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Effects of Sotagliflozin on Health Status in Patients With Worsening Heart Failure

Results From SOLOIST-WHF

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ABSTRACT

BACKGROUND Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve health status in heart failure (HF) across the left ejection fraction ejection spectrum. However, the effects of SGLT1 and SGLT2 inhibition on health status are unknown.

OBJECTIVES These prespecified analyses of the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial examined the effects of sotagliflozin vs placebo on HF-related health status.

METHODS SOLOIST-WHF randomized patients hospitalized or recently discharged after a worsening HF episode to receive sotagliflozin or placebo. The primary endpoint was total number of HF hospitalizations, urgent HF visits, and cardiovascular death. Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) score was a prespecified secondary endpoint. This analysis evaluated change in the KCCQ-12 score from baseline to month 4.

RESULTS Of 1,222 patients randomized, 1,113 (91%) had complete KCCQ-12 data at baseline and 4 months. The baseline KCCQ-12 score was low overall (median: 41.7; Q1-Q3: 27.1-58.3) and improved by 4 months in both groups. Sotagliflozin vs placebo reduced the risk of the primary endpoint consistently across KCCQ-12 tertiles ($P_{trend} = 0.54$). Sotagliflozin-treated patients vs those receiving placebo experienced modest improvement in KCCQ-12 at 4 months (adjusted mean change: 4.1 points; 95% CI: 1.3-7.0 points; $P = 0.005$). KCCQ-12 improvements were consistent across prespecified subgroups, including left ventricular ejection fraction <50% or ≥50%. More patients receiving sotagliflozin vs those receiving placebo had at least small (≥5 points) improvements in KCCQ-12 at 4 months (OR: 1.38; 95% CI: 1.06-1.80; $P = 0.017$).

CONCLUSIONS Sotagliflozin improved symptoms, physical limitations, and quality of life within 4 months after worsening HF, with consistent benefits across baseline demographic and clinical characteristics. (Effect of Sotagliflozin on Cardiovascular Events in Participants With Type 2 Diabetes Post Worsening Heart Failure [SOLOIST-WHF]; NCT03521934) (JACC. 2024;84:1078-1088) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Patients with heart failure (HF) across the spectrum of left ventricular ejection fraction (LVEF) experience an especially high burden of symptoms, physical limitations and a poor quality of life.[1] HF is characterized by intermittent episodes of worsening heart failure (WHF) requiring acute care and commonly hospitalization, during which symptom burden may be increased.[2] Improving health status is an increasingly recognized goal in the treatment of patients with HF, particularly during and shortly after a WHF event.[3] In fact, many patients with HF value improvement in symptoms and physical limitations at least as much as survival.

SEE PAGE 1089

Prior trials of sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown that these therapies improve HF-related health status among patients with reduced, mildly reduced, and preserved ejection fractions.[4-7] However, these assessments were largely derived from the study of ambulatory patients with chronic HF. A dedicated trial found that the SGLT2 inhibitor empagliflozin improved health status among hospitalized patients with WHF,[8] but this trial was modest in size and was not powered to examine the effect on clinical endpoints.[9] The dual SGLT1 and SGLT2 inhibitor sotagliflozin has properties additive to those of SGLT2 inhibition in terms of reducing postprandial glucose levels by delaying intestinal glucose absorption and increasing distal intestinal carbohydrate delivery that augment the endogenous incretin action.[10] Sotagliflozin was shown to improve clinical endpoints among patients recently hospitalized with WHF in the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial, which included an international patient population across the spectrum of LVEF.[11] The impact of sotagliflozin on patient-reported health status, as measured by using the Kansas City Cardiomyopathy Questionnaire (KCCQ), has not been previously described. The objective of this analysis was to evaluate the effect of sotogliflozin vs placebo on health status in patients with worsening HF.

METHODS

TRIAL DESIGN AND PATIENTS. The design, protocol modifications, and primary results of the SOLOIST-WHF trial have been published previously.[11] SOLOIST-WHF was a phase 3, international, double-blind, placebo-controlled, event-driven trial that enrolled patients aged 18 to 85 years with type 2 diabetes who were recently hospitalized for WHF across the spectrum of LVEF. Enrolled patients were randomized to receive once-daily sotagliflozin 200 mg (with a possible dose escalation to 400 mg) or placebo. Investigational product was started prior to or within 3 days of hospital discharge. Randomization was stratified according to baseline LVEF (<50% and ≥50%) and geographic region.

The SOLOIST-WHF trial protocol was approved by the relevant health authority, Institutional Review Board, or ethics committee at each participating site. An independent data and safety monitoring board oversaw the trial. Written informed consent was obtained from all patients.[11]

ENDPOINTS AND STUDY PROCEDURES. The primary endpoint was a composite of total hospitalizations and urgent visits for HF (first and subsequent events) and cardiovascular death. Adjudication of events was planned but could not be completed because of the loss of funding; the decision was therefore made by trial leadership to analyze investigator-reported events.

Change in HF-related health status was quantified by the 12-item KCCQ short form (KCCQ-12). KCCQ is a self-adminstered instrument that quantifies HF-related symptoms, function, and quality of life over the prior 2 weeks; the instrument has been validated for consistency across patient subgroups, including LVEF categories.[12] The instrument has been internally and externally validated against a longer form[13] (which consists of 23 questions across the following

ABBREVIATIONS AND ACRONYMS

ARR = absolute risk reduction

HF = heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

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

SGLT = sodium-glucose cotransporter

WHF = worsening heart failure

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domains: symptoms (frequency, severity, and recent change), physical function, quality of life, and social function. Scores are transformed to a range of 0 to 100, in which higher scores reflect better health status. Change in KCCQ-12 from baseline to 4 months was a key prespecified secondary endpoint of SOLOIST-WHF. KCCQ-12 scores were also collected at 2 weeks, 4 weeks, and 8 months after randomization. The KCCQ-12 was completed by patients, without assistance from site study staff (as validated).

STATISTICAL ANALYSES. Patients were grouped based on the tertiles of baseline KCCQ-12: 1) KCCQ-12 <31.25; 2) 31.25 ≤KCCQ-12 <51.6; and 3) KCCQ-12 ≥51.6. Baseline characteristics are summarized as median (Q1-Q3) or count (%). Cochran-Armitage and Jonckheere trend tests were used to test for differences in baseline characteristics across KCCQ-12 tertiles.

The effects of sotagliflozin vs placebo on the trial's primary endpoint of total hospitalizations and urgent visits for HF (first and subsequent events) and cardiovascular death were assessed across tertiles of KCCQ-12. A competing risk proportional hazards model was used for total events (stratified according to LVEF at baseline and geographic region of enrollment), in which noncardiovascular deaths were treated as a competing terminal event and included a test of linear trend across tertiles for the estimated log treatment HRs. The test of linear trend represents an interaction test accounting for the ordinal nature of the tertiles. Analyses were repeated across baseline KCCQ-12 score modeled as a continuous variable in a Poisson regression model containing a natural cubic spline of baseline KCCQ-12 score, treatment assignment, and the interaction between the spline and treatment assignment. The model included log follow-up time as an offset, and knots were specified at the 25th, 50th, and 75th percentiles.

To evaluate the effects of sotagliflozin vs placebo on the KCCQ-12, we estimated the differences between treatment groups in mean KCCQ-12 score at 4 months (prespecified) and at additional time points (post hoc) in surviving patients; an analysis of covariance was used, with treatment group as a factor and adjusted for baseline KCCQ-12 score, baseline LVEF, and geographic region. No imputation was used for missing data.

Responder analyses were conducted, comparing the proportions of patients with a clinically important deterioration (worsening of 5 points or more), as well as clinically important improvements in KCCQ-12 score at 4 months' postrandomization using logistic regression models. Clinically important improvements were defined similar to prior analyses assessing HF-related health status in patients receiving SGLT2 inhibitors, with increases of ≥5, ≥10, and ≥20 points corresponding to at least small, moderate, and large improvements, respectively.[6,14-16] We estimated the numbers needed-to-treat for these thresholds of KCCQ-12 by calculating the inverse of the difference in proportions.

Finally, the effects of sotagliflozin vs placebo on KCCQ-12 at 4 months was examined across relevant subgroups, stratifying patients according to several demographic and clinical characteristics, including LVEF. These models included formal interaction analyses. Interaction *P* values were obtained from a global test of the treatment-subgroup interaction.

All analyses were performed in SAS version 9.4 (SAS Institute, Inc). A *P* value <0.05 was considered statistically significant without adjustment for multiple comparisons.

RESULTS

PATIENT CHARACTERISTICS. Overall, 1,113 patients (91% of both the sotagliflozin and placebo groups) had available KCCQ-12 data at baseline and 4 months' postrandomization; of these, 13%, 2%, and 40% in the sotagliflozin group and 16%, 3%, and 40% in the placebo group were missing KCCQ-12 data at 2 weeks, 4 weeks, and 8 months, respectively. The median baseline KCCQ-12 was 41.7 (Q1-Q3: 27.1-58.3). Baseline KCCQ-12 tertiles were as follows: tertile 1: <31.25; tertile 2: 31.25 to <51.6; and tertile 3: ≥51.6. Follow-up occurred over a median of 9.0 months.

The baseline characteristics of patients according to KCCQ-12 tertiles are shown in Table 1. Compared with patients with higher KCCQ-12 scores at baseline (better health status), those with greater baseline symptomatic impairment were more often women, had higher body mass index, and were more likely to be enrolled in North America, but they did not have a higher prevalence of comorbidities. LVEF was similar across KCCQ-12 tertiles, but patients with greater symptomatic impairment did have higher baseline levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Although a nominally lower percentage of patients with lower baseline KCCQ-12 scores were taking beta-blockers, concomitant medication use was generally similar across the subgroups.

CLINICAL ENDPOINTS AND EFFECTS OF SOTAGLIFLOZIN. In the placebo group, patients with the highest baseline KCCQ-12 experienced lower rates of the primary endpoint of cardiovascular death or WHF events (54.3, 60.9, and 37.4 per 100 patient-years [py] in the first, second, and third KCCQ-12 tertiles, respectively; $P_{trend} < 0.0163$). Sotagliflozin vs placebo reduced the

TABLE 1 Clinical Characteristics According to Tertile of Baseline KCCQ-12

	Baseline KCCQ-12 Tertile				
	Tertile 1 (<31.25) (n = 363)	Tertile 2 (31.25 to <51.6) (n = 378)	Tertile 3 (≥51.6) (n = 372)	Total (N = 1,113)	P_{trend}
Age, y	70 (63–77)	70 (63–76)	70 (64–76)	70 (63–76)	0.75
Female	139 (38.3)	141 (37.3)	101 (26.5)	381 (34.2)	0.0014
Geographic region					<0.0001
Eastern Europe	148 (40.8)	161 (42.6)	150 (40.3)	459 (41.2)	
Western Europe	68 (18.7)	94 (24.9)	106 (28.5)	268 (24.1)	
Latin America	85 (23.4)	78 (20.6)	93 (25.0)	256 (23.0)	
North America	36 (9.9)	17 (4.5)	14 (3.8)	67 (6.0)	
Rest of world	26 (7.2)	28 (7.4)	9 (2.4)	63 (5.7)	
HbA_{1c}, %	7.1 (6.4–8.4)	7.1 (6.5–8.2)	7.0 (6.3–8.2)	7.1 (6.4–8.3)	0.28
BMI, kg/m^2	32.0 (27.6–36.1)	30.8 (27.0–34.4)	29.8 (26.6–33.0)	30.8 (27.0–34.5)	<0.0001
KCCQ-12	21.4 (15.1–27.1)	41.4 (35.4–46.4)	66.1 (58.3–75.6)	41.7 (27.1–58.3)	<0.0001
eGFR, mL/min/1.73 m^2	49.1 (39.6–61.3)	51.0 (40.0–65.1)	50.7 (40.3–64.3)	50.0 (39.9–63.4)	0.33
LVEF, %	35 (27–48)	37 (28–47)	35 (29–47)	35 (28–47)	0.57
NT-proBNP, pg/mL	1930 (1,012–3,987)	1842 (836–3,698)	1,542 (779–3,202)	1,804 (854–3,619)	0.0042
SBP, mm Hg	122 (112–133)	122 (111–134)	122 (112–135)	122 (111–134)	0.25
DBP, mm Hg	72 (66–80)	72 (67–80)	74 (68–80)	73 (67–80)	0.35
Medical history					
Chronic obstructive pulmonary disease	62 (17.1)	55 (14.6)	48 (12.9)	165 (14.8)	0.11
Myocardial infarction	91 (25.1)	90 (23.8)	87 (23.4)	268 (24.1)	0.59
Atrial fibrillation/flutter	178 (49.0)	179 (47.4)	169 (45.4)	526 (47.3)	0.33
Left ventricular hypertrophy	16 (4.4)	11 (2.9)	10 (2.7)	37 (3.3)	0.19
Peripheral artery disease	34 (9.4)	42 (11.1)	47 (12.6)	123 (11.1)	0.16
Peripheral revascularization	8 (2.2)	19 (5.0)	15 (4.0)	42 (3.8)	0.20
Peripheral venous disease	42 (11.6)	33 (8.7)	41 (11.0)	116 (10.4)	0.82
Baseline medications					
Any RAAS inhibitor	331 (91.2)	352 (93.1)	345 (92.7)	1,028 (92.4)	0.43
Beta-blocker	330 (90.9)	351 (92.9)	353 (94.9)	1,034 (92.9)	0.0355
Loop diuretic	343 (94.5)	363 (96.0)	355 (95.4)	1,061 (95.3)	0.55
Any glucose-lowering medication	313 (86.2)	335 (88.6)	310 (83.3)	958 (86.1)	0.25

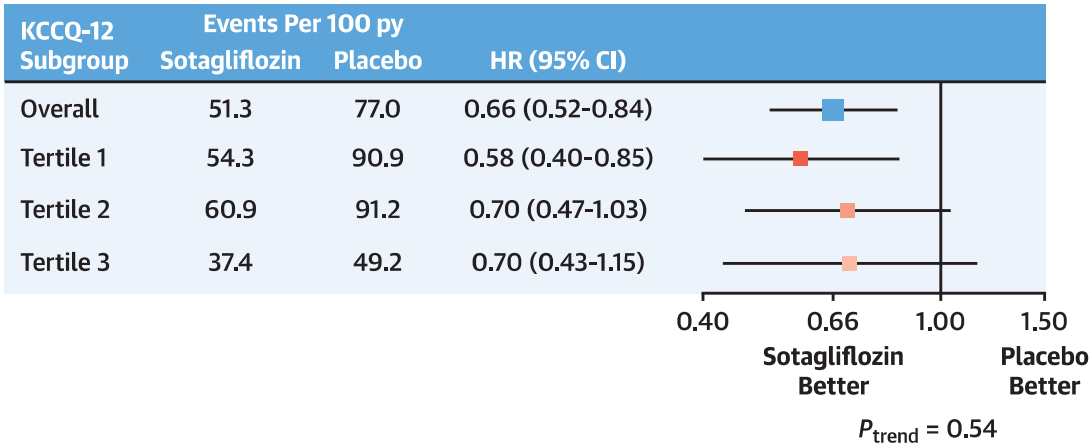
Values are median (Q1–Q3) or n (%), including patients with a baseline and month 4 Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) assessment.

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular rate; HbA_{1c} = glycosylated hemoglobin; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; SBP = systolic blood pressure.

risk of the primary endpoint consistently across KCCQ-12 tertiles (P_{trend} = 0.54) (Figure 1). Absolute risk reductions (ARRs) were greater in those with the greatest symptoms at baseline (tertile 1: ARR = 36.6 events per 100 py; tertile 2: ARR = 30.3 events per 100 py; and tertile 3: ARR = 11.8 events per 100 py). The effects of randomization to sotagliflozin vs placebo on the primary clinical endpoint were also consistent across KCCQ-12 modeled as a continuous variable ($P_{interaction}$ = 0.93) (Figure 2).

HEALTH STATUS. Patients randomized to receive sotagliflozin experienced a greater improvement in KCCQ-12 than those in the placebo group from baseline to 4 months (adjusted mean change: 4.1 points; 95% CI: 1.3-7.0 points; P = 0.005) (Central Illustration). The treatment benefits of sotagliflozin vs placebo on KCCQ-12 began to numerically emerge at 4 weeks postrandomization; benefits observed at 4 months persisted at 8 months postrandomization (adjusted mean change: 4.6 points; 95% CI: 0.6-9.2 points; P = 0.047). The effects of sotagliflozin vs placebo on KCCQ-12 at 4 months across various demographic and clinical subgroups are shown in Figure 3. The directional treatment benefit of sotagliflozin on health status was consistent across most subgroups, including age, sex, geographic region, kidney function, and timing of study drug administration (during or after hospitalization). Patients with lower NT-proBNP levels had similar improvements in health status compared with those with higher presenting NT-proBNP levels ($P_{interaction}$ = 0.84). Treatment with sotagliflozin vs placebo showed a 3.5-point (95% CI: 0.3-6.8 points) improvement in KCCQ-12 score in those with LVEF <50% and a 6.5-point (95% CI: 0.2-12.8 points) improvement in KCCQ-12 score in those with LVEF ≥50% ($P_{interaction}$ = 0.41).

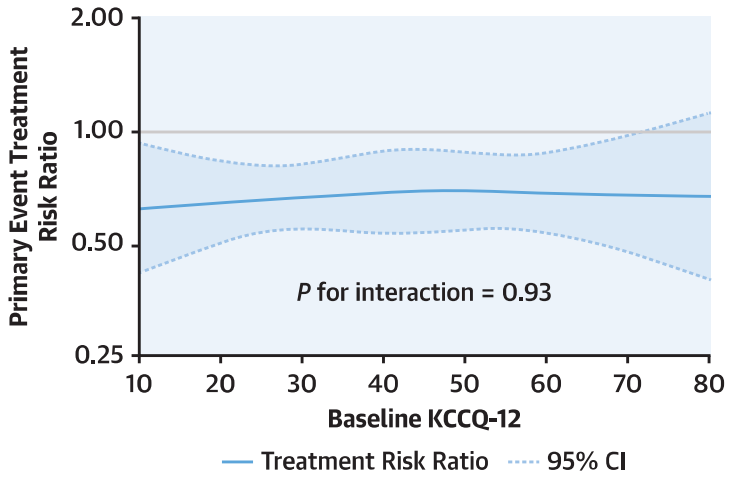
FIGURE 1 Effects of Sotagliflozin vs Placebo on the Primary Endpoint According to KCCQ-12 Tertile



Effect of treatment with sotagliflozin vs placebo on the primary endpoint of the composite of total hospitalizations and urgent visits for heart failure (first and subsequent events) and cardiovascular death by health status, as indicated by Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) tertile. py = person years.

The results of the responder analysis are presented in Figure 4. Numerically fewer patients treated with sotagliflozin had a clinically significant deterioration (≥5 point decline), and numerically more patients treated with sotagliflozin had at least small, moderate, or large improvements in KCCQ-12 scores. Treatment with sotagliflozin was associated with a statistically greater odds of an at least 5-point improvement in KCCQ-12 score from randomization to 4 months (OR: 1.38; 95% CI: 1.06-1.80; $P = 0.017$), corresponding to a number needed-to-treat with sotagliflozin of 17 patients to produce at least small improvements in KCCQ-12 scores at 4 months. Other elements of the responder analysis favored treatment with sotagliflozin vs placebo but were not statistically significant. Findings were largely consistent among those with higher and lower LVEF (Supplemental Figure 1).

FIGURE 2 Sotagliflozin vs Placebo on Primary Endpoint Across Baseline KCCQ-12



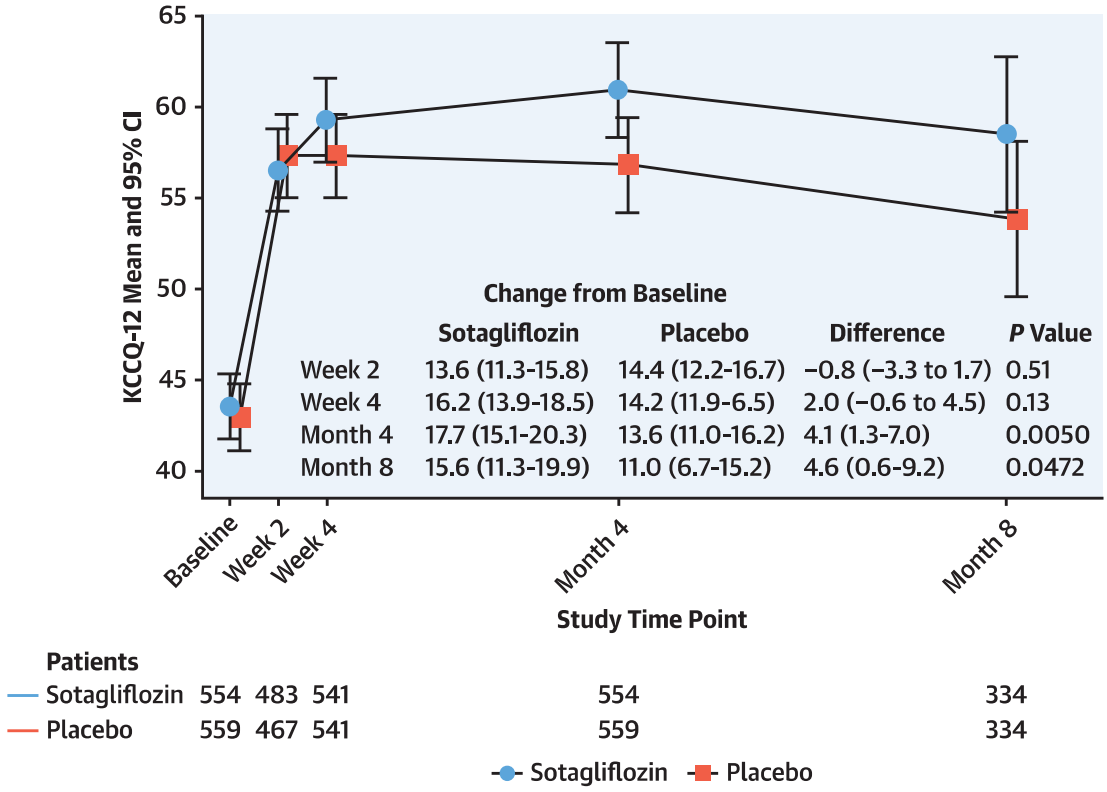
Effect of treatment with sotagliflozin vs placebo on the primary endpoint of the composite of total hospitalizations and urgent visits for heart failure (first and subsequent events) and cardiovascular death by health status based on Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) modeled as a continuous variable.

DISCUSSION

In this prespecified analysis from the SOLOIST-WHF trial, the benefits of sotagliflozin on reducing clinical events were consistent across the full spectrum of baseline KCCQ-12 scores, with greater absolute risk reductions observed in the most symptomatic patients. Treatment with sotagliflozin led to improvements in HF-related symptoms, physical limitations, and quality of life compared with placebo in a highly symptomatic population with recent WHF. Improvements in health status with sotagliflozin treatment appeared evident by 4 months' postrandomization and were consistent across major subgroups of interest, inclusive of those with lower and higher baseline LVEF.

This work has important implications. First, SOLOIST-WHF enrolled a highly symptomatic patient population with recent WHF. In this way, it contrasts with prior global outcomes trials of SGLT2 inhibitors in HF, which predominantly enrolled populations with

CENTRAL ILLUSTRATION **Mean Kansas City Cardiomyopathy Questionnaire-12 Score Over Time by Treatment Allocation**



Bhatt AS, et al. JACC. 2024;84(12):1078–1088.

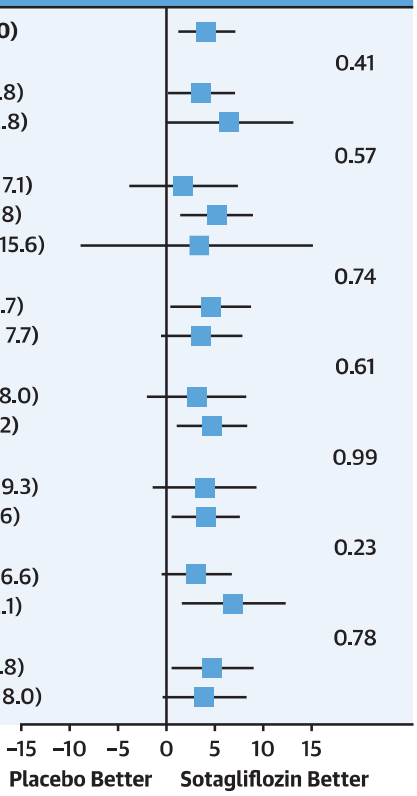
Change in Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) score between baseline and 4 months was a prespecified secondary endpoint; KCCQ-12 data were also collected at 2 weeks, 4 weeks, and 8 months among survivors and analyzed post hoc.

chronic stable HF with fewer symptoms and physical limitations at baseline. For example, the baseline median KCCQ-total symptom score from the pooled analysis of DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) was 75 compared with a baseline median KCCQ-12 score of 42 in SOLOIST-WHF.[4] Trials enrolling patients with chronic HF from North America (vs other parts of the world) have generally found lower baseline KCCQ scores in both patients with HF with reduced ejection fraction[17] and HF with preserved ejection fraction,[5] potentially reflective of greater HF symptom burden and a higher predominance of related comorbid conditions that may affect physical limitations (eg, obesity).[18] The high level of symptoms observed in SOLOIST WHF approximates that of the EMPULSE (Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized) trial, which randomized patients following stabilization of acute HF to receive empagliflozin vs placebo and where the median baseline KCCQ-total symptom score was 38.[9] Taken together, these data substantiate the high symptomatic burden faced by patients with HF during acute exacerbations. They also highlight the importance of therapeutic development aimed at durably improving symptoms, physical functions, and quality of life in addition to clinical events.

Second, we observed consistent treatment benefits with respect to clinical endpoints across the full spectrum of baseline health status impairment. Although patients with more symptoms at baseline may be expected to have larger magnitude of symptomatic improvement with decongestive and guideline-supported treatment strategies,[19] severely impaired health status may also be a marker of end-stage forms of myopathy,[20] which may be poorly

FIGURE 3 Change From Baseline in KCCQ at 4 Months by Subgroups

Subgroup	Sotagliflozin Change (95% CI)	Placebo Change (95% CI)	Difference Change (95% CI)	$P_{interaction}$
Overall	**17.7 (15.1-20.3)**	**13.6 (11.0-16.2)**	**4.1 (1.3-7.0)**	
LVEF				0.41
<50%	17.0 (14.4-19.7)	13.5 (10.8-16.2)	3.5 (0.3-6.8)	
≥50%	19.3 (14.7-24.0)	12.8 (8.2-17.4)	6.5 (0.2-12.8)	
Region				0.57
North/Latin America	25.2 (21.1-29.3)	23.5 (19.5-27.5)	1.7 (−3.7 to 7.1)	
Europe	16.3 (13.6-19.0)	11.1 (8.4-3.8)	5.2 (1.6-8.8)	
Rest of World	10.6 (2.0-19.2)	7.2 (−1.6 to 15.9)	3.4 (−8.8 to 15.6)	
First Dose				0.74
Before Discharge	17.3 (13.8-20.9)	12.7 (9.3-16.1)	4.6 (0.5-8.7)	
After Discharge	17.9 (14.7-21.1)	14.3 (11.1-17.5)	3.6 (−0.4 to 7.7)	
Sex				0.61
Female	15.6 (11.7-19.4)	12.5 (8.8-16.3)	3.5 (−1.9 to 8.0)	
Male	19.1 (16.0-22.2)	14.4 (11.3-17.5)	4.7 (1.1-8.2)	
Age				0.99
<65 years	18.6 (14.6-22.6)	14.6 (10.3-18.9)	4.0 (−1.3 to 9.3)	
≥65 years	17.4 (14.4-20.3)	13.3 (10.4-16.1)	4.1 (0.6-7.6)	
Estimated GFR				0.23
<60 mL/min/1.73 m^2	16.7 (13.9-19.6)	13.7 (10.7-16.6)	3.1 (−0.4 to 6.6)	
≥60 mL/min/1.73 m^2	20.5 (16.2-24.7)	13.6 (9.7-17.5)	6.9 (1.7-12.1)	
NT-proBNP				0.78
≤1,800 pg/mL	20.0 (16.6-23.4)	15.3 (12.0-18.5)	4.7 (0.6-8.8)	
>1,800 pg/mL	15.5 (12.2-18.8)	11.6 (8.2-15.0)	3.9 (−0.2 to 8.0)	



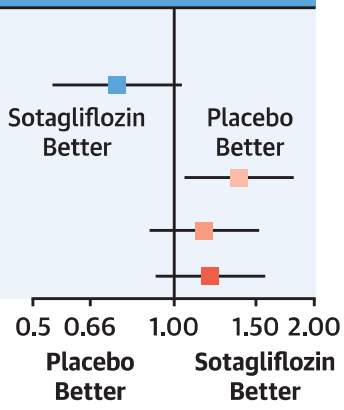
GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

responsive to conventional guideline-directed medical therapies.[21] Therefore, it is conceivable that such severely symptomatic patients may have less clinical benefit from sotagliflozin vs placebo. However, in SOLOIST-WHF, we observed no attenuation in the clinical benefits of sotagliflozin across the spectrum of KCCQ when modeled categorically or continuously. In fact, absolute risk reductions in death/worsening HF were highest among those with greatest symptom burden at baseline. These results add to the available knowledge regarding the benefit of dual SGLT1 and SGLT2 inhibition across the broad spectrum of disease severity. These data also add to the consistency of clinical benefits across care settings and HF type observed with prior SGLT2 inhibitor trials,[22] and they are novel in establishing the clinical efficacy of dual SGLT1 and SGLT2 inhibition across a broad spectrum of health status impairment.

In addition to the substantial improvements in KCCQ expected after a WHF episode in both randomized groups, incremental improvements in health status among those randomized to receive sotagliflozin were evident at 4 months' postrandomization and persistent at 8 months' postrandomization. The incremental benefits with sotagliflozin seen on top of usual care symptom burden improvement after WHF are particularly notable. Treatment with sotagliflozin resulted in a greater odds of clinically meaningful (at-least small) improvements in health status. Prior trials of SGLT2 inhibitors in chronic HF across the spectrum of LVEF have shown modest effects on improvement in health status.[6,14-16] However, health status benefits were generally greater in patients with type 2 diabetes in these trials, consistent with the larger benefits seen in the SOLOIST-WHF population who all had a history of diabetes.[14,15] However, data on patients with acute HF across the spectrum of LVEF have been generally limited. The EMPULSE trial observed a 4.5-point placebo-corrected change in KCCQ-total symptom score with treatment with empagliflozin vs placebo after stabilization of acute HF, similar to the 4.1 points in the current analysis.[8]

FIGURE 4 Responder Analysis of Clinically Meaningful Changes in Health Status

	Sotagliflozin	Placebo	OR (95% CI)	*P* Value
Month 4 Deterioration:				
5+ Points	16.4%	20.2%	0.75 (0.55-1.03)	0.0752
Month 4 Improvement:				
5+ Points	70.8%	64.9%	1.38 (1.06-1.80)	0.0177
10+ Points	60.1%	57.8%	1.16 (0.89-1.51)	0.26
20+ Points	46.8%	43.8%	1.20 (0.92-1.55)	0.18



However, EMPULSE was modestly sized, had a fixed, short-term follow-up, and was not powered to definitively examine clinical endpoints. The data from SOLOIST-WHF substantiate the improvement of health status and clinical endpoints with dual SGLT1 and SGLT2 inhibition in this larger global trial with longer clinical follow-up.

Furthermore, the benefits of sotagliflozin on health status remained consistent across major subgroups of interest, including LVEF. In fact, patients with LVEF ≥50% appeared to derive greater numerical improvements in KCCQ-12 compared with those with lower ejection fraction (although not statistically significant), potentially consistent with the greater symptom burden in those with HF with preserved ejection fraction; no attenuation in the clinical or health status benefits were observed with higher ejection fraction. In addition, patients in whom sotagliflozin was given before discharge also had substantial improvements in health status, substantially larger than those observed in patients randomized to receive placebo. Together with the clinical benefits and favorable safety profiles observed in SOLOIST-WHF, these data highlight the importance of early initiation of this therapy after stabilization of WHF and the potential for this treatment to facilitate early symptom relief and quality-of-care transitions from hospital to home.

These data provide additive information to the growing body of evidence showing the efficacy of dual SGLT1 and SGLT2 inhibition with sotagliflozin in both patients with atherosclerotic vascular disease[23] and HF[11] across the spectrum of diabetes severity.[24] Incremental to the SGLT2 inhibitor effects in the renal proximal tubule, sotagliflozin also provides selective modulation of kidney and gastrointestinal SGLT1. Because both the gastrointestinal and the proximal tubule of the kidney have important regulatory function in blood glucose management, future studies are needed to determine whether the improvements observed in clinical endpoints and health status are mediated by predominantly by SGLT1 inhibition, SGLT2 inhibition, or both.[25,26] It must also be determined whether additional selective SGLT1 inhibition provides unique benefits in reducing particular forms of cardiovascular events, including myocardial infarction and stroke.[27] In HF in particular, dual SGLT1 and SGLT2 inhibition has now been shown to reduce primary and recurrent HF events, with favorable early effects on HF-related morbidity and mortality, with clinical benefits apparent within weeks of initiation.[28-30] The health status results here are consistent with early observed benefit of this therapy, and together with clinical endpoints benefits, suggest that early initiation of this therapy should be considered in eligible patients shortly after a WHF event.

STUDY LIMITATIONS. First, although the KCCQ-12 change at 4 months was a prespecified secondary endpoint in SOLOIST-WHF, additional analyses of the change in KCCQ-12 at earlier and later time points

were post hoc; while numerical trends began to emerge at 4 weeks' postrandomization, these differences were not statistically significant. Second, some patients had missing health status assessments during follow-up; no imputation was done for missing values, and bias in those without follow-up KCCQ-12 could have affected the results. KCCQ-12 data were collected from randomization only through 8 months; the impact of treatment with sotagliflozin on longer term health status was not assessed in the context of this study. However, the health status follow-up in SOLOIST-WHF was similar to that of other SGLT2 inhibitor trials in chronic HF[4] and substantially longer than prior trials in WHF.[8] Finally, the use of KCCQ-12 precluded the ability to examine domain-specific changes in health status with sotagliflozin treatment; however, prior validation exercises have shown a high concordance with KCCQ-12 and all KCCQ-23 clinical domains.[12]

CONCLUSIONS

Treatment with the dual SGLT1 and SGLT2 inhibitor sotagliflozin after a WHF episode improved HF-related symptoms, physical limitations, and quality of life within 4 months of treatment initiation. Benefits were consistent across baseline health status, ejection fraction, demographic characteristics, and clinical characteristics.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sotagliflozin improved clinical endpoints in patients with WHF across the full spectrum of baseline symptom burden as measured by the KCCQ-12.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Sotagliflozin improved symptom burden, physical limitations, and quality of life and increased the proportion of patients experiencing at least small improvements in health status.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The benefits of sotagliflozin on HF-related quality of life were consistent across major subgroups of interest, including across the left ventricular ejection fraction spectrum.

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KEY WORDS dual SGLT1 and SGLT2 inhibitor, health status, KCCQ, sotagliflozin, worsening heart failure

APPENDIX For a supplemental figure, please see the online version of this article.