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CLINICAL RESEARCH

Heart Failure Drug Treatment—Inertia, Titration, and Discontinuation

A Multinational Observational Study (EVOLUTION HF)

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ABSTRACT

BACKGROUND Guidelines recommend early initiation of multiple guideline-directed medical therapies (GDMTs) to reduce mortality/rehospitalization in patients with heart failure and reduced ejection fraction. Understanding GDMT use is critical to improving clinical practice.

OBJECTIVES This study sought to describe GDMT use in Japan, Sweden, and the United States in contemporary real-world settings.

METHODS EVOLUTION HF (Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data) is an observational cohort study using routine-care databases. Patients initiating any GDMT within 12 months of a hospitalization for heart failure (hHF) discharge were included. Dapagliflozin (the only sodium-glucose cotransporter-2 inhibitor approved at study onset), sacubitril/valsartan, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) were considered separately. Doses and discontinuation were assessed in the 12 months following initiation. Target dose was defined as ≥100% of the guideline-recommended dose.

RESULTS Overall, 266,589 patients were included. Mean times from hHF to GDMT initiation were longer for novel GDMTs (dapagliflozin or sacubitril/valsartan) than for other GDMTs: 39 and 44 vs 12 to 13 days (Japan), 44 and 33 vs 22 to 31 days (Sweden), and 33 and 19 vs 18 to 24 days (United States). Pooled across countries, proportions of patients who discontinued therapy (not including switches from ACE inhibitor or ARB to sacubitril/valsartan) within 12 months were 23.5% (dapagliflozin), 26.4% (sacubitril/valsartan), 38.4% (ACE inhibitors), 33.4% (ARBs), 25.2% (beta-blockers), and 42.2% (MRAs). Corresponding target dose achievements were 75.7%, 28.2%, 20.1%, 6.7%, 7.2%, and 5.1%, respectively.

CONCLUSIONS Initiation of novel GDMTs is delayed compared with other GDMTs. Few patients received target doses of GDMTs requiring uptitration. Persistence was higher for dapagliflozin than other GDMTs.
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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

AKI = acute kidney injury

ARB = angiotensin receptor blocker

CKD = chronic kidney disease

GDMT = guideline-directed medical therapy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

hHF = hospitalization for heart failure

MRA = mineralocorticoid receptor antagonist

SGLT2 = sodium-glucose cotransporter-2

Heart failure (HF) is a global public health issue, representing a substantial economic burden.[1] The period during and immediately after hospitalization for heart failure (hHF) represents a vulnerable phase characterized by a high risk of death and rehospitalization.[2,3]

Early treatment optimization with guideline-directed medical therapies (GDMTs) in patients with HF is critical to reducing mortality, preventing rehospitalization, and improving quality of life.[4-14] Several paradigm-shifting clinical trials in patients with heart failure with reduced ejection fraction (HFrEF) have demonstrated strong beneficial effects of novel GDMTs (the angiotensin receptor-neprilysin inhibitor sacubitril/valsartan and sodium-glucose cotransporter-2 [SGLT2] inhibitors) on cardiovascular death and/or hHF.[7,9-12,15] Importantly, SGLT2 inhibitors have shown early effects on mortality/morbidity on top of standard treatment across the left ventricular ejection fraction range.[7,9-11,15]

The current European and U.S. guidelines on HF recommend early initiation of multiple GDMTs after a HFrEF diagnosis, and subsequent uptitration for some drugs.[16-18] However, guideline recommendations are often not sufficiently implemented, for example, because of real or perceived risk of side effects or insufficient reimbursement. Discontinuation, use of suboptimal doses, and lengthy sequencing strategies have also been observed as challenges to the implementation of recommendations.[2]

The understanding of contemporary GDMT implementation is critical to improve clinical practice, particularly after the inclusion of novel GDMTs in recent guidelines.[16,17] Previous studies have focused mainly on cross-sectional description of medication use,[19] and occasionally on dose;[20,21] few have investigated discontinuation and persistence[22-25] or considered contemporary real-world data across different countries. EVOLUTION HF (Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data) is a multinational, observational study that aims to provide insights into use of GDMTs after hHF.

The aim of the present analysis was to describe the initiation, uptitration, and discontinuation of GDMTs after hHF in patients in Japan, Sweden, and the United States, using the contemporary, real-world EVOLUTION HF cohort.

METHODS

STUDY DESIGN. EVOLUTION HF is a multinational, observational, longitudinal cohort study that uses secondary data extracted from well-established electronic health records or claims data sources in Japan (Medical Data Vision claims registry), Sweden (nationwide administrative registries), and the United States (Optum de-identified Market Clarity Data) (Supplemental Methods).

STUDY POPULATION. Patients ≥18 years of age were included in the analysis if they had at least 12 months of continual database presence, had a recorded hHF (incident or recurrent hospitalization, defined as a hospitalization with a registered HF diagnosis), and were new users of any medications listed as part of GDMT during the qualifying hHF or within 12 months after discharge (**Central Illustration, Figure 1A,** Supplemental Table 1). Patients were considered as new users of a specific GDMT if they had never received a drug in the same GDMT class or had not been using a drug in the same GDMT class in the 12 months before the index date (ie, restarting a GDMT after a gap of more than 12 months was considered as new use). The index date was defined as the date of any new GDMT initiation, and titration and discontinuation of that GDMT was assessed in the 12-month period following this date. For patients initiating a new GDMT during the qualifying hHF, the index date was the date of discharge. Patients were excluded if they had a type 1 diabetes diagnosis at or prior to index (**Figure 1A,** Supplemental Table 1).

GUIDELINE-DIRECTED MEDICAL THERAPIES. GDMTs were defined as the SGLT2 inhibitor dapagliflozin, the angiotensin receptor-neprilysin inhibitor sacubitril/valsartan, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). Only dapagliflozin was considered in the SGLT2 inhibitor class because other SGLT2 inhibitors

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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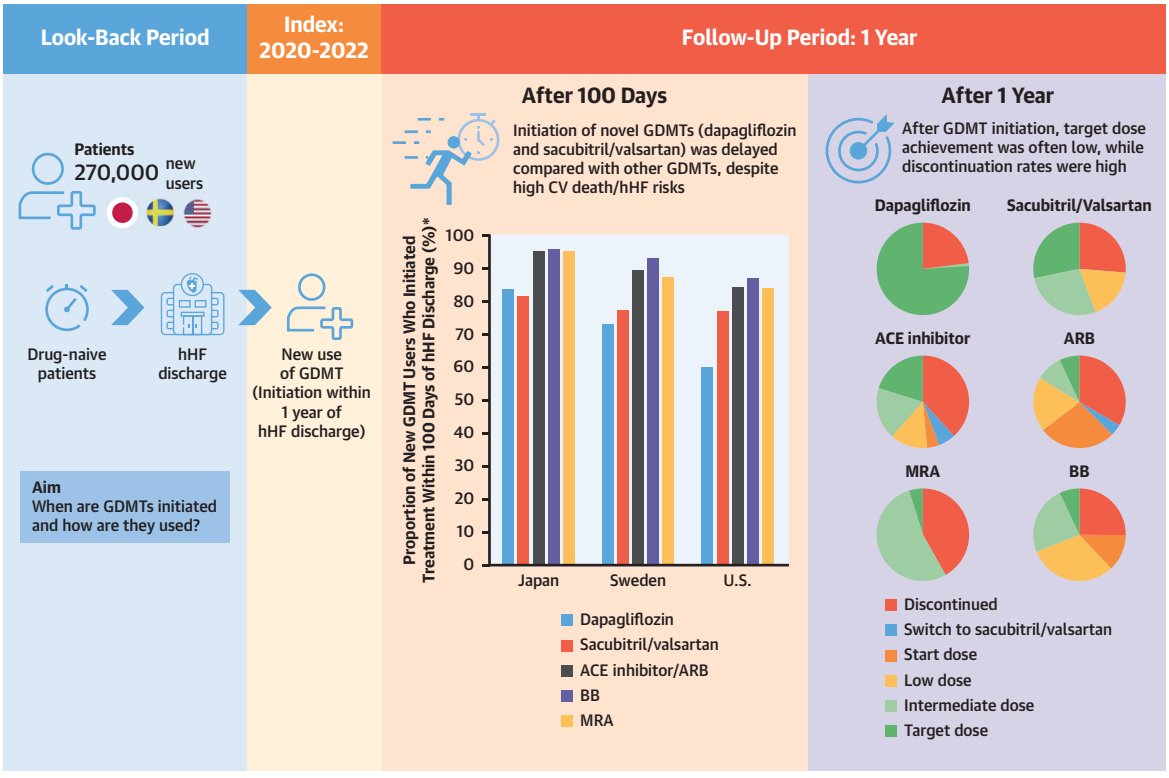
CENTRAL ILLUSTRATION **Initiation, Titration to Target Dose, and Discontinuation of GDMTs Among New Users of GDMTs After hHF, in Japan, Sweden, and the United States**



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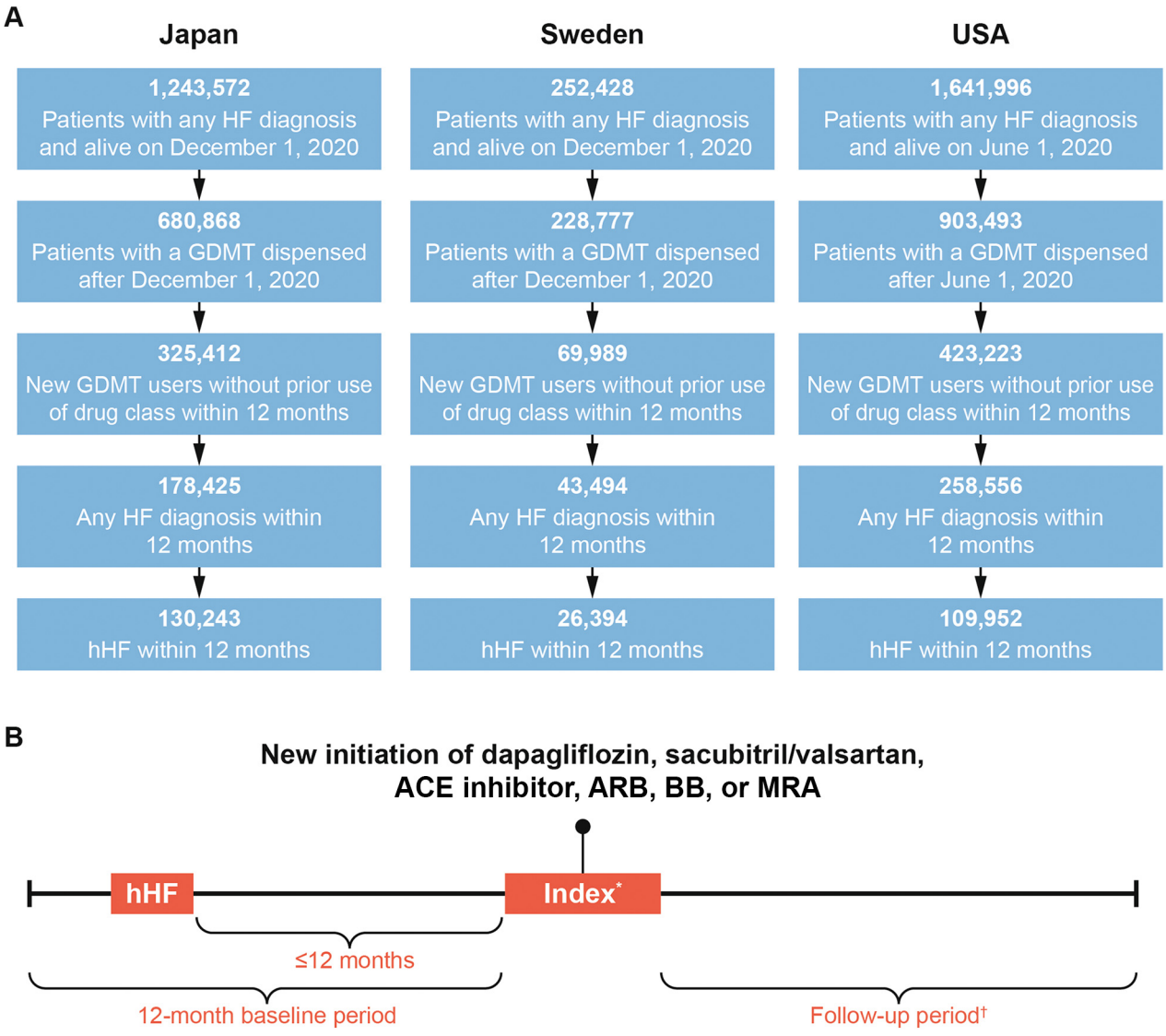
*By design, in each GDMT category, 100% of patients initiated treatment within 1 year of hHF discharge. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta-blocker; CV = cardiovascular; GDMT = guideline-directed medical therapy; hHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist.

or SGLT1/2 inhibitors were not approved for HFrEF (United States) or were approved late during the study period (Japan and Sweden). Dapagliflozin and empagliflozin were approved for HFrEF in Japan in November 2020 and November 2021, in Sweden in November 2020 and June 2021, and in the United States in May 2020 and February 2022, respectively.

The study period covered the first full month after approval of dapagliflozin for HFrEF (Japan: December 2020; Sweden: December 2020; United States: June 2020) up to the latest available update of the databases (Japan: February 2022; Sweden: March 2022; United States: September 2021). The follow-up period (Figure 1B) was defined as the time from index to the data-extraction date or date of death (if available).

TIMING OF GDMT INITIATION. Patients newly initiating more than 1 class of drug were described independently for each class and might have had several index dates if they initiated any of the 5 GDMTs (ACE inhibitor/ARB, beta-blocker, MRA, sacubitril/valsartan, and dapagliflozin) on different dates; hence, the same patient may be considered multiple times if they are a new user of more than 1 GDMT during the study period. Data were also extracted in a 12-month lookback period prior to the index date for all patients (baseline period) (Figure 1B). Patient characteristics were described at the index date (initiation of any GDMT) and included demographics, comorbidities, use of concomitant drugs, time since first HF diagnosis, and time since the qualifying hHF. The date of the first HF diagnosis was defined as the date of the first HF diagnosis code recorded in the database during or any time before the qualifying hHF. Presence of comorbidities was assessed using relevant diagnosis codes recorded during the 12-month baseline period. Use of comedications (non-GDMTs) was defined as at least 1 dispensation during the 12-month baseline period. Left ventricular ejection fraction was

FIGURE 1 EVOLUTION HF Study Design



(A) Patients included in this analysis. **(B)** Study timeline. *Patients newly initiating more than 1 drug class may have several index dates if they initiate guideline-directed medical therapies (GDMTs) on different dates. †The follow-up period was defined as the time from index to data-extraction date or date of death (if available). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta-blocker; EVOLUTION HF = Utilization of Dapagliflozin and Other Guideline Directed Medical Therapies in Heart Failure Patients: A Multinational Observational Study Based on Secondary Data; HF = heart failure; hHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist.

not available in these administrative registries, but because inclusion required initiation of at least 1 HFrEF GDMT following a recent hHF, all patients were assumed to have an indication for HFrEF. Detailed variable definitions are provided in Supplemental Tables 2 to 4.

GDMT TITRATION AND DISCONTINUATION ANALYSIS. For the titration and discontinuation analyses, only dose optimization after hospital discharge was considered. Additionally, only the most frequently used GDMTs within each respective class were considered for each country (Supplemental Table 5), and starting and target doses were considered according to local guidelines (Supplemental Table 6). Target dose was defined as ≥100% of dose recommended by local guidelines, intermediate dose as 50% to 99% of the recommended dose, and low dose as <50% of the

recommended dose. Dose categories were defined consistently across all GDMTs, with the exception of MRAs, for which guideline starting doses (12.5 mg in Japan and 25 mg in Sweden and the United States) were classified as intermediate. Although dapagliflozin does not require uptitration, we refer to the guideline recommended 10-mg dose as the target dose to distinguish it from the 5-mg dose that may be used, for example, for non-HF indications. Proportions of patients on starting, target, intermediate, and low doses, and who discontinued each drug, are reported relative to the number of patients initiating that drug. Drug utilization in different subgroups was also explored (older vs younger patients; women vs men; patients with vs without diabetes; patients with acute kidney injury [AKI] vs without any kidney disease).

STATISTICAL ANALYSIS. Continuous variables were reported using mean ± SD, median (IQR), and minimum and maximum values, as appropriate. Categorical variables were reported as absolute frequency and percentage. Cumulative percentages of patients initiating GDMTs after hHF discharge were calculated using the Kaplan-Meier method. Where appropriate, descriptive data are presented separately for patients initiating novel GDMTs (dapagliflozin or sacubitril/valsartan) and those initiating other GDMTs (ACE inhibitors/ARBs, beta-blockers, or MRAs).

ETHICAL APPROVAL. This study was performed in accordance with ethical principles that are consistent with the International Council for Harmonisation Good Clinical Practice, Good Pharmacoepidemiology Practice, and the applicable legislation on non-interventional studies and/or observational studies. Institutional Review Board approvals were not needed because EVOLUTION HF only involves secondary analysis of deidentified data. In Japan, ethical approval and informed consent do not apply to the use of de-identified secondary data according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. In Sweden and the United States, the EVOLUTION HF study followed local data source requirements for protocol and ethical approvals. Individual patient consent was not required.

RESULTS

BASELINE CHARACTERISTICS. Overall, 266,589 patients who initiated at least 1 GDMT within 12 months of hHF discharge were included from Japan (n = 130,243), Sweden (n = 26,394), and the United States (n = 109,952) (Table 1). Duration of the hHF stay was notably longer (median duration range across GDMTs: 15-19 days) in Japan than in Sweden and the United States (4-5 days in both countries). In the 3 countries, patients initiating novel GDMTs (dapagliflozin or sacubitril/valsartan) were younger than those initiating other GDMTs (ACE inhibitors/ARBs, beta-blockers, or MRAs). The proportions of women were markedly lower among patients initiating novel GDMTs than among those initiating other GDMTs.

The most prevalent comorbidities were atrial fibrillation, kidney disease, diabetes, and ischemic heart disease, and these tended to be more prevalent among initiators of novel GDMTs than among initiators of other GDMTs. Of note, among U.S. patients, 37.3% to 47.5% had a recorded history of AKI during the 12-month baseline period, compared with 2.4% to 3.4% in Japan and 4.9% to 7.6% in Sweden.

TIME TO GDMT INITIATION AFTER INCIDENT HF DIAGNOSIS. The median time from first HF diagnosis to a new initiation of a GDMT (as a first GDMT or in addition to others) was markedly longer for patients initiating novel GDMTs than for those initiating other GDMTs in all 3 countries: 229 and 352 days vs 13 to 34 days in Japan, 347 and 212 days vs 11 to 71 days in Sweden, and 938 and 679 days vs 560 to 658 days in the United States (Table 1).

TIME TO GDMT INITIATION AFTER RECENT hHF. In all 3 countries, mean time from the qualifying hHF to a new initiation of a GDMT (as a first GDMT or in addition to others) was longer for novel GDMTs (dapagliflozin and sacubitril/valsartan) than for other GDMTs: 39 and 44 days vs 12 to 13 days in Japan, 44 and 33 days vs 22 to 31 days in Sweden, and 33 and 19 days vs 18 to 24 days in the United States. The cumulative proportions of patients initiating a GDMT within 30 and 100 days of hHF discharge were lower among patients initiating novel GDMTs than among those initiating other GDMTs (Central Illustration, Figure 2, Table 1). In Japan, on day 30 after discharge, 74.6% and 72.7% of patients initiated dapagliflozin or sacubitril/valsartan, respectively, compared with 91.2% to 92.2% for other GDMTs. In Sweden, the corresponding numbers were 54.9% and 59.5% vs 72.9% to 85.2%, and in the United States, they were 37.3% and 62.0% vs 73.7% to 80.4%, respectively.

GDMT INITIATION IN THE TREATMENT JOURNEY. Upon initiation of a novel GDMT, large proportions of patients were already using 1 or more GDMTs, with use of 3 other GDMTs being common (Figure 3, Table 1). Among patients initiating sacubitril/valsartan, across the 3 countries 80.0% to 96.5% used a beta-blocker, 63.1% to 81.8% an ACE inhibitor or ARB, and 44.1% to 74.6% an MRA. Corresponding numbers

TABLE 1 Patient Characteristics at Study Index

	Japan (N = 130,243)				
	Dapagliflozin (n = 7,443)	Sacubitril/Valsartan (n = 12,971)	ACE Inhibitor/ARB (n = 64,831)	BB (n = 68,798)	MRA (n = 49,141)
Age, y	75 ± 13	76 ± 13	78 ± 13	77 ± 13	80 ± 12
Female	2,515 (33.8)	4,919 (37.9)	28,829 (44.5)	30,324 (44.1)	24,786 (50.0)
Time from first HF diagnosis to GDMT initiation, d	229 (7-1,689)	352 (17-1,873)	13 (2-655)	14 (2-734)	34 (3-1,074)
Time from hHF to GDMT initiation, d	0 (0-32), 39 ± 79	0 (0-45), 44 ± 84	0 (0-0), 13 ± 48	0 (0-0), 12 ± 46	0 (0-0), 13 ± 46
Length of hHF stay, d	15 (9-25)	15 (9-25)	15 (9-26)	16 (9-27)	19 (11-31)
Comorbidities					
Atrial fibrillation	3,212 (43.2)	5,605 (43.2)	19,980 (30.8)	24,683 (35.9)	19,115 (38.9)
Cancer	685 (9.2)	1,098 (8.5)	6,493 (10.0)	7,364 (10.7)	6,365 (13.0)
Any kidney disease	2,001 (26.9)	3,741 (28.8)	13,495 (20.8)	15,561 (22.6)	10,538 (21.4)
Acute kidney injury	208 (2.8)	381 (2.9)	1,539 (2.4)	2,134 (3.1)	1,679 (3.4)
COVID-19	100 (1.3)	134 (1.0)	1,105 (1.7)	1,325 (1.9)	870 (1.8)
Diabetes[a]	2,489 (33.4)	4,192 (32.3)	16,162 (24.9)	18,330 (26.6)	13,736 (28.0)
Ischemic heart disease	2,125 (28.6)	3,374 (26.0)	13,878 (21.4)	15,760 (22.9)	8,852 (18.0)
Peripheral artery disease	424 (5.7)	767 (5.9)	3,123 (4.8)	3,637 (5.3)	2,434 (5.0)
Stroke	521 (7.0)	1,065 (8.2)	7,071 (10.9)	7,381 (11.4)	4,911 (10.0)
GDMT					
BB	5,643 (75.8)	10,374 (80.0)	33,945 (52.4)	0 (0)	27,283 (55.5)
ACE inhibitor/ARB	5,326 (71.6)	10,418 (80.3)	0 (0)	34,865 (50.7)	25,052 (51.0)
MRA	3,588 (48.2)	5,908 (45.5)	15,983 (24.7)	17,594 (25.6)	0 (0)
Sacubitril/valsartan	1,140 (15.3)	0 (0)	438 (0.7)	1,892 (2.8)	1,847 (3.8)
Dapagliflozin	0 (0)	4,920 (37.9)	6,270 (9.7)	7,133 (10.4)	5,777 (11.8)
Number of GDMTs					
1	399 (5.4)	556 (4.3)	23,807 (36.7)	25,646 (37.3)	12,282 (25.0)
2	1,524 (20.5)	1,962 (15.1)	29,478 (45.5)	29,936 (43.5)	19,020 (38.7)
3	2,808 (37.7)	4,643 (35.8)	10,334 (15.9)	11,319 (16.5)	15,259 (31.1)
4	2,291 (30.8)	4,265 (32.9)	1,161 (1.8)	1,738 (2.5)	2,298 (4.7)
5	421 (5.7)	1,545 (11.9)	51 (0.1)	159 (0.2)	282 (0.6)
Other HF treatments					
Loop diuretic	6,538 (87.8)	11,231 (86.6)	41,011 (63.3)	44,006 (64.0)	45,029 (91.6)
Ivabradine	180 (2.4)	316 (2.4)	218 (0.3)	241 (0.4)	188 (0.4)
Nitrate	3,490 (46.9)	6,503 (50.1)	24,371 (37.6)	27,007 (39.3)	16,810 (34.2)
Vitamin K antagonist	925 (12.4)	1,735 (13.4)	4,275 (6.6)	5,223 (7.6)	5,129 (10.4)
$P2Y_{12}$ receptor antagonists	1,948 (26.2)	3,346 (25.8)	14,276 (22.0)	14,972 (21.8)	7,750 (15.8)
Device treatment (pacemaker or defibrillator)	287 (3.9)	514 (4.0)	1,575 (2.4)	1,874 (2.7)	976 (2.0)

Values are mean ± SD, n (%), or median (IQR). Patients were considered as new users of a specific GDMT if they had never received a drug in the same GDMT class or had not been using a drug in the same GDMT class in the 12 months before the index date (ie, restarting a GDMT after a gap of more than 12 months was considered as new use). [a]Based on use of any glucose-lowering drug, except sodium-glucose cotransporter-2 inhibitors, within 12 months.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta-blocker; GDMT = guideline-directed medical therapy; HF = heart failure; hHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist.

Continued on the next page

in patients initiating dapagliflozin were similar: 75.8% to 95.6% used a beta-blocker, 67.8% to 80.0% an ACE inhibitor or ARB, and 48.2% to 72.2% an MRA.

Use of loop diuretic agents and nitrates was also prevalent across the 3 countries (**Table 1**). Among patients initiating sacubitril/valsartan across the 3 countries, 76.3% to 86.6% used loop diuretic agents and 25.8% to 51.2% used oral nitrates, whereas corresponding numbers were 76.8% to 87.8% and 25.4% to 51.0% among patients initiating dapagliflozin, respectively.

GDMT TITRATION AND DISCONTINUATION. GDMT titration and discontinuation were assessed in users of the most common GDMTs in each class in each country (Supplemental Table 5). A total of 104,022 patients were included in this analysis (Supplemental Tables 7 to 9).

In all 3 countries, underdosing/slow uptitration, low target dose achievement, and early discontinuation of ACE inhibitors, ARBs, beta-blockers, MRAs, and sacubitril/valsartan were common during the 12-month follow-up (**Figure 4**). Among patients

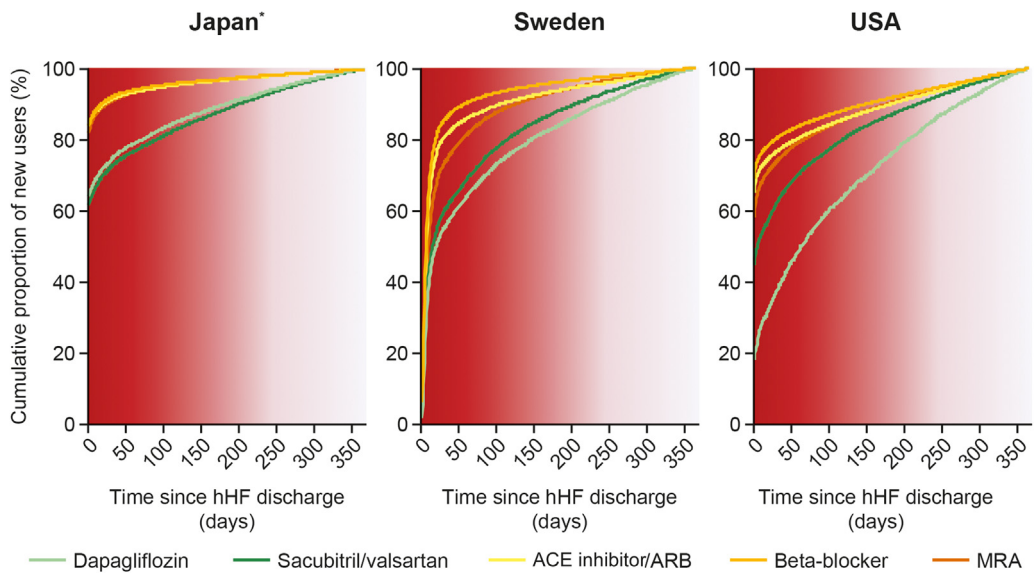
TABLE 1 Continued

Sweden (N = 26,394)					United States (N = 109,952)				
Dapagliflozin (n = 5,483)	**Sacubitril/Valsartan (n = 3,854)**	**ACE Inhibitor/ARB (n = 8,511)**	**BB (n = 9,658)**	**MRA (n = 14,315)**	**Dapagliflozin (n = 1,962)**	**Sacubitril/Valsartan (n = 12,200)**	**ACE Inhibitor/ARB (n = 48,067)**	**BB (n = 63,335)**	**MRA (n = 30,550)**
73 ± 12	70 ± 12	75 ± 14	74 ± 14	77 ± 12	61 ± 13	64 ± 14	68 ± 14	69 ± 14	66 ± 14
1,590 (29.0)	999 (25.9)	3,554 (41.8)	3,775 (39.1)	6,163 (43.0)	635 (32.4)	4,146 (34.0)	21,504 (44.7)	29,043 (45.9)	13,095 (42.9)
347 (36-2,310)	212 (21-2,017)	14 (5-513)	11 (5-121)	71 (9-1,190)	938 (206-2,265)	679 (52-2,050)	506 (4-1,815)	521 (3-1,848)	658 (19-1,963)
20 (6-113), 44 ± 69	15 (6-87), 33 ± 56	7 (4-20), 30 ± 64	7 (4-15), 22 ± 50	10 (5-37), 31 ± 58	64 (7-178), 33 ± 64	6 (0-87), 19 ± 47	0 (0-22), 24 ± 62	0 (0-7), 19 ± 56	0 (0-36), 18 ± 50
4 (2-7)	4 (2-7)	5 (3-8)	5 (3-8)	5 (3-8)	4 (2-7)	4 (2-7)	4 (2-8)	5 (2-8)	5 (2-8)
Comorbidities									
3,087 (56.3)	1,947 (50.5)	4,276 (50.2)	4,410 (45.7)	8,305 (58.0)	883 (45.0)	5,698 (46.7)	20,835 (43.3)	29,032 (45.8)	14,783 (48.4)
585 (10.7)	366 (9.5)	915 (10.8)	1,020 (10.6)	1,669 (11.7)	210 (10.7)	1,528 (12.5)	6,761 (14.1)	9,982 (15.8)	4,321 (14.1)
1,150 (21.0)	598 (15.5)	1,457 (17.1)	1,549 (16.0)	2,409 (16.8)	1,240 (63.2)	7,041 (57.7)	26,811 (55.8)	37,933 (59.9)	18,082 (59.2)
418 (7.6)	216 (5.6)	417 (4.9)	573 (5.9)	763 (5.3)	932 (47.5)	5,247 (43.0)	17,944 (37.3)	26,287 (41.5)	13,311 (43.6)
318 (5.8)	201 (5.2)	527 (6.2)	568 (5.9)	842 (5.9)	156 (8.0)	945 (7.7)	4,237 (8.8)	5,993 (9.5)	2,309 (7.6)
1,670 (30.5)	1,095 (28.4)	1,475 (17.3)	1,821 (18.9)	3,492 (24.4)	1,124 (57.3)	4,176 (34.2)	11,546 (24.0)	13,862 (21.9)	10,945 (35.8)
1,976 (36.0)	1,410 (36.6)	2,485 (29.2)	2,806 (29.1)	3,961 (27.7)	1,001 (51.0)	6,167 (50.5)	18,670 (38.8)	23,068 (36.4)	12,984 (42.5)
216 (3.9)	141 (3.7)	259 (3.0)	308 (3.2)	510 (3.6)	382 (19.5)	2,159 (17.7)	8,255 (17.2)	10,931 (17.3)	5,397 (17.7)
253 (4.6)	181 (4.7)	486 (5.7)	504 (5.2)	725 (5.1)	381 (19.4)	2,415 (19.8)	9,996 (20.8)	12,601 (19.9)	5,909 (19.3)
GDMT									
5,241 (95.6)	3,720 (96.5)	7,398 (86.9)	0 (0)	12,936 (90.4)	1,801 (91.8)	11,224 (92.0)	37,401 (77.8)	0 (0)	26,047 (85.3)
4,385 (80.0)	3,152 (81.8)	0 (0)	7,615 (78.8)	11,789 (82.4)	1,327 (67.6)	7,700 (63.1)	0 (0)	27,945 (44.1)	19,356 (63.4)
3,956 (72.2)	2,876 (74.6)	3,013 (35.4)	3,683 (38.1)	0 (0)	1,152 (58.7)	5,380 (44.1)	7,304 (15.2)	7,678 (12.1)	0 (0)
1,946 (35.5)	0 (0)	176 (2.1)	804 (8.3)	1,438 (10.0)	925 (47.1)	0 (0)	1,508 (3.1)	2,568 (4.1)	3,982 (13.0)
0 (0)	1,528 (39.6)	922 (10.8)	1,366 (14.1)	2,575 (18.0)	0 (0)	872 (7.1)	712 (1.5)	835 (1.3)	1,039 (3.4)
Number of GDMTs									
15 (0.3)	26 (0.7)	802 (9.4)	1,074 (11.1)	410 (2.9)	37 (1.9)	530 (4.3)	9,620 (20.0)	30,580 (48.3)	2,408 (7.9)
170 (3.1)	215 (5.6)	4,737 (55.7)	4,966 (51.4)	2,279 (15.9)	188 (9.6)	2,803 (23.0)	31,316 (65.2)	27,385 (43.2)	8,606 (28.2)
1,403 (25.6)	910 (23.6)	2,527 (29.7)	2,923 (30.3)	9,626 (67.2)	587 (29.9)	4,921 (40.3)	6,327 (13.2)	5,096 (8.0)	17,562 (57.5)
3,028 (55.2)	2,002 (51.9)	408 (4.8)	624 (6.5)	1,764 (12.3)	757 (38.6)	3,768 (30.9)	771 (1.6)	263 (0.4)	1,876 (6.1)
867 (15.8)	701 (18.2)	37 (0.4)	71 (0.7)	236 (1.6)	393 (20.0)	178 (1.5)	33 (0.1)	11 (0)	98 (0.3)
Other HF treatments									
4,212 (76.8)	2,942 (76.3)	5,580 (65.6)	6,161 (63.8)	11,389 (79.6)	1,721 (87.7)	10,359 (84.9)	33,183 (69.0)	40,791 (64.4)	26,618 (87.1)
29 (0.5)	34 (0.9)	18 (0.2)	17 (0.2)	25 (0.2)	34 (1.7)	96 (0.8)	88 (0.2)	89 (0)	135 (0.4)
1,392 (25.4)	996 (25.8)	1,925 (22.6)	2,048 (21.2)	3,304 (23.1)	1,000 (51.0)	6,249 (51.2)	17,520 (36.4)	19,542 (30.9)	13,437 (44.0)
710 (12.9)	499 (12.9)	735 (8.6)	649 (6.7)	1,673 (11.7)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)
1,100 (20.1)	834 (21.6)	1,669 (19.6)	1,996 (20.7)	2,276 (15.9)	564 (28.7)	3,357 (27.5)	9,378 (19.5)	10,231 (16.0)	6,494 (21.3)
585 (10.7)	392 (10.2)	364 (4.3)	524 (5.4)	753 (5.3)	96 (4.9)	484 (4.0)	407 (0.8)	479 (0.8)	535 (1.8)

initiating sacubitril/valsartan, 26.6%, 14.7%, and 40.3% of patients discontinued by 12 months in Japan, Sweden, and the United States, respectively, and 20.3%, 44.4%, and 12.6% of patients achieved target dose (defined as ≥100% of dose recommended by local guidelines), respectively. Among those initiating ACE inhibitors, 10.2%, 5.4%, and 3.1% switched to sacubitril/valsartan by 12 months in Japan, Sweden, and the United States, respectively. Corresponding estimates for ARBs were 6.1%, 3.3%, and 5.3%, respectively. Among those initiating an ACE inhibitor, 1.2%, 0.9%, and 2.9% switched to an ARB during follow-up in Japan, Sweden, and the United States, respectively. Corresponding estimates for patients switching from an ARB to an ACE inhibitor were 0.4%, 2.6%, and 3.1%, respectively.

For dapagliflozin, which does not require uptitration, 70.9%, 83.6%, and 46.5% of patients were on target dose at 12 months postinitiation in Japan, Sweden, and the United States, respectively. In Japan and Sweden, discontinuation tended to be lower for dapagliflozin than for other GDMTs: 24.4% vs 26.6% to 68.9% and 16.4% vs 14.1% to 27.5%, respectively. In the United States, the opposite was observed with 53.5% discontinuation for dapagliflozin vs 35.1% to 47.2% for other GDMTs. For all GDMTs, discontinuation was more prevalent in the United States than in Japan and Sweden. Although dapagliflozin is

FIGURE 2 Cumulative Proportions of Patients Initiating GDMTs After hHF



The **colored background** depicts risk of rehospitalization for heart failure (higher risk **[dark red]** vs lower risk **[light red]**). *The curves for beta-blockers, MRAs, and ACE inhibitors/ARBs overlap. Abbreviations as in Figure 1.

available in 2 dose strengths (5 and 10 mg), only the 10-mg dose is indicated for HFrEF treatment. Therefore, negligible dapagliflozin dose adjustments of 4.7%, 0%, and 0% were observed across Japan, Sweden, and the United States, respectively. When data from the 3 countries were pooled, discontinuation of dapagliflozin (23.5%) was lower than for all the other GDMTs, which ranged from 25.2% for beta-blockers to 42.2% for MRAs (**Central Illustration, Figure 5**). For GDMTs that require uptitration, the proportion of patients on target dose at 12 months ranged from 5.1% for MRAs (target dose considered 50 mg daily for spironolactone) to 28.2% for sacubitril/valsartan. For dapagliflozin, 75.7% of patients were on target dose at 12 months.

SUBGROUP ANALYSES. The median time from first HF diagnosis to GDMT initiation was longer in patients with any kidney disease than in those without kidney disease for all GDMTs (**Figure 6**). Median time from first HF diagnosis to GDMT initiation was also generally longer in patients with diabetes than in those without diabetes, except for Japanese patients initiating dapagliflozin for which the opposite was observed. In Japan and Sweden, median time from first HF diagnosis to GDMT initiation was longer in men than in women. In the United States, median time from first HF diagnosis to GDMT initiation was longer in women than in men for all GDMTs, except for dapagliflozin, for which the opposite was observed.

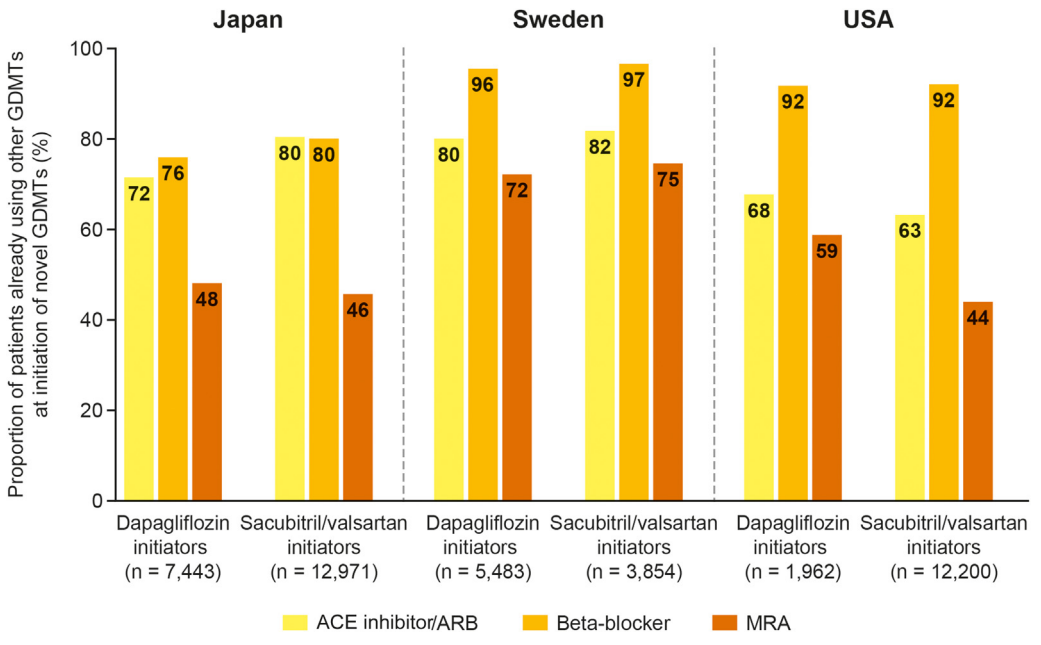
Discontinuation was higher and target dose achievement was lower in women vs men for patients initiating dapagliflozin, sacubitril/valsartan, ACE inhibitors, and ARBs (Supplemental Figure 1). Similar results were seen among patients with vs without type 2 diabetes and among patients with a reported diagnosis of AKI vs those without any kidney disease (Supplemental Figures 2 and 3). The differences in discontinuation and target dose achievement in patients below 70 years of age vs 70 years of age and over were small (Supplemental Figure 4).

DISCUSSION

LATE INITIATION OF GDMTs. Results from this study show that novel GDMTs are initiated late in both the HF disease and treatment journey. Despite the paradigm-shifting trial results for novel GDMTs,[7,9-12] early initiation of novel GDMTs in real-world settings remains a clinical challenge. However, SGLT2 inhibitors have entered clinical guidelines only recently, and changes in treatment strategies may improve over time.

The delay in GDMT initiation was generally more pronounced in patients with vs without comorbidities such as kidney disease and type 2 diabetes. Use of

FIGURE 3 **Proportions of Patients Already Using ACE Inhibitor/ARB, Beta-Blocker, or MRA at Initiation of Novel GDMTs (Dapagliflozin and Sacubitril/Valsartan)**



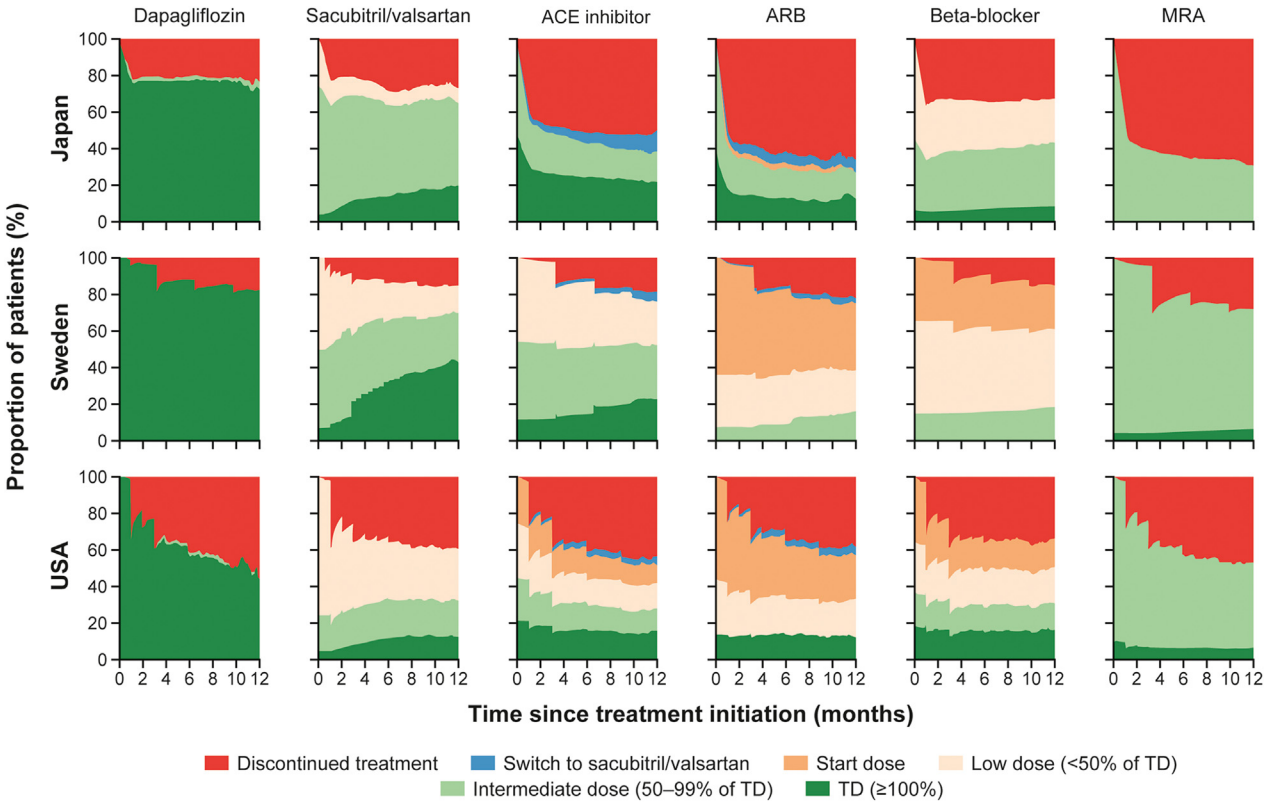
Abbreviations as in Figure 1.

novel GDMTs is especially important in patients with chronic kidney disease (CKD) because they have beneficial clinical effects for the treatment of CKD. In the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial, despite an early decline in estimated glomerular filtration rate, dapagliflozin demonstrated highly beneficial clinical effects on renal or cardiovascular events.[26] Although all patients in the present study had HF, it is notable that the cardiorenal benefits of dapagliflozin in patients with CKD in the DAPA-CKD trial were independent of history of HF or type 2 diabetes.[27] Sacubitril/valsartan also showed kidney benefits in patients with HFrEF and CKD, with a slower rate of decrease in estimated glomerular filtration rate compared with enalapril, despite causing a small increase in urinary albumin-to-creatinine ratio.[28]

Use of novel GDMTs is also beneficial in patients with type 2 diabetes and HFrEF.[7,29] Dapagliflozin was first approved as a glucose-lowering therapy in patients with type 2 diabetes, and has demonstrated cardiovascular benefits in these patients, with a 27% reduction in risk of hHF compared with placebo.[30] These benefits extended to patients with HFrEF, with or without type 2 diabetes, in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial.[7] Similarly, the cardiovascular benefits of sacubitril/valsartan compared with enalapril were observed irrespective of glycemic status in patients with HFrEF in the PARADIGM-HF (Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial.[29]

HIGH DISCONTINUATION RATES. Across all 3 countries, ACE inhibitors, ARBs, beta-blockers, MRAs, and sacubitril/valsartan showed low persistence. These results confirm the findings of a smaller study conducted before dapagliflozin was approved for the treatment of HF.[2] Discontinuation of GDMTs, including ACE inhibitors/ARBs, beta-blockers, and MRAs, after hHF has been observed to be associated with a 30% increase in 1-year all-cause mortality compared with maintaining GDMT therapy.[31] In the present study, dapagliflozin demonstrated higher persistence rates than the other GDMTs across all countries. Discontinuation rates were generally higher and uptitration poorer in the United States than in Japan and Sweden. This may be explained, at least in part, by the higher prevalence of patients with a recorded history of AKI in the United States (37.3%-47.5%) than in Japan (2.4%-3.4%) and Sweden (4.9%-7.6%). However, it should be noted that these numbers may not be representative of the true

FIGURE 4 Titration to Target Dose and Discontinuation of the Most Frequently Used Treatments in Each GDMT Class Among New Users of GDMTs After hHF



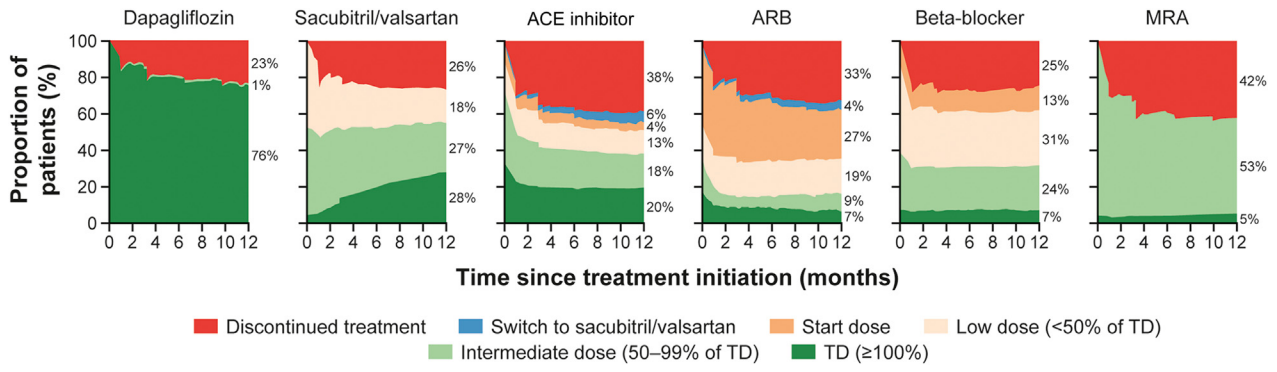
TD = target dose; other abbreviations as in Figure 1.

prevalence of AKI and may reflect differences in diagnosis coding across countries. Other explanations could include a lack of coverage for and the cost of drugs.

A small proportion of patients initiating ACE inhibitors and ARBs switched to sacubitril/valsartan during follow-up. In contrast to ACE inhibitors, switching from ARBs to sacubitril/valsartan does not require a washout period, which could prompt more frequent switches to sacubitril/valsartan in ARB users than in ACE inhibitor users. However, the proportions of patients who switched treatments were similar in ARB and ACE inhibitor users. A large proportion of patients initiating sacubitril/valsartan were already taking ACE inhibitors or ARBs at baseline, suggesting that these patients may have switched from ACE inhibitor/ARB to sacubitril/valsartan at index. Similarly, a small proportion of patients initiating ACE inhibitors and ARBs at index also initiated ARBs or ACE inhibitors, respectively, during follow-up, suggesting that these patients switched between these 2 classes.

LIMITED TITRATION TO TARGET DOSE. In general, patients initiating dapagliflozin showed lower discontinuation rates compared with those initiating other GDMTs. Most patients on dapagliflozin received the dose recommended by guidelines. In contrast, target dose achievement in the 12 months following initiation was generally low for patients initiating GDMTs requiring uptitration, in line with previous findings.[2] The explanation for this is likely multifactorial; clinical inertia may contribute, alongside challenges with the tolerability of these drugs at guideline-recommended doses, with inhibition of the renin-angiotensin system being associated with an increased risk of dry cough, hypotension, hyperkalemia, and decline in kidney function and the use of beta-blockers being associated with an increased risk of dry cough and bradycardia. However, though guideline-recommended doses of ACE inhibitors, ARBs, and beta-blockers are markedly lower in Japan than in Sweden and the United States (Supplemental Table 6), rates of discontinuation remained high in this country.

FIGURE 5 Titration to Target Dose and Discontinuation of the Most Frequently Used Treatments in Each GDMT Class Among New Users of GDMTs After hHF, Pooled Across Japan, Sweden, and the United States



Percentages may not sum to exactly 100% because of rounding. TD = target dose; other abbreviations as in Figure 1.

In the present study, patient characteristics such as female sex and pre-existing comorbidities such as diabetes and AKI were associated with higher discontinuation rates, potentially highlighting differences in tolerability and a need for a particular clinical attention in these subgroups of patients. Dose titration and discontinuation profiles were similar in patients below 70 years of age and those 70 years of age and over, suggesting that age might have little impact on treatment tolerability.

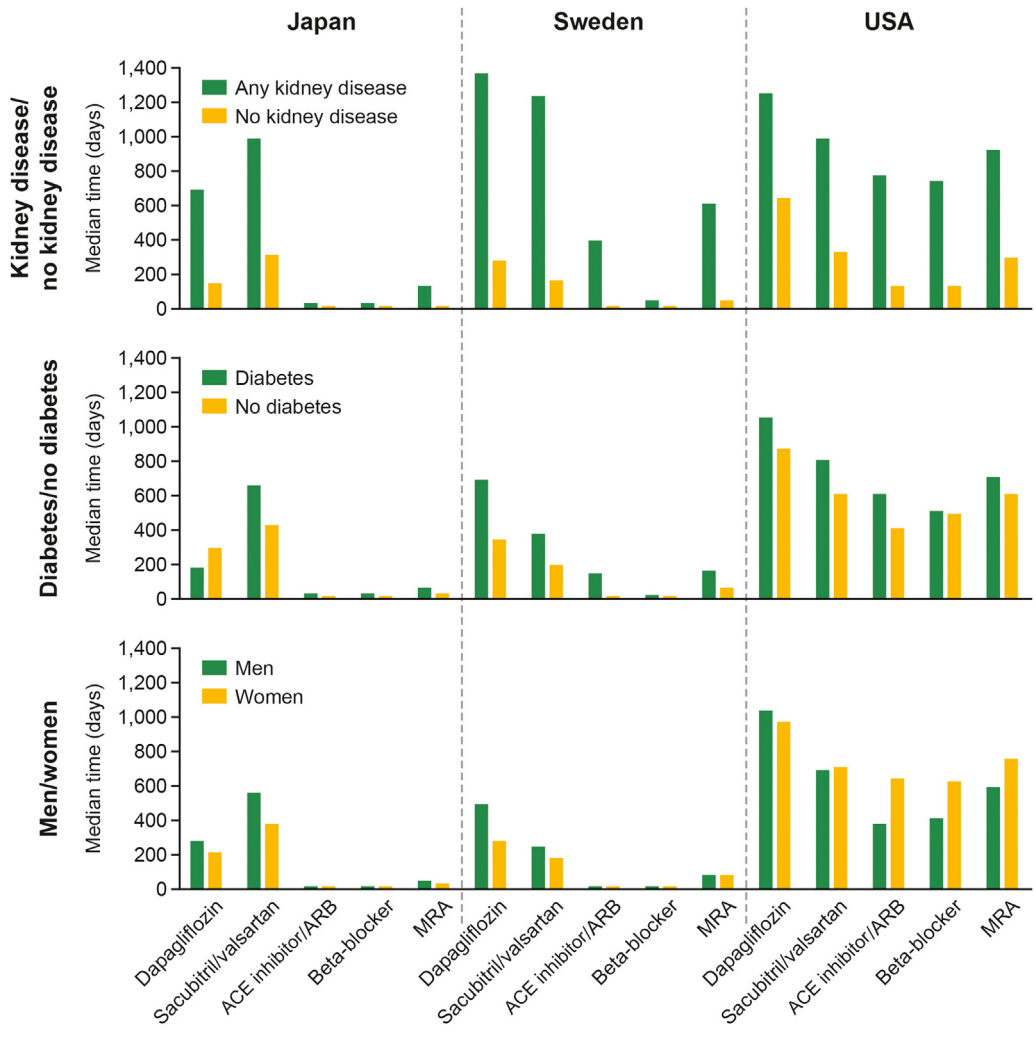
TIMING OF GDMT INITIATION. Initiation of GDMTs during hHF has been shown to lower the risk of rehospitalization and death. In particular, initiation of GDMTs including ACE inhibitors/ARBs, beta-blockers, and MRAs during hHF admission was associated with a 59% reduced risk of 1-year all-cause mortality compared with no therapy.[31] Lower 30-day mortality and risk of hospital readmission have also been observed in patients who continue or initiate an ACE inhibitor/ARB during hHF than in those who discontinue or do not initiate an ACE inhibitor/ARB.[4] However, we found that initiation of GDMTs, particularly novel GDMTs, was delayed after hHF, therefore leaving large proportions of patients at increased risk of death and rehospitalization. Most patients initiating novel therapies were also already on background therapy with 3 or more GDMTs.

STUDY STRENGTHS. Strengths of our study include the large sample size and the consistency of the results across 3 countries with different health care infrastructure and economics. To our knowledge, EVOLUTION HF is also the first study to assess the real-world use of dapagliflozin for the treatment of HFrEF since its inclusion in guidelines. In addition, availability of dosing information in the databases strengthened our analysis by providing insights on target dose achievement. Finally, longitudinal patient-level data allowed the assessment of not only time to initiation, but also persistence, which is particularly important given that treatment discontinuation has rarely been studied but may be at least as pressing an issue as delayed initiation.

STUDY LIMITATIONS. Limitations might include limited generalizability to other countries with significantly different health care systems or different local guidelines for the treatment of HF. Also, new HF guidelines were published during the study period, which may have influenced the results.

Ejection fraction assessments were not available; it was therefore not possible to determine whether patients had HFrEF rather than HF with mildly reduced ejection fraction or heart failure with preserved ejection fraction (HFpEF), although we included only patients who initiated HFrEF GDMTs, suggesting that they had an indication. However, several GDMTs have other indications (eg, for hypertension, type 2 diabetes, CKD). If patients initiated these GDMTs for a non-HF indication, it would not be possible to determine whether they had HFrEF, HF with mildly reduced ejection fraction, or HFpEF. This limitation may be particularly relevant to patients who only initiated 1 GDMT during the study period. Similarly, the noninitiation of some HFrEF treatments after hHF might also be explained by the lack of an HFrEF indication, for example, in a patient who had HFpEF and therefore no indication for a beta-blocker, sacubitril/valsartan, or MRA but who initiated an SGLT2 inhibitor for type 2 diabetes or CKD. Some patients with HFrEF may also have been missed from the analysis if they did not receive

FIGURE 6 Median Time from First HF Diagnosis to GDMT Initiation for Subgroups of New Users of GDMTs After hHF



Patients were considered as new users of a specific GDMT if they had never received a drug in the same GDMT class or had not been using a drug in the same GDMT class in the 12 months before the index date (ie, restarting a GDMT after a gap of more than 12 months was considered as new use). Abbreviations as in Figure 1.

any GDMT; however, this group is likely to be small. Time from first HF diagnosis to new drug initiation should be interpreted with caution because restarting a GDMT after a gap of more than 12 months was considered as new use.

Vital signs (eg, heart rate and blood pressure) and laboratory values (eg, creatinine, potassium) were not available, which precluded assessment of contraindications to GDMTs. Similarly, we could not assess whether discontinuation or lack of uptitration were appropriate. Finally, the use of dapagliflozin may not be fully representative of SGLT2 inhibitor use in general. In Sweden and Japan, some patients may have received empagliflozin instead of dapagliflozin following hHF, but these patients are not captured in the present analysis. Empagliflozin was approved for use in patients with HFrEF in Sweden and Japan late in the study period (June 2021 and November 2021, respectively) but may have been used for type 2 diabetes indications during the present study period. Studies on other SGLT2 inhibitors as part of GDMT are encouraged once these SGLT2 inhibitors are approved for HFrEF treatment, and once sufficient patient numbers and follow-up times are available.

CONCLUSIONS

In Japan, Sweden, and the United States, initiation of novel GDMTs (dapagliflozin and sacubitril/valsartan in this study) after hHF is markedly delayed compared with initiation of other GDMTs. The delay in novel GDMT initiation was more pronounced in high-risk patients with comorbidities such as kidney disease, and/or diabetes. For GDMTs requiring uptitration, few patients received the target dose in the 12 months after initiation, and many discontinued treatment. Conversely, dapagliflozin was associated with relatively low rates of discontinuation. These results show an urgent need for earlier use of novel GDMTs to improve patient outcomes, particularly of dapagliflozin, which has been shown to reduce mortality in patients with HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HF guidelines recommend early and rapid initiation of the 4 pillars of GDMT that reduce morbidity and mortality in patients with HFrEF.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Despite substantial clinical benefits achieved with optimal implementation of GDMT, EVOLUTION HF demonstrates that there is still delayed initiation of novel GDMTs (dapagliflozin and sacubitril/valsartan). An SGLT2 inhibitor, namely dapagliflozin 10 mg once daily in this study, showed the lowest discontinuation rates compared with other the GDMT classes, which often also require lengthy titrations.

TRANSLATIONAL OUTLOOK: There is an urgent need for effective strategies to achieve rapid implementation of the 4 pillars of GDMT in patients with HF, both in inpatient and in outpatient settings.

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KEY WORDS guideline-directed medical therapy, real-world data, treatment discontinuation, treatment initiation, treatment persistence

APPENDIX For expanded Methods and references as well as supplemental tables and figures, please see the online version of this paper.