# Effect of Sotagliflozin on Early Mortality and Heart Failure-Related Events

SOLOIST-WHF Investigators; Pitt, Bertram; Bhatt, Deepak L.; Szarek, Michael; Cannon, Christopher P.; Leiter, Lawrence A.; McGuire, Darren K.; Lewis, Julia B.; Riddle, Matthew C.; Voors, Adriaan A.

*Published in:*
JACC: Heart Failure

*DOI:*
10.1016/j.jchf.2023.05.026



*Document Version*
Publisher's PDF, also known as Version of record

*Publication date:*
2023

JACC: HEART FAILURE VOL. 11, NO. 8, 2023


CLINICAL RESEARCH

# Effect of Sotagliflozin on Early Mortality and Heart Failure-Related Events

## A Post Hoc Analysis of SOLOIST-WHF

Bertram Pitt, MD,[a] Deepak L. Bhatt, MD, MPH,[b] Michael Szarek, PHD,[c,d,e] Christopher P. Cannon, MD,[f] Lawrence A. Leiter, MD,[g] Darren K. McGuire, MD, MHSC,[h] Julia B. Lewis, MD,[i] Matthew C. Riddle, MD,[j] Adriaan A. Voors, MD, PHD,[k] Marco Metra, MD,[l] Lars H. Lund, MD,[m] Michel Komajda, MD,[n] Jeffrey M. Testani, MD, MTR,[o] Christopher S. Wilcox, MD,[p] Piotr Ponikowski, MD,[q] Renato D. Lopes, MD, PHD,[r] Justin A. Ezekowitz, MBBCH,[s] Franklin Sun, MS,[t] Michael J. Davies, PHD,[u] Subodh Verma, MD, PHD,[g] Mikhail N. Kosiborod, MD,[u] Ph. Gabriel Steg, MD,[v] on behalf of the SOLOIST-WHF Investigators

## ABSTRACT

**BACKGROUND** Approximately 25% of patients admitted to hospitals for worsening heart failure (WHF) are readmitted within 30 days.

**OBJECTIVES** The authors conducted a post hoc analysis of the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post-WHF) trial to evaluate the efficacy of sotagliflozin versus placebo to decrease mortality and HF-related events among patients who began study treatment on or before discharge from their index hospitalization.

**METHODS** The main endpoint of interest was cardiovascular death or HF-related event (HF hospitalization or urgent care visit) occurring within 90 and 30 days after discharge for the index WHF hospitalization. Treatment comparisons were by proportional hazards models, generating HRs, 95% CIs, and *P* values.

**RESULTS** Of 1,222 randomized patients, 596 received study drug on or before their date of discharge. Sotagliflozin reduced the main endpoint at 90 days after discharge (HR: 0.54 [95% CI: 0.35-0.82]; $P = 0.004$) and at 30 days (HR: 0.49 [95% CI: 0.27-0.91]; $P = 0.023$) and all-cause mortality at 90 days (HR: 0.39 [95% CI: 0.17-0.88]; $P = 0.024$). In subgroup analyses, sotagliflozin reduced the 90-day main endpoint regardless of sex, age, estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction, or mineralocorticoid receptor antagonist use. Sotagliflozin was well-tolerated but with slightly higher rates of diarrhea and volume-related events than placebo.

**CONCLUSIONS** Starting sotagliflozin before discharge in patients with type 2 diabetes hospitalized for WHF significantly decreased cardiovascular deaths and HF events through 30 and 90 days after discharge, emphasizing the importance of beginning sodium glucose cotransporter inhibitor treatment before discharge.


From the [a]Department of Internal Medicine (Emeritus), University of Michigan School of Medicine, Ann Arbor, Michigan, USA; [b]Mount Sinai Heart, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [c]School of Public Health, SUNY Downstate Health Sciences University, Brooklyn, New York, USA; [d]University of Colorado School of Medicine, Aurora, CO, USA; [e]CPC Clinical Research, Aurora, Colorado, USA; [f]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [g]Li Ka Shing Knowledge Institute, St. Michael's Hospital, and University of Toronto, Toronto, Ontario, Canada; [h]University of Texas Southwestern Medical Center, and Parkland Health and Hospital System, Dallas, Texas, USA; [i]Vanderbilt University Medical Center, Nashville, Tennessee, USA; [j]Oregon Health & Science University, Portland, Oregon, USA; [k]University of

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2023.05.026

JACC: HEART FAILURE VOL. 11, NO. 8, 2023
AUGUST 2023:879–889

**ABBREVIATIONS AND ACRONYMS**

**AE** = adverse event

**DKA** = diabetic ketoacidosis

**eGFR** = estimated glomerular filtration rate

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**LVEF** = left ventricular ejection fraction

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**Q** = quartile

**SGLT** = sodium glucose cotransporter

**T2D** = type 2 diabetes

**WHF** = worsening heart failure

Heart failure (HF) is the second most common cause of hospitalizations for patients >65 years of age in the United States, posing a significant cost burden on society.[1,2] The morbidity and mortality impact on patients is also severe. Up to 62% of patients discharged after an episode of worsening heart failure (WHF) are readmitted to the hospital within 1 year.[3,4] Nearly one-half of such patients are readmitted within 90 days and approximately a one-quarter within 30 days of hospital discharge,[3-7] with mortality rates during the first 30 days after discharge as high as 17%.[8-10] Tools for adequate risk prediction, and various tested strategies to decrease these risks, have been largely unsuccessful.[10-15] Meanwhile, U.S. health care reimbursement policy penalizes hospitals with high rates of 30-day HF readmissions.[16] These factors all point to a substantial unmet need for approaches that will decrease HF hospital readmissions and HF-related events such as visits to an urgent care center.

SEE PAGE 890

Sodium glucose cotransporter (SGLT) inhibitors decrease the risk of cardiovascular death and HF hospitalizations in patients with chronic HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF).[17-21] Based on this evidence, SGLT inhibitors are recommended for the treatment of HF across the spectrum of left ventricular ejection fraction (LVEF) in U.S. and European guidelines.[22,23] However, many patients admitted to the hospital with WHF have not previously received recommended therapies, and these patients are often discharged without or with only low doses of recommended HF agents.[3,24-26]

Few studies have examined the safety and effects of SGLT inhibitors on cardiovascular mortality and hospital-related outcomes when these agents are started in the setting of in-hospital HF.[17,27,28] The safety and efficacy of the relatively selective SGLT2 inhibitors such as empagliflozin and dapagliflozin when started in hospital after an episode of hospitalization for acute HF or WHF are promising, but as yet inconclusive. The dual SGLT1 and SGLT2 inhibitor sotagliflozin has been shown to decrease cardiovascular outcomes when administered before hospital discharge for WHF.[17] In addition, in the SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Participants With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial of patients with chronic kidney disease and type 2 diabetes (T2D), sotagliflozin was shown to significantly decrease the incidence of nonfatal and fatal stroke and nonfatal and fatal myocardial infarction by 30%,[29] an effect that has not been noted in studies of the more selective SGLT2 inhibitors in patients with chronic kidney disease.[30,31] The potential mechanisms accounting for the effect of sotagliflozin on stroke and myocardial infarction including an effect of SGLT1 inhibition on the intestinal microbiome have been reviewed recently.[32] In view of the potential difference in effectiveness of sotagliflozin in comparison with the more selective SGLT2 inhibitors and the fact that its effects on early and 30- and 90-day outcomes after discharge have not been analyzed in detail previously, we conducted a post hoc analysis of data from the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial focusing on the effects of sotagliflozin 30 and 90 days after discharge. In the SOLOIST-WHF trial, 48.8% of the total patient population received their first dose of study medication (either sotagliflozin or placebo) before discharge.[17] We evaluated the efficacy and safety of sotagliflozin specifically in this subset of patients who began study treatment on or before the date of hospital discharge from their index WHF admission and assessed

Groningen-University Medical Center Groningen, Groningen, the Netherlands; [l]Azienda Socio Sanitaria Territoriale Spedali Civili and University of Brescia, Brescia, Italy; [m]Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [n]Paris Sorbonne University and Groupe Hospitalier Paris Saint Joseph, Paris, France; [o]Yale University, New Haven, Connecticut, USA; [p]Georgetown University, Washington, DC, USA; [q]Wroclaw Medical University, Wroclaw, Poland; [r]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA; [s]University of Alberta and Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; [t]Lexicon Pharmaceuticals Inc., The Woodlands, Texas, USA; [u]Department of Cardiovascular Medicine, Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA; and the [v]Université Paris-Cité, Institut Universitaire de France, INSERM U-1148, FACT (French Alliance for Cardiovascular Trials) and AP-HP (Assistance Publique-Hôpitaux de Paris), Hopital Bichat Paris, Paris, France.

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.

Manuscript received November 29, 2022; revised manuscript received April 5, 2023, accepted May 1, 2023.

outcomes during the 90- and 30-day periods after discharge (not from randomization), when patients are at highest risk of death or readmission for HF-related events.[33,34]

## METHODS

The SOLOIST-WHF trial was a phase III, international, double-blind, randomized, placebo-controlled trial involving patients (aged 18-85 years) with T2D who were recently admitted for WHF, regardless of LVEF. Participants were assigned randomly to once-daily sotagliflozin 200 mg (with a possible dose escalation to 400 mg) or placebo. In the main trial, study medication was to be started before or within 3 days of discharge for the index WHF event. Randomization was stratified according to baseline LVEF (<50% or ≥50%) and geographic region. Over a median follow-up of 9.0 months, cardiovascular events, including hospital readmissions for HF events, were documented. The study conformed to the Declaration of Helsinki; the protocol was approved by the relevant health authority, institutional review board, or ethics committee at each participating study site; and all participants provided written, informed consent. Full design details as well as overall efficacy and safety results have been published previously.[17]

**POPULATION AND ENDPOINTS.** In the main trial, the primary endpoint was the total number of cardiovascular deaths and hospitalizations and urgent visits for HF (first and subsequent events) between the time of randomization and the end of study, a median of 9 months later.[17] The main endpoint of this post hoc, exploratory analysis was first occurrence of cardiovascular death or HF-related event (hospitalizations or urgent care visits for HF) within 90 days and within 30 days after hospital discharge (*not* randomization), specifically in the subgroup of patients who began study treatment on or before the date of discharge for their index hospitalization for WHF. Additional endpoints included first nonfatal HF-related event (ie, hospitalization or urgent visit for HF), cardiovascular death, all-cause death, first occurrence of all-cause hospitalization, and first occurrence of all-cause death or hospitalization. For a given patient, if their date of first dose of study treatment was the same as their index hospitalization discharge date, it was assumed that the dose was received before discharge. A sensitivity analysis was performed to determine the event rates at 90 and 30 days from the randomization date.

**STATISTICAL METHODS.** Categorical variables are expressed as counts and percentages, while continuous variables are expressed as median (Q1 to Q3). Cumulative incidences of events at 90 and 30 days were estimated by cumulative incidence functions. Treatment comparisons for events through 30 days, through 90 days, and through all postdischarge follow-up were performed using competing-risks proportional hazards models stratified by geographic region and baseline LVEF (<50%, ≥50%) to generate HRs and corresponding 95% CIs and *P* values. Deaths that were not part of a given endpoint were treated as competing terminal events. To determine whether the treatment effect on the main endpoint was different before and after 90 and 30 days after discharge, a competing-risks proportional hazards model that allowed the treatment HR to vary before and after 90 and 30 days after discharge was compared with the model in which the treatment HR was assumed constant over the total duration of postdischarge follow-up to test whether a nonconstant HR provided a better fit to the observed data. Possible heterogeneity of the sotagliflozin treatment effect on the main endpoint through 90 days after discharge for subgroups defined by baseline demographic and clinical characteristics was assessed by the significance of interaction terms in proportional hazards models. The sensitivity analysis evaluating time from randomization used the same statistical approach.

Safety data were summarized as treatment-emergent adverse events (AEs), serious AEs, and events of special interest, which were defined for a given patient as events occurring between the date of first dose and either date of last dose plus 10 days of study treatment or 90 or 30 days after discharge, whichever was earlier.

## RESULTS

Of the 1,222 randomized patients, 290 sotagliflozin recipients and 306 placebo recipients started study drug a median of 7 days (Q1-Q3: 4-9 days) after admission and before discharge. Within this subgroup, 142 patients began study drug ≥1 day before discharge (median, 2 days; Q1-Q3: 1-4 days) and 454 patients on the day of discharge. Baseline characteristics of the 596 patients are summarized in **Table 1** by treatment group. The median age was 70 years, 34.7% were female, and 96.1% were White. The median LVEF, estimated glomerular filtration rate (eGFR), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were 35%, 50.6 mL/min/1.73 $m^2$, and 1,686 pg/mL, respectively. Baseline characteristics were similar between the treatment groups.

These 596 patients were followed for cardiovascular death or HF-related event for a median of

JACC: HEART FAILURE VOL. 11, NO. 8, 2023
AUGUST 2023:879-889

**TABLE 1 Demographics and Patient Characteristics at Baseline**

| | Sotagliflozin (n = 290) | Placebo (n = 306) | Total (N = 596) |
|---|---|---|---|
| Age, y | 69 (63-75) | 70 (64-76) | 70 (64-76) |
| Female | 96 (33.1) | 111 (36.3) | 207 (34.7) |
| Race | | | |
| White | 281 (96.9) | 292 (95.4) | 573 (96.1) |
| Black | 3 (1.0) | 6 (2.0) | 9 (1.5) |
| Asian | 5 (1.7) | 5 (1.6) | 10 (1.7) |
| Other | 0 | 1 (0.3) | 1 (0.2) |
| Unknown | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| Hispanic or Latino ethnicity | 56 (19.3) | 75 (24.5) | |
| Geographic region[a] | | | |
| North America | 8 (2.8) | 9 (2.9) | 17 (2.9) |
| Latin America | 46 (15.9) | 65 (21.2) | 111 (18.6) |
| Western Europe | 68 (23.4) | 64 (20.9) | 132 (22.1) |
| Eastern Europe | 156 (53.8) | 153 (50.0) | 309 (51.8) |
| Rest of world | 12 (4.1) | 15 (4.9) | 27 (4.5) |
| LVEF <50%[a] | 232 (80.0) | 243 (79.4) | 475 (79.7) |
| LVEF, % | 36 (30-46) | 35 (29-45) | 35 (30-45) |
| BMI, kg/m$^2$ | 30.4 (26.8-34.3) | 30.9 (27.4-34.5) | 30.7 (27.1-34.5) |
| BMI ≥30 kg/m$^2$ | 150 (51.7) | 169 (55.2) | 319 (53.5) |
| SBP, mm Hg | 122 (112-133) | 122 (113-133) | 122 (112-133) |
| DBP, mm Hg | 73 (68-80) | 73 (68-80) | 73 (68-80) |
| Duration of diabetes, y | 10.0 (4.3-16.7) | 10.1 (4.9-15.6) | 10.1 (4.7-15.9) |
| Hemoglobin A1c, % | 7.1 (6.4-8.4) | 7.2 (6.4-8.1) | 7.1 (6.4-8.2) |
| NT-proBNP, pg/mL | 1,701 (742-3,632) | 1,634 (811-3,694) | 1,686 (776-3,687) |
| eGFR, mL/min/1.73 m$^2$ | 49.4 (39.8-61.0) | 53.5 (42.1-64.6) | 50.6 (40.6-62.3) |
| Any RAAS inhibitor | 269 (92.8) | 281 (91.8) | 550 (92.3) |
| ACE inhibitor | 123 (42.4) | 124 (40.5) | 247 (41.4) |
| ARB | 116 (40.0) | 129 (42.2) | 245 (41.1) |
| MRA | 197 (67.9) | 198 (64.7) | 395 (66.3) |
| ARNI | 48 (16.6) | 48 (15.7) | 96 (16.1) |
| Beta-blocker | 266 (91.7) | 284 (92.8) | 550 (92.3) |
| Loop diuretic | 279 (96.2) | 290 (94.8) | 569 (95.5) |
| Other diuretic | 29 (10.0) | 27 (8.8) | 56 (9.4) |
| First dose of study treatment | | | |
| Day of discharge | 223 (76.9) | 231 (75.5) | 454 (76.2) |
| Before day of discharge | 67 (23.1) | 75 (24.5) | 142 (23.8) |
| Days prior | 2 (1-4) | 2 (1-4) | 2 (1-4) |

Value are median (Q1-Q3) or n (%). [a]Randomization stratification factor; used as strata variables in proportional hazards models.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; SBP = systolic blood pressure.

7.2 months (Q1-Q3: 3.4-12.3 months) after discharge. At 90 days after discharge, the estimated cumulative incidence of this endpoint was 10.8% in the sotagliflozin group and 19.9% in the placebo group, a 46% risk reduction for sotagliflozin (HR: 0.54 [95% CI: 0.35-0.82]; $P = 0.004$) (**Table 2**, **Central Illustration**). At 30 days, the corresponding estimated cumulative incidences were 5.2% and 10.2%, a 51% risk reduction (HR: 0.49 [95% CI: 0.27-0.91]; $P = 0.023$). Through 90 days, there was a 52% reduction in the composite risk of all-cause death and HF-related events (HR: 0.48 [95% CI: 0.32-0.74]; $P = 0.0008$) and a 53% reduction in all-cause death and HF events through 30 days (HR: 0.47 [95% CI: 0.26-0.87]; $P = 0.0157$). Sotagliflozin significantly decreased the risk of HF-related events by 48% and 52% during the 90- and 30-day postdischarge periods, respectively, and all-cause death over 90 days by 61%; treatment differences were not significant for the other endpoints (**Table 2**). Similar results were obtained when the data were analyzed from the time of randomization (Supplemental Table 1).

Over the entire postdischarge follow-up period, sotagliflozin decreased the risk of the main endpoint by 31% (HR: 0.69 [95% CI: 0.51-0.94]; $P = 0.017$) (Supplemental Table 1, Supplemental Figure 1). Allowing the treatment HR to be different through 90 days and after 90 days suggested the sotagliflozin treatment benefit was more apparent in the earlier period (HR: 0.54) compared with the later period (HR after 90 days: 0.91 [95% CI: 0.59-1.41]; $P = 0.68$). Furthermore, a model allowing the treatment HR to differ through and after 90 days seemed to fit the data better than the model with an assumed constant treatment effect ($P = 0.09$ for model fit improvement), supporting the observation of a more pronounced early benefit. Similar results were observed when allowing the treatment HR to differ through 30 days and after 30 days.

In subgroup analyses for the main endpoint through 90 days after discharge (**Figure 1**), there was no significant heterogeneity ($P > 0.05$ for interaction) in the effectiveness of sotagliflozin across subgroups including age <65 or ≥65 years, sex, baseline LVEF <50% or ≥50%, baseline NT-proBNP level <1,686 or ≥1,686 pg/mL, and baseline eGFR <60 or ≥60 mL/min/1.73 m$^2$.

The safety profile of sotagliflozin during the postdischarge period was generally consistent with that observed in the main study.[17] At 90 days (**Table 3**), diarrhea was reported in 3.4% of the sotagliflozin group and 1.3% of the placebo group and AEs associated with volume depletion in 7.2% and 5.6%, respectively (**Table 3**). Diabetic ketoacidosis (DKA) was reported in 1 patient (0.3%) receiving sotagliflozin and no patients receiving placebo. At 30 days (Supplemental Table 2), diarrhea was reported in 3.1% and 0.3% and volume depletion in 6.6% and 4.6% of the sotagliflozin and placebo groups, respectively. No cases of DKA were reported within 30 days after discharge. The incidence of other AEs and serious AEs was similar between treatment groups (**Table 3**, Supplemental Table 2).

## DISCUSSION

In the SOLOIST-WHF trial primary analysis, the administration of sotagliflozin resulted in a significantly lower number of cardiovascular deaths and hospitalizations and urgent visits for HF relative to placebo in patients admitted for a WHF event.[17] Sotagliflozin was also found to decrease total hospitalizations and increase days alive and out of the hospital in the SOLOIST-WHF population.[21] In the present post hoc analysis of the 48.8% of SOLOIST-WHF participants who received study drug before or at the time of discharge from their index event, sotagliflozin decreased the relative risk of a composite of cardiovascular mortality and HF-related hospitalizations and urgent visits for HF by >40% within 90 and within 30 days of discharge from the index WHF hospitalization and also significantly decreased total mortality at 90 days after discharge. A similar analysis from the time of randomization conducted to avoid any potential bias resulting from an analysis from the time of discharge revealed almost identical outcomes. Decreases in 90-day postdischarge cardiovascular mortality and HF events were observed across subgroups including sex, age, baseline eGFR, NT-proBNP, LVEF, and mineralocorticoid receptor antagonist use (**Figure 1**). The consistent reduction in this composite endpoint in patients with HFpEF (LVEF ≥50%) was particularly noteworthy.

As in the main SOLOIST-WHF trial, sotagliflozin was relatively well-tolerated, with a safety profile that is largely consistent with selective SGLT2 inhibitors, including an increased incidence of AEs associated with volume depletion. In this analysis, rates of urinary tract and genital infections were similar between the treatment groups. The increased incidence of diarrhea in the present analysis (as in other sotagliflozin studies) is attributable to the partial inhibition of SGLT1 in the intestine with sotagliflozin.[35,36] A single case of DKA occurred in a sotagliflozin-treated patient within the 90-day postdischarge period included in this analysis, whereas over the entire 9 months of the SOLOIST-WHF trial, there were 2 cases of DKA in the sotagliflozin group and 4 in the placebo group.[17]

A >40% decrease in postdischarge cardiovascular mortality and HF events, as observed in this post hoc analysis, may have important implications for patients' readmission rates, health status, and cost of care. A poor health status, defined by a Kansas City Cardiomyopathy Questionnaire-12 item (KCCQ) score of ≤50, has been reported in ≤43% of patients after an acute HF hospitalization.[37] In SOLOIST-WHF, significant improvements in KCCQ-12 were found after 4 months of sotagliflozin treatment.[17] It is reasonable to postulate that health status and quality of life likely improved with sotagliflozin within 30 and 90 days after hospital discharge, because HF hospitalizations and urgent visits negatively affect the quality of life of not only patients, but also of family and caregivers. Also important is the potential for decreased health care costs. A recent Medicare claims analysis demonstrated that hospital readmissions accounted for 36% of postacute care spending within 90 days of an index hospitalization.[38] Although no formal cost-effectiveness study has yet been conducted in SOLOIST-WHF, the finding of consistent decreases across subgroups in HF hospitalizations and urgent visits would likely have a major impact on the cost of care for HF patients. Moreover, in the United States, where hospitals are penalized by Medicare for high rates of 30-day HF readmissions,[16] decreasing HF events may have an even broader positive impact.

The results from EMPULSE (Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure) are broadly consistent with our observations from SOLOIST. In EMPULSE, 530 patients who were hospitalized for acute HF, including worsening and new onset HF, received empagliflozin or placebo and were followed for 90 days after hospital discharge.[27] Empagliflozin treatment resulted in a significantly greater clinical benefit as determined by a win ratio composite of

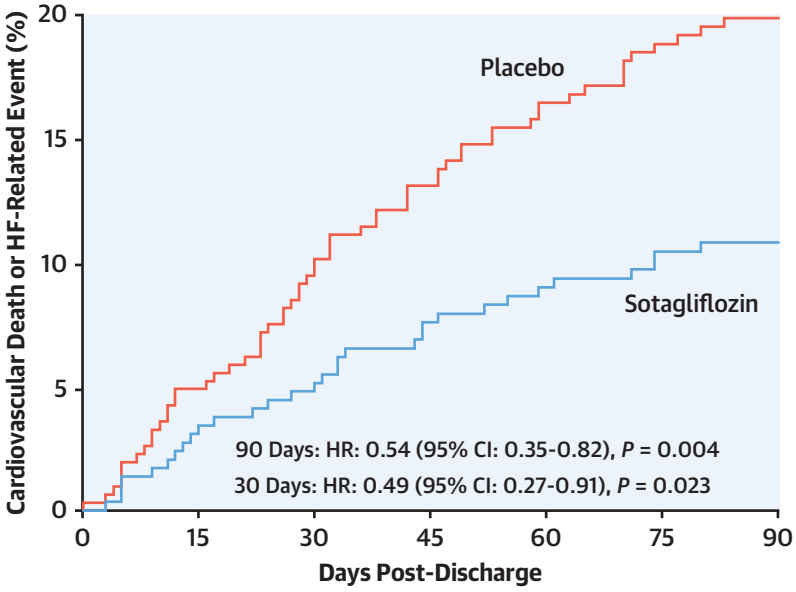
**TABLE 2 Cumulative Incidence and Relative Treatment Effects for Each Endpoint Over the 90- and 30-Day Postdischarge Observation Periods in Patients Who Started Study Medication Before Discharge From the Index Worsening HF Hospitalization**

| | Sotagliflozin (n = 290) | Placebo (n = 306) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Through 90 days | | | | |
| Cardiovascular death or HF-related event | 31 (10.8) | 60 (19.9) | 0.54 (0.35-0.82) | 0.004 |
| All-cause death or HF-related event | 31 (10.8) | 65 (21.2) | 0.48 (0.32-0.74) | 0.008 |
| HF-related event | 25 (8.7) | 51 (16.9) | 0.52 (0.32-0.83) | 0.006 |
| Cardiovascular death | 9 (3.1) | 17 (5.7) | 0.53 (0.23-1.23) | 0.14 |
| All-cause death | 9 (3.1) | 22 (7.4) | 0.39 (0.17-0.88) | 0.024 |
| All-cause hospitalization | 75 (26.5) | 81 (26.8) | 0.98 (0.71-1.34) | 0.89 |
| All-cause death or hospitalization | 77 (26.6) | 86 (28.1) | 0.92 (0.68-1.26) | 0.62 |
| Through 30 days | | | | |
| Cardiovascular death or HF-related event | 15 (5.2) | 31 (10.2) | 0.49 (0.27-0.91) | 0.023 |
| All-cause death or HF-related event | 15 (5.2) | 32 (10.5) | 0.47 (0.26-0.87) | 0.016 |
| HF-related event | 12 (4.1) | 26 (8.5) | 0.48 (0.24-0.95) | 0.036 |
| Cardiovascular death | 4 (1.4) | 7 (2.3) | 0.55 (0.16-1.94) | 0.36 |
| All-cause death | 4 (1.4) | 8 (2.6) | 0.48 (0.14-1.62) | 0.23 |
| All-cause hospitalization | 36 (12.4) | 44 (14.4) | 0.84 (0.54-1.31) | 0.44 |
| All-cause death or hospitalization | 38 (13.1) | 47 (15.4) | 0.81 (0.53-1.25) | 0.35 |

Values are n (%) unless otherwise indicated. Note: percentages are cumulative incidences at 90 or 30 days, estimated by cumulative incidence functions.

HF = heart failure.

**CENTRAL ILLUSTRATION** **Risk of Cardiovascular Death and HF-Related Events Over 30 and 90 Days**



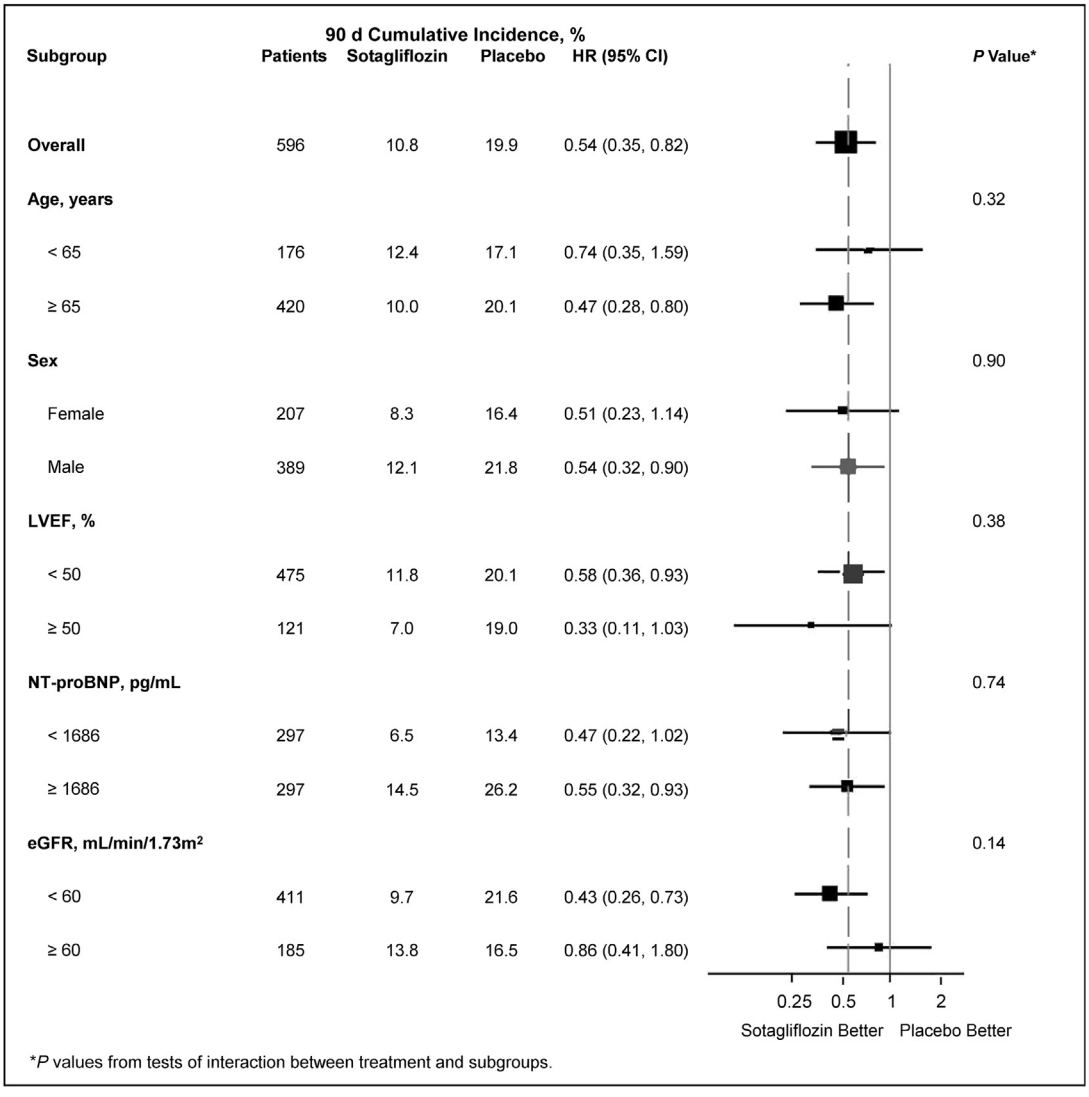

**Pitt B, et al. J Am Coll Cardiol HF. 2023;11(8):879-889.**

Estimated cumulative incidence for the main endpoint, consisting of the composite of cardiovascular death and heart failure (HF)-related events (hospitalizations and urgent visits for HF) in the sotagliflozin and placebo groups.

clinical endpoints and patient-reported outcomes, including a 31% nonsignificant decrease in the composite of cardiovascular mortality and HF hospitalizations at 90 days (HR: 0.69; 95% CI: 0.45-1.08). Improvements in the KCCQ-23 were also observed in EMPULSE, which further supports the benefits of starting SGLT inhibitor therapy before discharge.[27] Recent results from the subset of patients in DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) who were recently hospitalized with HF and a mildly reduced or preserved ejection fraction also suggest that SGLT inhibitors safely decreased the risk of WHF or cardiovascular death similarly in patients with and without a history of recent HF hospitalization.[39] It should, however, be pointed out that, in patients randomized to dapagliflozin in DELIVER during a recent HF hospitalization, the event curves did not diverge during the first 6 months of treatment, suggesting no early benefit in this group. Furthermore, neither EMPULSE nor DELIVER showed a decreased in total mortality at 90 days.

Previous pharmacological trials in patients hospitalized for acute or WHF before hospital discharge generally support our findings of the benefits of starting HF therapy in the hospital.[27,40,41] Initiation of an SGLT inhibitor such as sotagliflozin along with other guideline-recommended HF therapies in patients hospitalized for WHF is relatively well-tolerated and should improve patients' health status and decreased cardiovascular mortality and HF events, as well as health care costs. Starting evidence-based treatment during an HF hospitalization is also predictive of a higher likelihood appropriate HF therapy being maintained in the long term.[36] Conversely, when medication initiation is postponed until after discharge of patients hospitalized for WHF, there is a 75% chance guideline-recommended HF therapies will not be started within the next year.[42-45] Prompt initiation of the 4-pillar regimen (consisting of an SGLT inhibitor, renin-angiotensin system inhibitor, beta-blocker, and a mineralocorticoid receptor antagonist), which is recommended for patients with HFrEF,[22,23] may prolong the lifespan of this vulnerable group by 2 to 8 years.[46] HF guidelines also recommend use of SGLT inhibitors for patients with HFpEF as well as HFrEF.[22,23] Nevertheless, these agents are frequently not prescribed for HF because

**FIGURE 1** **90-Day Cumulative Incidence for the Composite of Cardiovascular Death and HF-Related Events by Subgroups**




HR with 95% CIs for the overall analysis population and selected subgroups over 90 days after discharge from the index worsening heart failure (HF) event in patients who began study drug before discharge from index event. eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

physicians may be unfamiliar with them or think of them as diabetes drugs and outside the bounds of their medical specialty.[47] Given the high mortality rate within the first 30 days after discharge,[8-10] decreases in 30- and 90-day post-discharge HF-related events and total mortality in this analysis should give clinicians confidence in the benefits of SGLT inhibitors as part of the 4-pillar strategy for HFrEF, as well as for HF patients with less severe EF deficits.

**STUDY LIMITATIONS.** The results of this analysis need further confirmation owing to the relatively small number of events—particularly deaths—and the fact that this is a post hoc analysis. As previously published, SOLOIST-WHF was stopped prematurely, endpoints were not centrally adjudicated, and the original primary endpoint was modified before database lock.[17] Without a trial directly comparing sotagliflozin with a more selective SGLT2 inhibitor, such

**TABLE 3 Incidence of AEs and EOSIs Over the 90-Day Postdischarge Observation Period in Patients Who Started Study Medication Before Discharge From the Index WHF Hospitalization**

| | Sotagliflozin (n = 290) | Placebo (n = 306) |
|---|---|---|
| AEs | | |
| Any AE | 158 (54.5) | 158 (51.6) |
| Any SAE | 74 (25.5) | 78 (25.5) |
| Any related AE | 31 (10.7) | 21 (6.9) |
| Any related SAE | 6 (2.1) | 2 (0.7) |
| Any AE leading to permanent treatment discontinuation | 8 (2.8) | 3 (1.0) |
| EOSI | | |
| Bone fractures | 3 (1.0) | 2 (0.7) |
| Diabetic ketoacidosis | 1 (0.3) | 0 |
| Genital mycotic infections | 1 (0.3) | 0 |
| Urinary tract infections | 19 (6.6) | 17 (5.6) |
| Volume depletion | 21 (7.2) | 17 (5.6) |
| Diarrhea | 10 (3.4) | 4 (1.3) |
| Pancreatitis | 0 | 0 |
| Venous thrombotic events | 2 (0.7) | 0 |
| AE leading to amputation | 0 | 0 |
| Severe hypoglycemia | 2 (0.7) | 1 (0.3) |

Values are n (%).

AE = adverse event; EOSI = event of special interest; SAE = serious adverse event; WHF = worsening heart failure.

as empagliflozin or dapagliflozin, it is difficult to reach any definitive conclusions about the advantages of dual SGLT1 and SGLT2 inhibition on HF mechanisms and outcomes. It would, however, seem that sotagliflozin is at least as effective as the selective SGLT2 inhibitors and possibly more effective as evidenced by the prior finding of a significant 30% decreased in stroke and myocardial infarction in patients with chronic kidney disease and T2D,[29] as well as the significant decreased in total mortality 90 days from the time of discharge in the present analysis in patients hospitalized with WHF.

## CONCLUSIONS

This post hoc analysis of a subset of the SOLOIST-WHF trial population suggests that sotagliflozin, when administered before hospital discharge after an episode of hospitalization for WHF in patients with T2D, decreases the 30- and 90-day rates of cardiovascular mortality and HF-related events by >40%, as well as total mortality, by 90 days after discharge. These findings are the first to demonstrate a decrease in mortality and HF events for a SGLT inhibitor treatment initiated during WHF hospitalization and underscore the benefits of early initiation of evidence-based HF therapy. These results suggest that dual inhibition of SGLT1 and SGLT2 is safe and may provide added benefit to patients with WHF.

**ACKNOWLEDGMENTS** The authors thank Manon Girard, MSc, for contributions to the statistical analysis, and Amanda M. Justice for editorial support (limited to formatting, referencing, and collation of coauthor comments), which were funded by Lexicon Pharmaceuticals, Inc.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by Sanofi and Lexicon Pharmaceuticals. Dr Pitt has received consulting fees from Lexicon, Bayer, AstraZeneca, Boehringer Ingelheim, Merck, and Phasebio; has received consulting fees and/or stock options from Viror, KBP Biosciences, Cereno Scientific, Tricida, SCPharmaceuticals, SQinnovatiions, G-3 Pharmaceuticals, Protonintel, and Brainstorm medical; holds U.S. Patent 9931412 on site specific delivery of eplerenone to the myocardium; and U.S. Patent pending 63/045,783 on histone-modulating agents for the protection and treatment of organ damage. Dr Bhatt is the Chair of SOLOIST with research funding paid by Lexicon to Brigham and Women's Hospital; he is on the Advisory Board for AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; is on the Board of Directors for AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, and TobeSoft; is Inaugural Chair for the American Heart Association Quality Oversight Committee; is a consultant for Broadview Ventures; is on the Data Monitoring Committees for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); has received honoraria from American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; is on the RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; is on the AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME

steering committees), Wiley (steering committee); *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned it to Lexicon; neither he nor Brigham and Women's Hospital receive any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, and 89Bio; has received royalties from Elsevier (Editor, *Braunwald's Heart Disease*); is site co-investigator for Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; is a trustee for the American College of Cardiology; and has done unfunded research for FlowCo and Takeda. Dr Szarek has received salary support from CPC, a nonprofit academic research organization affiliated with the University of Colorado, that receives research grant/consulting funding from Abbott, Agios, Alexion Pharma, Alnylam, Amgen, Angionetics, ARCA Biopharma, Array, AstraZeneca, Atentiv, Audentes, Bayer, Better Therapeutics, Brigham and Women's Hospital, Bristol-Myers Squibb, Cardiol Therapeutics, CellResearch, Cook Medical, Cook, CSL Behring, Eidos Therapeutics, EP Trading Co, Esperion Therapeutics, Everly Health, Faraday, Fortress Biotech, HDL Therapeutics, Heartflow, Hummingbird Bioscience, Insmed, Janssen, Kowa Research, Lexicon, Merck, MedPace, Medtronic, Moderna, Novate Medical, NovoNordisk, Pfizer, PhaseBio, PPD Development, Prairie Education and Research, Prothena Biosciences, Regeneron, Regio Biosciences, Sanifit Therapeutics, Sanofi, Smith and Nephew, Stealth BioTherapeutics, University of Colorado, University of Pittsburgh, Worldwide Clinical Trials, Wraser, and the Yale Cardiovascular Research Group; has received fees for performing analyses, steering committee fees, and travel support from Sanofi and Regeneron; has received consulting fees from CiVi, Esperion, and Amarin; has received Data Safety and Monitoring Board membership fees from Resverlogix and Janssen; and is a member of the *JACC* editorial board. Dr Cannon has received research grants from Amgen, Better Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, Novo Nordisk, Pfizer; consulting fees from Aegerion/Amryt, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Lexicon, Merck, Pfizer, Rhoshan, and Sanofi; and service on the Data and Safety Monitoring Boards for the Veteran's Administration, Applied Therapeutics, and NovoNordisk. Dr Leiter has received research funding from, has provided CME on behalf of, and/or has acted an adviser to AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Lexicon, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, and Servier. Dr McGuire has received honoraria for trial leadership from Lexicon, Sanofi, Boehringer Ingelheim, Merck & Co, Pfizer, AstraZeneca, Novo Nordisk, Esperion, Lilly USA, CSL Behring; and has received honoraria for consultancy from Lilly USA, Boehringer Ingelheim, Novo Nordisk, CSL Behring, Bayer, GlaxoSmithKline, and Lexicon. Dr Lewis has received consultant fees from Sanofi. Dr Riddle has received honoraria for consulting from Adocia, Anji, Xeris, DalCor, and Theracos. Dr Voors has received consultancy and speaker fees and research support from AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, BMS, Cyrokinetics, Merck, Myokardia, Novartis, NooNordisk, and Roche diagnostics. Dr Metra has received personal fees from Actelion, Amgen, Livanova, and Vifor pharma as a member of Executive or Data Monitoring Committees of sponsored clinical trials; from AstraZeneca, Bayer, Boheringer Ingelhelm, Edwards Lifesciences, Novartis for participation in advisory boards and/or speeches at sponsored meetings. Dr Lund has received support from the Karolinska Institutet, the Swedish Research Council [grant 523-2014-2336], and the Swedish Heart Lung Foundation [grants 20150557, 20190310] and grants from AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis, and MSD; consulting honoraria from Vifor, AstraZeneca, Bayer, Pharmacosmos, MSD, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier, Edwards Lifesciences, and Alleviant; and speaker honoraria from Abbott, OrionPharma, MedScape, Radcliffe, AstraZeneca, Novartis, Boehringer Ingelheim, and Bayer; and has patents with AnaCardio and stock ownership in AnaCardio. Dr Komajda has received honoraria from Servier, Novartis, Boehringer Ingelheim, AstraZeneca, Bayer, and Sanofi as adviser/member of clinical trials committees. Dr Testani has received grants and/or personal fees from 3ive labs, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca, Novartis, Cardionomic, MagentaMed, Reprieve Inc, FIRE1, W. L. Gore & Associates, Sanofi, Sequana Medical, Otsuka, Abbott, Merck, Windtree Therapeutics, Lexicon pharmaceuticals, Precardia, Relypsa, Regeneron, BD, Edwards Lifesciences, and Lilly; and has a patent treatment of diuretic resistance issued to Yale and Corvidia Therapeutics Inc, a patent methods for measuring Renalase issued to Yale, and a patent treatment of diuretic resistance pending with Reprieve Inc. Dr Ponikowski has received consultancy fees and speaker honoraria from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Amgen, Servier, Novartis, Bayer, MSD, Pfizer, Impulse Dynamics, Renal Guard Solutions, BMS, AbbottVascular, and the Radcliffe Group. Dr Lopes has received research grants or contracts from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, Sanofi-Aventis; funding for educational activities or lectures from Pfizer, Daiichi Sankyo, and Novo Nordisk; and funding for consulting or other services from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk. Dr Ezekowitz has received research support for trial leadership from Bayer, Merck & Co, Novo Nordisk, Cytokinetics, Applied Therapeutics, American Regent; and honoraria for consultancy from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Otsuka, Bayer, and Novartis. Dr Davies and Mr Sun are employed by and may have stock or stock options in Lexicon Pharmaceuticals, Inc. Dr Verma has received research and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, CMS, HLS, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, and Sanofi; and is the President of the Canadian Medical and Surgical Knowledge Translation Research Group and holds the Tier 1 Canada Research Chair in Cardiovascular Surgery. Dr Kosiborod has received research grants from AstraZeneca and Boehringer Ingelheim; served as a consultant or advisory board member for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Sanofi, Vifor Pharma; has received other research support from AstraZeneca; and honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Steg has received research grants from Amarin, Bayer, Sanofi, and Servier; speaker or consultant fees from Amarin, Amgen, AstraZeneca, Bayer, Bristol-Myers-Squibb, Janssen, Kowa, Idorsia, Lexicon, Merck, Novartis, Novo-Nordisk, PhaseBio, Pfizer, Regeneron, Sanofi, Servier; and is a Senior Associate Editor of *Circulation*. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Deepak L. Bhatt, Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box 1030, New York, New York 10029, USA. E-mail: DLBhattMD@post.Harvard.edu. Twitter: https://twitter.com/DLBhattMD.

JACC: HEART FAILURE VOL. 11, NO. 8, 2023
AUGUST 2023:879–889

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Initiation of sotagliflozin before discharge in patients with T2D admitted with decompensated HF markedly reduced their risk of cardiovascular death or hospitalization for HF at both 30 and 90 days. Barring contraindications, SGLT inhibitors should be routinely started in such patients before discharge.

**TRANSLATIONAL OUTLOOK:** Dual SGLT1 and SGLT2 inhibition afforded by sotagliflozin might provide additional clinical benefits beyond selective SGLT2 inhibition, though adequately powered randomized clinical trials of sufficient duration will be necessary to test this hypothesis.

## REFERENCES

**1.** McDermott KW, Roemer M. Most frequent principal diagnoses for inpatient stays in U.S. hospitals, 2018. Accessed June 14, 2022. https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet

**2.** Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606–619.

**3.** Tromp J, Bamadhaj S, Cleland JGF, et al. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): a cohort study. *Lancet Glob Health*. 2020;8:e411–e422.

**4.** Cheng RK, Cox M, Neely ML, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J*. 2014;168:721–730.

**5.** Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360:1418–1428.

**6.** Sepehrvand N, Islam S, Dover DC, et al. Epidemiology of worsening heart failure in a population-based cohort from Alberta, Canada: evaluating eligibility for treatment with vericiguat. *J Card Fail*. 2022;28:1298–1308.

**7.** Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. *Risk Manag Healthc Policy*. 2017;10:63–70.

**8.** Chang PP, Chambless LE, Shahar E, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol*. 2014;113:504–510.

**9.** Chang PP, Wruck LM, Shahar E, et al. Trends in hospitalizations and survival of acute decompensated heart failure in four US Communities (2005-2014): ARIC Study Community Surveillance. *Circulation*. 2018;138:12–24.

**10.** Pokorney SD, Al-Khatib SM, Sun JL, et al. Sudden cardiac death after acute heart failure hospital admission: insights from ASCEND-HF. *Eur J Heart Fail*. 2018;20:525–532.

**11.** Yazdan-Ashoori P, Lee SF, Ibrahim Q, Van Spall HG. Utility of the LACE index at the bedside in predicting 30-day readmission or death in patients hospitalized with heart failure. *Am Heart J*. 2016;179:51–58.

**12.** Wang H, Robinson RD, Johnson C, et al. Using the LACE index to predict hospital readmissions in congestive heart failure patients. *BMC Cardiovasc Disord*. 2014;14:97.

**13.** Au AG, McAlister FA, Bakal JA, Ezekowitz J, Kaul P, van Walraven C. Predicting the risk of unplanned readmission or death within 30 days of discharge after a heart failure hospitalization. *Am Heart J*. 2012;164:365–372.

**14.** van Walraven C, Dhalla IA, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. *CMAJ*. 2010;182:551–557.

**15.** Sharma V, Kulkarni V, McAlister F, et al. Predicting 30-day readmissions in patients with heart failure using administrative data: a machine learning approach. *J Card Fail*. 2022;28:710–722.

**16.** Centers for Medicare and Medicaid Services. Hospital Readmissions Reduction Program (HRRP). Accessed June 15, 2022. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program

**17.** Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128.

**18.** Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

**19.** McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

**20.** Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

**21.** Szarek M, Bhatt DL, Steg PG, et al. Effect of sotagliflozin on total hospitalizations in patients with type 2 diabetes and worsening heart failure: a randomized trial. *Ann Intern Med*. 2021;174:1065–1072.

**22.** McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

**23.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421.

**24.** Ambrosy AP, Parikh RV, Sung SH, et al. A natural language processing-based approach for identifying hospitalizations for worsening heart failure within an integrated health care delivery system. *JAMA Netw Open*. 2021;4:e2135152.

**25.** Loudon BL, Noordali H, Gollop ND, Frenneaux MP, Madhani M. Present and future pharmacotherapeutic agents in heart failure: an evolving paradigm. *Br J Pharmacol*. 2016;173:1911–1924.

**26.** Verma S, Anker SD, Butler J, Bhatt DL. Early initiation of SGLT2 inhibitors is important, irrespective of ejection fraction: SOLOIST-WHF in perspective. *ESC Heart Fail*. 2020;7:3261–3267.

**27.** Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28:568–574.

**28.** Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22:713–722.

**29.** Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384:129–139.

**30.** The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in

patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127.

**31.** Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446.

**32.** Pitt B, Bhatt DL, Metra M. Does SGLT1 inhibition add to the benefits of SGLT2 inhibition in the prevention and treatment of heart failure? *Eur Heart J*. 2022;43:4754–4757.

**33.** Butler J, Yang M, Manzi MA, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;73:935–944.

**34.** Pitt B, Bhatt DL. Does SGLT1 inhibition add benefit to SGLT2 inhibition in type 2 diabetes? *Circulation*. 2021;144:4–6.

**35.** Powell DR, DaCosta CM, Smith M, et al. Effect of LX4211 on glucose homeostasis and body composition in preclinical models. *J Pharmacol Exp Ther*. 2014;350:232–242.

**36.** Powell DR, Smith MG, Doree DD, et al. LX2761, a sodium/glucose cotransporter 1 inhibitor restricted to the intestine, improves glycemic control in mice. *J Pharmacol Exp Ther*. 2017;362:85–97.

**37.** McNaughton CD, McConnachie A, Cleland JG, et al. Quality of life assessed 6 months after hospitalisation for acute heart failure: an analysis from REPORT-HF (international REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure). *Eur J Heart Fail*. 2022;24:1020–1029.

**38.** Reinhardt SW, Clark KAA, Xin X, et al. Thirty-day and 90-day episode of care spending following heart failure hospitalization among Medicare beneficiaries. *Circ Cardiovasc Qual Outcomes*. 2022;15:e008069.

**39.** Cunningham JW, Vaduganathan M, Claggett BL, et al. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. *J Am Coll Cardiol*. 2022;80:1302–1310.

**40.** Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548.

**41.** Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396:1895–1904.

**42.** Rao VN, Murray E, Butler J, et al. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2021;78:2004–2012.

**43.** Carnicelli AP, Lippmann SJ, Greene SJ, et al. Sacubitril/valsartan initiation and postdischarge adherence among patients hospitalized for heart failure. *J Cardiac Fail*. 2021;27:826–836.

**44.** Curtis LH, Mi X, Qualls LG, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. *Am Heart J*. 2013;165:979–986.e1.

**45.** Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. *JAMA Cardiol*. 2021;6:743–744.

**46.** Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121–128.

**47.** Sharma A, Aziz H, Verma S, et al. Permission to prescribe: do cardiologists need permission to prescribe diabetes medications that afford cardiovascular benefit? *Curr Opin Cardiol*. 2021;36:672–681.

**KEY WORDS** dual SGLT1 and SGLT2 inhibitor, heart failure-related events, hospital readmission, mortality, sotagliflozin, SGLT2 inhibitor

**APPENDIX** For supplemental tables and a figure, please see the online version of this paper.