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ORIGINAL RESEARCH PAPER

Mortality, Outcomes, Costs, and Use of Medicines Following a First Heart Failure Hospitalization

EVOLUTION HF

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ABSTRACT

BACKGROUND There are few contemporary data on outcomes, costs, and treatment following a hospitalization for heart failure (hHF) in epidemiologically representative cohorts.

OBJECTIVES The study sought to describe rehospitalizations, hospitalization costs, use of guideline-directed medical therapy (GDMT) (renin-angiotensin system inhibitors, sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors), and mortality after hHF.

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, longitudinal cohort study using data from electronic health records or claims data sources in Japan, Sweden, the United Kingdom, and the United States. Adults with a first hHF discharge between 2018 and 2022 were included. One-year event rates per 100 patient-years (ERs) for death and rehospitalizations (with a primary diagnosis of heart failure (HF), chronic kidney disease [CKD], myocardial infarction, stroke, or peripheral artery disease) were calculated. Hospital health care costs were cumulatively summarized. Cumulative GDMT use was assessed using Kaplan-Meier estimates.

RESULTS Of 263,525 patients, 28% died within the first year post-hHF (ER: 28.4 [95% CI: 27.0-29.9]). Rehospitalizations were mainly driven by HF (ER: 13.6 [95% CI: 9.8-17.4]) and CKD (ER: 4.5 [95% CI: 3.6-5.3]), whereas the ERs for myocardial infarction, stroke, and peripheral artery disease were lower. Health care costs were predominantly driven by HF and CKD. Between 2020 and 2022, use of renin-angiotensin system inhibitors, sacubitril/valsartan, beta-blockers, and mineralocorticoid receptor antagonists changed little, whereas uptake of sodium-glucose cotransporter-2 inhibitors increased 2- to 7-fold.

CONCLUSIONS Incident post-hHF rehospitalization risks and costs were high, and GDMT use changed little in the year following discharge, highlighting the need to consider earlier and greater implementation of GDMT to manage risks and reduce costs. (J Am Coll Cardiol HF 2023;■:■-■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitor

CKD = chronic kidney disease

GDMT = guideline-directed medical therapy

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

hHF = hospitalization for heart failure

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

RAS = renin-angiotensin system

SGLT2 = sodium-glucose cotransporter-2

Heart failure (HF) is common, and its prevalence is expected to rise with aging populations and improved diagnosis.[1,2] HF is associated with an impaired quality of life, poor outcomes, and places a substantial economic burden on health care systems.[3]

Treatment strategies to improve prognosis vary depending on left ventricular ejection fraction (LVEF). For patients with heart failure with preserved ejection fraction (HFpEF), guideline-recommended treatments are currently limited. In contrast, for patients with chronic HF with reduced ejection fraction (HFrEF), initiation of several guideline-directed medical therapies (GDMTs) reduces hospitalizations for heart failure (hHFs) and mortality and is cost-effective, with effects beginning to appear within a few days or weeks of initiation.[4,5]

However, in routine clinical practice, the implementation of GDMT (renin-angiotensin system [RAS] inhibitors, angiotensin receptor-neprilysin inhibitors [ARNIs] [ie, sacubitril/valsartan], beta-blockers, mineralocorticoid receptor antagonists [MRAs], and sodium-glucose cotransporter-2 [SGLT2] inhibitors) in patients with chronic HFrEF is often suboptimal, whether in the outpatient setting or following an hHF.[6-10] Failure to implement GDMT has an adverse effect on outcomes.[11,12]

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 provides insights into the management of patients after discharge from an hHF.[6] The present analysis provides a contemporary description of rehospitalization rates, hospital health care costs, use of key therapies, and mortality after a first hHF in Japan, Sweden, the United Kingdom, and the United States (**Central Illustration**).

METHODS

STUDY DESIGN. EVOLUTION HF[6] is a multinational, observational, longitudinal cohort study that uses data extracted from well-established electronic health records or claims data sources in Japan (hospital sourced), Sweden (hospital sourced and national registries), the United Kingdom (primary care sourced), and the United States (hospital sourced and prescription claims data) (Supplemental Methods, Supplemental Figure 1).

STUDY POPULATIONS AND STUDY PERIODS. Adults were included if they had a first-ever registered inpatient hHF during the study period of 2018 through 2022 (Supplemental Table 1). Patients with new-onset hHF were included to increase the validity of an HF diagnosis and the likelihood that the investigated medicines were initiated for HF treatment (rather than for other indications). To ensure that only patients with new-onset HF were included, patients were excluded if they had any prior HF diagnosis during all the available periods for each database and were required to have records in the 12 months prior to the event. Patients with a prior type 1 diabetes diagnosis were also excluded. HF was defined by the following International Classification of Diseases-10th Revision diagnosis codes in all countries: I50, I11.0, I13.0, and I13.2 (Supplemental Table 2).

COHORTS. Two cohorts were created within each country: one (cohort 1) to study clinical outcomes and hospital health care costs, and another (cohort 2) to describe contemporary use of HF medicines after hHF discharge (**Figure 1**). For both cohorts, the index date (start of follow-up) was defined as the date of discharge from a first registered inpatient hHF, and follow-up periods were defined as the time from the index date to the data-extraction date, date of death, or 12 months after discharge, whichever came first. Data were also censored 14 days after the last registered activity (ie, a dispensed medicine) in the database to avoid including patients who had been lost to follow-up.

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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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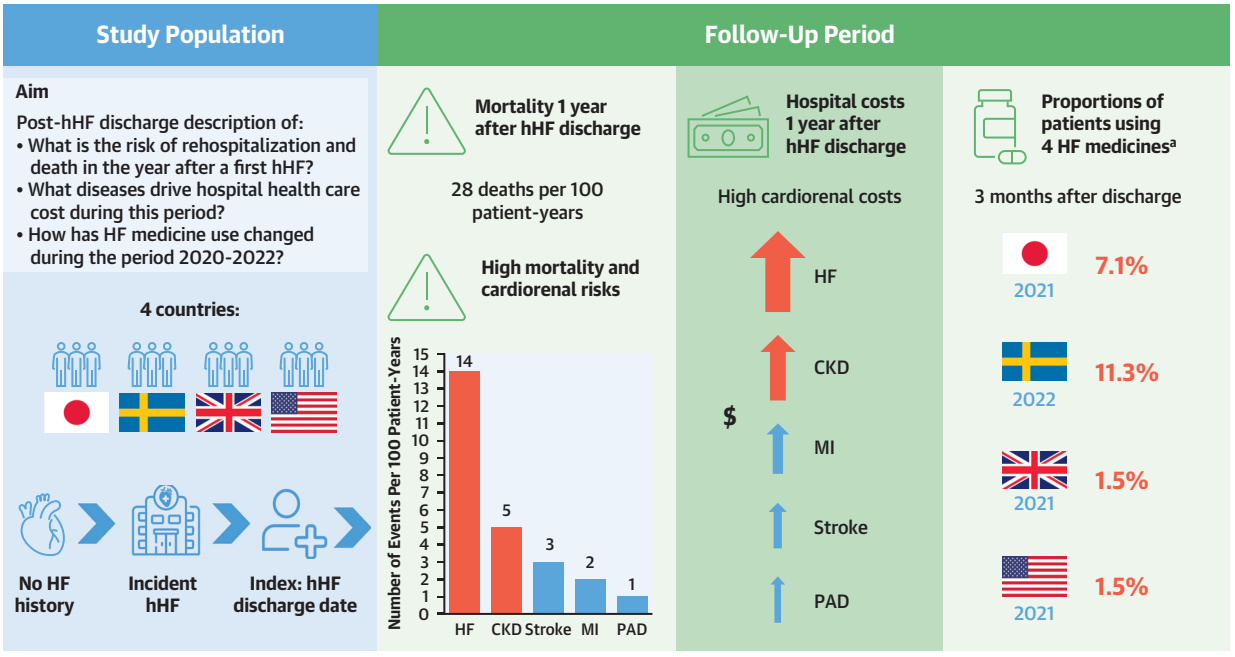
CENTRAL ILLUSTRATION **Risks, Costs, and HF Medicine Use After a First hHF**



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[a]Concurrent use of a renin-angiotensin system inhibitor, beta-blocker, mineralocorticoid receptor antagonist, and sodium-glucose cotransporter-2 inhibitor.
CKD = chronic kidney disease; HF = heart failure; hHF = hospitalization for heart failure; MI = myocardial infarction; PAD = peripheral artery disease.

Cohort 1 (clinical outcomes and costs during 2018-2020). This cohort was created to allow sufficient follow-up while avoiding the potential influence of the COVID-19 pandemic on the results (Figure 1). Patients were included if the date of discharge from their index hHF took place between January 1, 2018, and January 1, 2020. Patient characteristics, 1-year readmission rates, and hospital health care costs are reported for this cohort. However, postdischarge mortality data were available only from Sweden and the United Kingdom.

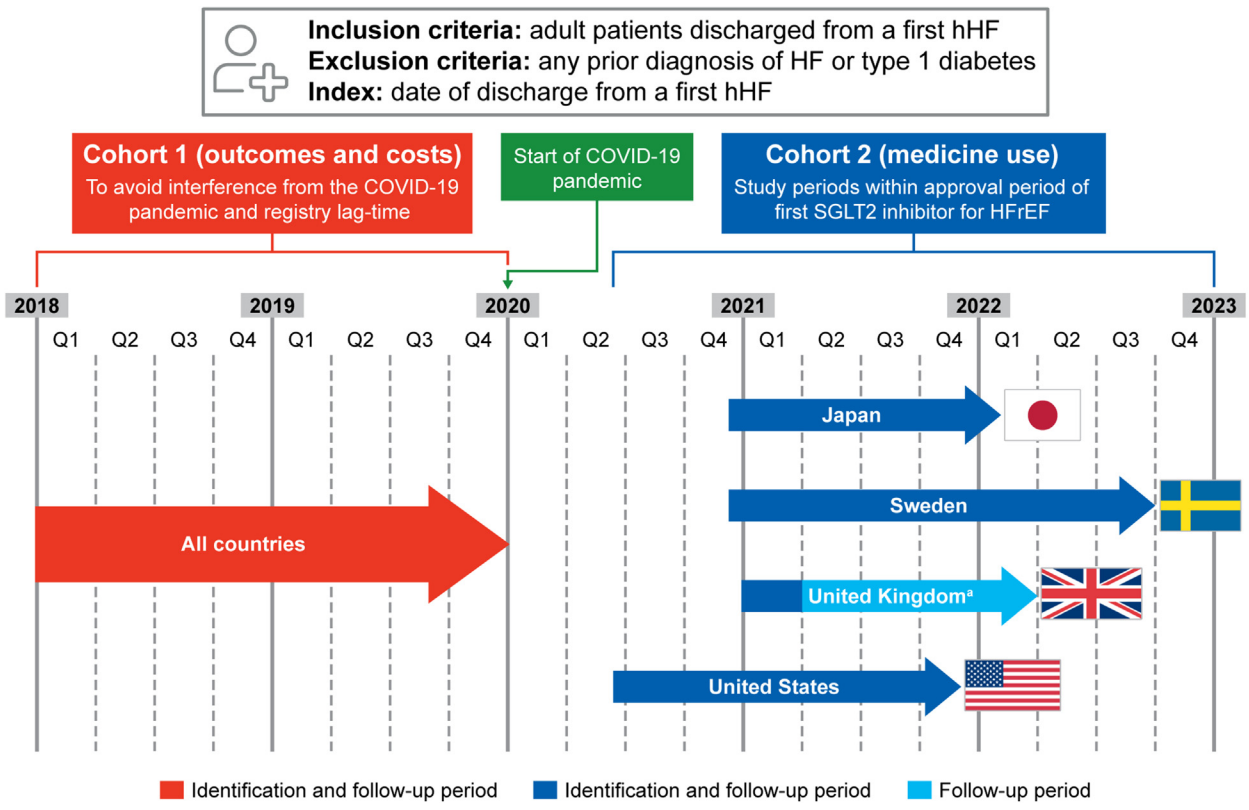
Cohort 2 (contemporary use of medicines during 2020-2022). In this cohort, use of HF medicines following discharge from a first hHF within each country is reported for the years 2020 through 2022 (Figure 1). The study periods for the individual countries within this cohort covered the first full month after approval of the SGLT2 inhibitor dapagliflozin for HFrEF in each country (Japan: December 2020; Sweden: December 2020; United Kingdom: January 2021; United States: June 2020), up to the latest available update of the databases. Because cohort 1 and cohort 2 were independent, the association between GDMT use and outcomes was not studied.

BASELINE CHARACTERISTICS. For patients in both cohorts, baseline data were extracted for at least 12 months before each study period start date to allow a 12-month "lookback" period from the index hHF admission for all patients (baseline periods). Patient characteristics were described prior to the first hHF admission, and included demographics, comorbidities, measurements of blood pressure, and estimated glomerular filtration rate (Supplemental Tables 2 and 3). Use of medicines was based on at least 1 filled prescription during the year prior to the first hHF admission (Supplemental Table 4).

OUTCOMES. Outcomes for each cohort were assessed from first hHF discharge date during the respective follow-up periods for each country.

Clinical outcomes (cohort 1). The clinical outcomes studied were rehospitalizations with a primary diagnosis of HF, chronic kidney disease (CKD) (including diagnoses of acute kidney failure, unspecified kidney failure, diabetic kidney disease,

FIGURE 1 Study Design and Timelines



Cohort 1 (N = 263,525) study period began on January 1, 2018. Cohort 2 (N = 119,350) study period began from date of approval of first SGLT2 inhibitor for HFrEF in each country (Japan: December 2020; Sweden: December 2020; United Kingdom: January 2021; United States: June 2020). Both cohorts include 12-month baseline periods prior to index. [a]United Kingdom patients were identified during Q1 2021 only and followed up for up to 12 months. HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; Q = quarter; SGLT2 = sodium-glucose co-transporter-2.

hypertensive CKD, dialysis, glomerular diseases, renal tubulointerstitial disease, or other),[13] myocardial infarction, stroke, or peripheral artery disease, and cardiovascular and all-cause mortality during the 12 months after index (Supplemental Table 2). The index hHF was not included when counting outcome events.

Hospital health care costs (cohort 1). Costs for planned and unplanned inpatient and outpatient hospital visits associated with any diagnosis, separately, of HF, CKD, myocardial infarction, stroke, and peripheral artery disease were cumulatively summarized for the 12 months following the index date for each patient.[1,14,15] The index hHF was not included. For this analysis, multiple diagnoses could be registered for a given hospitalization. For detailed methods, see Supplemental Methods.

Use of HF medicines (cohort 2). HF medicines were defined as those represented by GDMT (ie, those with a strong, evidence-based recommendation): RAS inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [ARBs]), the ARNI sacubitril/valsartan, beta-blockers, MRAs, and SGLT2 inhibitors (dapagliflozin and empagliflozin). Kaplan-Meier estimates were reported for time to initiation and time to the concurrent use of 2 or more medicines, 3 or more medicines, and 4 medicines in the 12 months following index hHF discharge. All HF medicine prescriptions filled in the month prior to the index hHF and during follow-up were analyzed. GDMT initiation prior to the index hHF may have occurred for indications other than HF, and such medicines may be continued after the index hHF without the need to refill the prescription. Therefore, GDMTs initiated in the month prior to or during the index hHF were counted as use at index and had day 0 as the day of initiation, with day 1 being the date of discharge (index date).

At the time of this analysis, angiotensin-converting enzyme inhibitors, ARBs, sacubitril/valsartan, beta-blockers, MRAs, and SGLT2 inhibitors had been given class I recommendations for the treatment of HFrEF in both European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines; none of these treatments had been given class I recommendations for the treatment of HFpEF.[4,5] Information on LVEF was not available for the majority of patients included in this analysis. As such, we cannot report on whether prescribing adhered to guidelines, but rather only on which medicines were prescribed and when.

STATISTICAL ANALYSIS. Continuous variables were reported using median (IQR). Categorical variables were reported as absolute frequency and percentage. All analyses of event rates are descriptive, and no formal between-group comparisons were made. The event rates are described separately by country, and DerSimonian and Laird random-effects meta-analysis was used when pooling data, taking heterogeneity between countries into consideration.[16] Tau was used to describe heterogeneity, corresponding with the estimated SD of the underlying data across countries. Cumulative percentages of patients using HF medicines after index were calculated using the Kaplan-Meier method. Event rates were calculated as events per 100 patient-years based on time to first event.

ETHICAL APPROVAL. This study was performed in accordance with ethical principles that are consistent with the International Council for Harmonisation Good Clinical Practice Guideline, the Guidelines for Good Pharmacoepidemiology Practice, and the applicable legislation on noninterventional studies and/or observational studies. Institutional Review Board approvals were not needed because EVOLUTION HF only involves secondary analysis of de-identified 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, EVOLUTION HF followed local data source requirements for protocol and ethical approvals. Individual patient consent was not required.

RESULTS

BASELINE CHARACTERISTICS. Cohort 1 included 263,525 patients who had a first hHF from Japan (n = 87,787), Sweden (n = 37,340), the United Kingdom (n = 64,635), and the United States (n = 73,763) (**Figure 1**, **Table 1**). Median age was lower in the United States (68 years) than in Japan, Sweden, and the United Kingdom (78, 81, and 81 years, respectively), and the overall proportion of women was 44% to 50%. Baseline characteristics for cohort 2 (Supplemental Table 5) were similar to those of cohort 1 (**Table 1**).

CLINICAL OUTCOMES (COHORT 1). Event rates were generally similar across all countries (**Table 2**). The most frequent event was all-cause rehospitalization (96.8 events per 100 patient-years), followed by all-cause death (28.4 events per 100 patient-years-data from Sweden and the United Kingdom only), cardiovascular death (16.2 events per 100 patient-years-data from Sweden and the United Kingdom only), rehospitalizations for HF (13.6 events per 100 patient-years), all-cause in-hospital death (12.9 events per 100 patient-years), and rehospitalizations for CKD (4.5 events per 100 patient-years). Rehospitalizations for atherosclerotic cardiovascular diseases were less frequent than rehospitalizations for HF and CKD (myocardial infarction: 2.0 events per 100 patient-years; stroke: 3.0 events per 100 patient-years; and peripheral artery disease: 0.9 events per 100 patient-years). In-hospital all-cause mortality was similar for all 4 countries (**Table 2**). Rates per 100 patient-years for all-cause rehospitalizations were 99.3, 102.0, 106.0, and 80.1 for Japan, Sweden, the United Kingdom, and the United States, respectively (pooled: 96.8 [95% CI: 85.6-108.1]). For the first rehospitalization in our cohorts, the most frequent primary diagnosis was a cardiovascular event.

Full data for all-cause mortality, both in and out of hospital, were only available for Sweden and the United Kingdom (29.2 and 27.7 deaths per 100 patient-years, respectively). In Sweden and the United Kingdom, 13.8 and 18.6 deaths per 100 patient-years, respectively, were registered as having cardiovascular causes based on International Classification of Diseases codes. Event rates for all outcomes were generally higher in older patients (≥70 years of age) than in younger patients (<70 years of age) (Supplemental Table 6).

HOSPITAL HEALTH CARE COSTS (COHORT 1). All countries had hospital health care cost data available, and the cost levels varied between countries. Following hHF, hospital health care costs for cardiorenal events (HF or CKD) were consistently higher than those for atherosclerotic events (myocardial infarction or stroke), across all countries (**Figure 2**).

USE OF HF MEDICINES (COHORT 2). The initiation of RAS inhibitors and beta-blockers within 3 months of first hHF discharge was approximately 60% to 80% across countries and index quarters, and remained

TABLE 1 Characteristics of 263,525 Patients Prior to a First hHF

	Japan (n = 87,787)	Sweden (n = 37,340)	United Kingdom (n = 64,635)	United States (n = 73,763)
Age, y	78 (68-86)	81 (73-88)	81 (71-88)	68 (58-79)
Women	38,529 (44)	18,205 (49)	32,130 (50)	34,806 (47)
Index hospitalization length, d[a]	17 (10-27)	6 (4-10)	8 (4-17)	5 (4-9)
Comorbidities				
Chronic kidney disease	15,998 (18)	6,177 (17)	25,883 (40)	34,347 (47)
Acute kidney injury	2,141 (2)	1,756 (5)	14,665 (23)	23,886 (32)
Atrial fibrillation	23,272 (27)	17,651 (47)	29,607 (46)	25,646 (35)
Cancer	10,011 (11)	4,821 (13)	8,317 (13)	11,044 (15)
Type 2 diabetes	10,980 (13)	8,182 (22)	19,195 (30)	23,290 (32)
Ischemic heart disease[b]	40,207 (46)	12,465 (33)	26,142 (40)	44,592 (60)
Myocardial infarction	17,242 (20)	8,317 (22)	16,480 (25)	22,842 (31)
Peripheral artery disease	3,658 (4)	1,222 (3)	3,806 (6)	9,724 (13)
Stroke	8,099 (9)	2,197 (6)	4,793 (7)	12,925 (18)
Laboratory measurements[c]				
eGFR, mL/min/1.73 m^2	72 (48-87)	NA	60 (46-76)	66 (45-85)
eGFR measurement available	3,207	NA	50,782	63,048
eGFR <60 mL/min/1.73 m^2	1,180 (37)	NA	23,317 (46)	27,066 (43)
Systolic blood pressure, mm Hg[d]	NA	NA	130 (120-141)	138 (123-153)
Systolic blood pressure measurement available	NA	NA	56,150	61,273
Medications				
RAS inhibitor	18,043 (21)	20,511 (55)	31,484 (49)	34,156 (46)
Sacubitril/valsartan	0 (0)	44 (<1)	148 (<1)	210 (<1)
Beta-blockers	16,333 (19)	21,484 (58)	26,501 (41)	38,001 (52)
MRA	5,970 (7)	2,857 (8)	4,385 (7)	3,120 (4)
SGLT2 inhibitor	966 (1)	404 (1)	640 (1)	986 (1)
Loop diuretic agents	32,762 (37)	14,829 (40)	25,869 (40)	28,533 (39)
Ivabradine	0 (0)	9 (<1)	454 (1)	12 (<1)
Nitrates	24,926 (28)	5,600 (15)	8,156 (13)	19,640 (27)
Vitamin K antagonists	2,094 (2)	4,607 (12)	6,789 (11)	4,584 (6)
Receptor $P2Y_{12}$ antagonists	13,977 (16)	2,981 (8)	7,579 (12)	10,064 (14)

Values are median (IQR) or n (%). The table shows characteristics of patients discharged from a first hHF between January 1, 2018, and January 1, 2020 (cohort 1; N = 263,525). [a]Maximum duration was capped at 100 days; patients with index hospitalization longer than 100 days were excluded as outliers. [b]Includes angina pectoris, unstable angina, myocardial infarction, and percutaneous coronary intervention/coronary artery bypass grafting. [c]Laboratory measurements represent the last registered value in the year prior to a first hHF. [d]Systolic blood pressure not measured at admission.

eGFR = estimated glomerular filtration rate; hHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist; NA = not available; RAS = renin-angiotensin system; SGLT2 = sodium-glucose cotransporter-2.

relatively unchanged from first to last relevant calendar quarters (**Figure 3**, Supplemental Figure 2). MRA use at 3 months was approximately 20% to 40% in the first index quarter and changed little over time, except in Sweden, in which a slight increase was noted in the final quarter. Sacubitril/valsartan use was low (<10% at 3 months), with small changes over time. Use of SGLT2 inhibitors was 2% to 11% at 3 months after discharge in the first quarter, increasing to 8% to 35% in the last quarter for Japan, Sweden, and the United States (no last index quarter data were available for the United Kingdom).

Use of 2 or more concurrent HF medicines was approximately 40% to 80% at 3 months across the countries and showed a slight increase from the first to last quarter (**Figure 4**, Supplemental Figure 3). The use of 3 or more concurrent HF medicines was approximately 10% to 30% at 3 months across the countries, with a notable increase from the first to last quarter. For patients enrolled in the last index quarter, the concurrent use of 4 GDMTs at 3 months after hHF discharge was 10% in Japan, 21% in Sweden, 2% in the United Kingdom (first quarter results only), and 3% in the United States (Supplemental Figure 3).

DISCUSSION

This is the largest and most contemporary study of patients following an incident hHF. Despite differences in study designs and patient population definitions, the characteristics of patients prior to an incident hHF in our study showed similarities with other studies (Supplemental Discussion). We found

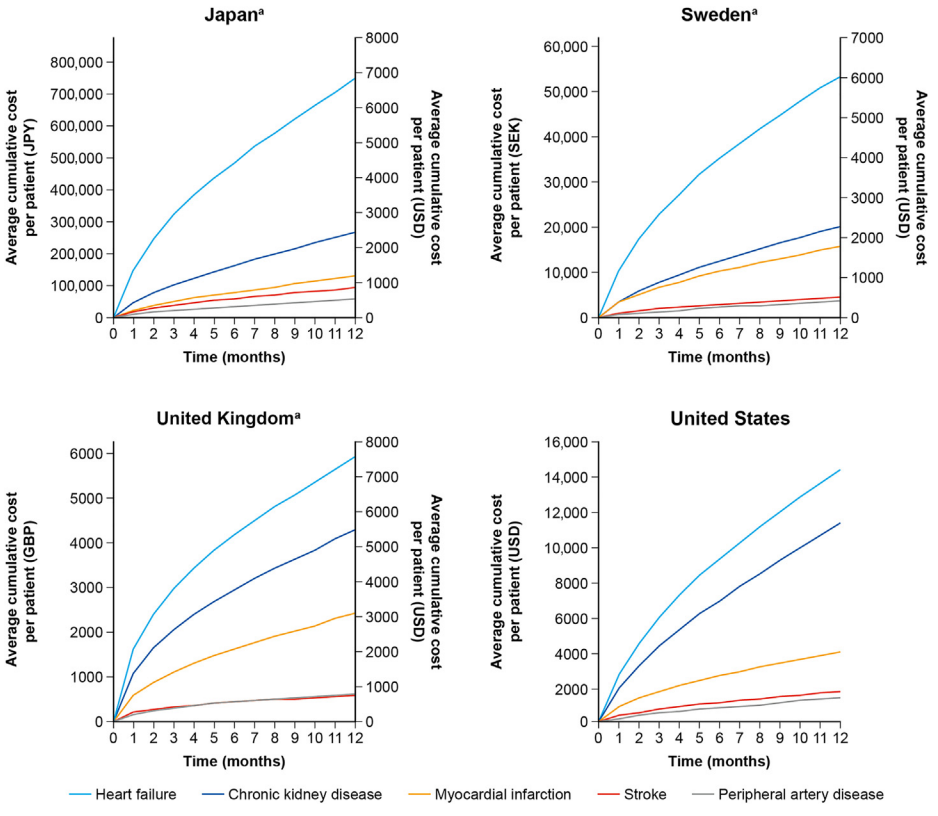
TABLE 2 Rehospitalization Risk and Mortality After Discharge From a First hHF

	Event Rates (Events per 100 Patient-Years)[a]					
	Japan (n = 87,787)	Sweden (n = 37,340)	United Kingdom (n = 64,635)	United States (n = 73,763)	Pooled (95% CI) (N = 263,525)[b]	Tau
Cardiorenal complications						
Heart failure	13.1	19.1	12.2	10.0	13.6 (9.8-17.4)	3.87
Chronic kidney disease	3.5	4.9	5.4	4.0	4.5 (3.6-5.3)	0.87
Atherosclerotic cardiovascular disease						
Myocardial infarction	0.4	2.8	2.9	1.9	2.0 (0.9-3.1)	1.15
Stroke	2.6	3.8	3.5	2.0	3.0 (2.2-3.8)	0.81
Peripheral artery disease	1.2	1.3	0.7	0.4	0.9 (0.5-1.3)	0.40
Mortality						
All-cause death (in hospital)	9.3	13.4	18.6	10.3	12.9 (8.8-17.0)	4.21
All-cause death (in and out of hospital)	NA[c]	29.2	27.7	NA[c]	28.4 (27.0-29.9)	1.01
Cardiovascular death (in and out of hospital)	NA[d]	13.8	18.6	NA[d]	16.2 (11.5-20.9)	3.36
All-cause rehospitalizations	99.3	102.0	106.0	80.1	96.8 (85.6-108.1)	11.49

Event rates for hospitalizations with a main diagnosis of heart failure, chronic kidney disease, myocardial infarction, stroke, peripheral artery disease, all-cause death, and cardiovascular death for patients in Japan, Sweden, the United Kingdom, and the United States, excluding the index hHF (cohort 1; N = 263,525). [a]Based on the first event during the 12 months following the index hHF discharge (excluding the index hHF). [b]Random-effects models were used to calculate pooled values; the heterogeneity measure tau corresponds to the estimated SD of the underlying data. [c]Data on deaths outside of hospital not available. [d]Cause of death registries not available.

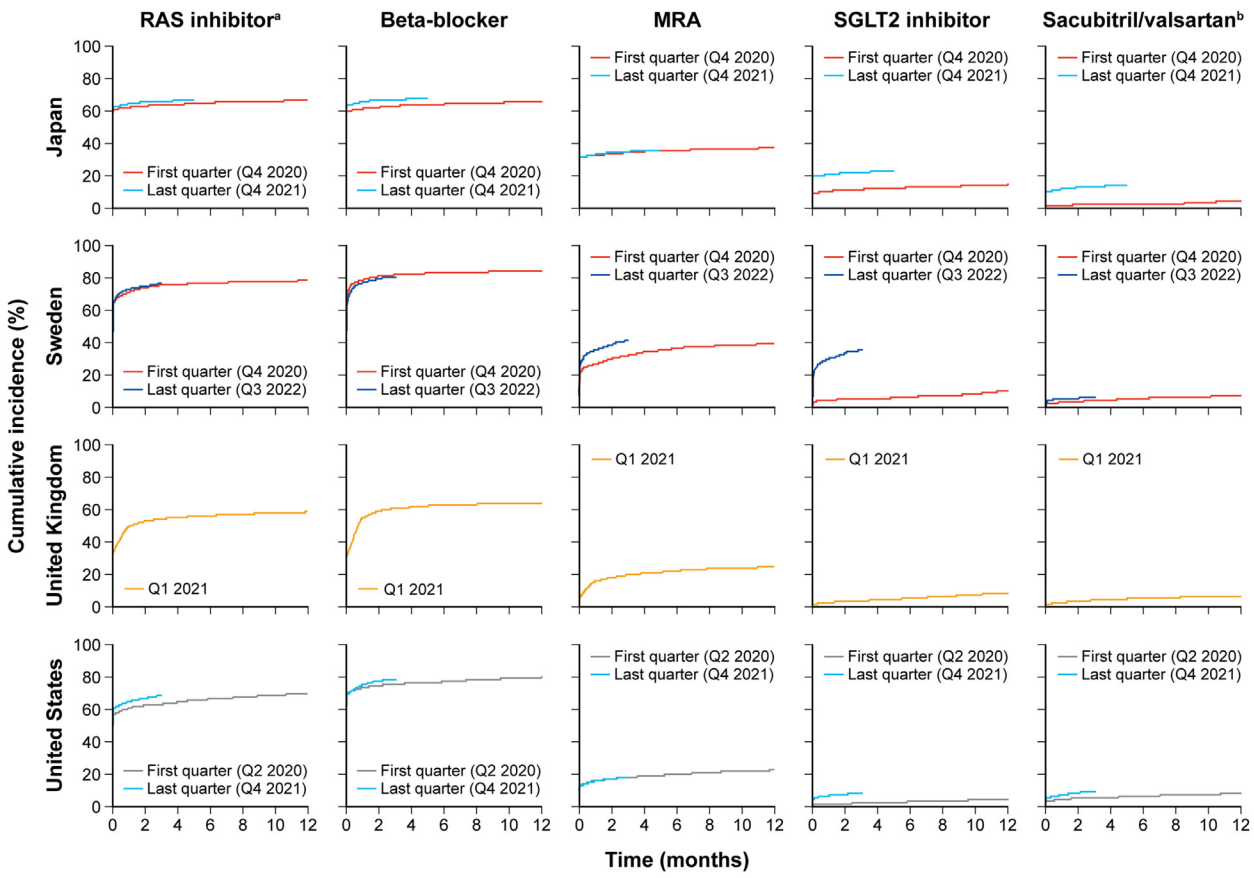
Abbreviations as in Table 1.

FIGURE 2 Health Care Costs 12 Months After a First hHF Discharge



Average cumulative hospital health care costs per patient in 263,525 unique patients (enrolled 2018-2020) in the 12 months after a first hospitalization for heart failure (hHF) discharge reported in USD and local currency. Index hHF costs were not included. [a]Conversion rates from January 1, 2019 used (1 JPY = 0.0091 USD; 1 SEK = 0.1127 USD; 1 GBP = 1.2752 USD); currency was converted simply by applying conversion rates, without considering differences in purchasing power. GBP = British pound sterling; JPY = Japanese yen; SEK = Swedish krona; USD = United States dollars.

FIGURE 3 HF Medicine Use After a First hHF Discharge

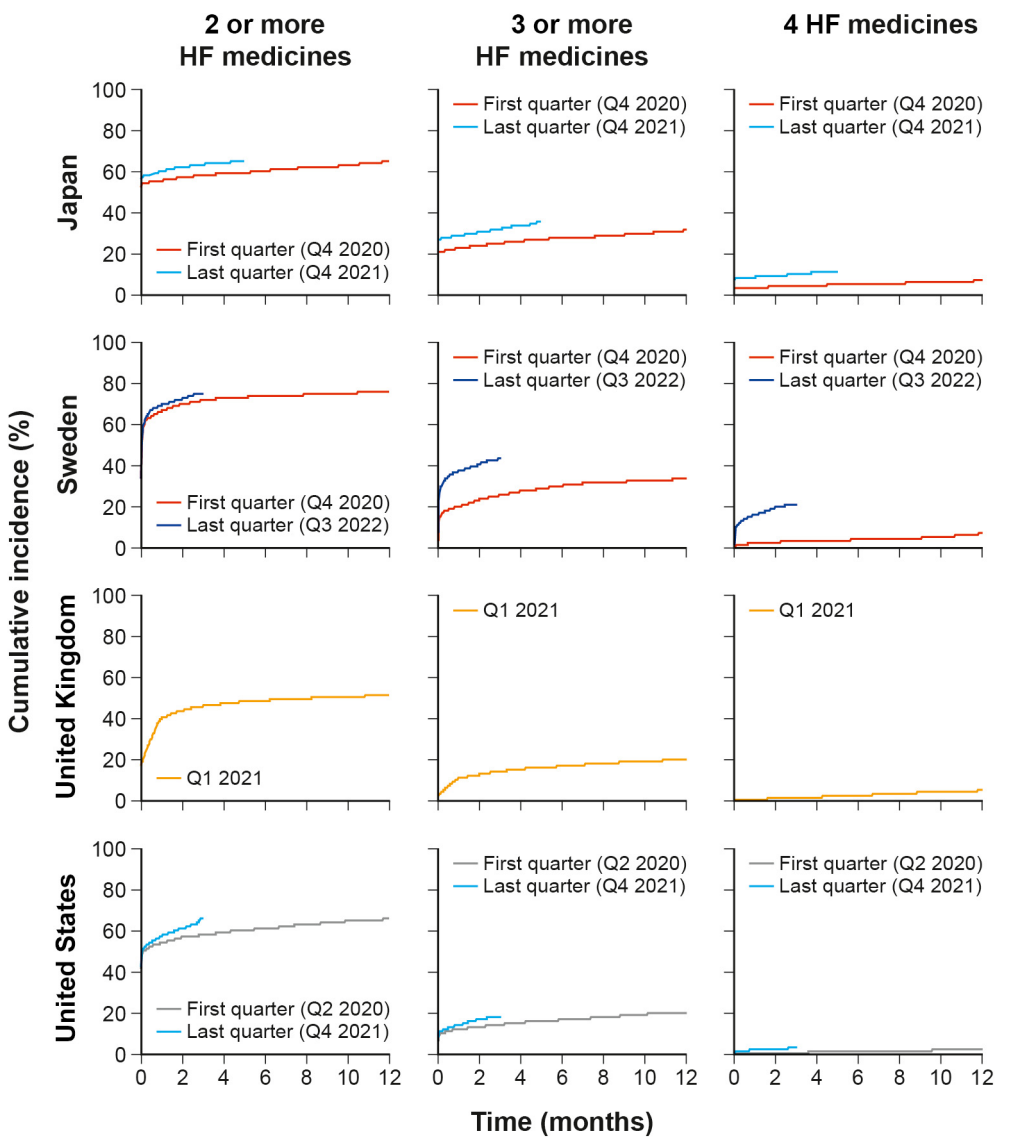


Cumulative incidences of patients using a renin-angiotensin system (RAS) inhibitor (including sacubitril/valsartan), beta-blocker, mineralocorticoid receptor antagonist (MRA), SGLT2 inhibitor (dapagliflozin or empagliflozin), and sacubitril/valsartan following a first hHF among 119,350 unique patients (enrolled 2020-2022) by the first and last calendar quarters of index hHF within each country. Patients were only enrolled during one quarter in the United Kingdom (quarter 1 [Q1] 2021); no last quarter was available. The last calendar quarter is the most recent calendar quarter with more than 3 months of follow-up data available (cohort 2, N = 119,350). [a]Includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and sacubitril/valsartan. [b]The sacubitril/valsartan group is a subgroup of the RAS inhibitor group. Abbreviations as in Figure 1.

that patients discharged following their first hHF were at a high risk of rehospitalization and death. Substantial hospital health care costs accumulated in the year following hHF discharge, which were mainly driven by HF and CKD readmissions. During years 2020 to 2022, we found that established HF medicines like RAS inhibitors, sacubitril/valsartan, beta-blockers, and MRAs showed relatively few changes in use. The largest change in use was the uptake of SGLT2 inhibitors, with a 2- to 7-fold increase in use from the first to the last calendar quarter. However, relatively few patients were treated with all 4 foundational therapies despite many of them being likely to have indications for them, such as HFrEF (all 4), HFpEF (MRA, SGLT2 inhibitor, ARNI), hypertension (MRA, RAS inhibitor, beta-blocker), rate control for atrial fibrillation (beta-blocker), and diabetes (SGLT2 inhibitor).

MORTALITY AND REHOSPITALIZATION EVENTS. Following discharge from a first hHF, rehospitalization and mortality were higher in this real-world cohort than in observational studies of patients with acute hHF.[17,18] Although speculative, this may partly be because the EVOLUTION HF population exclusively included cases of incident hHF. This population, prior to hospitalization, was undiagnosed and therefore not treated optimally. Indeed, most new cases of HF are diagnosed during a hospital admission. These patients may have rapid progression of disease and severe comorbid conditions (such as respiratory infections or acute coronary syndrome) that precipitated the event. It is to be expected that

FIGURE 4 Concurrent HF Medicine Use After a First hHF Discharge



Cumulative incidences of patients using concurrent HF medicines (RAS inhibitor [including sacubitril/valsartan], beta-blocker, MRA, and SGLT2 inhibitor [dapagliflozin or empagliflozin]) following a first hHF among 119,350 unique patients (enrolled 2020-2022) by the first and last calendar quarters of index hHF within each country. Patients were only enrolled during one quarter in the United Kingdom (Q1 2021); no last quarter was available. The last calendar quarter is the most recent calendar quarter with more than 3 months of follow-up available (cohort 2, N = 119,350). Abbreviations as in Figures 1 and 3.

the sickest patients will die first, enriching subsequent years with survivors who have a less adverse prognosis. Epidemiological studies have long shown that mortality is higher in the first 6 to 12 months after the onset of HF,[19] although registry data do not always concur (eg, REPORT-HF [International Registry to assess mEdical Practice with lOngitudinal obseRvation for Treatment of Heart Failure]). The most common rehospitalization events were for HF- and CKD-related events, with lower hospitalization rates for atherosclerotic cardiovascular diseases (myocardial infarction, stroke, and peripheral artery disease).

The pooled mortality of 28% within the first year was high compared with other studies,[17,18] and the results from Sweden and the United Kingdom suggest that more than half of the deaths occur outside of hospital following a first hHF. The high risks of rehospitalization and death observed following a first

hHF indicate an urgent need for early initiation of multiple concurrent GDMTs.

HOSPITAL HEALTH CARE COSTS. The cumulative cost analyses account for repeated events during follow-up, rather than for only first events. These demonstrated that, over a 12-month period, hospital health care costs increased quite rapidly, mainly driven by hospitalizations involving HF and CKD. Although we studied patients with a first hHF (a substantial proportion of whom are likely to have had heart failure with mildly reduced ejection fraction [HFmrEF] and HFpEF), it is possible that more rapid initiation of GDMTs may reduce future hospitalization events and may delay the progression of CKD.[20,21]

HF MEDICINE UPTAKE FOLLOWING A FIRST hHF. When assessing the initiation of individual GDMT medications, large proportions of patients were using a RAS inhibitor or beta-blocker immediately after hHF discharge. This probably reflects the widespread use of these therapies for comorbid conditions prior to admission as well as historical conventions about the sequence of medicine initiation. However, in the first year after discharge, few patients were initiated on sacubitril/valsartan[22,23] or SGLT2 inhibitors. Low use of SGLT2 inhibitors in 2021 to 2022 is not particularly surprising, as they only recently received approval, robust guideline recommendations for the management of HF, especially HFpEF, and agreements for reimbursement.

SGLT2 inhibitors reduce the combined risk of hHF or cardiovascular death in patients with HFrEF, HFmrEF, and HFpEF.[24-27] Most patients encountered in clinical practice are eligible for treatment with SGLT2 inhibitors according to trial and label criteria.[28] It is to be hoped that SGLT2 inhibitor use for the treatment of HF will increase with greater awareness and successful implementation strategies. In an analysis from SwedeHF (the Swedish Heart Failure Registry), after the HF benefits of SGLT2 inhibitors became known from the cardiovascular outcomes trials, SGLT2 inhibitor use was noted to increase rapidly in patients with type 2 diabetes and HF.[29]

High clinical risk has been associated with suboptimal GDMT use by other studies. The recent randomized STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies) study demonstrated the benefits of rapid initiation of 3 concurrent GDMTs vs usual care following hHF, including patients with a broad range of LVEF, and underlines the feasibility of early and rapid optimization of multiple medical therapies in HF.[30]

Among patients hospitalized with HF, a substantial proportion are likely to have HFrEF or HFmrEF.[1,2] The uptake of all 4 GDMTs may have been higher in patients with HFrEF. We recognize that guidelines do not include recommendations for the use of beta-blockers in patients with HFpEF (these may even worsen outcomes and symptoms in some patients)[31,32] and that the class of recommendations are lower for ARNIs, MRAs, or ARBs than SGLT2 inhibitors.[4,5] Nevertheless, many patients will receive RAS inhibitors and beta-blockers for indications other than HF. There are few trial data to support use of all 4 medicines in new-onset hospitalized HF, and no data for HFpEF. However, we assessed initiation for up to 1 year postdischarge from a first hHF and about half of such patients would be expected to have HFrEF.[2] In addition, patients with HFmrEF have similar indications to those with HFrEF, and therefore the proportion of patients not eligible for all 4 medicines is probably lower than 50%. Therefore, it is not unreasonable to expect greater use of all 4 medicines than observed to date.

There are a number of potential barriers to optimal GDMT use, such as patients' willingness to take medicines; real or anticipated side effects and tolerability;[33,34] age, frailty, and comorbidities;[7,8,35] health care professional inertia; the cost to patients; a lack of reimbursement and payer coverage; a lack of optimized multidisciplinary health care structures for GDMT optimization and follow-up; and a lack of strategic care plans and staff to implement them, which creates uncertainty about who will implement therapy and when. Initiatives to improve GDMT uptake and subsequently patient outcomes might include better patient and clinician education and understanding of HF and its management;[11,36] assurance of access to appropriate care and follow-up;[35,37,38] expansion of payer coverage; use of registries and audit;[12] adherence to performance measures and quality indicators;[11] better multidisciplinary care coordination in HF; use of electronic medical record alerts;[39] and use of HFrEF therapeutic scores (eg, quad score) to promote GDMT.[40]

STUDY STRENGTHS AND LIMITATIONS. Strengths of our study include the large sample size and the availability of data across 4 countries with different health care infrastructures and funding models, although these might have limited generalizability to other health care systems.

Limitations of our study include that patient information on LVEF was not available. A substantial

proportion of patients will have had HFmrEF or HFpEF and, despite relevant comorbidities, may not have been indicated for all 4 GDMTs. In Japan and the United States, complete coverage of mortality data is lacking, which might have affected the competing risk for rehospitalization. To minimize this, patients were censored 14 days after the last registered activity. Validation of outcomes per se in this study was not performed. However, event rates across outcomes and countries were similar, and external validation has been reported in some of the countries. Vital signs (eg, heart rate or clinical examination findings) and some relevant laboratory values (eg, creatinine, potassium) were often not available, which precluded some assessments of contraindications to GDMTs. Information about side effects and tolerability leading to treatment discontinuation was not available. Finally, natriuretic peptides were not available in all countries and, where available, these tests were either not done or their results were not recorded.

CONCLUSIONS

In patients following a first hHF, postdischarge rates for rehospitalization and death were high. Rehospitalization rates and hospital health care costs were mainly driven by HF and CKD, highlighting the unmet need and causes of the related high health care burden. Optimized GDMT use may reduce risks and costs during the vulnerable post-hHF period and improve patient outcomes. During 2020 to 2022, rates of prescribing for established HF medicines like RAS inhibitors, sacubitril/valsartan, beta-blockers, and MRAs has remained relatively unchanged. Conversely, SGLT2 inhibitor use, albeit still low, increased several-fold, likely due to recent approvals and guideline updates. Even with the likelihood that a substantial proportion of patients in this study have HFpEF or HFmrEF (which have weaker indications for multiple GDMTs than patients with HFrEF), the low rates of uptake for all 4 GDMTs underline the need for further optimization of implementation strategies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Following a first hHF, there are high rates of rehospitalization and death, as well as high costs. The 4 foundational pharmacological classes of medicines for HFrEF had low implementation rates in broad, generalizable HF populations in Japan, Sweden, the United Kingdom, and the United States. This may be partially explained by weaker indications and recommendations for these treatments for HFmrEF and HFpEF and also de novo and acute HF. Nevertheless, outcomes may be improved with better use of 4 GDMT medications after hHF in appropriate patients.

TRANSLATIONAL OUTLOOK: There are many barriers to the rapid initiation of GDMTs after a first hHF. These may include perceptions regarding the safety and efficacy of GDMTs in the acute setting, a lack of strategic care plans and a lack of staff with the expertise and experience to implement them, negative patient and clinician perceptions about particular GDMTs, and challenges posed by a lack of access to optimal HF care. This study highlights the need to address these barriers to optimal care in order to improve patient outcomes and to use health care resources wisely. This will require effective planning, organization and implementation, and transparent auditing.

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