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Sodium-Glucose Cotransporter 2 Inhibitor Use for Heart Failure in US Ambulatory Cardiovascular Care

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IMPORTANCE Sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy reduces risk of heart failure (HF) events and cardiovascular death among individuals with HF. Trends of SGLT2i use in cardiovascular ambulatory care in the US remain unknown.

OBJECTIVE To evaluate the rate of SGLT2i use among patients with HF in the cardiovascular ambulatory care setting.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study conducted from July 1, 2019, through June 30, 2023. Included for analysis were patients with HF enrolled in the National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) registry, a national ambulatory cardiovascular care quality improvement registry. Study data were analyzed from February 15, 2024, through January 15, 2025.

MAIN OUTCOMES AND MEASURES Patient-level and practice-level prescription of SGLT2i therapy.

RESULTS Of 759 915 patients (mean [SD] age, 70 [14] years; 359 270 women [47.3%]; 49 252 Black individuals [14.6%]; 278 303 White individuals [82.7%]) with HF at 191 US sites, 76 927 (10.1%) were prescribed SGLT2i. Among patients with available ejection fraction (EF) data, 20 544 (17.9%) with HF with reduced EF (HFrEF) and 36 615 (8.9%) with HF with mildly reduced EF (HFmrEF) or HF with preserved EF (HFpEF) were prescribed SGLT2i. Rates of SGLT2i use for all patients with HF increased from 4.6% in the third quarter of 2019 to 16.2% in the second quarter of 2023, from 5.1% to 28.5% for those with HFrEF, and from 4.5% to 12.8% for those with HFmrEF or HFpEF (*P* for trend <.001). SGLT2i was less commonly used for older persons (IQR age, 80 years vs 63 years; OR, 0.76; 95% CI, 0.75-0.77), female sex (OR, 0.79; 95% CI, 0.77-0.81), and higher systolic blood pressure (OR, 0.78; 95% CI, 0.77-0.79), whereas history of type 2 diabetes was associated with markedly higher use (OR, 3.21; 95% CI, 3.15-3.28). After adjustment for patient- and practice-level characteristics, significant variation in SGLT2i use across sites was present (90th vs 10th percentile risk practice, adjusted OR, 4.40; 95% CI, 3.76-5.52).

CONCLUSIONS AND RELEVANCE Although this study found that SGLT2i use had increased among ambulatory patients with HF during the study period, the majority of eligible patients did not receive this therapy. Older age, female sex, and higher blood pressures were associated with lower SGLT2i use with significant unexplained variation in use across practices. Systematic efforts to improve SGLT2i therapy use are warranted.

Supplemental content

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The DAPA-HF[1] and EMPEROR-Reduced[2] trials in 2019 and 2020, respectively, found that patients with heart failure with reduced ejection fraction (HFrEF) randomized to sodium-glucose cotransporter 2 inhibitors (SGLT2i) had lower rates of cardiovascular (CV) death and heart failure hospitalizations (HHF). In 2021 and 2022, the EMPEROR-Preserved and DELIVER trials found that patients with heart failure with preserved (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF) treated with SGLT2i had lower rates of HHF with less evident reduction in CV death rate.[3,4] The 2022 US HF clinical practice guidelines included a class of recommendation 1 for SGLT2i use in patients with HFrEF and a class of recommendation 2a in patients with HFmrEF/HFpEF.[5] In August 2023, a focused update to the European HF clinical practice guidelines issued SGLT2i a class of recommendation 1 for SGLT2i use among patients with HFmrEF/HFpEF.[6] Projected clinical benefits of SGLT2i to the US population related to the prevention of worsening HF events and HF hospitalizations if prescribed among eligible patients are anticipated to be substantial.[7]

In the context of an evolving evidence base, prior studies of real-world SGLT2i therapy use have centered on acute HF hospitalizations, demonstrating that prescription rates of SGLT2i at hospital discharge were low, particularly among older patients and women, with significant variation across hospitals.[8-10] These studies, however, merely assessed prescription rates of SGLT2i therapy, and information on patients actually receiving treatment were not assessed. Moreover, national practice patterns of SGLT2i use in the cardiovascular ambulatory care setting have not been examined, nor have prior studies accounted for differential degrees of left ventricular dysfunction. Accordingly, using the National Cardiovascular Data Registry (NCDR) Practice Innovation and Clinical Excellence (PINNACLE) Registry, we sought to characterize (1) trends in use of SGLT2i therapy by different left ventricular ejection fraction (LVEF) categories (HFrEF vs HFmrEF or HFpEF), (2) factors underlying SGLT2i therapy prescription, and (3) variation across practices among patients with HF.

Key Points

Question What is the prevalence, temporal change, and variability of sodium-glucose cotransporter 2 inhibitor (SGLT2i) use among patients with heart failure (HF) in US ambulatory cardiovascular care?

Findings In this cohort study including 759 915 patients across 191 practices, fewer than 1 of 6 patients received prescriptions for SGLT2i therapy after regulatory approval across the ejection fraction spectrum. Prescriptions significantly increased over the study period and varied widely across practices independent of patient and practice characteristics.

Meaning In this cohort study, SGLT2i use for HF in US ambulatory cardiovascular care was low, increased over time, and was highly variable across practices.

Methods

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Source

The NCDR PINNACLE Registry, which has been described previously,[11,12] served as the primary data source. Briefly, PINNACLE is a national, US-based outpatient registry, created in 2008, to enable systemic collection of clinical performance measures of cardiovascular care delivery. Participating centers routinely submit data to the NCDR, and the data are collected by modification of practice's electronic medical record data. Data quality is maintained through standardized data element definitions and periodic data quality evaluations.[11-13] The data are deidentified, and patient informed consent has been waived.

Study Population

Patients 18 years or older with clinical encounters between July 1, 2019, and June 30, 2023, with a diagnosis of HF and available SGLT2 prescribing information were included. Patients with a documented allergy or adverse drug reaction to SGLT2i therapy, a history of cardiac transplant, a current left ventricular assist device, chronic kidney disease stage V or greater, or those who received care at practices with 6 or fewer months of participation in PINNACLE were excluded (eFigure 1 in Supplement 1). Race and ethnicity were extracted from practices' electronic health records and included Black or African American, White, and other (ie, American Indian or Alaskan Native, Asian, Native Hawaiian or Pacific Islander race, and Hispanic or Latino ethnicity). Race was included due to low HF medications use in subgroups in prior analyses.[14]

Study Outcome

The outcome was the prescription of SGLT2i therapy (canagliflozin, dapagliflozin, empagliflozin). Prescription data were derived from PINNACLE encounter documentation. For patients with multiple encounters, the last encounter was used.

Statistical Analysis

In the primary analysis, patients with an HF diagnosis, irrespective of LVEF, were included. In the secondary analysis stratified by LVEF, patients whose EF data were missing (n = 233 861; 30.8%) were excluded. Patients with HF who had an EF available were categorized as having HFrEF if they had a left ventricular ejection fraction of 40% or less, or HFmrEF or HFpEF with a left ventricular ejection fraction of 41% or greater. Baseline demographics and characteristics were summarized according to study group and further stratified by SGLT2i therapy. Data were summarized as mean (SD) or median (IQR) for continuous variables and frequency (%) for categorical variables. Comparisons were performed using standardized differences, where a value of more than 0.1 is considered to be a significant difference.

We determined the proportion of patients who received SGLT2i in each quarter during the study period for the full study cohort. If patients had more than 1 clinical encounter during the quarter, the last study visit from each quarter was used for

analysis. We then used a linear trend test to assess raw trends of SLGT2i use over time.

Before statistical modeling, we imputed missing data using multiple imputations as implemented in the R package mice.[15] Race and New York Heart Association class were not imputed owing to significant missingness. Five imputed datasets were generated, incorporating random perturbations in the imputed values to reflect uncertainty due to missingness. Using the imputed datasets, we performed hierarchical logistic regression with the calendar quarter as a categorical independent variable (using the third quarter of 2019 as reference) and a random effect for site. Covariates used for adjustment included age, sex, insurance status, body mass index, systolic blood pressure, diastolic blood pressure, comorbidities (hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, prior myocardial infarction, prior coronary artery bypass graft surgery, peripheral vascular disease, prior stroke or transient ischemic attack, atrial fibrillation, an implantable cardioverter-defibrillator, cardiac resynchronization therapy, prior cardiac valve surgery, chronic kidney disease, smoking status), medical therapy (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysin inhibitor; β-blocker; potassium-sparing diuretic excluding mineralocorticoid receptor antagonists), practice geographics (geographic region inclusive of Northeast, Midwest, West, and South; percentage of patients seen at urban, suburban, and rural locations; average number of patients seen per clinician; percentage of Black patients; percentage below the poverty level, number of physicians). Restricted cubic splines were used to allow for nonlinear effects of continuous variables. Models were fit on each of the 5 imputed datasets and the results were pooled to obtain final effect estimates. Analyses were performed on the complete HF cohort and then repeated after stratification by as defined above.

Encounters between July 1, 2022, and June 30, 2023, were examined to better understand factors associated with SGLT2i use after publication of relevant clinical trials across the spectrum of EF. Associations between individual patient- and practice-related factors and the use of SGLT2i were evaluated using hierarchical logistic regression models accounting for patient demographics, clinical characteristics, and practice-related variables. Patient- and practice-level variables included in the model are described above. Analyses were repeated among patients with HFrEF and among those with HFmrEF or HFpEF. To quantify sources of variation leading to SGLT2i therapy use, we calculated reference effect measure ranges for practice- and patient-level effects.[16] To compare the relative contribution of practice and patient factors, odds ratios for a 90th percentile risk were compared to a 10th percentile risk for each set of factors. Confidence intervals for estimates were derived from hierarchical bootstrapping. Risk after accounting for both patient and practice factors was then assessed. These data are presented as forest plots. For purposes of clarity, the equivalent median odds ratio (OR) was calculated to assess practice variation not attributable to measured patient or practice characteristics. The median OR was calculated from the random effect standard deviation. Analyses were then repeated for the subgroups of patients with HFrEF and those with HFmrEF or HFpEF. All analyses were performed using SAS version9.4 (SAS Institute Inc) and R 4.3.3.

Results

There were 759 915 patients with HF eligible for SGLT2i therapy at 191 participating sites that participated (mean [SD] age, 70 [14] years; 399 785 men [52.7%]; 359 270 women [47.3%]; 49 252 Black individuals [14.6%]; 278 303 White individuals [82.7%]; 8616 other [2.6%] **Table 1**). There were 114 702 patients (15.1%) with HFrEF, 411 352 (54.1%) with HFmrEF or HFpEF, and 233 861 (30.8%) without an EF measurement. Over the entire study period, a total of 76 927 (10.1%) were prescribed SGLT2i therapy. Patients prescribed SGLT2i were significantly more likely to be younger (mean [SD] age, 68 [12] years vs 70 [14] years, standardized difference, 0.104), men (61.5% vs 51.7%, standardized difference 0.198), and had higher rates of hypertension (87.7% vs 80.0%, standardized difference 0.210). Furthermore, type 2 diabetes was significantly more common among patients who received SGLT2i therapy than among those who did not (61.3% vs 28.5%, standardized difference 0.699). Among patients with HF and type 2 diabetes, 19.5% (47 151 of 241 716) were prescribed SGLT2i therapy compared with 5.7% (29 776 of 518 199) for patients without type 2 diabetes. For the analysis stratified by LVEF, patients with missing EF data were excluded. Findings among patients with HFrEF were similar to those with HFmrEF or HFpEF (Table 1 and **Table 2**).

Temporal Trends in SGLT2i Prescription

Rates of SGLT2i use among patients with HF significantly increased from 4.6% (8315 of 180 732) during the third quarter of 2019 to 16.2% (26 654 of 164 692) during the second quarter of 2023 (*P* for trend <.01; **Figure 1**). Using the same time points, rates significantly increased from 5.1% (1657 of 32 833) to 28.5% (7602 of 26 636) among patients with HFrEF and from 4.5% (4338 of 96 054) to 12.8% (12 567 of 98 306) among patients with HFmrEF or HFpEF (*P* for trend both <.01). These trends persisted after adjustment for patient and site characteristics (eFigures 2-4 in Supplement 1).

Factors Associated With SGLT2i Prescription

Patient and practice characteristics associated with SGLT2i therapy use among patients with HF are shown in **Figure 2**. In multivariable models, factors associated with significantly lower rates of SGLT2i use included older age (IQR, 80 vs 63; adjusted OR, 0.76; 95% CI, 0.75-0.77), female sex (adjusted OR, 0.79, 95% CI, 0.77, 0.81), and higher systolic blood pressure (adjusted OR, 0.78; 95% CI, 0.77-0.79). A history of type 2 diabetes was the predominant patient-level factor significantly associated with higher rates of SGLT2i use (adjusted OR, 3.21; 95% CI, 3.15-3.28). Individual practice characteristics were not associated with SGLT2i use (Figure 2). A composite variable of practice-level characteristics was created and was not significantly associated with SGLT2i therapy use (adjusted OR, 1.34; 95% CI, 1.00-1.44) for the 90th percentile compared with the 10th percentile. Comparable findings were observed among

Table 1. Baseline Patient Characteristics Stratified by Sodium-Glucose Cotransporter 2 Inhibitor Use

Variable	Total cohort				Heart failure with reduced ejection fraction				Heart failure with mildly reduced or with preserved ejection fraction			
	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference
		Yes	No			Yes	No			Yes	No	
No. (%) of patients	759 915	76 927 (10)	682 988 (90)		114 702	20 544 (18)	94 158 (82)		411 352	36 615 (9)	374 737 (91)	
Age, mean (SD), y	70 (14)	68 (12)	70 (15)	0.104	71 (13)	67 (13)	71 (13)	0.327	72 (14)	70 (11)	72 (14)	0.106
Sex, No. (%)												
Female	359 270 (47.3)	29 588 (38.5)	329 682 (48.3)	0.198	36 877 (32.2)	5895 (28.7)	30 982 (32.9)	0.091	204 509 (49.7)	15 590 (42.6)	188 919 (50.4)	0.158
Male	399 785 (52.7)	47 178 (61.5)	352 607 (51.7)		77 811 (67.8)	14 649 (71.3)	63 162 (67.1)		206 695 (50.3)	21 023 (57.4)	185 672 (49.6)	
BMI, mean (SD)	31 (8)	32 (8)	30 (8)	0.228	30 (7)	31 (8)	29 (7)	0.221	31 (8)	32 (8)	30 (8)	0.277
Race, No. (%)												
Black or African American	49 252 (14.6)	5460 (16.9)	43 792 (14.4)	0.080	9181 (16.6)	1810 (20.8)	7371 (15.8)	0.135	26 364 (12.5)	2539 (14.2)	23 825 (12.3)	0.071
White	278 303 (82.7)	25 767 (79.9)	252 536 (83.0)		44 556 (80.7)	6630 (76.0)	37 926 (81.5)		179 978 (85.2)	14 870 (82.9)	165 108 (85.4)	
Other[a]	8616 (2.6)	987 (3.1)	7629 (2.5)		1431 (2.6)	267 (3.1)	1164 (2.5)		4756 (2.3)	511 (2.8)	4245 (2.2)	
Insurance status, No. (%)												
Medicare or Medicaid	97 307 (16.2)	9403 (13.9)	87 904 (16.5)	0.108	17 778 (17.8)	2625 (14.0)	15 153 (18.6)	0.156	46 144 (14.4)	4144 (12.6)	45 592 (14.6)	0.077
Private	495 880 (82.8)	57 405 (85.1)	438 475 (82.5)		81 090 (81.0)	15 794 (84.6)	65 296 (80.2)		291 888 (84.9)	28 474 (86.7)	263 414 (84.7)	
Uninsured	2776 (<1)	282 (<1)	2494 (<1)		744 (<1)	120 (<1)	624 (<1)		851 (<1)	62 (<1)	789 (<1)	
Comorbidities, No. (%)												
Diabetes	241 716 (31.8)	47 151 (61.3)	194 565 (28.5)	0.699	42 946 (37.4)	11 257 (54.8)	31 689 (33.7)	0.436	133 969 (32.6)	24 227 (66.2)	109 742 (29.3)	0.795
Atrial fibrillation or flutter	194 565 (37.3)	30 972 (40.3)	252 420 (37)	0.068	54 844 (47.8)	9299 (45.3)	45 545 (48.4)	0.062	162 120 (39.4)	15 273 (41.7)	146 847 (39.2)	0.051
Chronic kidney disease	100 572 (13.2)	12 891 (16.8)	87 691 (12.8)	0.111	21 576 (18.8)	3784 (18.4)	17 792 (18.9)	0.012	53 239 (12.9)	6258 (17.1)	46 981 (12.5)	0.128
Hypertension	613 870 (80.8)	67 458 (87.7)	546 412 (80.0)	0.210	95 860 (83.6)	17 508 (85.2)	78 352 (83.2)	0.055	348 457 (84.7)	33 568 (91.7)	314 889 (84.0)	0.236
Prior CAD	447 672 (58.9)	54 336 (70.6)	393 336 (57.6)	0.274	85 587 (74.6)	15 723 (76.5)	69 864 (74.2)	0.054	261 775 (63.6)	27 403 (74.8)	234 372 (62.5)	0.268
Prior stroke or TIA	106 719 (14.0)	13 137 (17.1)	93 582 (13.7)	0.094	20 428 (17.8)	3890 (18.9)	16 538 (17.6)	0.035	64 306 (15.6)	6951 (19.0)	57 355 (15.3)	0.098
Prior MI	115 876 (15.2)	16 041 (20.9)	99 835 (14.6)	0.164	30 997 (27.0)	5974 (29.1)	25 023 (26.6)	0.056	63 137 (15.4)	7429 (20.3)	55 744 (14.9)	0.143
Prior CABG	106 610 (14.2)	14 972 (19.5)	92 638 (13.6)	0.159	25 487 (22.2)	5036 (24.5)	20 451 (21.7)	0.066	65 017 (15.8)	7737 (21.1)	57 280 (15.3)	0.152
ICD	56 766 (7.5)	10 821 (14.1)	45 945 (6.7)	0.242	31 322 (27.3)	6932 (33.7)	24 390 (25.9)	0.172	15 706 (3.8)	2207 (6.0)	13 499 (3.6)	0.113
CRT	91 735 (12.1)	14 365 (18.7)	77 370 (11.3)	0.207	38 005 (33.1)	7875 (38.3)	30 130 (32.0)	0.133	39 943 (9.7)	4606 (12.6)	35 337 (9.4)	0.101
PVD	156 421 (20.6)	20 899 (27.2)	135 522 (19.8)	0.173	29 130 (25.4)	5581 (27.2)	23 549 (25.0)	0.049	90 846 (22.1)	10 877 (29.7)	79 969 (21.3)	0.193
Laboratory values, mean (SD)												
HR/min	74 (13)	76 (13)	74 (13)	0.105	75 (13)	76 (13)	75 (14)	0.054	73 (13)	75 (13)	73 (13)	0.123
SBP, mm Hg	129 (18)	126 (18)	129 (18)	0.171	124 (18)	122 (18)	125 (18)	0.161	129 (17)	128 (17)	130 (17)	0.116
DBP, mm Hg	75 (11)	73 (11)	75 (11)	0.145	73 (12)	72 (11)	73 (12)	0.043	74 (11)	73 (11)	75 (11)	0.135
GFR, mL/min	61 (23)	62 (24)	61 (23)	0.063	60 (23)	62 (24)	59 (23)	0.106	62 (23)	63 (24)	61 (22)	0.072
NYHA class, No. (%)[b]												
I-II	226 836 (91.5)	17 059 (89.3)	299 777 (91.7)	0.380	27 363 (87.68)	5010 (86.9)	22 353 (87.8)	0.150	126 497 (90.4)	8733 (89.4)	117 764 (90.4)	0.335
III	8395 (3.4)	1319 (6.9)	7076 (3.1)		2678 (8.6)	592 (10.3)	2086 (8.2)		4095 (2.9)	558 (5.7)	3537 (2.7)	
IV	12 620 (5.1)	723 (3.8)	11 897 (5.2)		1194 (3.8)	165 (2.9)	1029 (4.0)		9362 (6.7)	476 (4.9)	8886 (6.8)	

(continued)

Table 1. Baseline Patient Characteristics Stratified by Sodium-Glucose Cotransporter 2 Inhibitor Use (continued)

Variable	Total cohort				Heart failure with reduced ejection fraction				Heart failure with mildly reduced or with preserved ejection fraction			
	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference
		Yes	No			Yes	No			Yes	No	
Medication use, No. (%)												
β-Blocker	548 417 (72.2)	68 035 (88.4)	480 382 (70.3)	0.459	105 003 (91.5)	19 697 (95.9)	85 306 (90.6)	0.211	294 516 (71.6)	31 436 (85.9)	263 080 (70.2)	0.385
ACE, ARB, or ARN inhibitors	475 964 (62.6)	62 534 (81.3)	413 430 (60.5)	0.469	91 665 (79.9)	18 479 (89.9)	73 186 (77.7)	0.337	252 540 (61.4)	28 338 (77.4)	224 202 (59.8)	0.385

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers, ARN, angiotensin receptor-neprilysin; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HR, heart rate; ICD, implanted cardiac defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; SGLT2, sodium-glucose cotransporter 2; SBP, systolic blood pressure.

[a] Other included American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander.

[b] NYHA class I indicates no limitations on physical activity; II, slight limitations on physical activity; III, marked limitations on physical activity; IV, symptoms of heart failure at rest.

Table 2. Practice Characteristics Stratified by Sodium-Glucose Cotransporter 2 Inhibitor Use

Variable	Total cohort				Heart failure with reduced ejection fraction				Heart failure with mildly reduced or with preserved ejection fraction			
	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference	Total	SGLT2 inhibitor		Standardized difference
		Yes	No			Yes	No			Yes	No	
No. (%) of patients	759 915	76 927 (10)	682 988 (90)		114 702	20 544 (18)	94 158 (82)		411 352	36 615 (9)	374 737 (91)	
Geographic region, No. (%)												
South	384 489 (50.6)	38 086 (49.5)	346 403 (50.7)	0.140	57 740 (50.3)	10 298 (50.1)	47 442 (50.4)	0.095	200 174 (48.7)	17 556 (47.9)	182 618 (48.7)	0.138
Northeast	100 841 (13.3)	7717 (10.0)	93 124 (13.6)		10 238 (8.9)	1790 (8.7)	8448 (9.0)		67 047 (16.3)	4586 (12.5)	62 461 (16.7)	
Midwest	103 301 (13.6)	12 737 (16.6)	90 564 (13.6)		15 858 (13.8)	3357 (16.3)	12 501 (13.3)		61 158 (14.9)	6354 (17.4)	54 804 (14.6)	
West	171 284 (22.5)	18 387 (23.9)	152 897 (22.4)		30 866 (26.9)	57 740 (24.8)	25 767 (27.4)		82 973 (20.2)	8119 (22.2)	74 854 (20.0)	
No. of clinicians, mean (SD)	33 (32)	38 (34)	33 (32)	0.150	35 (34)	40 (35)	34 (33)	0.181	34 (34)	39 (36)	34 (34)	0.143
Patients seen by HCP, mean (SD), %	16 (18)	17, (19)	15 (18)	0.079	17 (18)	17 (17)	17 (19)	0.002	16 (18)	17 (18)	16 (18)	0.056
Monthly patients seen by clinician, mean (SD), No.	66 (27)	63 (24)	66 (27)	0.127	65 (26)	63 (24)	66 (27)	0.119	65 (28)	64 (25)	65 (28)	0.069
Black patients, mean (SD), %	14 (17)	14 (17)	14 (17)	0.020	13 (15)	14 (15)	12 (16)	0.097	13 (16)	13 (16)	13 (15)	0.033
Rural status, mean (SD)	30 (33)	30 (32)	29 (33)	0.036	32 (33)	33 (32)	31 (34)	0.044	30 (34)	31 (33)	30 (34)	0.031
Urban status, mean (SD)	27 (31)	24 (29)	27 (31)	0.085	26 (31)	24 (28)	27 (32)	0.090	27 (31)	24 (28)	27 (31)	0.111
Median household income, mean (SD), $	56 287 (15 068)	56 504 (15 143)	56 262 (15 060)	0.016	56 135 (15 619)	57 215 (15 208)	55 898 (15 698)	0.085	56 969 (15 323)	56 937 (15 293)	56 972 (15 326)	0.002
Poverty, mean (SD), %	15 (5)	15 (6)	15 (5)	0.037	15 (6)	15 (6)	15 (6)	0.003	15 (5)	15 (6)	15 (5)	0.061

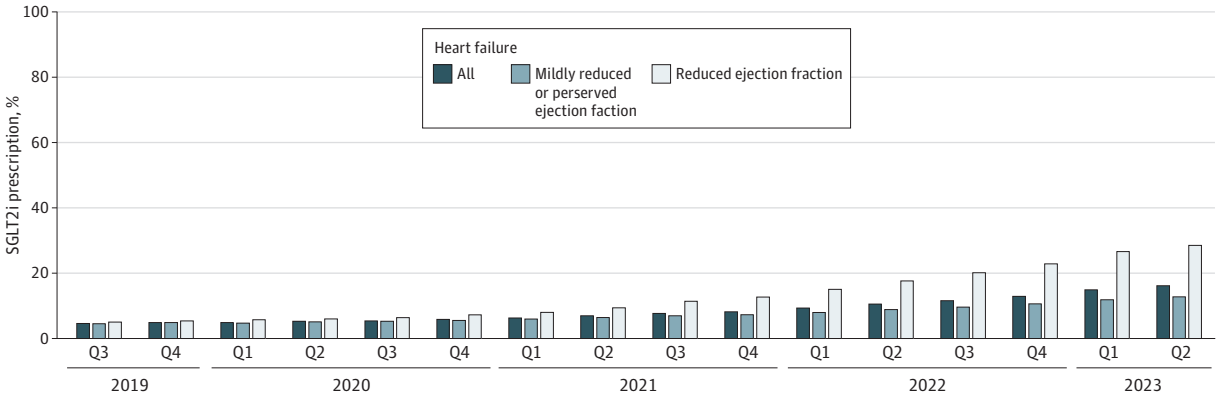
Abbreviation: HCP, health care professional; SGLT2, sodium-glucose cotransporter 2.

patients with HFrEF and HFmrEF or HFpEF (eFigures 4-5 in Supplement 1).

Practice-Level Variation in SGLT2i Prescription

There was significant practice-level variation in the use of SGLT2i therapy, ranging from 2% to 60% with a median of 15% (IQR, 10%-19%; **Figure 3**), from 4% to 60% with a median of 22% (IQR, 17%-29%) among patients with HFrEF (eFigure 6 in Supplement 1), and from 3% to 42% with a median of 12% (IQR, 9%-16%) among patients with HFmrEF or HFpEF (eFigure 7 in Supplement 1). The variation remained after adjustment for patient- and practice-level characteristics. Among patients with

Figure 1. Sodium-glucose Cotransporter 2 Inhibitor Therapy Over Time Among Patients With Heart Failure



Sodium-glucose cotransporter 2 inhibitor (SGLT2i) prescription increased over time, more markedly among patients with heart failure with reduced ejection fraction than those with mildly reduced or preserved ejection fraction. Q indicates quarter.

HF, the adjusted OR for SGLT2i therapy use among patients with HF in a 90th percentile risk practice compared with a 10th percentile risk practice after accounting for measured and patient practice factors was 4.40 (95% CI, 3.76-5.52). This equivalently corresponds to an adjusted median OR of 1.74 (95% CI, 1.64-1.89) for practice variation not attributable to measured patient or practice characteristics. Estimates among patients with HFrEF were an adjusted OR of 5.53 (95% CI, 4.23-8.10) and median OR of 1.89 (95% CI, 1.71-2.18) among patients with HFrEF and an adjusted OR of 4.05 (95% CI, 3.30-5.60) and median OR of 1.68 (95% CI, 1.56-1.90) among patients with HFmrEF or HFpEF.

Discussion

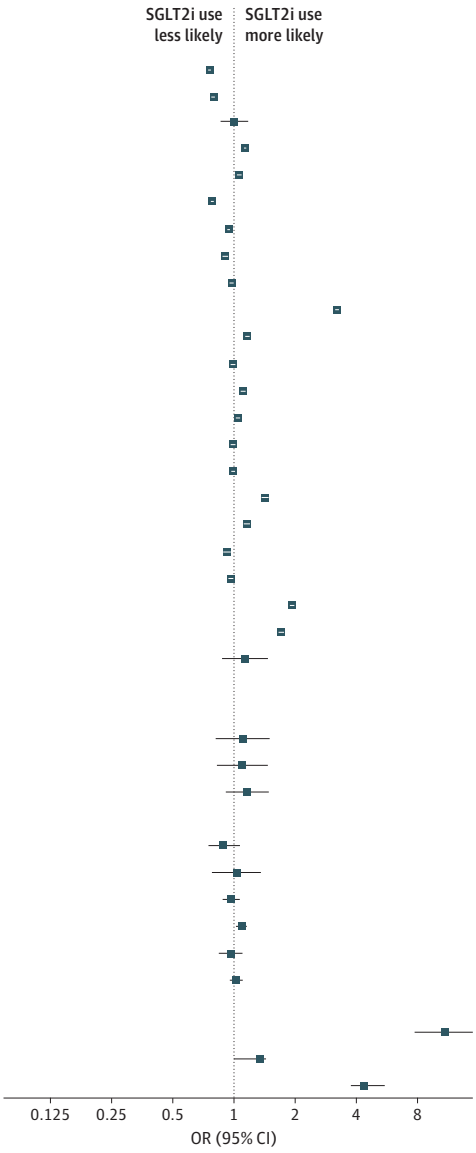
The current analysis has 3 main findings. First, in contemporary cardiovascular ambulatory care, a majority of patients with HF who were eligible for SGLT2i therapy did not receive it. In the second quarter of 2023 when SGLT2i therapy was approved for patients with HF irrespective of LVEF, less than 1 in 6 eligible HF patients were treated. SGLT2i underuse was more prominent in patients with HFmrEF or HFpEF compared with those with HFrEF. Second, during the time when SGLT2i use was approved across the spectrum of LVEF, use was significantly lower among older patients, women, and patients with comparatively high blood pressure and significantly higher among patients with type 2 diabetes. Third, rates of SGLT2i treatment significantly increased over time with substantial variation between practices. Taken together, these findings demonstrate opportunities to improve real-world use of SGLT2i therapy use and may inform the development of quality improvement initiatives.

In prior US-based studies among hospitalized patients eligible for SGLT2i therapy, 9 of 10 patients with HF, 4 of 5 patients with HFrEF, and 6 of 7 patients with HFmrEF and HFpEF were not prescribed SGLT2i therapy at hospital discharge.[8-10] The current analysis extends this finding to US cardiovascular ambulatory care and demonstrates a similarly low treatment rate in the outpatient population. It also demonstrates that SLGT2i use was lower in patients with HFmrEF or HFpEF compared with patients with HFrEF. Differential uptake in SGLT2i by LVEF could be related to the timing of evidence generation as clinical trials among patients with HFrEF preceded that in patients with HFmrEF or HFpEF, and the larger degree of clinical benefit observed with SGLT2i use in patients with lower EF with regard to cardiovascular mortality.[1-4] Nevertheless, even among patients with HFrEF, less than 1 in 3 patients were treated with SGLT2i in the second quarter of 2023. Barriers such as formulary restriction, prior authorization requirements, and high co-payment likely contribute to the overall low SGLT2i uptake.[17]

Low adoption of new elements of guideline-directed medical therapy for HF has been previously described. In the CHAMP-HF registry, 13% of patients with ambulatory HFrEF received angiotensin receptor-neprilysin inhibitor 3 years after US Food and Drug Administration (FDA) approval.[18] Although the overall use of SGLT2i was low, the absolute increase in the rate of SGLT2i treatment seen in the current analysis was relatively large, increasing from 4.6% in 2019 to 16.2% in 2023, a trend that was more pronounced among patients with HFrEF (5.1% to 28.5%). This trend emerged within 3 years of dapagliflozin's FDA approval for HFrEF in May 2020, and within 1 year of empagliflozin's approval for patients with HFmrEF or HFpEF in February 2022.[19,20] The relatively large increase in SGLT2i use over the study period may stem partly from the low-baseline usage rate, corresponding with greater room for improvement, along with the favorable safety profile of SGLT2i and the use of fixed dosing in patients with HF.[21] Furthermore, the approval of empagliflozin for patients with HFmrEF and HFpEF, was a significant breakthrough in a condition with limited treatment options, likely contributing to the relatively quick uptake of SGLT2i.[19] This trend is reflected in recent Get With The Guidelines (GWTG) data, which show an increase in SGLT2i prescription rate at hospital discharge for patients with HFmrEF or HFpEF, rising to 23% in the third quarter of 2023 from 4% in the first quarter of 2021.[10] If current trends continue, it would take approximately 4 years

Figure 2. Factors Associated With Sodium-Glucose Cotransporter 2 Inhibitor Among Patients With Heart Failure

Characteristics	OR (95% CI)
Patient	
Age (IQR, 80 vs 63 y)	0.76 (0.75-0.77)
Female	0.79 (0.77-0.81)
No insurance	1.00 (0.86-1.17)
BMI (IQR, 34.5 vs 25.5)	1.13 (1.12-1.15)
Current smoker	1.06 (1.03-1.09)
Systolic BP (IQR, 140 vs 118 mm Hg)	0.78 (0.77-0.79)
Diastolic BP (IQR, 81 vs 68 mm Hg)	0.94 (0.93-0.96)
Hypertension	0.91 (0.88-0.94)
Dyslipidemia	0.97 (0.95-1.00)
Diabetes	3.21 (3.15-3.28)
Coronary artery disease	1.16 (1.14-1.19)
Prior myocardial infarction	0.99 (0.96-1.02)
Prior CABG surgery	1.11 (1.08-1.14)
Peripheral vascular disease	1.05 (1.02-1.07)
Prior stroke or transient iscemic attack	0.99 (0.96-1.02)
Atrial fibrillation	0.99 (0.97-1.01)
Implantable (cardioverter-defibrillator)	1.42 (1.37-1.48)
Cardiac resynchronization therapy	1.16 (1.12-1.20)
Prior cardiac valve surgery	0.92 (0.88-0.96)
Chronic kidney disease	0.96 (0.94-0.99)
ACEI/ARB/ARNI	1.93 (1.88-1.98)
β-Blocker	1.71 (1.66-1.76)
Diuretic (potassium−sparing)	1.13 (0.87-1.47)
Practice	
Geographic region	
Northeast vs South	1.10 (0.81-1.50)
Midwest vs South	1.10 (0.82-1.47)
West vs South	1.16 (0.91-1.48)
Patients seen, %	
Urban location (IQR, 55% vs 0%)	0.89 (0.75-1.07)
Suburban location (IQR, 100% vs 0%)	1.03 (0.78-1.36)
Average monthly patients per practitioner (IQR, 70 vs 40)	0.97 (0.88-1.07)
Black patients (IQR, 13.9% vs 1.5%)	1.09 (1.02-1.16)
Average below poverty level across locations (IQR, 19.6% vs 9.4%)	0.96 (0.84-1.10)
No. of physicians (IQR, 15 vs 2)	1.03 (0.95-1.10)
Reference effect measures (90th vs 10th percentile)	
Patient characteristics	10.90 (7.74-14.97)
Practice characteristics	1.34 (1.00-1.44)
Unmeasured practice variation	4.40 (3.76-5.52)

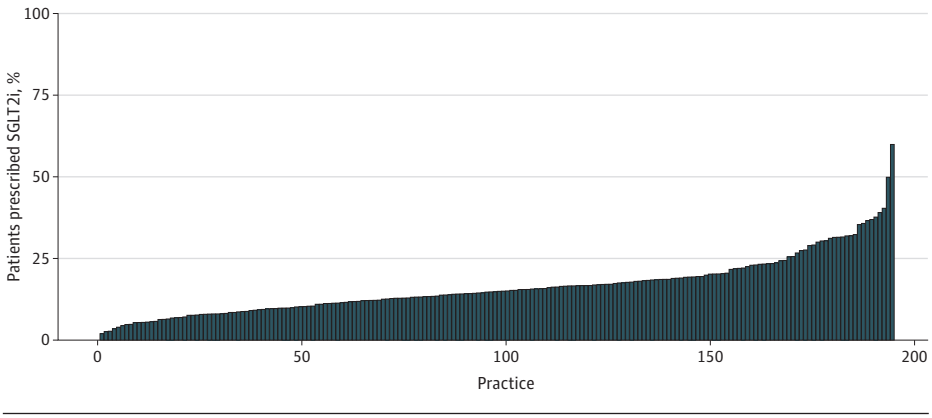


ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BP, blood pressure; CABG, coronary artery bypass graft; MI, myocardial infarction; OR, odds ratio.

for at least 90% of eligible patients with HFrEF and approximately 7 years for 90% of eligible patients regardless of ejection fraction to be treated with SGLT2i.

In the current analysis, older age, female sex, and high blood pressure were significantly associated with lower rates of SGLT2i prescription, whereas a history of type 2 diabetes was strongly associated with higher SGLT2i use. Secondary analyses of the seminal trials demonstrated SGLT2i efficacy with adequate safety across broad spectrums of age,[22-25] irrespective of sex,[26-28] across a wide range of baseline blood pressure,[29-32] and irrespective of baseline diabetes status.[33-35] Our analysis shows that older patients and women in the real world are less likely to receive SGLT2i therapy not only among hospitalized patients but also in the cardiovascular ambulatory care setting irrespective of EF.[8,9] Importantly, women with HF tend to experience a higher symptom burden and may potentially derive greater benefit from SGLT2i therapy.[36,37] Blood pressure was not examined in the prior hospital-based analyses of SGLT2i,[8,9] and it does not significantly influence prescription among other elements of guideline-directed medical therapy for HFrEF.[38] The fact that comparatively high systolic blood pressure is associated with an approximately 20% reduction in the likelihood of SGLT2i treatment in ambulatory cardiovascular care is notable, particularly that SLGT2i use is associated with improved blood pressure control.[39] Whether residual confounding due to pill burden underlies this

Figure 3. Practice-Level Variation in Percentage of Patients Prescribed Sodium-Glucose Cotransporter 2 Inhibitor



Sodium-glucose contransporter 2 inhibitor (SGLT2i) prescription varied widely across practices.

finding requires further study. The markedly higher prescription rate of SGLT2i among patients with type 2 diabetes likely reflects their initial recognition as antihyperglycemic drugs.[40] SGLT2i is now a pillar of HF therapy as the benefit of SGLT2i in HF extends beyond CV mortality and HF hospitalization to improving quality of life measures regardless of diabetes status.[41]

Variability in performance across practices indicates opportunities for improvement at low-performing sites. High-performing sites may be using care processes that could be emulated by low-performing sites, including quality improvement efforts around key steps required for SGLT2i therapy prescription such as clinician recognition of patient candidacy, meaningful communication between patients and clinicians, and patients' interest in medication adherence. Organizations seeking to improve care quality may implement programs using strategies with demonstrated effectiveness such as educational outreach.[42] The current analysis suggests clinician education should center on patient candidacy with an emphasis on age, sex, blood pressure, and diabetes. Clinical inertia among outpatients with HF has been well documented and is often related to concerns regarding adverse effects, medication nonadherence, and clinician comanagement.[43] Adverse social determinants of health similarly impact likelihood of HF medication prescription.[44] Leveraging societal and practice resources may surmount the activation barriers to HF medication prescription. Additional elements of successful programs may include documentation of SGLT2i candidacy in the medical record,[45] engaging and activating patients via electronically delivered tools,[46] and/or multidisciplinary care.[47] Policy interventions may include incorporating SGLT2i therapy use in public reporting and/or pay-for-performance programs. In addition, given that SGLT2i therapy provides intermediate economic value,[5] sites may also consider subsidizing costs and increasing coverage to reduce out-of-pocket costs for highly effective medications.[17,48]

Limitations

This study has several limitations. First, participating practices may be more interested in quality improvement than non-participating practices, which may limit external validity. However, our analysis included 191 practices from varying geographic regions and practice sizes. Second, contraindications or intolerances may have been present but were not documented, including concerns regarding insurance status, out-of-pocket costs, polypharmacy or frailty, may partially explain the observed low rates of use, and may benefit from future research. Third, LVEF missingness was significant (30.8%) and potentially nonrandom, leading to uncertainty in the observed effect estimates of the secondary analyses stratified by LVEF. However, the main findings were largely consistent in magnitude and directionality across subgroup analyses, and SGLT2i therapy eligibility is agnostic to LVEF in the current therapeutic era. Fourth, while canagliflozin was not studied in HF outcomes trials to date, it has been associated with reduced HF hospitalization, cardiovascular death, and improved quality of life.[20,49] Fifth, kidney function was not available from a significant number of patients, and it likely influenced SGLT2i therapy use. Sixth, ertugliflozin, bexagliflozin, and sotagliflozin were approved by the FDA during the study period but not captured in the PINNACLE dataset. Seventh, although additional analyses further stratifying HFmrEF and HFpEF into HFmrEF and HFpEF may be informative, the data were not available for analysis. Eighth, mineralocorticoid use was not captured in the PINNACLE registry. Finally, given the observational study design, the possibility of residual or unmeasured confounding exists and was quantified.

Conclusions

In a nationwide study of outpatients with HF, a majority eligible for SGLT2i therapy did not receive it, particularly those who were older, female, or with higher blood pressure. There was a significant increase in SGLT2i use over the study period, less among patients with HFmrEF or HFpEF compared with those with HFrEF, with substantial variation in use across practices. Systematic efforts to improve SGLT2i therapy use are warranted.

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