ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

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ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure or death from cardiovascular causes among patients with stable heart failure. However, the safety and efficacy of SGLT2 inhibitors when initiated soon after an episode of decompensated heart failure are unknown.

METHODS

We performed a multicenter, double-blind trial in which patients with type 2 diabetes mellitus who were recently hospitalized for worsening heart failure were randomly assigned to receive sotagliflozin or placebo. The primary end point was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial ended early because of loss of funding from the sponsor.

RESULTS

A total of 1222 patients underwent randomization (608 to the sotagliflozin group and 614 to the placebo group) and were followed for a median of 9.0 months; the first dose of sotagliflozin or placebo was administered before discharge in 48.8% and a median of 2 days after discharge in 51.2%. Among these patients, 600 primary end-point events occurred (245 in the sotagliflozin group and 355 in the placebo group). The rate (the number of events per 100 patient-years) of primary end-point events was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001). The rate of death from cardiovascular causes was 10.6 in the sotagliflozin group and 12.5 in the placebo group (hazard ratio, 0.84; 95% CI, 0.58 to 1.22); the rate of death from any cause was 13.5 in the sotagliflozin group and 16.3 in the placebo group (hazard ratio, 0.82; 95% CI, 0.59 to 1.14). Diarrhea was more common with sotagliflozin than with placebo (6.1% vs. 3.4%), as was severe hypoglycemia (1.5% vs. 0.3%). The percentage of patients with hypotension was similar in the sotagliflozin group and the placebo group (6.0% and 4.6%, respectively), as was the percentage with acute kidney injury (4.1% and 4.4%, respectively). The benefits of sotagliflozin were consistent in the prespecified subgroups of patients stratified according to the timing of the first dose.

CONCLUSIONS

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo. (Funded by Sanofi and Lexicon Pharmaceuticals; SOLOIST-WHF ClinicalTrials.gov number, NCT03521934.)

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors represent a major therapeutic advance.[1-3] They were initially developed to treat hyperglycemia in patients with diabetes mellitus. Subsequently, several SGLT2 inhibitors were shown to lower the risk of hospitalization for heart failure among patients with type 2 diabetes, who are at substantial risk for this complication.[4-22] In addition, some SGLT2 inhibitors have been shown to reduce the risk of death from cardiovascular causes or hospitalization for heart failure in patients with heart failure (with or without diabetes) and a reduced ejection fraction.[23,24]

The safety and potential efficacy of initiating SGLT2 inhibition soon after an episode of decompensated heart failure remain uncertain. Potential safety concerns include the risks of hypotension and precipitation of kidney failure among patients with fluctuating volume status and renal function who are receiving treatment with other drugs that might also affect the glomerular filtration rate (GFR). In addition, whether the benefits of SGLT2 inhibition extend to patients with heart failure with preserved ejection fraction remains unknown.

These considerations led to the design of the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial. Sotagliflozin is an SGLT2 inhibitor that also provides some gastrointestinal SGLT1 inhibition. SGLT2 inhibition increases glucose excretion in the urine, whereas SGLT1 inhibition reduces the postprandial glucose level by delaying intestinal glucose absorption.[25-30] We hypothesized that sotagliflozin would reduce the risks of death from cardiovascular causes, hospitalization for heart failure, and an urgent visit for heart failure among patients with diabetes mellitus and recent worsening of heart failure with either reduced or preserved ejection fraction when administered soon after an episode of decompensated heart failure.

Methods

Trial Design

The SOLOIST-WHF trial was a phase 3, double-blind, randomized, placebo-controlled trial. Sanofi was the original sponsor; sponsorship was transferred to Lexicon Pharmaceuticals as of January 30, 2020. The executive and steering committees (both consisting of academic physicians) and representatives from the sponsors developed the protocol and statistical analysis plan, available with the full text of this article at NEJM.org, and were responsible for the conduct and oversight of the trial and for the interpretation of the data. The sponsors were responsible for management and monitoring of the trial sites, regulatory reporting, and collection and management of the data. The 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. All the data analyses presented here were performed by an independent academic statistician (the second author), who had access to the raw data. The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol and statistical analysis plan.

Eligibility

Patients were eligible for enrollment in the trial if they were 18 to 85 years of age and had been hospitalized because of the presence of signs and symptoms of heart failure and received treatment with intravenous diuretic therapy. Patients were also required to have received a previous diagnosis of type 2 diabetes before the index admission or to have laboratory evidence to support a diagnosis of type 2 diabetes during the index admission. Exclusion criteria included end-stage heart failure or recent acute coronary syndrome, stroke, percutaneous coronary intervention or coronary-artery bypass surgery, or an estimated GFR of less than 30 ml per minute per 1.73 m^2 of body-surface area. Further details of the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from all patients.

Patients were excluded if they did not meet criteria for clinical stability before randomization. These criteria included no need for oxygen therapy, a systolic blood pressure of at least 100 mm Hg, no need for intravenous inotropic or vasodilator therapy (excluding nitrates), and having transitioned from intravenous to oral diuretic therapy. Patients were also required to have elevated natriuretic peptide levels at the time of randomization. Natriuretic peptide thresholds were, for

B-type natriuretic peptide, at least 150 pg per milliliter (≥450 pg per milliliter for patients with atrial fibrillation) or, for N-terminal pro–B-type natriuretic peptide (NT-proBNP), at least 600 pg per milliliter (≥1800 pg per milliliter for patients with atrial fibrillation).

TRIAL PROCEDURES

Patients who met all eligibility and stability criteria were randomly assigned, either before or within 3 days after hospital discharge, to receive 200 mg of sotagliflozin once daily (with a dose increase to 400 mg, depending on side effects) or placebo. Randomization was performed centrally with the use of interactive-response technology and was stratified according to left ventricular ejection fraction (<50% or ≥50%) and geographic region of enrollment (North America, Latin America, western Europe, eastern Europe, or rest of the world) at baseline. Follow-up visits were scheduled at 1, 2, and 4 weeks, at 4 months, and every 4 months thereafter. Further details of the trial design are provided in Figure S1 in the Supplementary Appendix.

END POINTS

All end points were measured from the time of randomization. The trial was originally designed with a primary end point of the first occurrence of either death from cardiovascular causes or hospitalization for heart failure, as described in the trial protocol. However, trial enrollment was closed early (on March 20, 2020) because of loss of funding from the sponsor, which resulted in a substantial reduction in power to test the original primary end point. Therefore, while remaining unaware of the trial-group assignments and without information from an interim analysis or sample-size recalculation, the executive and steering committees and sponsor changed the primary end point to the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent) in order to increase the power of the trial. Adjudication of events was planned but could not be completed because of the loss of funding; therefore, the decision was made by the executive and steering committees to analyze investigator-reported events. This change was codified in the first (and only) version of the statistical analysis plan, dated August 9, 2020.

The revised secondary end points were the total number of hospitalizations and urgent visits for heart failure; the incidence of death from cardiovascular causes; the incidence of death from any cause; the total number of deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes; the total number of deaths from cardiovascular causes, hospitalizations and urgent visits for heart failure, and events of heart failure during hospitalization; the change in score on the Kansas City Cardiomyopathy Questionnaire–12 item (KCCQ-12; scores range from 0 to 100, with higher scores indicating better quality of life) to month 4; and the change in the estimated GFR.[31] The prespecified end-point definitions are provided in the Supplementary Appendix. Adverse events of special interest that occurred during the treatment period were also recorded. The protocol definitions of adverse events of interest are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

In this event-driven trial, it was originally estimated that 947 adjudicated primary end-point events (first occurrence of either death from cardiovascular causes or hospitalization for heart failure) in patients with a left ventricular ejection fraction of less than 50% and 1341 adjudicated primary end-point events in all patients would provide the trial with more than 85% power to detect a 19% lower risk of a primary end-point event in the sotagliflozin group than in the placebo group among patients with a left ventricular ejection fraction of less than 50% and more than 90% power to detect the same risk reduction overall. This resulted in an estimated sample size of approximately 4000 patients; the enrollment of patients with a left ventricular ejection fraction of 50% or higher was limited to 1100, as prespecified in the protocol. Because trial enrollment was closed early, only 1222 patients were enrolled (256 with a left ventricular ejection fraction of ≥50%), which led to the decision to change the primary end point as described in the previous section.

All efficacy analyses were performed according to the intention-to-treat principle. To allow for analyses of the total number of events, competing-risks marginal models for recurrent events

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Sotagliflozin (N=608)	Placebo (N=614)
Median age (IQR) — yr	69 (63–76)	70 (64–76)
Female sex — no. (%)	198 (32.6)	214 (34.9)
Race or ethnic group — no. (%)†		
White	567 (93.3)	572 (93.2)
Black	25 (4.1)	25 (4.1)
Asian	8 (1.3)	7 (1.1)
Other	2 (0.3)	4 (0.7)
Unknown	6 (1.0)	6 (1.0)
Median glycated hemoglobin level (IQR) — %	7.1 (6.4–8.3)	7.2 (6.4–8.2)
Median body-mass index (IQR)‡	30.4 (26.3–34.3)	31.1 (27.3–34.5)
Median KCCQ-12 score (IQR)§	35 (28–44)	35 (26–44)
Median estimated GFR (IQR) — ml/min/1.73 m^2 of body-surface area	49.2 (39.5–61.2)	50.5 (40.5–64.6)
Geographic region — no. (%)¶		
Eastern Europe	244 (40.1)	246 (40.1)
Western Europe	155 (25.5)	155 (25.2)
Latin America	132 (21.7)	134 (21.8)
North America	39 (6.4)	41 (6.7)
Rest of the world	38 (6.2)	38 (6.2)
Diagnosis of diabetes — no. (%)		
During the index admission	17 (2.8)	14 (2.3)
Within 3 mo before randomization	25 (4.1)	20 (3.3)
Within 6 mo before randomization	35 (5.8)	34 (5.5)
Left ventricular ejection fraction		
Median value (IQR) — %	35 (28–47)	35 (28–45)
<50% — no. (%)¶	481 (79.1)	485 (79.0)
Median NT-proBNP (IQR) — pg/ml	1816.8 (854.7–3658.5)	1741.0 (842.5–3582.2)
Median blood pressure (IQR) — mm Hg		
Systolic	122 (111–135)	122 (112–133)
Diastolic	72 (66–80)	73 (66–80)
Any RAAS inhibitor — no. (%)	553 (91.0)	563 (91.7)
ACE inhibitor	254 (41.8)	241 (39.3)
ARB	245 (40.3)	270 (44.0)
ARNI	93 (15.3)	112 (18.2)
MRA	403 (66.3)	385 (62.7)
Beta-blocker — no. (%)	564 (92.8)	561 (91.4)
Loop diuretic — no. (%)	580 (95.4)	581 (94.6)
Other diuretic — no. (%)	66 (10.9)	62 (10.1)

Table 1. (Continued.)

Characteristic	Sotagliflozin (N=608)	Placebo (N=614)
Any glucose-lowering medication — no. (%)	522 (85.9)	522 (85.0)
Metformin	320 (52.6)	320 (52.1)
Sulfonylurea	114 (18.8)	114 (18.6)
DPP-4 inhibitor	96 (15.8)	102 (16.6)
Insulin	217 (35.7)	217 (35.3)
GLP-1 receptor agonist	17 (2.8)	23 (3.7)

* Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, DPP-4 dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide 1, IQR interquartile range, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, and RAAS renin–angiotensin–aldosterone system.
† Race and ethnic group were reported by the investigators. The category "other" includes native Hawaiian or other Pacific Islander or multiple races.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the Kansas City Cardiomyopathy Questionnaire–12 item (KCCQ-12) range from 0 to 100, with higher scores indicating better quality of life.
¶ Geographic region and left ventricular ejection fraction below 50% were categorized according to the respective randomization stratification factors.

(stratified according to left ventricular ejection fraction at baseline [<50% or ≥50%] and geographic region of enrollment [North America, Latin America, western Europe, eastern Europe, or rest of the world]), in which deaths that were not part of a given end point were treated as competing terminal events, were applied to generate hazard ratios (sotagliflozin vs. placebo) with Wald 95% confidence intervals and P values.[32] We used the robust sandwich variance estimate for the estimated standard error of the log hazard ratio to account for the dependence of event times within individual patients.[33] Event rates were calculated as the number of events per 100 patient-years of follow-up, and the accrual of events over time was estimated with the use of cumulative incidence functions.

A fixed hierarchical procedure was used to control for type I error in the analyses of the secondary end points; the hierarchical testing sequence is provided in the Supplementary Appendix. For tertiary and subgroup analyses, 95% confidence intervals were reported without adjustment for multiple testing, and inferences drawn from the intervals may not be reproducible. Change in the KCCQ-12 score from baseline to month 4 was assessed with the use of analysis of covariance, with trial group as a factor and baseline score and randomization stratification factors as covariates. Change in the estimated GFR over time was analyzed with the use of a repeated-measures, mixed-effects model, with absolute change in the estimated GFR from baseline as the outcome, the intercept as a random effect, and trial group, baseline value, and time as fixed effects. A sensitivity analysis of the change in KCCQ-12 score was also performed with the use of a mixed-effects model similar to that used for change in the estimated GFR. In addition, change in the KCCQ-12 score and change in the estimated GFR were jointly modeled with death from any cause to account for competing risk. Conventions used for missing data are described in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

A total of 1549 patients underwent screening, of whom 1222 (78.9%) were randomly assigned to a trial group (608 to the sotagliflozin group and 614 to the placebo group) at 306 sites in 32 countries (Fig. S2). The reasons for screening failure are listed in Table S1. The first patient underwent randomization on June 15, 2018, and the last on March 20, 2020.

The baseline characteristics of the patients are provided in Table 1. The median age of the

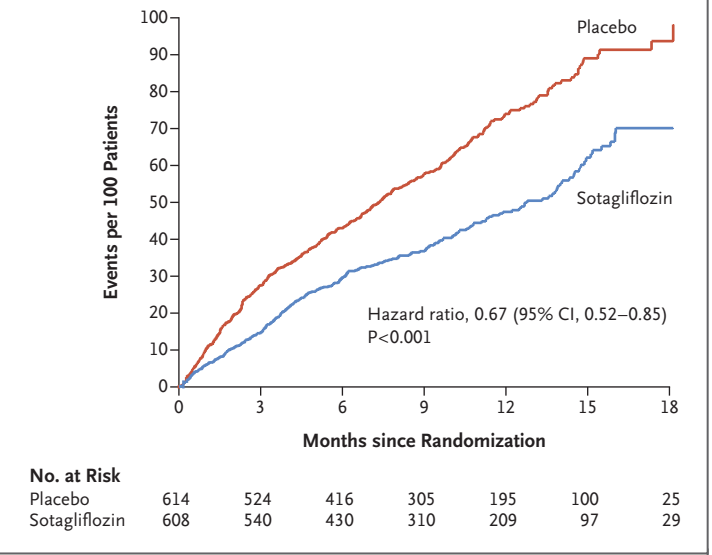

Figure 1. Primary Efficacy End-Point Events.

Shown are the rates of primary efficacy end-point events (deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure) in the sotagliflozin group and the placebo group. Total events after randomization are shown as estimated cumulative events per 100 patients instead of events per 100 patient-years to graphically show the time course of event accrual during follow-up. Competing deaths from noncardiovascular causes occurred in 14 patients in the sotagliflozin group and in 18 patients in the placebo group.

patients was 70 years, 33.7% were female, and 93.2% were White. A total of 79.1% of the patients had a left ventricular ejection fraction of less than 50%, the median estimated GFR was 49.7 ml per minute per 1.73 m^2, the median glycated hemoglobin level was 7.1%, and the median NT-proBNP level was 1799.7 pg per milliliter. The first dose of sotagliflozin or placebo was administered before discharge in 48.8% of the patients and after discharge in 51.2% (median, 2 days [interquartile range, 1 to 3] after discharge in both trial groups). The patients were well treated for heart failure with various classes of evidence-based medications, and 85.4% were receiving a glucose-lowering medication.

FOLLOW-UP

At the time of database lock (August 10, 2020), vital status was available for 97.1% of the patients; 43 patients (3.5%) did not complete the final trial visit, among whom vital status was unknown at the end of the trial for 35. In the sotagliflozin group, the median duration of follow-up was 9.2 months, the median duration of treatment was 7.8 months, and 81.7% of the patients were exposed to the trial agent for at least 80% of follow-up; the corresponding values in the placebo group were 8.9 months, 7.6 months, and 79.2% of the patients. Early discontinuation of the trial regimen for reasons other than death or early termination of the trial occurred in 79 patients (13.0%) in the sotagliflozin group and in 94 patients (15.3%) in the placebo group.

EFFICACY END POINTS

A total of 600 primary end-point events occurred among 1222 patients (245 in the sotagliflozin group and 355 in the placebo group). The rate of primary end-point events was 51.0 per 100 patient-years in the sotagliflozin group and 76.3 per 100 patient-years in the placebo group (hazard ratio, 0.67; 95% confidence interval [CI], 0.52 to 0.85; P<0.001), for an absolute difference of 25.3 events per 100 patient-years (95% CI, 5.1 to 45.6).[34] The cumulative incidence curves for the primary efficacy end point are shown in Figure 1. The results of subgroup analyses of the primary efficacy end point according to stratification factors and select prespecified subgroups showed a consistent treatment effect across the subgroups stratified according to geographic region of enrollment (North America or Latin America, Europe, or rest of the world), left ventricular ejection fraction (<50% or ≥50%), timing of the first dose of sotagliflozin or placebo (before or after discharge), sex, age (<65 years or ≥65 years), and renal function (estimated GFR, <60 ml per minute per 1.73 m^2 or ≥60 ml per minute per 1.73 m^2) (Fig. 2). The results for all prespecified and additional post hoc subgroups are provided in Table S2.

The secondary end points are listed in hierarchical testing order in Table 2. The results of the analysis of the first secondary end point (the total number of hospitalizations and urgent visits for heart failure) were consistent with the results of the primary end-point analysis. The incidence of death from cardiovascular causes or of death from any cause did not differ significantly between the trial groups. To address the possible concern that the primary end point might be subject to double counting of urgent visits for heart failure leading to hospitalization, we examined the total number of deaths from cardiovascular causes and hospitalizations for

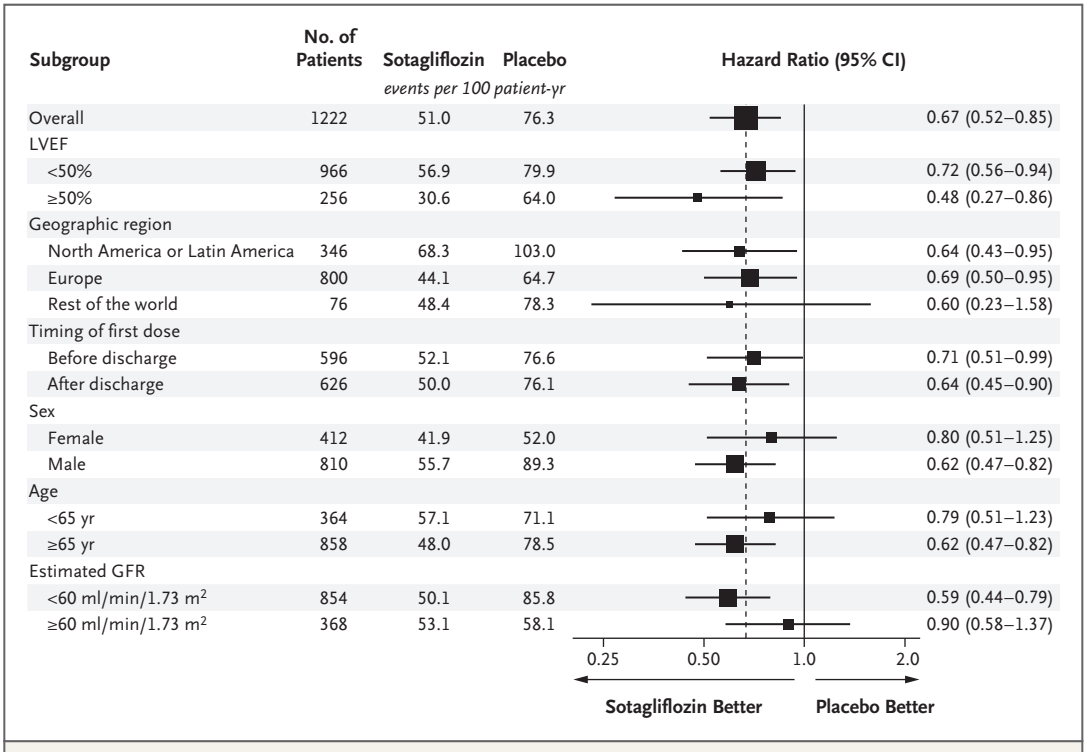

Figure 2. Primary Efficacy End-Point Events in Select Prespecified Subgroups.

Shown are the hazard ratios with 95% confidence intervals for primary end-point events in select prespecified subgroups. The confidence intervals have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible. Left ventricular ejection fraction (LVEF) was categorized according to the randomization stratification factor. GFR denotes glomerular filtration rate.

heart failure, excluding urgent visits for heart failure. The results were consistent with those of the primary end-point analysis (hazard ratio, 0.68; 95% CI, 0.53 to 0.88) (Fig. S3). In addition, in a time-to-event analysis of the original primary end point of the trial (the first occurrence of either death from cardiovascular causes or hospitalization for heart failure), the results were consistent with those of the revised primary end point, with a hazard ratio for death from cardiovascular causes or hospitalization for heart failure of 0.71 (95% CI, 0.56 to 0.89) (Fig. 3). The between-group difference in the change in the KCCQ-12 score was 4.1 points (95% CI, 1.3 to 7.0) in favor of the sotagliflozin group, and the between-group difference in the change in the estimated GFR during follow-up was −0.16 ml per minute per 1.73 m^2 (95% CI, −1.30 to 0.98) in favor of the placebo group.

The results of sensitivity analyses that used a joint model of the change in the KCCQ-12 score and death from any cause, a joint model of the change in the estimated GFR and death from any cause, and a mixed model of the change in the KCCQ-12 score were similar to those of the primary analysis (Table S3). Among the investigator-reported events that were submitted for adjudication (before the loss of sponsor funding), 174 of 225 (77.3%) in the sotagliflozin group and 221 of 286 (77.3%) in the placebo group were confirmed on adjudication (Table S4).

SAFETY END POINTS

Serious adverse events that led to withdrawal of sotagliflozin or placebo occurred in 3.0% of the patients in the sotagliflozin group and in 2.8% of the patients in the placebo group (Table S5). The most common adverse events other than heart failure that occurred in the sotagliflozin group and the placebo group were hypotension (6.0% vs. 4.6%), urinary tract infection (4.8% vs. 5.1%), and diarrhea (6.1% vs. 3.4%) (Table S6).

Table 2. Primary End Point and Secondary End Points.

End Point	Sotagliflozin (N=608)	Placebo (N=614)	Hazard Ratio or Difference (95% CI)*	P Value
Primary end point: deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure — total no. of events (rate)†	245 (51.0)	355 (76.3)	0.67 (0.52 to 0.85)	<0.001
Secondary end points in order of hierarchical testing				
Hospitalizations and urgent visits for heart failure — total no. of events (rate)†	194 (40.4)	297 (63.9)	0.64 (0.49 to 0.83)	<0.001
Deaths from cardiovascular causes — total no. of events (rate)†	51 (10.6)	58 (12.5)	0.84 (0.58 to 1.22)	0.36‡
Deaths from cardiovascular causes, hospitalizations for heart failure, nonfatal myocardial infarctions, and nonfatal strokes — total no. of events (rate)†	247 (51.4)	330 (71.0)	0.72 (0.56 to 0.92)	
Deaths from cardiovascular causes, hospitalizations and urgent visits for heart failure, and events of heart failure during hospitalization — total no. of events (rate)†	263 (54.7)	375 (80.6)	0.68 (0.54 to 0.86)	
Deaths from any cause — total no. of events (rate)†	65 (13.5)	76 (16.3)	0.82 (0.59 to 1.14)	
Least-squares mean change in KCCQ-12 score to month 4	17.7	13.6	4.1 (1.3 to 7.0)	
Least-squares mean change in estimated GFR — ml/min/1.73 m^2	−0.34	−0.18	−0.16 (−1.30 to 0.98)	

* Hazard ratios (sotagliflozin vs. placebo) are shown for all end points except change in KCCQ-12 score to month 4 and change in estimated GFR, for which differences in the least-squares mean values are shown (sotagliflozin minus placebo).
† Rate was calculated as the number of events per 100 person-years of follow-up.
‡ The hierarchical analysis was stopped after the first P value indicating nonsignificance.

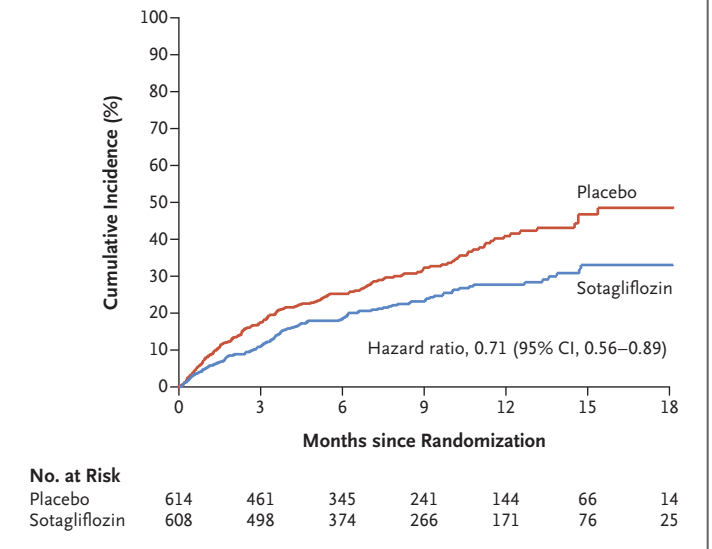

Figure 3. First Occurrence of Either Death from Cardiovascular Causes or Hospitalization for Heart Failure.

Shown is the cumulative incidence of the first occurrence of either death from cardiovascular causes or hospitalization for heart failure in the sotagliflozin group and the placebo group. Competing deaths from noncardiovascular causes occurred in 10 patients in the sotagliflozin group and in 13 patients in the placebo group.

Details of renal and urinary disorders are shown in Table S7. Acute kidney injury occurred in 4.1% of the patients in the sotagliflozin group and in 4.4% of patients in the placebo group. Severe hypoglycemia was more common with sotagliflozin than with placebo (1.5% vs. 0.3%). Additional adverse events of special interest, including bone fractures, diabetic ketoacidosis, genital mycotic infections, adverse events leading to amputation, and others, are shown in Table S8.

DISCUSSION

The SOLOIST-WHF trial showed that among patients with diabetes who had worsening heart failure, the primary end point of the total number of cardiovascular deaths and hospitalizations and urgent visits for heart failure was significantly lower with the SGLT2 and SGLT1 inhibitor sotagliflozin than with placebo. This finding was consistent across multiple prespecified subgroups, including those stratified according to the timing of the first dose of sotagliflozin or placebo (before or after discharge) and left ventricular ejection fraction (reduced or mid-range [<50%] or preserved [≥50%]).

Accumulating evidence from randomized clinical trials supports the use of SGLT2 inhibitors in patients who have stable heart failure (with or without diabetes) and a reduced ejection fraction.[4-22,35] The current trial showed that initiation of SGLT2 inhibition before or shortly after discharge in patients who were hospitalized for worsening heart failure was also beneficial. Despite the low estimated GFR (median, 49.7 ml per minute per 1.73 m^2) and the recent hospitalization for worsening heart failure in this population, the percentage of patients who had hypotension was similar in the sotagliflozin group and the placebo group, although severe hypoglycemia was more common in the sotagliflozin group. Early initiation of therapy represents an important opportunity to improve outcomes, as indicated by the high rate of primary end-point events at 90 days after randomization among the patients receiving placebo.

The SOLOIST-WHF trial had also intended to evaluate whether the benefits of SGLT2 inhibition extend to patients with heart failure with preserved ejection fraction. However, although such patients were enrolled in the trial and there was no evidence of heterogeneity of treatment effect according to ejection fraction, early termination of the trial and the small sample size of this subgroup made it difficult to draw any firm conclusion in this regard. Two additional trials, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER; ClinicalTrials.gov number, NCT03619213) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved; NCT03057951), are examining SGLT2 inhibitors in patients with heart failure with preserved ejection fraction, with or without diabetes mellitus.

The mechanisms of the benefit of SGLT2 inhibition are still being elucidated. Enhanced renal glucose excretion is a well-established mechanism of action, leading to a natriuretic and diuretic effect. Weight loss, improved myocardial energetics, decreases in uric acid level, adaptive cellular reprogramming, and salutary effects on endothelial progenitor cells have been described.[36-41] Reductions in blood pressure and in left ventricular hypertrophy have also been reported.[42-44] It is not clear, however, in the current trial what, if any, clinical benefits were derived through the inhibition of SGLT1 with sotagliflozin therapy, and further direct comparative trials with a selective SGLT2 inhibitor are needed to evaluate whether there is any incremental value of SGLT1 blockade beyond SGLT2 inhibition.

Limitations of this trial included loss of funding from the sponsor that led to the trial being stopped before enrollment of the initial planned sample size.[45-49] Although the trial suggested that there was a beneficial effect with respect to the original primary end point of the first occurrence of either death from cardiovascular causes or hospitalization for heart failure, the earlier-than-planned closure of the trial limited the statistical power to assess the secondary end points, such as death from cardiovascular causes. The initial trial design had called for the adjudication of events, but because of the loss of funding, this was not completed, and while the investigators remained unaware of the trial outcomes, the primary end point was changed to be based on investigator-defined events.[50,51]

In this trial involving patients with diabetes and a recent episode of acute decompensated heart failure, sotagliflozin therapy — whether initiated before or shortly after hospital discharge — resulted in a lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.

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APPENDIX

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