporter 2 inhibitors and discontinuation

In the overall population use of SGLT2i was 37% (3012 patients), but progressively increased during the observation time period from 20.5% to 59.0% (from 13.4% to 44.4% for dapagliflozin, from 7.2% to 14.7% for empagliflozin; *Figure 1*).

Regarding trends for the pre-specified subgroups, SGLT2i increased from 46.2% and 12.5% to 69.8% and 55.4% in patients with and without T2DM, from 14.7% and 22.3% to 58.0% and 59.8% in eGFR <60 versus ≥60 ml/min/1.73 m^2, from 21.0% and 18.9% to 61.6% and 52.0% in males versus females, from 24.2% and 18.0% to 60.8% and 57.7% in patients with versus without recent HF hospitalization, from 26.1% and 19.8% to 54.7% and 59.6% in inpatients versus outpatients, and from 20.2% and 21.2% to 59.2% and 58.7% in patients with HF duration <6 versus ≥6 months, respectively. Therefore, temporal trends in SGLT2i use across these subgroups were overall similar to the overall study population, and in inpatients versus outpatients but with slightly less use at the beginning and slightly higher use at the end of the observation period in outpatients (*Figure 2*). The differences in the regional distribution of SGLT2i use across Sweden (median odds ratio 1.88) are reported online in supplementary *Table S3*. Discontinuation rate at 6 and 12 months was 13.1% and 20.0%, respectively.

Patient characteristics according to sodium–glucose cotransporter 2 inhibitor use (*Table 1*)

Compared to non-users, SGLT2i users were younger, more likely male, referred to specialty care and nurse-led HF clinics. They presented characteristics of more severe HF, as shown by their higher likelihood of reporting a hospitalization for HF within the last 12 months, more symptoms (i.e. more likely New York Heart

Table 1 Baseline characteristics of the overall study population and divided according to treatments use versus non-use

Variable	SGLT2i non-use	SGLT2i use	*p*-value
n (%)	5180 (63)	3012 (37%)	
Dapagliflozin	0	2180 (72.4)	<0.001
Empagliflozin	0	853 (28.3)	<0.001
Demographic/organizational characteristics			
Male sex[a]	3664 (70.7)	2305 (76.5)	<0.001
Age ≥75 years[a]	2467 (47.6)	1148 (38.1)	<0.001
Inpatient	691 (13.3)	372 (12.4)	0.211
Follow-up referral HF nurse clinic[a]	4627 (92.8)	2815 (96.0)	<0.001
Follow-up referral specialty care[a]	4390 (86.9)	2786 (94.0)	<0.001
Period of registration[b]			<0.001
2020 4th trimester	713 (13.8)	102 (3.4)	
2021 1st trimester	1036 (20.0)	212 (7.0)	
2021 2nd trimester	1016 (19.6)	227 (7.5)	
2021 3rd trimester	793 (15.3)	306 (10.2)	
2021 4th trimester	704 (13.6)	603 (20.0)	
2022 1st trimester	549 (10.6)	680 (22.6)	
2022 2nd trimester	322 (6.2)	719 (23.9)	
2022 3rd trimester	47 (0.9)	163 (5.4)	
HF hospitalization <12 months[a]	2081 (40.2)	1409 (46.8)	<0.001
HF duration ≥6 months[a]	2456 (48.1)	1384 (46.6)	0.210
EF <30%[a]	2041 (39.4)	1422 (47.2)	<0.001
NYHA class III–IV[a]	1629 (37.0)	1035 (39.9)	0.020
MAP >90 mmHg[a]	2381 (48.1)	1155 (40.0)	<0.001
HR >70 bpm[a]	2616 (53.3)	1458 (51.1)	0.068
Laboratory			
eGFR <60 ml/min/1.73 m^2[a]	1604 (32.1)	924 (31.4)	0.548
NT-proBNP ≥ median[a]	2255 (51.5)	1240 (46.1)	<0.001
Potassium[a]			0.881
Hyperkalaemia (>5 mEq/L)	178 (3.6)	111 (3.8)	
Normokalaemia (3.5–5.0 mEq/L)	4682 (94.1)	2749 (93.9)	
Hypokalaemia (<3.5 mEq/L)	115 (2.3)	69 (2.4)	
Comorbidities			
BMI ≥30 kg/m^2 [a]	1023 (24.7)	683 (28.8)	<0.001
Smoking[a]	439 (10.6)	267 (11.2)	0.502
T2DM[a]	984 (19.0)	1190 (39.5)	<0.001
AF[a]	2800 (54.1)	1507 (50.0)	<0.001
Ischaemic heart disease[a]	2434 (47.0)	1580 (52.5)	<0.001
Anaemia[a,c]	1271 (28.1)	578 (21.7)	<0.001
Hypertension[a]	3325 (64.2)	2045 (67.9)	0.001
Peripheral artery disease[a]	423 (8.2)	249 (8.3)	0.905
Stroke/TIA[a]	617 (11.9)	364 (12.1)	0.843
Valve disease[a]	952 (18.4)	492 (16.3)	0.021
Malignant cancer <3 years[a]	669 (12.9)	317 (10.5)	0.002
COPD[a]	560 (10.8)	288 (9.6)	0.080
Liver disease[a]	123 (2.4)	80 (2.7)	0.474
Dialysis	60 (1.1)	16 (0.5)	0.008
Charlson comorbidity index, median (IQR)	2.0 [1.0–4.0]	2.0 [1.0–4.0]	0.250
Charlson comorbidity index			0.710
0–1	1630 (31.5)	934 (31.0)	
2–3	1951 (37.7)	1111 (36.9)	
4–7	1275 (24.6)	769 (25.5)	
≥8	324 (6.3)	198 (6.6)	

Table 1 (Continued)

Variable	SGLT2i non-use	SGLT2i use	*p*-value
Treatments			
ACEi/ARB/ARNi[a]	4874 (94.2)	2931 (97.4)	<0.001
Beta-blockers[a]	4779 (92.3)	2877 (95.5)	<0.001
MRA[a]	2769 (53.5)	2169 (72.1)	<0.001
Diuretics[a]	3476 (67.1)	2023 (67.2)	0.954
Digoxin[a]	418 (8.1)	233 (7.7)	0.622
Antiplatelet therapy[a]	1497 (28.9)	1000 (33.2)	<0.001
Anticoagulant therapy[a]	2837 (54.8)	1614 (53.7)	0.319
Statins[a]	2644 (51.1)	1872 (62.2)	<0.001
Nitrates[a]	289 (5.6)	172 (5.7)	0.838
ICD/CRT[a]	752 (14.5)	599 (19.9)	<0.001
Family type living alone[a]	2335 (45.1)	1338 (44.5)	0.566
Children[a]	4321 (83.4)	2471 (82.0)	0.117
Education[a]			0.001
Compulsory school	1687 (32.9)	866 (29.2)	
Secondary school	2273 (44.3)	1426 (48.0)	
University	1169 (22.8)	678 (22.8)	
Income ≥ median[a]	2547 (49.2)	1577 (52.4)	0.006

Values are given as n (%), unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP; N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; TIA, transient ischaemic attack.
[a]Included in multiple imputation model and adjusted for in logistic regression models.
[b]Included in imputation and logistic regression models as a continuous single month/year variable and not as categorical variable by trimesters.
[c]Defined as haemoglobin <130 g/dl in men and 120 g/dl in women.

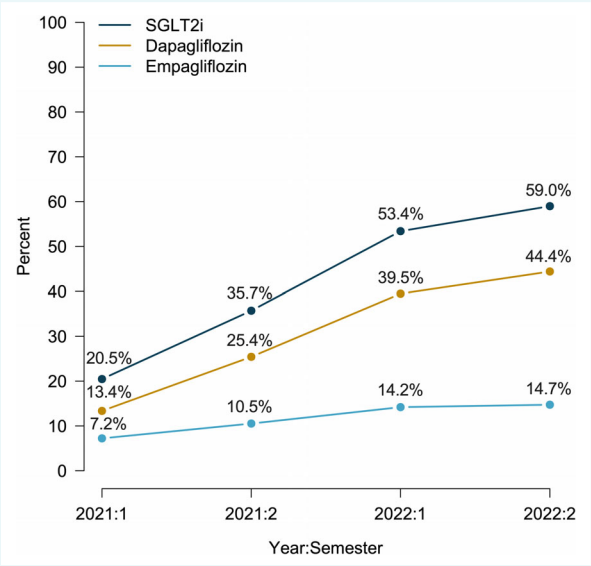


Figure 1 Temporal trends in use of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in the overall population. Note that the percentages for dapagliflozin and empagliflozin can add up to more than the total percentage for SGLT2i due to cross-over.

Association [NYHA] class III–IV), lower ejection fraction (<30% vs. 30–39%), and lower blood pressure, although they had slightly lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. eGFR and the proportion of patients with eGFR <60 ml/min/1.73 m^2 were similar across the two groups. Among comorbidities, SGLT2i users were more likely obese (i.e. body mass index >30 kg/m^2), with T2DM, ischaemic heart disease and hypertension, but were less likely having atrial fibrillation, anaemia and history of cancer within the previous 3 years. Level of education and income were higher in SGLT2i users. Patients treated with SGLT2i were more likely treated with renin–angiotensin system inhibitors/angiotensin receptor–neprilysin inhibitor (RASi/ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA), antiplatelet agents, statins and HF devices, while use of diuretics was similar to SGLT2i non-users.

Independent predictors of sodium–glucose cotransporter 2 inhibitor use

As shown in *Figure 3*, after adjustments, patient characteristics associated with higher likelihood of SGLT2i use in the overall cohort were male sex, recent HF hospitalization (i.e. <12 months), follow-up referral to specialty care and nurse-led

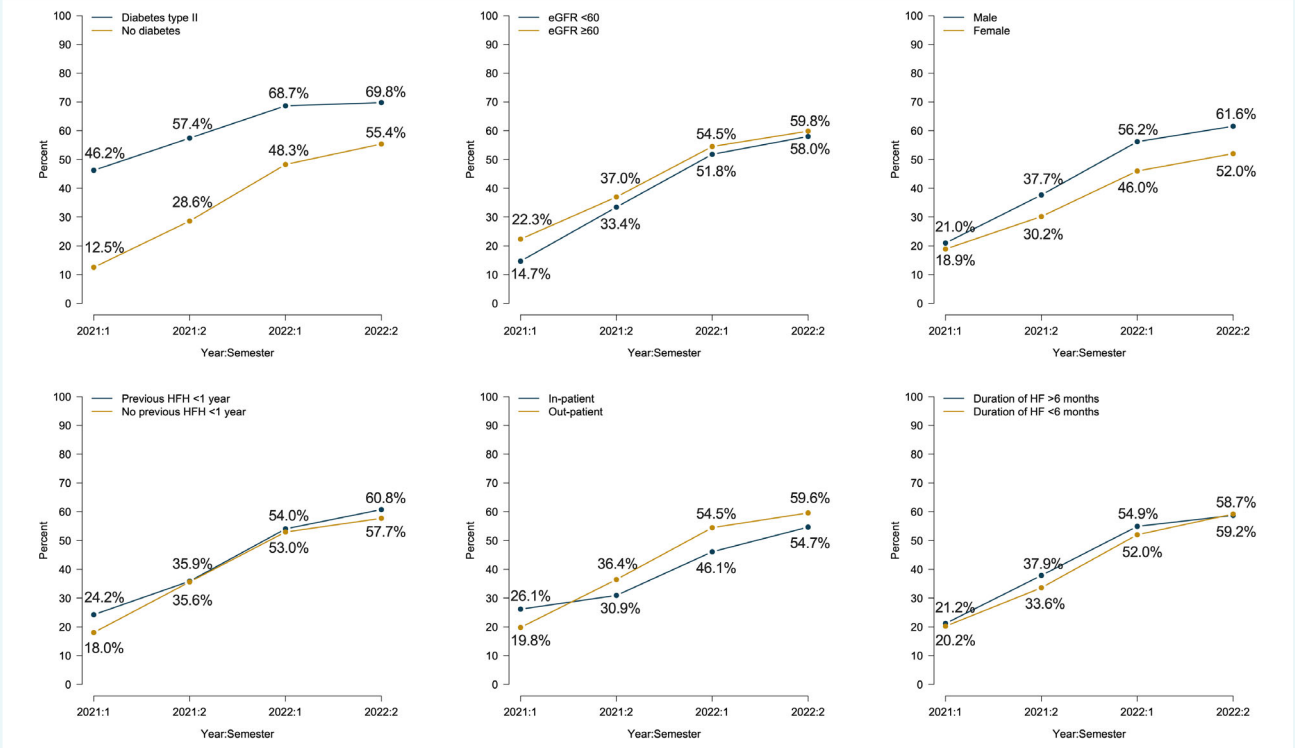


Figure 2 Temporal trends in use of sodium–glucose cotransporter 2 inhibitors across subgroups. (*A*) Renal function; (*B*): type 2 diabetes; (*C*) sex; (*D*) recent heart failure (i.e. <12 months) hospitalization (HFH); (*E*) location (i.e. inpatients vs. outpatients); (*F*) duration of heart failure (HF) (<6 vs. ≥6 months). eGFR, estimated glomerular filtration rate.

HF clinics, ejection fraction <30%, history of T2DM, higher education level, a more recent registration in SwedeHF, treatment with RASi/ARNi, beta-blockers, MRA, anticoagulants, statins and HF devices. Older age, mean arterial pressure >90 mmHg, atrial fibrillation and anaemia were instead less likely associated with use of SGLT2i, and no association was observed with renal function.

Some differences in the association between specific patient characteristics and SGLT2i use were observed across the pre-specified subgroups (online supplementary *Figures* S2–S6). Recent HF hospitalization, ejection fraction <30% and history of atrial fibrillation were associated with SGLT2i use only in patients with an eGFR ≥60 ml/min/1.73 m^2, whereas heart rate ≤70 bpm and use of diuretics with less likely SGLT2i use only in those with eGFR <60 ml/min/1.73 m^2. Liver disease and use of oral anticoagulants were associated with more likely use of SGLT2i only in patients with eGFR <60 ml/min/1.73 m^2. T2DM and use of MRA were associated with more likely SGLT2i use across the eGFR range, but more strongly in eGFR ≥60 ml/min/1.73 m^2.

Older age (≥75 years) was more strongly associated with less likely use, but use of RASi/ARNi with more likely SGLT2i use in patients with versus without T2DM, whereas specialty care follow-up and later year of registration were more strongly associated with use in those without T2DM. Ejection fraction <30% and anticoagulant use were associated with more likely use, and eGFR <60 ml/min/1.73 m^2 with less likely use in patients without but not in those with T2DM. Ischaemic heart disease, use of antiplatelet agents and statins, higher level of education were associated with more likely use of SGLT2i only in patients with T2DM. Higher NT-proBNP levels, peripheral artery disease and use of diuretics were instead associated with less likely SGLT2i use only in patients with T2DM.

NYHA class III–IV and eGFR <60 ml/min/1.73 m^2 were associated with more likely use in patients without but not in those with a recent HF hospitalization (i.e. <12 months), whereas higher NT-proBNP levels were associated with less likely use only in patients with a recent HF hospitalization. Older age (≥75 years) was more strongly associated with less likely use in those with a recent HF hospitalization.

HF devices were associated with more likely SGLT2i use in both sexes, but more strongly in females, whereas ischemic heart disease was associated with more likely use only in males.

Older age (≥75 years) was more strongly associated with less likely use of SGLT2i in inpatients versus outpatients; more recent registration was more strongly associated with less likely use in outpatients; history of atrial fibrillation was associated with less likely use, and liver disease and higher level of education with more likely use of SGLT2i in inpatients but not in outpatients.

Finally, NYHA class III–IV was associated with more likely use in patients with HF duration ≥6 months, history of atrial fibrillation and chronic obstructive pulmonary disease with less likely use in those with HF duration <6 months. Use of MRA and more recent period of registration were associated with more likely use of

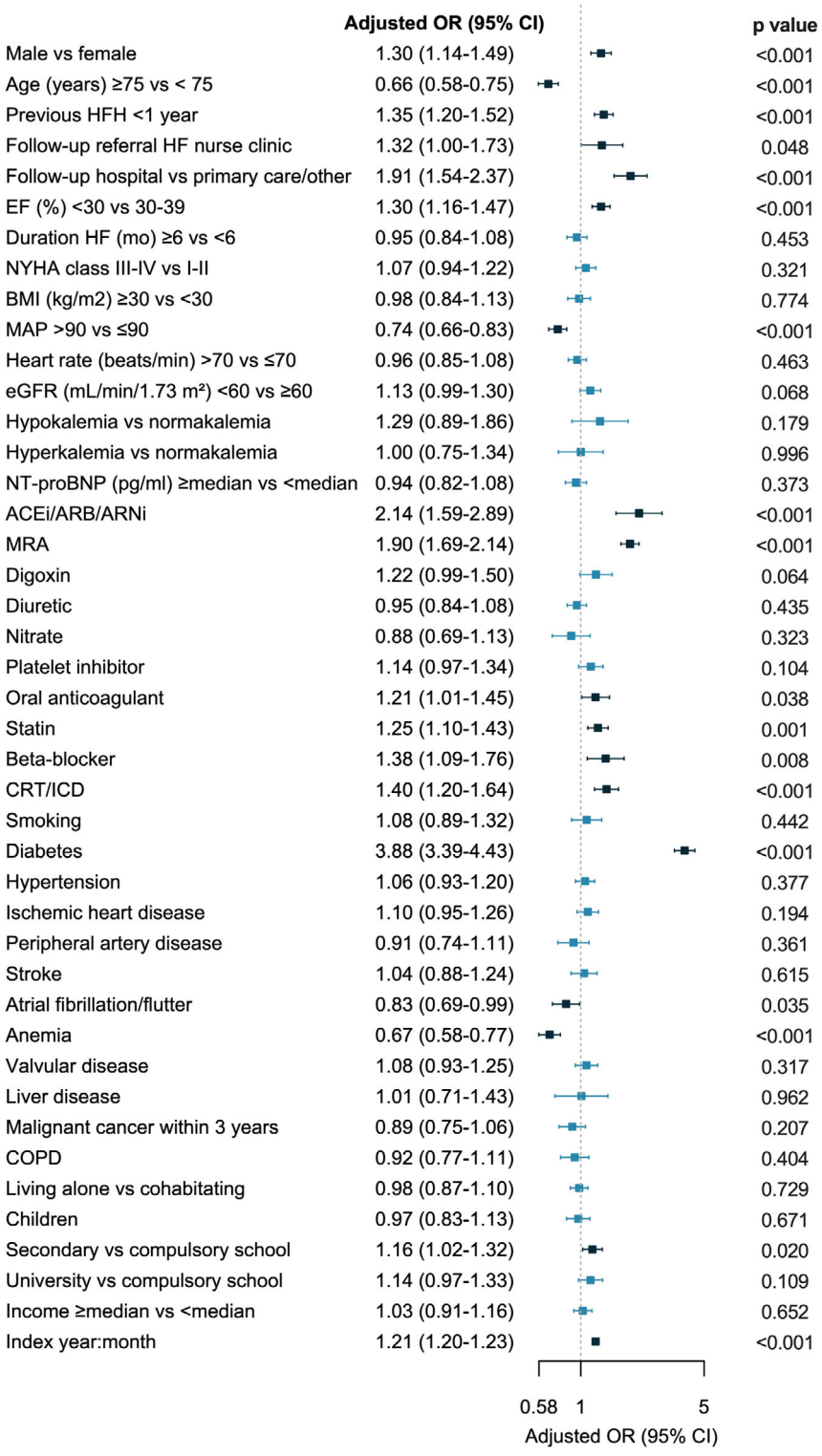


Figure 3 Predictors of treatment with sodium–glucose cotransporter 2 inhibitors in the overall cohort. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilyisin inhibitor; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; EF, ejection fraction; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.

SGLT2i across the HF duration, but more strongly in patients with HF duration <6 months.

Discussion

The efficacy of SGLT2i in terms of mortality/morbidity demonstrated on top of other evidence-based treatments in RCTs advocates their extensive implementation in patients with HFrEF, as recommended by the most recent European and American guidelines.[4,6] However, in clinical practice there are multiple barriers that have traditionally limited the use of previous GDMT, and that could similarly curb the implementation of more novel drugs. In this study we provided a comprehensive and one of the first overviews on the contemporary use of SGLT2i in a large nationwide cohort of patients with HFrEF, demonstrating a progressive increase in their use from 2020 to 2022, reaching 59% in the second semester of 2022. Moreover, we identified several patient characteristics independently associated with a less likely SGLT2i use, which might help defining strategies to counteract the underuse of recommended treatments (*Graphical Abstract*).

Temporal trends in sodium–glucose cotransporter 2 inhibitor use and discontinuation

With the publication of several RCTs showing the efficacy of novel GDMT (i.e. ARNi and SGLT2i), the paradigm of the treatment for chronic HFrEF shifted from a sequential to a default strategy of early initiation of foundational quadruple therapy,[11] followed by the up-titration to maximal tolerated doses.[12] SGLT2i are the most recent pharmacological class to demonstrate a reduction in mortality and morbidity in HFrEF, and entered the latest HF guidelines with a class I recommendation.[4,6] They were previously in use for the treatment of T2DM and their gradual implementation in patients with HF and T2DM has been reported in SwedeHF since 2013.[13] Their safety profile, the limited effect on blood pressure, their beneficial effect on renal function and on the risk of hyperkalaemia,[14] and the single dose not requiring up-titration make SGLT2i the ideal candidate for rapid implementation in daily clinical practice.[15,16] The eligibility for this treatment in daily practice according to the regulatory labels ranged between ≈50% and ≈80% across different studies,[17–19] and a low rate of discontinuation has been observed in RCTs.[20] However, in the real-world setting, as in our study, the rate of treatment discontinuation within the first 2 months was high, although less compared with other HFrEF foundational therapies.[9,21] Increasing patients' awareness of GDMT efficacy and of the outcome associated with untreated or partially treated HF, as well as increasing the self-competence of handling adverse/tolerability events are necessary steps for minimizing the discontinuation of GDMT and its negative impact on outcome.[22]

Secondary analyses of the landmark RCTs on SGLT2i in HF highlight an early effect in terms of mortality/morbidity reduction with dapagliflozin and empagliflozin, and two positive RCTs on patients with acute decompensated HF contribute to strongly support an early introduction of these drugs on top of other medications, even in the hospital setting.[23–25] However, in a large multicentre observational study, novel drugs, including SGLT2i, were initiated later after HF hospitalization compared with older GDMT in patients with HFrEF, regardless of the country of origin.[9]

In the current study we observed a progressive implementation in use of SGLT2i over time in Sweden, with the steeper increase after the release of the 2021 European guidelines on HF which introduced for the first time SGLT2i as class I recommended treatment for HFrEF.[4] In the second half of 2022, 59% of the HFrEF population enrolled in SwedeHF was on treatment with empagliflozin or dapagliflozin, resulting in an implementation process for SGLT2i much faster as compared with other GDMT, and attesting, thus, that the rapid introduction of GDMT is feasible in the real world.

Patient characteristics associated with sodium–glucose cotransporter 2 inhibitor use/non-use

Initiation of novel drugs in daily care can be hampered by several barriers.[26,27] Despite the rapid implementation, in our study >40% of patients eligible for SGLT2i were still in need of initiation.[28]

Underuse of GDMT in women with HFrEF has been formerly reported in real-world studies.[29,30] However, extensive adjustment for multiple covariates in SwedeHF, probably mitigating the effect of confounders, did not confirm any sex-related disparity in the use of conventional GDMT in Sweden,[31] that has been instead observed for SGLT2i in the present study. Post-hoc analyses of the two landmark RCTs on SGLT2i in HFrEF suggested a comparable effect across sexes, advocating dedicated strategies to promote implementation with novel treatments regardless of sex.[7,32] Our observation that the trend of SGLT2i increased more in men compared with women advocates for prompt intervention.

Follow-up in HF specialty care and better socio-economic status are known to be associated with better optimization of treatments in HFrEF even in universal healthcare systems,[33,34] and our results are consistent with previous evidence. The high proportion of patients included in SwedeHF who were managed in specialty care or with the support of nurse-led HF clinics (>90% in this study) might explain the observed high SGLT2i implementation. Consistently, in the STRONG-HF trial, a more intensive care resulted into a better implementation of HF treatments in terms of use and achievement of target doses.[12] Partially in contrast with the results of the STRONG-HF trial,[12] we observed a more intense implementation of SGLT2i over time in outpatients compared with inpatients, highlighting how in the real world the optimization of GDMT in hospital remains an unmet need.[35]

We also reported the regional differences in SGLT2i implementation across Sweden, which emphasize the importance of large-scale educational strategies in order to achieve homogeneous implementation of treatments, and to avoid low performances in less central and/or secondary centres. We cannot exclude that, in other Swedish hospitals not enrolling patients in SwedeHF, and thus where access to dedicated HF care might be more limited, SGLT2i implementation might be lower than what observed in the current analysis.

The association between SGLT2i use and being on treatment with other HF and cardiovascular medications, including HF devices, might imply that (i) patients receiving SGLT2i received overall better care, and/or that (ii) SGLT2i were initiated primarily in patients who were already on treatment with other HF medications reflecting a sequential rather than a parallel approach to HFrEF treatment, which is consistent with the evidence of later initiation of novel versus conventional GDMT,[9] and/or that (iii) patients who were still symptomatic and with very low ejection fraction despite the use of three medications were more promptly initiated with an SGLT2i, which might be consistent with the association between SGLT2i use, lower ejection fraction and lower blood pressure observed in our analysis.

The higher likelihood of treatment with a SGLT2i associated with T2DM was expected given the prior recommendation for SGLT2i in this setting, reflecting the fact that patients with HF and T2DM have a double indication for this treatment, which might have promoted a more rapid implementation.[13] However, it is worth noting that the rate of SGLT2i use in patients with and without T2DM progressively converged and became similar in the second semester of 2022, suggesting a more careful adherence to novel evidence by the managing clinicians.

Counterintuitively, use of SGLT2i was not associated with renal function, although they have been shown to improve renal and cardiovascular outcomes in patients with HF or chronic kidney disease, and the implementation of other GDMTs has been demonstrated to be more limited even with only slight reductions in renal function in daily clinical practice,[36] which candidates SGLT2i as one of the simplest treatments to be used in the setting of chronic kidney disease.[37]

Older age has been extensively reported in real-world settings as one of the more impactful variables associated with underuse and underdosing of GDMT, even though guidelines recommend HF treatments irrespective of age.[4,28,38] Atrial fibrillation and anaemia are associated with multiple comorbidities affecting patients with HF that typically reduce the adherence to evidence-based recommendations.[39] It is also likely that in patients with atrial fibrillation the priority given to the initiation of a beta-blocker and its dose titration for rate control might delay the introduction of other medications. Finally, reversal causality might alternatively explain, at least partially, the association between anaemia and lower drug use since SGLT2i have been reported to increase haemoglobin and improve iron use.[40,41]

Among subgroups identified as having a higher probability of SGLT2i underuse, diuretics were associated with less likely SGLT2i use in patients with eGFR <60 versus ≥60 ml/min/1.73 m^2, perhaps for the perceived risk of potential kidney injury due to excessive diuresis. In patients with T2DM, additional comorbidities such as ischaemic heart disease and peripheral artery disease were associated with less likely use, whereas ejection fraction <30%, which can be considered a marker of severity of HF, had no influence on drug use in contrast with patients without T2DM where it was associated with higher probability of receiving a SGLT2i. It is conceivable that the timing of SGLT2i initiation in HFrEF patients with T2DM is not influenced by HF severity as already prioritized given the diabetic status.

Limitations

Despite the extensive adjustments, the effect of residual unmeasured confounders cannot be ruled out. Use of treatments was defined at the index date and a later introduction cannot be excluded. The limited sample size due to the more limited time frame for patient inclusion could have prevented to observe statistically significant associations between specific covariates and use of SGLT2i in multivariable analyses. No data on tolerability and adverse events were available. However, discontinuation rates after treatment initiation have been reported. Finally, generalizability of our results is partially limited by the coverage, with the potential risk of overestimating the use of SGLT2i in the current analysis, since patients enrolled in SwedeHF have different characteristics and are better treated compared with the overall HF population in Sweden.[42]

Conclusions

In this nationwide cohort of patients with HFrEF, we showed that use of SGLT2i increased three-fold over 2-year time. This represents a more rapid translation of trial results, guidelines, regulatory labelling and reimbursement into the clinical setting compared to former GDMT. However, there is still room for implementation of novel HF treatments, and we highlighted some important patient characteristics strongly associated with underuse of SGLT2i. Efforts are warranted to continue the process of implementation, reduce discontinuations, and to counteract the inequities in introduction of both existing and future effective treatments.

Supplementary Information

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

Acknowledgements

We thank all staff members at care units reporting to the SwedeHF registry for their contribution.

Funding

This study received support through a grant from the Swedish Heart and Lung Foundation (project number 20220680) to Dr. Savarese. The grant source had no role in the design or analysis, nor in the interpretation of findings, manuscript preparation, or decision to submit the results.

Conflict of interest: D.S. reports personal fees from AstraZeneca, Novartis, Merck and Janssen. L.H.L. reports no conflicts related to the present work. Unrelated to the present work, L.H.L. reports grants, consulting, honoraria from Abbott, Alleviant, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Edwards, FineHeart, MedScape/WebMD, Merck/MSD, Novartis, Novo Nordisk, OrionPharma, Pharmacosmos, Radcliffe Cardiology, Roche, Sanofi, Servier, Translational Medicines Academy, Vifor; Stock ownership: AnaCardio. U.D. reports research grants from AstraZeneca, Boehringer Ingelheim, Pfizer, Vifor, Boston

Scientific, Roche Diagnostics and honoraria/consultancies from Amgen, Pfizer and AstraZeneca, all outside the present work. G.S. reports personal fees from Novartis, Impulse Dynamics and Biotronik, and speaker and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini and Akcea Therapeutics, outside the submitted work. G.S. reports grants and personal fees from Vifor, Boehringer Ingelheim, AstraZeneca, Novartis, Cytokinetics, Pharmacosmos, personal fees from Servier, Medtronic, TEVA, INTAS, Abbott; grants from Boston Scientific, Merck, Bayer, outside the submitted work. All other authors have nothing to disclose.

References

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, *et al.* Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. *Lancet*. 2018;**391**:572–580. https://doi.org/10.1016/S0140-6736(17)32520-5
2. Taylor CJ, Ordonez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, *et al.* Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: Population based cohort study. *BMJ*. 2019;**364**:l223. https://doi.org/10.1136/bmj.l223
3. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *Eur J Heart Fail*. 2016;**18**:503–511. https://doi.org/10.1002/ejhf.496
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
5. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;**171**:368–376. https://doi.org/10.1016/j.ijcard.2013.12.028
6. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
7. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.*; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
8. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.*; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;**383**:1413–1424. https://doi.org/10.1056/NEJMoa2022190
9. Savarese G, Kishi T, Vardeny O, Adamsson Eryd S, Bodegård J, Lund LH, *et al.* Heart failure drug treatment-inertia, titration, and discontinuation: A multinational observational study (EVOLUTION HF). *JACC Heart Fail*. 2023;**11**:1–14. https://doi.org/10.1016/j.jchf.2022.08.009
10. Savarese G, Vasko P, Jonsson A, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: A living, ongoing quality assurance and research in heart failure. *Ups J Med Sci*. 2019;**124**:65–69. https://doi.org/10.1080/03009734.2018.1490831
11. Bauersachs J. Heart failure drug treatment: The fantastic four. *Eur Heart J*. 2021;**42**:681–683. https://doi.org/10.1093/eurheartj/ehaa1012
12. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al.* Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised, trial. *Lancet*. 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
13. Becher PM, Schrage B, Ferrannini G, Benson L, Butler J, Carrero JJ, *et al.* 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. *Eur J Heart Fail*. 2021;**23**:1012–1022. https://doi.org/10.1002/ejhf.2131
14. Verma S, Dhingra NK, Pandey AK, Cosentino F. Emerging role for SGLT2 inhibitors in mitigating the risk of hyperkalaemia in heart failure. *Eur Heart J*. 2022;**43**:2994–2996. https://doi.org/10.1093/eurheartj/ehac304
15. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, *et al.* Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2022;**24**:431–441. https://doi.org/10.1002/ejhf.2397
16. Rao VN, Murray E, Butler J, Cooper LB, Cox ZL, Fiuzat M, *et al.* In-hospital initiation of sodium-glucose cotransporter-2 inhibitors for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2021;**78**:2004–2012. https://doi.org/10.1016/j.jacc.2021.08.064
17. Thorvaldsen T, Ferrannini G, Mellbin L, Benson L, Cosentino F, McMurray JJV, *et al.* Eligibility for dapagliflozin and empagliflozin in a real-world heart failure population. *J Card Fail*. 2022;**28**:1050–1062. https://doi.org/10.1016/j.cardfail.2022.04.011
18. Monzo L, Ferrari I, Cicogna F, Tota C, Calo L. Sodium-glucose co-transporter-2 inhibitors eligibility in patients with heart failure with reduced ejection fraction. *Int J Cardiol*. 2021;**341**:56–59. https://doi.org/10.1016/j.ijcard.2021.08.035
19. Piccinni C, Dondi L, Calabria S, Ronconi G, Pedrini A, Lapi F, *et al.* How many and who are patients with heart failure eligible to SGLT2 inhibitors? Responses from the combination of administrative healthcare and primary care databases. *Int J Cardiol*. 2023;**371**:236–243. https://doi.org/10.1016/j.ijcard.2022.09.053
20. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, *et al.* Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: Insights from DAPA-HF. *Circulation*. 2020;**141**:100–111. https://doi.org/10.1161/CIRCULATIONAHA.119.044133
21. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, *et al.* Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: A multinational observational study (US, UK and Sweden). *Eur J Heart Fail*. 2021;**23**:1499–1511. https://doi.org/10.1002/ejhf.2271
22. Tran RH, Aldemerdash A, Chang P, Sueta CA, Kaufman B, Asafu-adjei J, *et al.* Guideline-directed medical therapy and survival following hospitalization in patients with heart failure. *Pharmacotherapy*. 2018;**38**:406–416. https://doi.org/10.1002/phar.2091
23. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, *et al.* Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;**6**:499–507. https://doi.org/10.1001/jamacardio.2020.7585
24. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, *et al.* The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat Med*. 2022;**28**:568–574. https://doi.org/10.1038/s41591-021-01659-1
25. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire D, *et al.*; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;**384**:117–128. https://doi.org/10.1056/NEJMoa2030183
26. Sharma A, Verma S, Bhatt DL, Connelly KA, Swiggum E, Vaduganathan M, *et al.* Optimizing foundational therapies in patients with HFrEF: How do we translate these findings into clinical care? *JACC Basic Transl Sci*. 2022;**7**:504–517. https://doi.org/10.1016/j.jacbts.2021.10.018
27. Seferovic PM, Polovina M, Adlbrecht C, Bělohlávek J, Chioncel O, Goncalvesová E, *et al.* Navigating between Scylla and Charybdis: Challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2021;**23**:1999–2007. https://doi.org/10.1002/ejhf.2378
28. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, *et al.* Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail*. 2022;**24**:1047–1062. https://doi.org/10.1002/ejhf.2483
29. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, *et al.* Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;**73**:29–40. https://doi.org/10.1016/j.jacc.2018.09.081
30. Hsich EM. Sex differences in advanced heart failure therapies. *Circulation*. 2019;**139**:1080–1093. https://doi.org/10.1161/CIRCULATIONAHA.118.037369
31. Stolfo D, Uijl A, Vedin O, Strömberg A, Faxén UL, Rosano GMC, *et al.* Sex-based differences in heart failure across the ejection fraction spectrum: Phenotyping, and prognostic and therapeutic implications. *JACC Heart Fail*. 2019;**7**:505–515. https://doi.org/10.1016/j.jchf.2019.03.011
32. Packer M, Butler J, Zannad F, Pocock SJ, Filippatos G, Ferreira JP, *et al.*; EMPEROR Study Group. Empagliflozin and major renal outcomes in heart failure. *N Engl J Med*. 2021;**385**:1531–1533. https://doi.org/10.1056/NEJMc2112411
33. Lindberg F, Lund LH, Benson L, Schrage B, Edner M, Dahlström U, *et al.* Patient profile and outcomes associated with follow-up in specialty vs. primary care in heart failure. *ESC Heart Fail*. 2022;**9**:822–833. https://doi.org/10.1002/ehf2.13848
34. Liljeroos M, Stromberg A. Introducing nurse-led heart failure clinics in Swedish primary care settings. *Eur J Heart Fail*. 2019;**21**:103–109. https://doi.org/10.1002/ejhf.1329

35. Schrage B, Lund LH, Benson L, Braunschweig F, Ferreira JP, Dahlström U, *et al.* Association between a hospitalization for heart failure and the initiation/discontinuation of guideline-recommended treatments: An analysis from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2023;**25**:1132–1144. https://doi.org/10.1002/ejhf.2928
36. Janse RJ, Fu EL, Dahlstrom U, Benson L, Lindholm B, van Diepen M, *et al.* Use of guideline-recommended medical therapy in patients with heart failure and chronic kidney disease: From physician's prescriptions to patient's dispensations, medication adherence and persistence. *Eur J Heart Fail*. 2022;**24**:2185–2195. https://doi.org/10.1002/ejhf.2620
37. Mark PB, Sattar N. Implementation, not hesitation, for SGLT2 inhibition as foundational therapy for chronic kidney disease. *Lancet*. 2022;**400**:1745–1747. https://doi.org/10.1016/S0140-6736(22)02164-X
38. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al.* Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol*. 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
39. Savarese G, Jonsson A, Hallberg AC, Dahlström U, Edner M, Lund LH. Prevalence of, associations with, and prognostic role of anemia in heart failure across the ejection fraction spectrum. *Int J Cardiol*. 2020;**298**:59–65. https://doi.org/10.1016/j.ijcard.2019.08.049
40. Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, *et al.* Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: Findings from EMPEROR-Reduced. *Eur J Heart Fail*. 2022;**24**:708–715. https://doi.org/10.1002/ejhf.2409
41. Docherty KF, Curtain JP, Anand IS, Bengtsson O, Inzucchi SE, Køber L, *et al.*; DAPA-HF Investigators and Committees. Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail*. 2021;**23**:617–628. https://doi.org/10.1002/ejhf.2132
42. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, *et al.* Association between enrolment in a heart failure quality registry and subsequent mortality-a nationwide cohort study. *Eur J Heart Fail*. 2017;**19**:1107–1116. https://doi.org/10.1002/ejhf.762