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Effect of Sotagliflozin on Total Hospitalizations in Patients With Type 2 Diabetes and Worsening Heart Failure

A Randomized Trial

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Background: In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial, sotagliflozin, a sodium–glucose cotransporter-1 and sodium–glucose cotransporter-2 inhibitor, reduced total occurrences of cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure relative to placebo by 33%.

Objective: To determine whether sotagliflozin increased the prespecified efficacy outcome of days alive and out of the hospital (DAOH) in the SOLOIST-WHF trial.

Design: Randomized, double-blind, placebo-controlled trial. (ClinicalTrials.gov: NCT03521934)

Setting: 306 sites in 32 countries.

Participants: 1222 patients with type 2 diabetes and reduced or preserved ejection fraction who were recently hospitalized for worsening heart failure.

Intervention: 200 mg of sotagliflozin once daily (with a possible dose increase to 400 mg) or matching placebo.

Measurements: The primary analysis included hospitalizations for any reason on the basis of investigator-reported incidence and duration of admissions after randomization. Days alive and out of the hospital and its converse (days dead and days in the hospital) were analyzed using prespecified Poisson regression models.

Results: Although similar proportions of patients in the sotagliflozin and placebo groups were hospitalized at least once (38.5% vs. 41.4%), fewer patients in the sotagliflozin group were hospitalized more than once (16.3% vs. 22.1%). There were 64 and 76 deaths in the sotagliflozin and placebo groups, respectively. The DAOH rate in the sotagliflozin group was 3% higher than in the placebo group (rate ratio [RR], 1.03 [95% CI, 1.00 to 1.06]; $P = 0.027$). This difference was primarily driven by a reduction in the rate of days dead (RR, 0.71 [CI, 0.52 to 0.99]; $P = 0.041$) rather than by a reduction in the rate of days hospitalized for any cause. For every 100 days of follow-up, patients in the sotagliflozin group were alive and out of the hospital for 3% or 2.9 more days than those in the placebo group (91.8 vs. 88.9 days); this difference reflected a 2.6-day difference in days dead (6.3 vs. 8.9 days) and a 0.3-day difference in days in the hospital (1.9 vs. 2.2 days).

Limitation: Other than heart failure, the primary reason for each hospitalization was unspecified.

Conclusion: Sotagliflozin increased DAOH, a metric that may provide an additional patient-centered outcome to capture the totality of disease burden. Future studies are needed to quantify the consequences of increasing DAOH in terms of health economics and patient quality of life.

Primary Funding Source: Sanofi at initiation and Lexicon Pharmaceuticals at completion.

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Elevated risk for hospitalization among patients with a history of diabetes and heart failure is a clinically meaningful component of their total disease burden (1). In clinical trials, treatment with a sodium–glucose cotransporter-2 (SGLT2) inhibitor has been shown to reduce the risk for first hospitalization for heart failure or total (first and potentially subsequent) hospitalizations for heart failure in patients with diabetes and/or heart failure (2–11). Although there is emerging evidence that this drug class can also reduce first or total hospitalizations for any reason (3, 10), these prior reports have accounted for the incidence of each admission but not the duration.

The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial compared sotagliflozin, a sodium–glucose cotransporter-1 (SGLT1) and SGLT2 inhibitor, with placebo in patients with type 2 diabetes and reduced or preserved left ventricular ejection fraction who were recently hospitalized for worsening heart failure. Despite early termination of the study due to loss of funding from the sponsor during the onset of the COVID-19 pandemic (12), sotagliflozin reduced the primary efficacy end point, total occurrences of cardiovascular deaths, hospitalizations for heart failure, and

See also:

Web-Only
Supplement

urgent visits for heart failure (9, 13). All-cause death was also numerically less frequent in the sotagliflozin group.

In this prespecified analysis of the study, we extended on these previous findings by comparing days alive and out of the hospital (DAOH) and percent DAOH (PDAOH) between the sotagliflozin and placebo groups. Days alive and out of the hospital and PDAOH combine information on hospitalizations and death into a single outcome while accounting for the duration of each hospitalization—an aspect of disease burden that has not been reported in prior trials of SGLT2 inhibitors. We also evaluated the effect of sotagliflozin in post hoc joint models of total hospitalizations and death. Our hypothesis was that sotagliflozin extends DAOH and reduces the risk for hospitalizations for any reason after hospitalization for heart failure.

METHODS

Details of the primary efficacy and safety results of the study, including the protocol and analysis plan, have been published (9). Ethics committee approval was obtained at all participating institutions. Eligible patients were aged 18 to 85 years, had provided written informed consent, had been hospitalized with signs and symptoms of heart failure within 2 weeks before randomization and received intravenous diuretic therapy, and had a previous diagnosis of type 2 diabetes before the index hospitalization or laboratory evidence of type 2 diabetes during the index hospitalization. Patients were randomly assigned in a 1:1 ratio to receive either 200 mg of sotagliflozin once daily (with a goal of a dose increase to 400 mg) or matching placebo, stratified by left ventricular ejection fraction (<50% vs. ≥50%) and geographic region (North America, Latin America, western Europe, eastern Europe, or rest of the world). Randomization was double blinded; the patients, investigators, and other parties involved in the study were masked to the true treatment assignments.

Hospitalization Assessments

Investigators reported all incidence and duration of admissions to the hospital or emergency department after randomization on a designated case report form, although the primary reason for each hospitalization was not recorded. The investigator-reported efficacy end point events of hospitalization for heart failure, collected on a separate case report form, were, therefore, merged with the hospitalizations data to determine if the reason for hospitalization was heart failure or for other reasons, which remained unspecified. The duration of each hospitalization was determined from the difference in dates of admission and discharge recorded by the investigators on the form; if a patient died in the hospital, the hospitalization was ended on the date of death. Follow-up was truncated at the common study end date described below so that hospitalizations and deaths occurring after this date were not included in the analyses. Likewise, index hospitalizations were excluded, and although 596 patients first received the study drug (that is, were randomly assigned and dosed) during their index hospitalization, discharge occurred a median of 1 day (95th percentile = 5 days) after their first dose, and therefore these patients were at risk for rehospitalization within days of randomization. Furthermore, consistent with the primary efficacy end point of the study, independent adjudication of the hospitalization data was not done.

Definition of DAOH

Days alive and out of the hospital and PDAOH were prespecified as "other" efficacy end points in the study's statistical analysis plan, which was finalized before unblinding of the data. Total potential follow-up time for each patient was defined as the number of days from the date of randomization until the date the patient was last known to be alive if before 1 May 2020, or a prespecified common study end date of 1 May 2020 (the date by which all final visits were to be completed) if the patient died before this date or was last known to be alive after this date. The total number of days spent in the hospital for a given patient was derived from their cumulative duration of hospitalizations per the investigator reports. If a patient died, the number of days dead was calculated as the number of days between their date of death and the common study end date. Days alive and out of the hospital were calculated by subtracting days in the hospital and days dead from days of total potential follow-up; if a patient survived without hospitalization (no known death or hospitalization before 1 May 2020), DAOH was equal to the days of follow-up for that patient. In addition, PDAOH was calculated as DAOH divided by total potential follow-up time.

Statistical Analysis

Days alive and out of the hospital, days dead, and days in the hospital were compared between treatment groups using prespecified Poisson regression models with a log link function and Pearson χ^2 scaling of SEs to account for potential overdispersion. In addition to treatment group, interpatient differences in follow-up durations were accounted for by inclusion of the logarithm of potential follow-up time for each patient as an offset variable in the model so that results could be framed in terms of a comparison of the rates of these outcomes, quantified by rate ratios (RRs) with corresponding 95% CIs and *P* values. To explore the possible effects of regional health care environments, additional post hoc analyses of DAOH were done in subgroups defined by predefined geographic region (North America or Latin America, Europe, or rest of the world; the countries within each region are listed in the **Table of Supplement 1**, available at Annals.org). In addition, consistent with previous analyses of DAOH (14, 15), to account for possible bias due to differential follow-up, an additional post hoc sensitivity analysis of DAOH included outcomes through the first 90 days after randomization (>90% of surviving patients were followed for at least this duration). **Supplement 1** provides additional details on how these models were implemented.

Although β regression would be a customary approach to analyze percentage data, such as PDAOH, the standard model can only be applied with observed percentages

greater than 0% and less than 100%. Given the expectation that a substantial fraction of patients would survive without hospitalization until the end of follow-up (that is, PDAOH = 100%), PDAOH was therefore compared between treatment groups with a prespecified one-inflated β regression model, which is an extension of the standard model. In the current application, the model jointly estimates the treatment odds ratio of surviving until the end of the study without hospitalization (that is, PDAOH = 100%) and the treatment odds ratio of higher mean PDAOH among the subset of patients who died and/or had at least 1 hospitalization during follow-up (that is, PDAOH <100%) (16, 17). **Supplement 1** provides additional details on the one-inflated β regression model and how the model was implemented.

The primary post hoc analysis of total hospitalizations as a time-to-event outcome involved incident hospitalizations for any reason, whereas sensitivity analyses restricted total hospitalizations to those for heart failure and for reasons other than heart failure. We applied a joint semiparametric model that estimated the effect of sotagliflozin relative to placebo on total hospitalizations and separately on all-cause death as well as the association between hospitalizations and death (18, 19). Joint modeling allowed for the possibility that patients may have multiple hospitalizations, quantified the association between hospitalizations and death, and accounted for competing deaths that prevent follow-up for hospitalization, thereby resulting in an unbiased relative estimate (that is, hazard ratio [HR]) for incident hospitalization risk. Treatment effects on hospitalizations and death are summarized by HRs and corresponding 95% CIs and *P* values. Point estimates and corresponding 95% CIs and *P* values were also calculated for the association parameters. **Supplement 1** provides additional details on the model. Note that unlike DAOH and PDAOH, the duration of each hospitalization was not included in the joint model; an event was only determined by when a given hospitalization began.

To facilitate convergence of the semiparametric model, for a given patient, a hospitalization that occurred on the same day as death was excluded, and a maximum of 1 hospitalization was allowed to occur on a given day. With these conventions, all hospitalizations and death for a given patient had distinct event times from randomization.

To illustrate the cumulative incidence of events over time and facilitate comparisons with similar summaries generated for the primary efficacy end point of the study (9), nonparametric mean cumulative function curves were created for total hospitalizations for any reason, total hospitalizations for heart failure, and total hospitalizations for reasons other than heart failure (20). The mean cumulative function represents the expected (mean) cumulative number of hospitalizations per 100 patients at a given point in time after randomization, without consideration of the duration of each hospitalization. The CIs for total event incidence rates were calculated with methods that accounted for the possibility of multiple events per patient (21).

All analyses were done according to intention to treat, including all patients and events from randomization to the common study end date. Continuous variables are expressed as mean (SD) or median (quartile 1 to quartile 3). Categorical variables are expressed as counts and percentages, with treatment group comparisons done using Cochran–Mantel–Haenszel tests with stratification by the randomization stratification factors. Two-tailed *P* values less than 0.05 were considered statistically significant, with no adjustment for multiple testing. Analyses were done in SAS, version 9.4 (SAS Institute); TIBCO Spotfire S+ 8.2 (TIBCO Software); and R, version 3.5 (R Foundation for Statistical Computing) by an independent academic statistician (M.S.) who had access to the raw data. The study protocol and analysis plan are provided in **Supplement 2**.

Role of the Funding Source

The study sponsors (Sanofi at initiation and Lexicon Pharmaceuticals at completion) were responsible for management and monitoring of the trial sites, regulatory reporting, and collection and management of the data.

Table 1. Patient Demographic and Clinical Characteristics at Baseline

Characteristic	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)
Median age (IQR), *y*	69 (63–76)	70 (64–76)
Female, *n* (%)	198 (32.6)	214 (34.9)
Geographic region, *n* (%)		
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)
Left ventricular ejection fraction <50%, *n* (%)	481 (79.1)	485 (79.0)
Median estimated glomerular filtration rate (IQR), *mL/min/1.73 m^2 of body surface area*	49.2 (39.5–61.2)	50.5 (40.5–64.6)
Median duration of diabetes before randomization (IQR), *y*	10.2 (5.0–16.8)	10.2 (5.2–16.9)
Diagnosis of diabetes during index admission, *n* (%)	17 (2.8)	14 (2.3)
Any glucose-lowering medication, *n* (%)	522 (85.9)	522 (85.0)
Metformin	320 (52.6)	320 (52.1)
Sulfonylurea	114 (18.8)	114 (18.6)
Dipeptidyl peptidase-4 inhibitor	96 (15.8)	102 (16.6)
Insulin	217 (35.7)	217 (35.3)
Glucagon-like peptide-1 receptor agonist	17 (2.8)	23 (3.7)

IQR = interquartile range.

Table 2. Number and Duration of Hospitalizations and Number of Deaths During Follow-up

Outcome	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)	*P* Value*
Total hospitalizations for any reason, *n*	464	583	
For heart failure	159	237	
For reasons other than heart failure	305	346	
Number of hospitalizations per patient during follow-up, *n* (%)			
None	374 (61.5)	360 (58.6)	
At least once	234 (38.5)	254 (41.4)	0.30
Once	135 (22.2)	118 (19.2)	0.20
More than once	99 (16.3)	136 (22.1)	0.009
Median total duration of hospitalization among patients hospitalized at least once (IQR), *d*	8 (3–21)	10 (3–24)	
Death during follow-up, *n* (%)	64 (10.5)	76 (12.4)	
Among patients with no hospitalization during follow-up, *n/N* (%)	18/374 (4.8)	17/360 (4.7)	0.97
Among patients hospitalized once during follow-up, *n/N* (%)	20/135 (14.8)	28/118 (23.7)	0.141
Among patients hospitalized more than once during follow-up, *n/N* (%)	26/99 (26.3)	31/136 (22.8)	0.55

IQR = interquartile range.
* *P* values from Cochran–Mantel–Haenszel tests with stratification by the randomization stratification factors (left ventricular ejection fraction and geographic region). Because multiple hospitalizations may be attributable to individual participants, formal statistical testing for unadjusted comparisons for the first 3 end points listed in the table are not presented; relevant treatment group comparison *P* values for these end points are presented in Table 5.

RESULTS

A CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study is provided (**Appendix Figure 1**, available at Annals.org). Baseline characteristics of the 1222 patients are summarized in **Table 1**. Most patients had reduced or mid-range left ventricular ejection fraction and impaired renal function, and most had been diagnosed with diabetes years before randomization, with a small number first diagnosed during their index hospitalization. The first dose of study treatment was administered before discharge in 49% of patients and a median of 2 days (interquartile range, 1 to 3 days) after discharge in the remaining patients. Of the 608 patients randomly assigned to receive 200 mg of sotagliflozin, 57% had their dose increased to 400 mg at some point during follow-up per the protocol allowance.

Patients were followed during the study for a median of 9.0 months (interquartile range, 4.9 to 13.2 months) through 1 May 2020. **Table 2** summarizes the number and duration of hospitalizations and the number of deaths after randomization. Of 1047 total hospitalizations, 396 (37.8%) were attributed to heart failure by the investigators, whereas the remaining 651 (62.2%) were for reasons other than heart failure. In total, there were 119 fewer hospitalizations with sotagliflozin, including 78 for heart failure and 41 for other reasons. Although a similar number of patients in each treatment group were hospitalized during the study, more patients in the placebo group (22.1%) than in the sotagliflozin group (16.3%) were hospitalized more than once.

The analysis of DAOH, days dead, and days in the hospital by treatment group is summarized in **Table 3**, with the distributions of DAOH by treatment group depicted in the **Figure**. The overall mean DAOH was 274 days out of a mean 303 days of potential follow-up in the trial (90.4% of the mean potential follow-up time). The DAOH rate in the sotagliflozin group versus the placebo group was 3% higher for total hospitalizations for any reason (RR, 1.03 [95% CI, 1.00 to 1.06]; $P = 0.027$). This difference was primarily because of a reduction in the rate of days dead (RR, 0.71 [CI, 0.52 to 0.99]; $P = 0.041$) rather than a reduction in the rate of days hospitalized. This indicated that for every 100 days of follow-up, patients in the sotagliflozin group were alive and out of the hospital 3% more days in relative terms or 2.9 days in absolute terms than those in the placebo group (91.8 vs. 88.9 days); this

Table 3. Days Alive and Out of the Hospital, Days Dead, and Days in the Hospital

Outcome	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)	Rate Ratio (95% CI)	*P* Value
Mean days alive and out of the hospital (SD) [rate per 100 d], *d**	280 (152) [91.8]	267 (155) [88.9]	1.03 (1.00–1.06)	0.027
Mean days dead (SD) [rate per 100 d], *d*†	19 (67) [6.3]	27 (85) [8.9]	0.71 (0.52–0.99)	0.041
Mean days in the hospital (SD) [rate per 100 d], *d*‡	6 (14) [1.9]	7 (14) [2.2]	0.86 (0.69–1.08)	0.21

* Calculated by subtracting days in the hospital and days dead from potential follow-up time; if a patient survived without hospitalization, days alive and out of the hospital was equal to the potential follow-up time for that patient.
† Calculated as the time interval between a patient's date of death and the common study end date (1 May 2020).
‡ Calculated from investigator reports of incidence and duration of hospitalizations. The rate ratio represents the rate in the sotagliflozin group relative to the placebo group (i.e., a rate ratio >1 indicates that the rate per 100 d in the sotagliflozin group is higher than that in the placebo group).

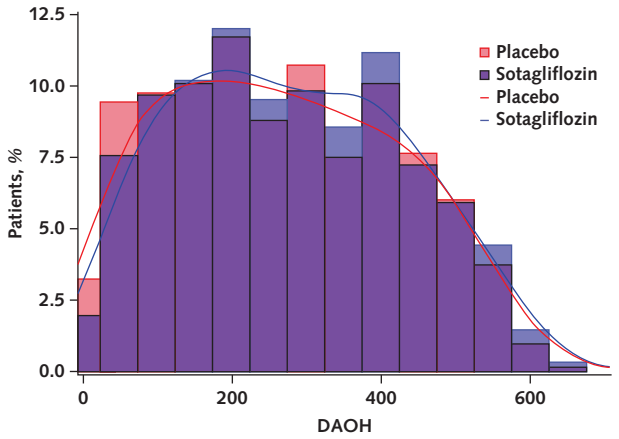
difference reflected a 2.6-day difference in fewer days dead (6.3 vs. 8.9 days) and a 0.3-day difference in fewer days in the hospital (1.9 vs. 2.2 days). The DAOH, days dead, and days in the hospital model results by geographic region are presented in **Appendix Table 1** (available at Annals.org); there was no statistical interaction between treatment and geographic region on these outcomes. Furthermore, results through the first 90 days after randomization were consistent with our primary findings (**Appendix Table 2**, available at Annals.org).

The analysis of PDAOH by treatment group is summarized in **Table 4**. Although patients in the sotagliflozin group were more likely to survive the follow-up period without hospitalization and have higher PDAOH among those who died or were hospitalized during the study, neither outcome was statistically significant.

The mean cumulative function plots for total hospitalizations for any reason are shown in **Appendix Figure 2**, *A* (available at Annals.org). The expected cumulative number of hospitalizations per 100 patients at 12 months was 115 in the placebo group, indicating that, on average, a patient in this group would have been expected to be rehospitalized at least once during 12 months of follow-up. However, given that only a minority of patients actually had a hospitalization after randomization, this indicates that the distribution of hospitalizations was skewed, with a relatively small fraction of patients having multiple hospitalizations during follow-up, as shown in **Table 2**. Mean cumulative functions for total hospitalizations attributed to heart failure and for reasons other than heart failure are presented in **Appendix Figure 2**, *B* and *C*, respectively.

Table 5 shows that 29.0 total hospitalizations (CI, 5.2 to 52.8 total hospitalizations) were avoided with sotagliflozin per 100 patient-years of follow-up; the rates of total hospitalizations by country and treatment group are summarized in **Appendix Table 3** (available at Annals.org). When jointly modeled with death, sotagliflozin treatment reduced total occurrences of hospitalizations for any reason by 24% (HR, 0.76 [CI, 0.63 to 0.93]; $P = 0.006$). Sotagliflozin also reduced hospitalizations attributed by the investigators to heart failure (HR, 0.61 [CI, 0.45 to 0.84]; $P = 0.002$) and, to a lesser extent, hospitalizations for other reasons (HR, 0.81 [CI, 0.65 to 1.02]; $P = 0.074$). Furthermore, the parameters describing the estimated association between death and hospitalization, summarized in **Appendix Table 4** (available at Annals.org), were considerably greater than 1, indicating that death is informative for the hospitalization rate. Specifically, conditional on treatment assignment, patients at the highest risk for death were also at elevated risk for hospitalization, so that death removed those patients at highest risk for hospitalizations from the risk set. This is shown in **Table 2**, where the risk for death among patients hospitalized at least once during the study was much greater than the risk for those not hospitalized.

Figure. Distributions of DAOH.



Histograms with kernel density curves show the distribution of DAOH by treatment group. DAOH = days alive and out of the hospital.

Discussion

The SOLOIST-WHF trial showed that sotagliflozin decreases total occurrences of cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure in patients with type 2 diabetes who were recently hospitalized for worsening heart failure (9). The current analysis extends these findings by establishing a favorable effect of sotagliflozin on more comprehensive measures of patients' disease burden, specifically extending DAOH primarily through a reduction in days dead. The reduction in the incidence rate of total hospitalizations–largely through a reduction in the proportion of patients hospitalized more than once–did not translate to a statistically significant reduction in days hospitalized.

Although DAOH was statistically significantly greater in the sotagliflozin group, the difference between treatment

Table 4. Percentage Days Alive and Out of the Hospital

Outcome	Sotagliflozin Group ($n = 608$)	Placebo Group ($n = 614$)	Odds Ratio (95% CI)	*P* Value
PDAOH = 100%, *n* (%)*	356 (58.6)	343 (55.7)	1.12 (0.89–1.40)	0.34
Mean PDAOH among patients <100% (SD), %†	81.9 (27.0)	78.7 (29.7)	1.24 (0.98–1.57)	0.073

PDAOH = percentage days alive and out of the hospital.

* Represents patients who survived the follow-up period without hospitalization. The odds ratio for PDAOH = 100% represents the odds of PDAOH = 100% in the sotagliflozin group relative to the placebo group (i.e., an odds ratio >1 indicates that patients in the sotagliflozin group were more likely to have PDAOH = 100% than those in the placebo group).

† Represents the duration of follow-up a patient was alive and out of the hospital as a percentage of potential total follow-up time. The odds ratio for PDAOH <100% represents the odds of higher PDAOH in the sotagliflozin group relative to the placebo group (i.e., an odds ratio >1 indicates that patients in the sotagliflozin group were more likely to have higher PDAOH–while still <100%–than those in the placebo group).

Table 5. Joint Semiparametric Model Results of Total Hospitalizations, Accounting for Multiple Hospitalizations per Patient and the Competing Risk for Death

Reason for Hospitalization	Events per 100 Patient-Years* (95% CI), *n*		Hazard Ratio (95% CI)	*P* Value
	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)		
For any reason	97.6 (83.4–111.8)	126.6 (107.6–145.6)	0.76 (0.63–0.93)	0.006
For heart failure	33.4 (25.5–41.3)	51.4 (41.7–61.1)	0.61 (0.45–0.84)	0.002
For reasons other than heart failure	64.2 (53.7–74.7)	75.1 (61.0–89.2)	0.81 (0.65–1.02)	0.074

* Patient-years of follow-up were 475.4 and 460.7 for the sotagliflozin and placebo groups, respectively. The joint semiparametric model allows for the possibility that patients may have multiple hospitalizations, quantifies the association between hospitalizations and death, and accounts for competing deaths that prevent subsequent follow-up for hospitalization. All-cause death results and association parameters are summarized in Appendix Table 4 (available at Annals.org).

groups was modest given that most patients in both groups survived to the end of the study without hospitalization. More important, in general, one may expect patients who otherwise would have died to be more likely to be hospitalized, resulting in a paradoxical increase in days hospitalized for an intervention that reduces days dead. Therefore, the fact that days hospitalized was not higher with sotagliflozin given the reduction in days dead could in itself be viewed as a favorable outcome. Of note is that the treatment effects on DAOH stemming from total hospitalizations did not seem to depend on geographic region of enrollment.

Consistent with the primary efficacy outcome of the study (9), the effect of sotagliflozin on the incidence rate of total hospitalizations seemed to be primarily due to reducing the risk for hospitalization for heart failure in a subset of patients; similar results regarding incident hospitalizations have been reported in studies of other SGLT2 inhibitors (10). Although not statistically significant, there were also numerically fewer hospitalizations for reasons other than heart failure, which is consistent with beneficial effects on ischemic events associated with hospitalizations (for example, myocardial infarction and ischemic stroke) previously reported with sotagliflozin (8) and in meta-analyses of other agents in this therapeutic class (22–24). More important, whereas results on DAOH have been described in patients with heart failure treated with other therapeutics (14) or in other disease settings (15, 25, 26), such results have not been previously described with SGLT2 inhibition. Therefore, the current report extends on prior findings by showing the degree to which this therapeutic class increases the proportion of time patients are alive and free of hospitalization.

A limitation of total hospitalizations and DAOH is that the analyses relied on investigator reports of hospitalizations on a dedicated case report form that did not request the primary reason for hospitalization. Although it was possible to determine hospitalizations for heart failure by cross-referencing the corresponding investigator-reported efficacy end point events, this left more than 60% of the total hospitalizations with an unspecified primary reason, and misclassification of the primary reason could have influenced the results. This also limited our ability to summarize duration of hospitalizations because of possible adverse effects of sotagliflozin that have been reported previously (for example, severe hypotension and diabetic ketoacidosis) (8, 9). Also, there may have been additional events that could have been included in the calculation of DAOH that either were not recorded on this form (for example, admission into a long-term care facility) or were unknown to the investigators, resulting in an underreporting of hospitalizations. Furthermore, study enrollment and duration of follow-up were curtailed because of loss of funding by the sponsor during the COVID-19 pandemic, and although the study primary end point was met, this combined with the potential unreported hospitalizations may have reduced statistical power for the current analyses. Finally, although DAOH and PDAOH were prespecified outcomes in the study analysis plan, total hospitalizations as an outcome was not, and none of these outcomes were prespecified in the final study protocol.

Future research in this area could focus on either different patient populations or subgroups within completed studies with higher rates of hospitalization, to gain more clarity on how reducing the risk for incident hospitalization translates to cumulative days in the hospital. It would also be important to quantify the consequences of increasing DAOH in terms of health economics and patient quality of life.

In conclusion, during a median 9-month follow-up in patients with type 2 diabetes and at high risk for recurrent hospitalization due to recent admission for worsening heart failure, sotagliflozin extended DAOH relative to placebo, and the effect did not seem to depend on geographic region of enrollment. Sotagliflozin also reduced the incidence of total hospitalizations primarily through a decrease in recurrent hospitalizations among a minority of patients. These metrics may provide additional patient-centered outcomes to capture the totality of disease burden and could have important implications for patient quality of life and health care costs.

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AD LIBITUM

Through the Fishbowl

The rays of the rising sun lit up the sparkling water
As men afar rowed in the quiet waters of the lake.
The lake which was close and yet so far.
From the glass windows of the ICU fishbowl,
I sat admiring the colors galore that had decorated the morning sky
A gentle reminder that summer was upon us
That the year-clock has yet again turned around
And the endless walks and mindless chatter is here
To fill our days and bring a smile to the pale faces.
Alas, I am interrupted by the sight of the nurse running in with a strip of paper
Another patient whose blood gas is a reminder and a question together
Did nature really mean this upon us?
Did mankind come too far?
To cure a disease will we create another
Just as evil, just as bizarre
And when we are finally done, exhausted and apart
The masks of our minds will continue to suffocate us.
Because we have forgotten what life was started to be,
And like the men rowing alone in the quiet lake, we shall silently sail through
No summer, no chatter, no laughter
A world post 2020, a world we did not look after.

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Appendix Table 1. Days Alive and Out of the Hospital, Days Dead, and Days Hospitalized for Total Hospitalizations for Any Reason, by Geographic Region

Outcome	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)	Rate Ratio (95% CI)	Interaction *P* Value
Mean days alive and out of the hospital (SD), *d*				0.52
North America or Latin America	274 (152)	265 (150)	1.01 (0.96–1.07)	
Europe	284 (153)	269 (158)	1.04 (1.01–1.08)	
Rest of the world	269 (153)	260 (147)	0.99 (0.89–1.11)	
Mean days dead (SD), *d*				0.42
North America or Latin America	20 (63)	21 (76)	0.94 (0.50–1.77)	
Europe	19 (69)	31 (91)	0.63 (0.43–0.92)	
Rest of the world	16 (61)	11 (51)	1.39 (0.25–7.76)	
Mean days in the hospital (SD), *d*				0.37
North America or Latin America	5 (11)	7 (14)	0.68 (0.44–1.07)	
Europe	6 (15)	6 (14)	0.97 (0.74–1.28)	
Rest of the world	6 (16)	8 (16)	0.69 (0.29–1.63)	

Appendix Table 2. Outcomes Through 90 Days After Randomization

Outcome	Sotagliflozin Group (*n* = 608)	Placebo Group (*n* = 614)	Rate Ratio (95% CI)	*P* Value
Mean days alive and out of the hospital (SD), *d*	84 (15)	82 (18)	1.09 (1.05–1.13)	<0.001
Mean days dead (SD), *d*	3 (16)	5 (20)	0.65 (0.47–0.90)	0.009
Mean days in the hospital (SD), *d*	2 (6)	2 (7)	0.91 (0.66–1.26)	0.56

Appendix Table 3. Total Hospitalizations for Any Reason, by Country

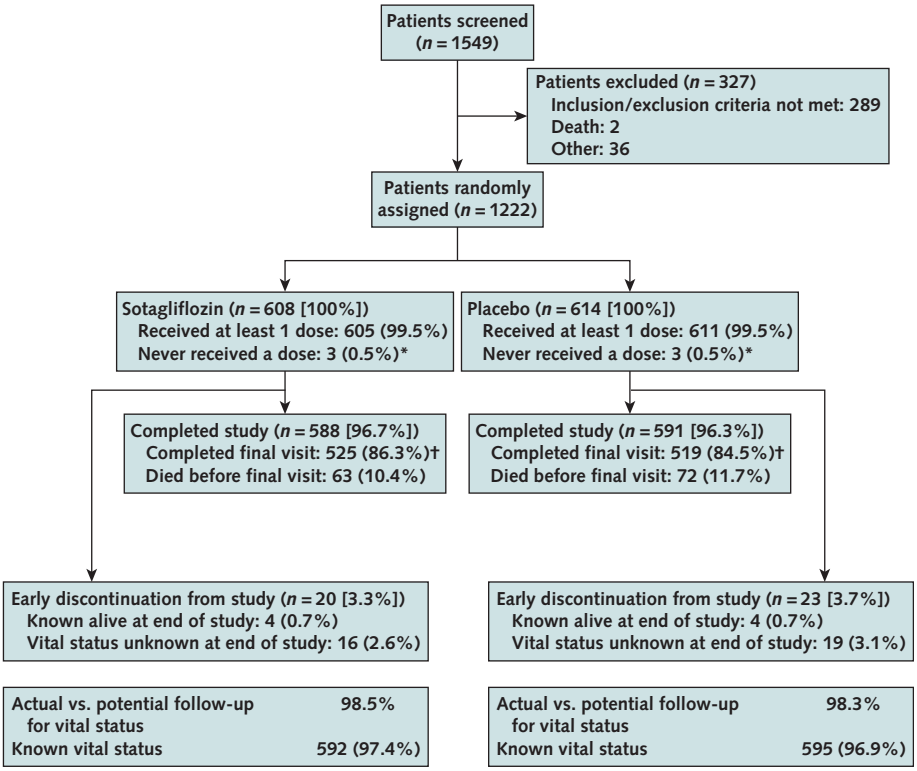
Country	Patients, *n*	Events per 100 Patient-Years, *n*	
		Sotagliflozin Group	Placebo Group
Argentina	166	73.5	105.8
Australia	3	81.2	221.7
Austria	18	195.8	419.6
Belgium	13	68.3	142.3
Brazil	59	87.3	155.5
Canada	8	167.7	0
Chile	41	54.9	42.2
Czech Republic	26	221.6	152.9
Denmark	25	136.8	56.9
Finland	3	1470.6	468.8
France	14	183.5	234.1
Germany	27	192.9	240.8
Greece	29	53.8	71.4
Hungary	81	94.5	117.8
Israel	49	134.4	153.4
Italy	33	30.0	81.5
Korea	13	35.8	166.2
Latvia	30	14.5	53.8
Lithuania	36	17.7	64.9
Netherlands	13	193.7	132.3
New Zealand	11	180.9	185.7
Poland	52	40.7	71.1
Portugal	16	47.9	215.7
Romania	14	82.3	225.7
Russia	168	61.5	53.8
Slovakia	18	118.2	0
Spain	87	79.2	133.1
Sweden	14	118.6	0
Switzerland	6	176.2	178.6
Turkey	65	127.8	150.1
United Kingdom	12	129.4	144.9
United States	72	268.2	389.5

Appendix Table 4. Additional Joint Semiparametric Model Results of Total Hospitalizations, Accounting for Multiple Hospitalizations per Patient and the Competing Risk for Death: All-Cause Death and Association Parameters*

Outcome	Treatment Hazard Ratio (95% CI)	*P* Value
All-cause death when jointly modeled with total hospitalizations for any reason	0.78 (0.54–1.12)	0.183
Association among hospitalizations: $\hat{\eta}$(95% CI) = 0.0050 (0.0046 to 0.0054)		<0.001
Association between hospitalizations and death: $\hat{\theta}$(95% CI) = 1.51 (1.19 to 1.83)		<0.001
All-cause death when jointly modeled with total hospitalizations for heart failure	0.77 (0.51–1.15)	0.20
Association among hospitalizations: $\hat{\eta}$(95% CI) = 0.0050 (0.0046 to 0.0054)		<0.001
Association between hospitalizations and death: $\hat{\theta}$(95% CI) = 3.41 (2.50 to 4.32)		<0.001
All-cause death when jointly modeled with total hospitalizations for reasons other than heart failure	0.76 (0.53–1.11)	0.153
Association among hospitalizations: $\hat{\eta}$(95% CI) = 0.0050 (0.0046 to 0.0054)		<0.001
Association between hospitalizations and death: $\hat{\theta}$(95% CI) = 1.74 (1.30 to 2.18)		<0.001

* The joint semiparametric model allows for the possibility that patients may have multiple hospitalizations, quantifies the association between hospitalizations and death, and accounts for competing deaths that prevent subsequent follow-up for hospitalization. Association between hospitalizations reflects the within-patient association between their hospitalization times; when $\eta = 0$, the hospitalization times for a given patient are independent of each other, whereas when $\eta > 0$, there is an association between the hospitalization times. Association between hospitalizations and death reflects the within-patient association between their hospitalization and all-cause death times; when $\theta = 0$, the hospitalization and all-cause death times for a given patient are independent of each other, whereas when $\theta > 0$, there is an association between the hospitalization and all-cause death times.

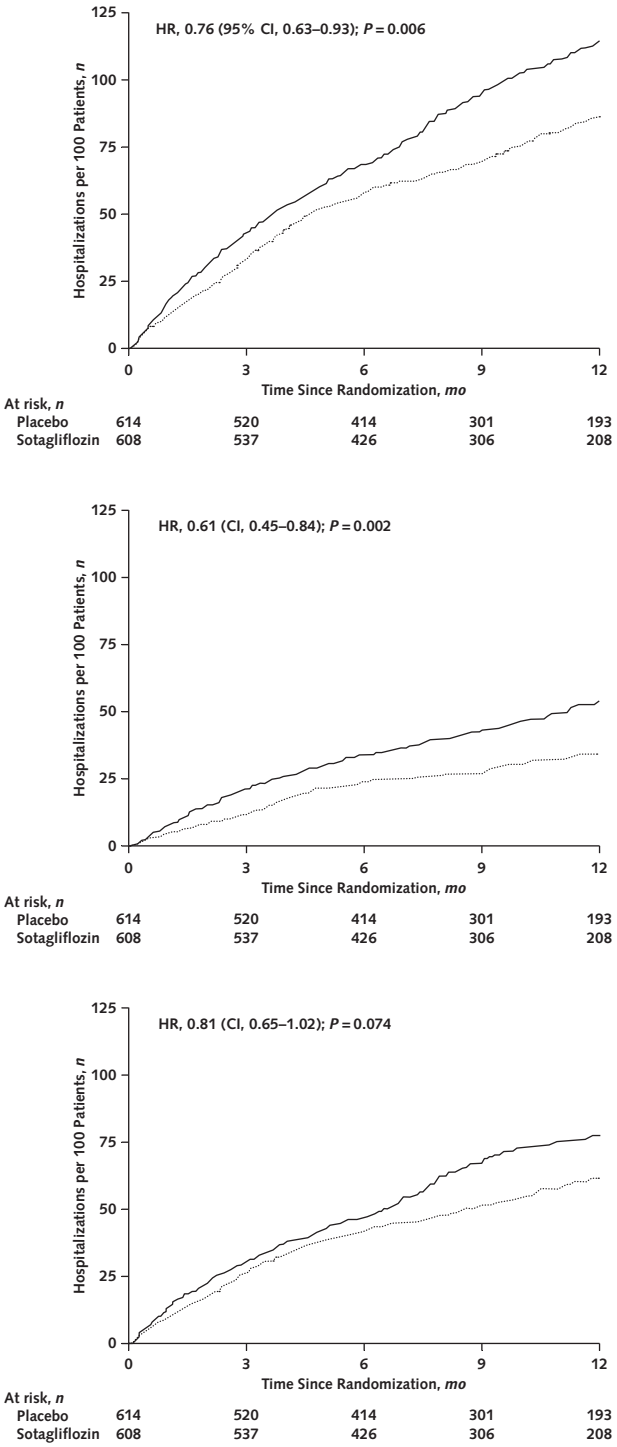
Appendix Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.



* Three patients in each treatment group were randomly assigned but never received a dose of the study drug. These 6 patients are included in all analyses per the intention-to-treat principle.

† Two patients in the sotagliflozin group and 4 patients in the placebo group were known to have died after completing final visits. One of these deaths in the sotagliflozin group and all 4 of the deaths in the placebo group occurred before 1 May 2020, and thus are included in the analyses.

Appendix Figure 2. Mean cumulative functions.



Mean cumulative function curves depict the expected number of total hospitalizations per 100 patients in the sotagliflozin and placebo groups at a given time after randomization. As summarized in Table 2, most patients in both treatment groups were not hospitalized after randomization, and similar proportions in both treatment groups were hospitalized at least once. Consequently, the differences between treatment groups shown in the figures were primarily due to a greater proportion of patients in the placebo group than in the sotagliflozin group being hospitalized more than once. HR = hazard ratio. **Top.** Total hospitalizations. **Middle.** Total hospitalizations attributed to heart failure. **Bottom.** Total hospitalizations attributed to reasons other than heart failure. Solid line denotes placebo group; dotted line denotes sotagliflozin group.