ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., Bertram Pitt, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., David Z.I. Cherney, M.D., Ph.D., Jamie P. Dwyer, M.D., Benjamin M. Scirica, M.D., M.P.H., Clifford J. Bailey, Ph.D., Rafael Díaz, M.D., Kausik K. Ray, M.D., Jacob A. Udell, M.D., M.P.H., Renato D. Lopes, M.D., Ph.D., Pablo Lapuerta, M.D., and P. Gabriel Steg, M.D., for the SCORED Investigators*

ABSTRACT

BACKGROUND

The efficacy and safety of sodium–glucose cotransporter 2 inhibitors such as sotagliflozin in preventing cardiovascular events in patients with diabetes with chronic kidney disease with or without albuminuria have not been well studied.

METHODS

We conducted a multicenter, double-blind trial in which patients with type 2 diabetes mellitus (glycated hemoglobin level, ≥7%), chronic kidney disease (estimated glomerular filtration rate, 25 to 60 ml per minute per 1.73 m^2 of body-surface area), and risks for cardiovascular disease were randomly assigned in a 1:1 ratio to receive sotagliflozin or placebo. The primary end point was changed during the trial to the composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure. The trial ended early owing to loss of funding.

RESULTS

Of 19,188 patients screened, 10,584 were enrolled, with 5292 assigned to the sotagliflozin group and 5292 assigned to the placebo group, and followed for a median of 16 months. The rate of primary end-point events was 5.6 events per 100 patient-years in the sotagliflozin group and 7.5 events per 100 patient-years in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.63 to 0.88; P<0.001). The rate of deaths from cardiovascular causes per 100 patient-years was 2.2 with sotagliflozin and 2.4 with placebo (hazard ratio, 0.90; 95% CI, 0.73 to 1.12; P=0.35). For the original coprimary end point of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, the hazard ratio was 0.84 (95% CI, 0.72 to 0.99); for the original coprimary end point of the first occurrence of death from cardiovascular causes or hospitalization for heart failure, the hazard ratio was 0.77 (95% CI, 0.66 to 0.91). Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with placebo.

CONCLUSIONS

In patients with diabetes and chronic kidney disease, with or without albuminuria, sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events. (Funded by Sanofi and Lexicon Pharmaceuticals; SCORED ClinicalTrials.gov number, NCT03315143.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bhatt at Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis St., Boston, MA 02115, or at dlbhattmd@post.harvard.edu.

*A complete list of the SCORED trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 16, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2030186

Copyright © 2020 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

Patients with diabetes mellitus are at high risk for both heart failure and ischemic events.[1-7] Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to be effective for the treatment of type 2 diabetes mellitus[8-10] and to lower the risk of hospitalization for heart failure among patients with or without previous heart failure.[11-22] Their effect on different types of ischemic events has been more heterogeneous across drugs, trials, and populations. Coexisting chronic kidney disease in patients with diabetes mellitus further raises the risk of heart failure and ischemic events.[23] Data from randomized trials support the use of SGLT2 inhibition in patients with chronic kidney disease with or without diabetes.[12,19] These trials have required the presence of macroalbuminuria for inclusion, in addition to reduced estimated glomerular filtration rate (eGFR).

These considerations led to the design of the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial. Sotagliflozin is an SGLT2 inhibitor that also inhibits gastrointestinal SGLT1. Inhibition of SGLT2 increases urinary glucose excretion, whereas inhibition of SGLT1 appears to delay glucose absorption and reduce postprandial glucose.[24-29] We conducted this trial to determine whether sotagliflozin was noninferior to placebo with respect to ischemic events and whether it was superior with respect to heart failure events. On the basis of emerging data about SGLT2 inhibitors, we aimed to examine whether sotagliflozin would reduce the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in patients with diabetes mellitus and chronic kidney disease, regardless of the degree of albuminuria.

Methods

Trial Design

This was a phase 3, randomized, double-blind, placebo-controlled trial that compared sotagliflozin (200 mg once daily, with an increase to 400 mg once daily if unacceptable side effects did not occur) with placebo in patients with type 2 diabetes mellitus, chronic kidney disease, and additional cardiovascular risk; all the patients also received standard-of-care treatments. Randomization was stratified according to criteria for heart failure (ejection fraction of ≤40% documented within the past year or hospitalization for heart failure during the previous 2 years) and geographic region (North America, Latin America, western Europe, eastern Europe, or rest of the world). The original plan was for approximately 10,500 patients to undergo randomization, and this plan was accomplished. Final trial visits were initiated in March 2020 before the target number of events had occurred because of loss of funding from the sponsor.[30] This led to a revision of end points, as indicated in the end-points section below and in the original and revised protocols, available with the full text of this article at NEJM.org. Details of the trial design are provided in Figure S1 in the Supplementary Appendix, available at NEJM.org. Patients were enrolled at 750 sites in 44 countries. The first patient underwent randomization on December 8, 2017, and the last on January 20, 2020.

The original sponsor was Sanofi. Sponsorship was transferred to Lexicon Pharmaceuticals as of January 30, 2020. The executive and steering committees, consisting of academic physicians, and representatives from the sponsors developed the protocol and statistical analysis plan (available with the protocol at NEJM.org) and were responsible for the conduct and oversight of the trial, as well as the interpretation of data. The sponsors provided sotagliflozin and placebo and were responsible for the collection and handling of the data and funded the statistical analysis performed by an independent academic statistician (the second author). The protocol was approved by the relevant health authority, institutional review board, or ethics committee at each trial site. The authors vouch for the completeness and accuracy of the data, for the accurate and full reporting of adverse events, and for the fidelity of the trial to the protocol and statistical analysis plan. An independent data and safety monitoring board oversaw the trial. There were confidentiality agreements between the sponsors and the authors. The sponsor had the right to review and comment on the manuscript, with no obligation of the authors to incorporate any comments, and the authors were not restricted from publishing the results of the trial.

Patients

Persons 18 years of age or older with type 2 diabetes mellitus with a glycated hemoglobin level of 7% or higher, chronic kidney disease (eGFR, 25 to

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

60 ml per minute per 1.73 m^2 of body-surface area), and additional cardiovascular risk factors were enrolled. The risk factors consisted of at least one major cardiovascular risk factor in those 18 years of age or older or at least two minor cardiovascular risk factors in those 55 years of age or older. An exclusion criterion was any plan to start an SGLT2 inhibitor during the trial. Inclusion criteria (including definitions of major and minor cardiovascular risk factors) and exclusion criteria are listed in the Supplementary Appendix. Written informed consent was obtained from all the patients.

END POINTS

The original coprimary end points, assessed in time-to-event analyses, were the first occurrence of a major adverse cardiovascular event (MACE, defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and the first occurrence of death from cardiovascular causes or hospitalization for heart failure. Because of the early closing of the trial and the fewer than planned number of events, with the investigators and sponsor unaware of the trial-group assignments and without end-point information from an interim analysis, the primary end point was changed on August 21, 2020, to the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure.

The original secondary end points were the first occurrence, in patients with a baseline eGFR of at least 30 ml per minute per 1.73 m^2, of a sustained decrease of at least 50% in the eGFR from baseline for at least 30 days, long-term dialysis, renal transplantation, or a sustained eGFR of less than 15 ml per minute per 1.73 m^2 for at least 30 days; the first occurrence, in patients with a baseline eGFR of at least 30 ml per minute per 1.73 m^2 and a baseline urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, of the above composite end point; the first occurrence of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit for heart failure; deaths from cardiovascular causes; and deaths from any cause. The revised secondary end points were the total number of hospitalizations for heart failure and urgent visits for heart failure; deaths from cardiovascular causes; 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 for heart failure, urgent visits for heart failure, and events of heart failure during hospitalization; the first occurrence of the composite of a sustained decrease of at least 50% in the eGFR from baseline for at least 30 days, long-term dialysis, renal transplantation, or a sustained eGFR of less than 15 ml per minute per 1.73 m^2 for at least 30 days; deaths from any cause; and the total number of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes. The use of total events allowed for a single patient to have more than one event contributing to the analysis. Subgroup analyses were prespecified. Because of loss of funding, planned adjudication of end-point events was not completed and investigator-reported events were used for end-point analyses.

STATISTICAL ANALYSIS

The original design of the trial intended to establish the noninferiority of sotagliflozin to placebo with respect to the first occurrence of a MACE and the superiority of sotagliflozin over placebo with respect to the first occurrence of death from cardiovascular causes or hospitalization for heart failure. We estimated that for 10,500 randomly assigned patients, 1189 events would be needed to test for noninferiority with respect to the first occurrence of a MACE, on the basis of the upper boundary of a two-sided 95% confidence interval for the hazard ratio being less than 1.3, and 844 events would be needed to test for superiority with respect to the first occurrence of death from cardiovascular causes or hospitalization for heart failure. In a hierarchical fashion, the coprimary end points and prespecified secondary end points were to be tested with a prespecified procedure to control for type I error. No formal power calculation was performed for the revised primary end point.

All efficacy analyses followed the intention-to-treat principle. To allow for analyses of total events, competing-risk marginal models for recurrent events that were stratified according to heart-failure criteria and geographic region, with deaths not included in a given end point treated as competing terminal events, were applied to generate hazard ratios with Wald 95% confidence intervals and P values.[31] Proportionality was confirmed by interaction terms between trial-group assignment and the logarithm of time. Event rates

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sotagliflozin (N=5292)	Placebo (N=5292)
Median age (IQR) — yr	69 (63–74)	69 (63–74)
Female sex — no. (%)	2347 (44.3)	2407 (45.5)
Race or ethnic group — no. (%)†		
White	4402 (83.2)	4347 (82.1)
Black	176 (3.3)	188 (3.6)
Asian	317 (6.0)	365 (6.9)
American Indian or Alaska Native	206 (3.9)	216 (4.1)
Native Hawaiian or other Pacific Islander	25 (0.5)	15 (0.3)
Multiple	109 (2.1)	95 (1.8)
Unknown	57 (1.1)	66 (1.2)
Median glycated hemoglobin (IQR) — %	8.3 (7.6–9.3)	8.3 (7.6–9.4)
Median body-mass index (IQR)	31.9 (28.1–36.2)	31.7 (28.0–36.1)
Estimated glomerular filtration rate		
Median (IQR) — ml/min/1.73 m^2	44.4 (37.0–51.3)	44.7 (37.0–51.5)
Distribution — no. (%)		
<30 ml/min/1.73 m^2	419 (7.9)	394 (7.4)
30 to <45 ml/min/1.73 m^2	2347 (44.3)	2308 (43.6)
≥45 ml/min/1.73 m^2	2526 (47.7)	2590 (48.9)
Geographic region — no. (%)		
Eastern Europe	1613 (30.5)	1613 (30.5)
Western Europe	711 (13.4)	709 (13.4)
Latin America	1586 (30.0)	1586 (30.0)
North America	746 (14.1)	747 (14.1)
Rest of the world	636 (12.0)	637 (12.0)
Ejection fraction of ≤40% within past year or hospitalization for heart failure during previous 2 years — no. (%)	1054 (19.9)	1054 (19.9)
History of heart failure — no. (%)‡	1640 (31.0)	1643 (31.0)
Ejection fraction of <40%	505 (9.5)	528 (10.0)
Ejection fraction of 40 to <50%	290 (5.5)	291 (5.5)
Ejection fraction of ≥50%	843 (15.9)	824 (15.6)
Ejection fraction unknown	2 (<0.1)	0
Cardiovascular risk factors — no. (%)		
At least one major	4682 (88.5)	4699 (88.8)
No major, at least two minor	405 (7.7)	413 (7.8)
No major and less than two minor	205 (3.9)	180 (3.4)
Previous myocardial infarction — no. (%)	1051 (19.9)	1057 (20.0)
Previous coronary revascularization — no. (%)	1208 (22.8)	1167 (22.1)
Previous stroke — no. (%)	472 (8.9)	474 (9.0)

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

Table 1. (Continued.)

Characteristic	Sotagliflozin (N = 5292)	Placebo (N = 5292)
Urinary albumin-to-creatinine ratio§		
Median (IQR)	74 (18–486)	75 (17–477)
Distribution — no. (%)		
<30	1864 (35.2)	1845 (34.9)
30 to <300	1770 (33.4)	1819 (34.4)
≥300	1658 (31.3)	1628 (30.8)
Median left ventricular ejection fraction (IQR) — %‡	60 (51–64)	60 (51–65)
Median NT-proBNP (IQR) — pg/ml	196.0 (75.1–564.6)	198.1 (74.6–560.7)
Median systolic blood pressure (IQR) — mm Hg	138 (127–149)	139 (127–149)
Median diastolic blood pressure (IQR) — mm Hg	78 (70–85)	78 (70–85)
Any RAAS inhibitor — no. (%)¶	4705 (88.9)	4660 (88.1)
ACE inhibitor	2009 (38.0)	2039 (38.5)
Angiotensin-receptor blocker	2619 (49.5)	2562 (48.4)
Angiotensin receptor–neprilysin inhibitor	66 (1.2)	65 (1.2)
Mineralocorticoid-receptor antagonist	810 (15.3)	776 (14.7)
Beta-blocker — no. (%)	3310 (62.5)	3306 (62.5)
Calcium-channel blocker — no. (%)	2228 (42.1)	2202 (41.6)
Loop diuretic — no. (%)	1869 (35.3)	1867 (35.3)
Other diuretic — no. (%)	1568 (29.6)	1605 (30.3)
Any glucose-lowering medication — no. (%)	5111 (96.6)	5136 (97.1)
Metformin	2907 (54.9)	2955 (55.8)
Sulfonylurea	1400 (26.5)	1486 (28.1)
DPP-4 inhibitor	1041 (19.7)	1044 (19.7)
Insulin	3389 (64.0)	3333 (63.0)
GLP-1 receptor agonist	310 (5.9)	323 (6.1)

* Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, DPP-4 dipeptidyl peptidase 4, GLP-1 glucagon-like peptide 1, IQR interquartile range, and NT-proBNP N-terminal pro–brain natriuretic peptide.
† Race and ethnic group were reported by the investigators.
‡ Ejection fraction was measured within 1 year before screening or during the screening period.
§ The ratio was calculated with albumin measured in milligrams and creatinine measured in grams.
¶ Some patients were taking more than one renin–angiotensin–aldosterone system (RAAS) inhibitor.

were summarized by the number of events per 100 patient-years of follow-up,[32] and accrual of events over time was summarized by cumulative incidence functions. For subgroup analyses, 95% confidence intervals are reported without adjustment for multiple comparisons, and no conclusions can be drawn from these data.

Total events of myocardial infarction and total events of stroke were evaluated post hoc. Testing for differences between the two groups in adverse events was performed post hoc; P values were obtained from Pearson chi-square tests. Change in the eGFR, glycated hemoglobin level, systolic blood pressure, diastolic blood pressure, and weight over time was analyzed post hoc by means of repeated-measures mixed-effects models with absolute change from baseline as the outcome, a random effect for intercept, and fixed effects for trial-group assignment, baseline value, and time. Changes in these outcomes were also jointly modeled with death from any cause to account for competing risk. Data for patients

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

Table 2. Primary End Point and Secondary End Points.*

End Point	Sotagliflozin (N = 5292)	Placebo (N = 5292)	Hazard Ratio (95% CI)†	P Value
	no. of events/100 patient-yr (no. of events)			
Primary end point: total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF	5.6 (400)	7.5 (530)	0.74 (0.63–0.88)	<0.001
Major secondary end points, in order of hierarchical testing				
Total no. or hospitalizations for HF and urgent visits for HF	3.5 (245)	5.1 (360)	0.67 (0.55–0.82)	<0.001
Deaths from cardiovascular causes	2.2 (155)	2.4 (170)	0.90 (0.73–1.12)	0.35‡
Total no. of deaths from cardiovascular causes, hospitalizations for HF, nonfatal myocardial infarctions, and nonfatal strokes	7.6 (541)	10.4 (738)	0.72 (0.63–0.83)	—
Total no. of deaths from cardiovascular causes, hospitalizations for HF, urgent visits for HF, and events of HF during hospitalization	6.4 (453)	8.3 (589)	0.76 (0.65–0.89)	—
First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of <15 ml/min/1.73 m^2 for ≥30 days	0.5 (37)	0.7 (52)	0.71 (0.46–1.08)	—
Deaths from any cause	3.5 (246)	3.5 (246)	0.99 (0.83–1.18)	—
Total no. of deaths from cardiovascular causes, nonfatal myocardial infarctions, and nonfatal strokes	4.8 (343)	6.3 (442)	0.77 (0.65–0.91)	—

* The term eGFR denotes estimated glomerular filtration rate, and HF heart failure.
† Results are presented as point estimates and 95% confidence intervals unadjusted for multiple comparisons, from which no definite conclusions regarding significant differences can be made.
‡ The hierarchical analysis stops after the first P value indicating nonsignificance.

who discontinued the trial were censored for time-to-event end points, and sensitivity analyses were performed, including imputation of the occurrence of events on the date that the patient was last known to be alive and imputation of the same for the sotagliflozin group only. Additional information on missing data is provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

A total of 19,188 patients were screened, of whom 10,584 were enrolled; 5292 were assigned to each trial group. Details regarding screening, randomization, and follow-up of the patients are shown in Figure S2. The median age of the patients was 69 years; 44.9% were female, and 82.7% were White. Vital status was available for 99.4% of the patients; 142 (1.3%) did not complete final trial visits, of whom 67 had unknown end-of-trial vital status. The median duration of exposure to sotagliflozin was 14.2 months (interquartile range, 10.3 to 18.9), and the median duration of exposure to placebo was 14.3 months (interquartile range, 10.3 to 18.9). The median duration of follow-up was 16.0 months (interquartile range, 12.0 to 20.3) in the sotagliflozin group and 15.9 months (interquartile range, 11.9 to 20.3) in the placebo group. In the sotagliflozin group, 3944 patients (74.5%) had an increase of the dose from 200 to 400 mg; in the placebo group, 4002 (75.6%) had the dose ostensibly increased. Early discontinuation of the trial regimen for reasons other than death or early trial termination occurred in 578 patients (10.9%) in the sotagliflozin group and 597 patients (11.3%) in the placebo group.

Baseline characteristics were similar in the two groups (Table 1). Of all randomly assigned patients, 19.9% had an ejection fraction of 40% or less within the past year or hospitalization for heart failure during the previous 2 years, and the median left ventricular ejection fraction was 60% (interquartile range 51 to 65). The median glycated hemoglobin level was 8.3%, median body-mass index (the weight in kilograms divided by the square of the height in meters) was 31.8, median eGFR was 44.5 ml per minute per 1.73 m^2 (interquartile range, 37.0 to 51.4), and median

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

urinary albumin-to-creatinine ratio was 74 (interquartile range, 17 to 481). Changes in the eGFR, glycated hemoglobin level, blood pressure, and weight are provided in Table S1.

END POINTS

There were 701 first and 930 total primary end-point events. The distribution of primary end-point events and competing deaths not from cardiovascular causes is shown in Table S2. The rates of total primary end-point events were 5.6 and 7.5 events per 100 patient-years in the sotagliflozin and placebo groups, respectively (hazard ratio, 0.74; 95% confidence interval [CI], 0.63 to 0.88; P<0.001) (Table 2). The estimated time-to-event curves for total primary end-point events are shown in Figure 1. Primary end-point events according to stratification factors and in selected prespecified subgroups are shown in Figure S3; however, the lack of a plan for adjustment of confidence intervals for multiple comparisons precludes conclusions from these data. Figure S4 shows the results for the same end point minus urgent visits for heart failure. Table S3 shows results for prespecified subgroups and post hoc subgroups according to baseline history of heart failure and ejection fraction and according to geographic region and country; again, no definite conclusions can be drawn from these data.

For the total number of hospitalizations for heart failure and urgent visits for heart failure (first secondary end point), the rate was 3.5 events per 100-patient years in the sotagliflozin group and 5.1 events per 100-patient years in the placebo group (hazard ratio, 0.67; 95% CI, 0.55 to 0.82; P<0.001) (Table 2). There was no significant difference between the sotagliflozin and placebo groups in deaths from cardiovascular causes (second secondary end point) (2.2 and 2.4 per 100 patient-years, respectively; hazard ratio, 0.90; 95% CI, 0.73 to 1.12), and the hierarchical analysis stopped at this point. However, results for the composite renal end point did not differ significantly between the two groups, nor did all-cause mortality. Table S4 lists the original analysis plan for hierarchical testing of primary and secondary end points. The original coprimary end point of the first event of death from cardiovascular causes or hospitalization for heart failure showed a hazard ratio of 0.77 (95% CI, 0.66 to 0.91) (Fig. S5). The other original coprimary end point of the first event of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke showed a hazard ratio of 0.84 (95% CI, 0.72 to 0.99) (Fig. 2). Results for additional post hoc secondary end points are shown in Table S5. Prespecified and post hoc evaluations of composite end points as a function of normo-, micro-, and macroalbuminuria are presented in Tables S6 and S7, with no adjustment of confidence intervals for multiple comparisons. For investigator-reported events submitted for adjudication before loss of trial funding, 337 of 501 events (67.3%) in the sotagliflozin group and 460 of 664 events (69.3%) in the placebo group were confirmed on adjudication (Table S8).

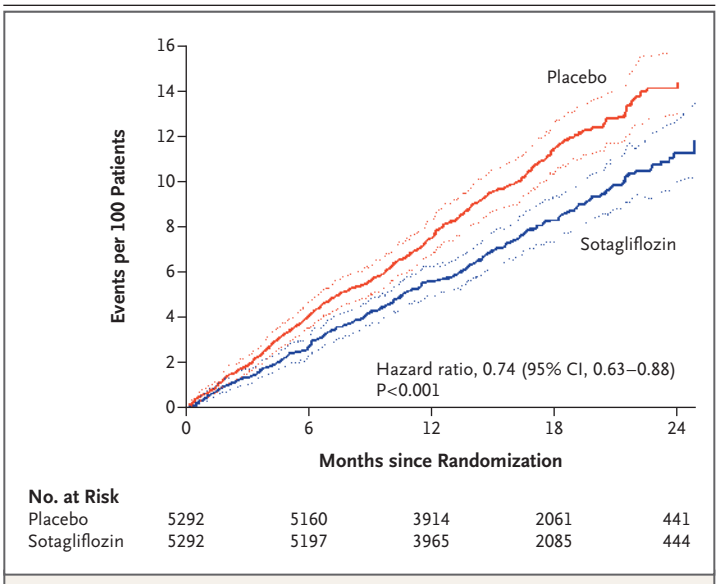


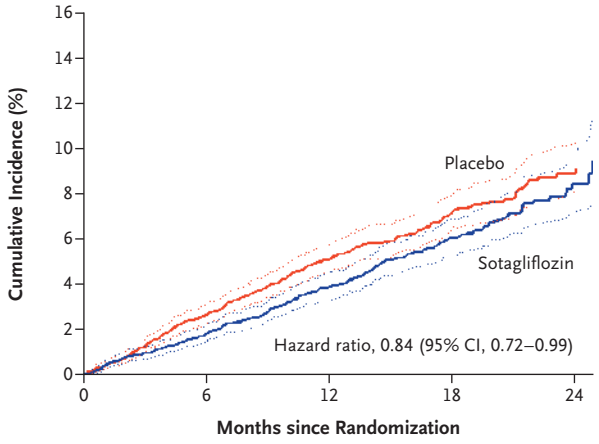
Figure 1. Total Number of Deaths from Cardiovascular Causes, Hospitalizations for Heart Failure, and Urgent Visits for Heart Failure.

Shown is a time-to-event analysis of the estimated number of events per 100 patients for the primary end point of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure in the sotagliflozin and placebo groups. 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. The number of competing deaths not from cardiovascular causes was 91 in the sotagliflozin group and 76 in the placebo group. Dotted lines indicate a 95% confidence interval for events per 100 patients.

ADVERSE EVENTS

There were no significant differences between the two groups in the percentage of patients with adverse events that occurred or worsened during the treatment period or with events leading to withdrawal of the trial regimen. The percentage of patients with a serious adverse event was 23.4%

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.



No. at Risk					
Placebo	5292	5090	3817	1985	421
Sotagliflozin	5292	5150	3892	2034	432

Figure 2. First Occurrence of Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke.

Shown is a time-to-event analysis of the original primary end point of the estimated cumulative incidence for the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in the sotagliflozin and placebo groups. The number of competing deaths not from cardiovascular causes was 80 in the sotagliflozin group and 69 in the placebo group. Dotted lines indicate a 95% confidence interval for the cumulative incidence.

in the sotagliflozin group and 25.2% in the placebo group (Table S9). Adverse events of special interest that were more common with sotagliflozin than with placebo were diarrhea (8.5% vs. 6.0%; P<0.001), diabetic ketoacidosis (0.6% vs. 0.3%; P=0.02), genital mycotic infections (2.4% vs. 0.9%; P<0.001), and volume depletion (5.3% vs. 4.0%; P=0.003) (Table 3). There were no significant between-group differences in bone fractures, urinary tract infections, severe hypoglycemia, acute kidney injury (2.2% in the sotagliflozin group and 2.1% in the placebo group; P=0.55), or amputations. The percentage of patients in whom hypertension developed was lower with sotagliflozin than with placebo (2.6% vs. 4.1%) (Table S10), whereas the percentage in whom hypotension developed was higher with sotagliflozin than with placebo (2.6% vs. 1.9%; P=0.009).

DISCUSSION

In our trial involving patients with type 2 diabetes mellitus, chronic kidney disease, and additional cardiovascular risks, the SGLT1/2 inhibitor sotagliflozin resulted in a lower risk of the composite primary end point of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo (5.6 vs. 7.5 events per 100 patient-years). Deaths from cardiovascular causes and renal end points did not differ significantly between the trial groups. Diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis occurred with sotagliflozin.

Unlike some previous trials, our trial did not require that patients have a urinary albumin-to-creatinine ratio of at least 200 or 300, and the trial examined cardiovascular events in a population with a median albumin-to-creatinine ratio of 74. Our trial also did not require a history of heart failure or reduced ejection fraction at baseline. Despite the low eGFR in our trial population (median, 44.5 ml per minute per 1.73 m^2), kidney injury did not differ significantly between the sotagliflozin and placebo groups.

Potential mechanisms of action of SGLT2 inhibition include renal and systemic natriuretic effects, enhanced myocardial energetics, adaptive cellular reprogramming, increased red-cell mass affecting improved oxygen supply, weight loss, reductions in blood pressure and left ventricular hypertrophy, decreases in uric acid, and beneficial effects on endothelial progenitor cells.[33-41] Sotagliflozin provides some degree of SGLT1 inhibition as well, slowing intestinal glucose absorption and reducing postprandial glycemia. Mendelian randomization data have raised the possibility that SGLT1 inhibition might be associated with decreased rates of cardiovascular events.[42] The SGLT1 blockade may have contributed to increased reports of diarrhea in our trial. Whether additional cardiovascular benefit is provided from SGLT1 inhibition above that provided by SGLT2 inhibition remains to be determined.

Limitations of this trial include premature cessation due to loss of funding that led to an inability to complete the intended duration of follow-up.[30,43-46] Owing to concerns about the potential for an inadequate number of events, the primary end point was changed to total number of events in an attempt to preserve statistical power. The change to a heart failure–related end point was made at a time when there was evidence that SGLT2 inhibitors as a class reduced heart failure, although sotagliflozin, with SGLT1/2 activity, had not been tested in this regard. The change

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

may have biased the findings toward benefit of the trial drug. The power to show a difference between the trial groups was not recalculated with the change of the end point; the trial remained adequately powered for the original and revised primary end points but not for secondary end points, such as death from cardiovascular causes and progression of kidney disease. The trial design had called for adjudication of events, but this was not completed; therefore, investigator-defined end-point events were used for all analyses. Approximately 31% of adjudicated heart-failure hospitalizations or urgent visits were not confirmed to be primary events (Table S8), leading to overestimation of the number of events.[47-49] Furthermore, hospitalization for reasons other than heart failure would remove patients from the risk of a primary end-point event, although fewer total hospitalizations in the sotagliflozin group than in the placebo group (1923 vs. 2094) spanning fewer total patient-years (104 vs. 119) suggest the absence of bias favoring sotagliflozin with respect to the primary end point.

The SGLT1/2 inhibitor sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo among patients with diabetes mellitus and chronic kidney disease, with or without albuminuria. The results in the sotagliflozin group did not differ significantly from those in the placebo group with respect to rates of death from cardiovascular causes or renal end points, and sotagliflozin was associated with serious adverse events. Longer trials are required to evaluate the effect and safety of sotagliflozin in patients with diabetes and chronic kidney disease.

Supported initially by Sanofi and then by Lexicon Pharmaceuticals. Dr. Ray received support from the National Institute for Health Research Imperial Biomedical Research Centre.

Table 3. Adverse Events of Special Interest, According to Composite Term.*

Event	Sotagliflozin (N=5291)	Placebo (N=5286)	P Value†
	no. of patients (%)		
Urinary tract infections	610 (11.5)	585 (11.1)	0.45
Diarrhea	448 (8.5)	315 (6.0)	<0.001
Volume depletion	278 (5.3)	213 (4.0)	0.003
Bone fractures	111 (2.1)	117 (2.2)	0.68
Genital mycotic infections	125 (2.4)	45 (0.9)	<0.001
Severe hypoglycemia	53 (1.0)	55 (1.0)	0.84
Malignant conditions	47 (0.9)	42 (0.8)	0.60
Venous thrombotic events	31 (0.6)	37 (0.7)	0.46
Adverse event leading to amputation	32 (0.6)	33 (0.6)	0.89
Diabetic ketoacidosis	30 (0.6)	14 (0.3)	0.02
Pancreatitis	12 (0.2)	20 (0.4)	0.16

* Shown are adverse events that first occurred or worsened in severity on or after the date of the first dose of sotagliflozin or placebo and within 10 days (1 day for hypoglycemia) after the last dose. Percentages are based on the safety population, which comprised all the patients who underwent randomization and who received at least one dose of sotagliflozin or placebo. Unlike Table S10, which shows adverse events according to single preferred terms, Table 3 groups multiple preferred terms together under one composite term; therefore, values may differ slightly between the two tables. The preferred terms that are included in each composite term are shown in the final statistical analysis plan. All adverse events are coded according to the *Medical Dictionary for Regulatory Activities*, version 23.0.

† P values were calculated with the Pearson chi-square test.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the members of our independent data and safety monitoring board (Hertzel C. Gerstein, M.D. [chair], Gary S. Francis, M.D., John E. Gerich, M.D., Johannes F.E. Mann, M.D., Weichung J. Shih, Ph.D., and James B. Young, M.D.) and the SCORED national coordinators; Phillip Banks, M.S., and Eshetu Tesfaye, Ph.D., from Lexicon Pharmaceuticals for independent validation of the analyses performed by Dr. Szarek; and the site investigators, the trial coordinators, and especially the patients who participated in the trial.

APPENDIX

The authors' affiliations are as follows: Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B., C.P.C., B.M.S.); Colorado Prevention Center Clinical Research and Department of Medicine, Division of Cardiovascular Medicine, University of Colorado Anschutz Medical Campus, Aurora (M.S.); the State University of New York Downstate School of Public Health, Brooklyn (M.S.); the University of Michigan, Ann Arbor (B.P.); Li Ka Shing Knowledge Institute and the Division of Endocrinology and Metabolism, St. Michael's Hospital, and the Departments of Medicine and Nutritional Sciences, University of Toronto (L.A.L.), and the Division of Nephrology (D.Z.I.C.) and the Cardiovascular Division, Department of Medicine, Women's College Hospital and Peter Munk Cardiac Centre (J.A.U.), University Health Network, University of Toronto — all in Toronto; the University of Texas Southwestern Medical Center and Parkland Health and Hospital System, Dallas (D.K.M.), and Lexicon Pharmaceuticals, The Woodlands (P.L.) — both in Texas; Vanderbilt University Medical Center, Nashville (J.B.L., J.P.D.); the Division of Endocrinology, Diabetes, and Clinical Nutrition, Oregon Health and Science University, Portland (M.C.R.); the Section of Endocrinology, Yale School of Medicine, New Haven, CT (S.E.I.); Saint Luke's Mid America Heart Institute, University of Missouri–Kansas City, Kansas City (M.N.K.); the School of Life and Health Sciences, Aston University, Birmingham (C.J.B.), and the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London (K.K.R.) — both in the United Kingdom; the Department of Medicine, Estudios Clínicos Latinoamérica, Instituto Cardiovascular de Rosario, Rosario, Argentina (R.D.); Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (R.D.L.); and Université de Paris, French Alliance for Cardiovascular Trials, Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, INSERM Unité 1148, Paris (P.G.S.).

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

REFERENCES

1. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7.
2. Steg PG, Bhatt DL, Wilson PWF, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197-206.
3. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-9.
4. Cavender MA, Steg PG, Smith SC Jr, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;132:923-31.
5. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
6. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:356-66.
7. Scirica BM, Bhatt DL, Braunwald E, et al. Prognostic implications of biomarker assessments in patients with type 2 diabetes at high cardiovascular risk: a secondary analysis of a randomized clinical trial. JAMA Cardiol 2016;1:989-98.
8. Bhatt DL, Verma S, Braunwald E. The DAPA-HF trial: a momentous victory in the war against heart failure. Cell Metab 2019;30:847-9.
9. Verma S, Bhatt DL. More CREDENCE for SGLT2 inhibition. Circulation 2019; 140:1448-50.
10. Connelly KA, Bhatt DL, Verma S. Can we DECLARE a victory against cardiorenal disease in diabetes? Cell Metab 2018;28:813-5.
11. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
12. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.
14. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
15. Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-88.
16. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528-36.
17. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
18. Vaduganathan M, Sathiyakumar V, Singh A, et al. Prescriber patterns of SGLT2i after expansions of U.S. Food and Drug Administration labeling. J Am Coll Cardiol 2018;72:3370-2.
19. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
20. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425-35.
21. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
22. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
23. Udell JA, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: observations from the SAVOR-TIMI 53 Trial. Diabetes Care 2015;38:696-705.
24. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 2017;377:2337-48.
25. Rodbard HW, Giaccari A, Lajara R, et al. Sotagliflozin added to optimised insulin therapy leads to HbA1c reduction without weight gain in adults with type 1 diabetes: a pooled analysis of inTandem1 and inTandem2. Diabetes Obes Metab 2020 July 3 (Epub ahead of print).
26. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care 2015;38:1181-8.
27. Powell DR, Zambrowicz B, Morrow L, et al. Sotagliflozin decreases postprandial glucose and insulin concentrations by delaying intestinal glucose absorption. J Clin Endocrinol Metab 2020;105(4):e1235-e1249.
28. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 study. Diabetes Care 2018;41:1970-80.
29. Danne T, Cariou B, Banks P, et al. HbA_{1c} and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. Diabetes Care 2018;41:1981-90.
30. Bagiella E, Bhatt DL, Gaudino M. The consequences of the COVID-19 pandemic on non-COVID-19 clinical trials. J Am Coll Cardiol 2020;76:342-5.
31. Andersen PK, Angst J, Ravn H. Modeling marginal features in studies of recurrent events in the presence of a terminal event. Lifetime Data Anal 2019;25:681-95.
32. Stukel TA, Glynn RJ, Fisher ES, Sharp SM, Lu-Yao G, Wennberg JE. Standardized rates of recurrent outcomes. Stat Med 1994;13:1781-91.
33. Hess DA, Terenzi DC, Trac JZ, et al. SGLT2 inhibition with empagliflozin increases circulating provascular progenitor cells in people with type 2 diabetes mellitus. Cell Metab 2019;30:609-13.
34. Chowdhury B, Luu AZ, Luu VZ, et al. The SGLT2 inhibitor empagliflozin reduces mortality and prevents progression in experimental pulmonary hypertension. Biochem Biophys Res Commun 2020;524: 50-6.
35. Kumar N, Garg A, Bhatt DL, et al. Empagliflozin improves cardiorespiratory fitness in type 2 diabetes: translational implications. Can J Physiol Pharmacol 2018;96:1184-7.
36. Sherman SE, Bell GI, Teoh H, et al. Canagliflozin improves the recovery of blood flow in an experimental model of severe limb ischemia. JACC Basic Transl Sci 2018;3:327-9.
37. Packer M. SGLT2 inhibitors produce cardiorenal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry: a paradigm shift in understanding their mechanism of action. Diabetes Care 2020;43:508-11.
38. Avogaro A, Fadini GP, Del Prato S. Reinterpreting cardiorenal protection of renal sodium-glucose cotransporter 2 inhibitors via cellular life history programming. Diabetes Care 2020;43:501-7.
39. Verma S, Mazer CD, Bhatt DL, et al. Empagliflozin and cardiovascular outcomes in patients with type 2 diabetes and left ventricular hypertrophy: a subanalysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2019;42(3):e42-e44.
40. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation 2019;140:1693-702.
41. Opingari E, Verma S, Connelly KA, et al. The impact of empagliflozin on kidney injury molecule-1: a subanalysis of the effects of Empagliflozin on Cardiac Structure, Function, and Circulating Biomarkers in Patients with Type 2 Diabetes CardioLink-6 trial. Nephrol Dial Transplant 2020;35:895-7.

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

42. Seidelmann SB, Feofanova E, Yu B, et al. Genetic variants in SGLT1, glucose tolerance, and cardiometabolic risk. J Am Coll Cardiol 2018;72:1763-73.
43. Gaba P, Bhatt DL. The COVID-19 pandemic: a catalyst to improve clinical trials. Nat Rev Cardiol 2020;17:673-5.
44. Gaudino M, Arvind V, Hameed I, et al. Effects of the COVID pandemic on active non-COVID clinical trials. J Am Coll Cardiol 2020;76:1605-6.
45. Selvaraj S, Greene SJ, Khatana SAM, Nathan AS, Solomon SD, Bhatt DL. The landscape of cardiovascular clinical trials in the United States initiated before and during COVID-19. J Am Heart Assoc 2020; 9(18):e018274.
46. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909-17.
47. Jatene T, Harrington RA, Stone GW, et al. Investigator-reported bleeding versus post hoc adjudication of bleeding: lessons from the CHAMPION PHOENIX Trial. J Am Coll Cardiol 2016;67:596-8.
48. Tyl B, Lopez Sendon J, Borer JS, et al. Comparison of outcome adjudication by investigators and by a central end point committee in heart failure trials: experience of the SHIFT heart failure study. Circ Heart Fail 2020;13(7):e006720.
49. Patel T, Tesfaldet B, Chowdhury I, et al. Endpoints in diabetes cardiovascular outcome trials. Lancet 2018;391:2412.
Copyright © 2020 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at IMPERIAL COLLEGE LONDON on November 27, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.