ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

RESULTS

We evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], <1.3; P<0.001 for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001).

CONCLUSIONS

In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE–TIMI 58 ClinicalTrials.gov number, NCT01730534.)

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*A complete list of the DECLARE–TIMI 58 investigators and executive committee and steering committee members is provided in the Supplementary Appendix, available at NEJM.org.

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Diabetes mellitus is estimated to affect more than 415 million adults worldwide. The prevalence is increasing, and it is expected that more than 640 million adults will have diabetes by 2040.[1] Patients with diabetes are at high risk for adverse outcomes from atherosclerotic cardiovascular disease,[2,3] heart failure,[4] and renal disease.[5] The high risk of heart failure in patients with diabetes is independent of coronary disease, and limited data are available to guide treatments for the prevention of heart failure.[6,7] As a result of this intersection of diabetes, atherosclerotic cardiovascular disease, and heart failure, the importance of determining diabetes therapies that are not only safe but also effective in reducing cardiovascular risk is paramount.[8-10]

Dapagliflozin is a selective inhibitor of sodium–glucose cotransporter 2 (SGLT2) that blocks glucose resorption in the proximal tubule of the kidney and promotes glucosuria.[11-13] Other SGLT2 inhibitors have shown favorable cardiovascular effects, including a reduction in the risk of hospitalization for heart failure, predominantly in patients with type 2 diabetes and established cardiovascular disease[14-16]; they have also been shown to delay the progression of kidney disease.[14,15,17-19] The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial evaluated the effects of dapagliflozin on cardiovascular and renal outcomes in a broad population of patients who had or were at risk for atherosclerotic cardiovascular disease.

Methods

Trial Design and Oversight

The DECLARE–TIMI 58 trial was a randomized, double-blind, multinational, placebo-controlled, phase 3 trial of dapagliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease.[20,21] The trial was designed collaboratively by the Thrombolysis in Myocardial Infarction (TIMI) Study Group, the Hadassah Medical Organization, the trial executive committee (see Section A in the Supplementary Appendix, available with the full text of this article at NEJM.org, for members of these groups), and the sponsor (AstraZeneca) and was conducted at 882 sites in 33 countries. The trial protocol, available at NEJM.org, was approved by the institutional review board at each participating site, and all participants provided written informed consent. The complete, raw database was provided to the TIMI Study Group, which independently conducted all analyses reported in this article. The executive committee made the decision to submit the manuscript for publication. The first author wrote the first draft of the manuscript, and all the authors participated in revisions. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and the statistical analysis plan.

As described previously,[20] the trial was originally designed with a primary safety outcome of major adverse cardiovascular events (MACE), in accordance with Food and Drug Administration (FDA) guidelines.[10] However, during the trial, compelling external scientific information from the EMPA-REG OUTCOME trial, which evaluated another SGLT2 inhibitor, showed greater benefit with respect to cardiovascular death and hospitalization for heart failure than with respect to MACE.[14] In response, and before the data and safety monitoring committee of our trial viewed data on MACE, the trial executive committee amended the protocol to include two primary efficacy outcomes: MACE and cardiovascular death or hospitalization for heart failure. The two outcomes would split an alpha level equally, and no change would be made in the primary safety outcome or the sample size. The decision was made by the executive committee without knowledge of any blinded or unblinded comparative data on MACE. This change was communicated to regulators, and the protocol was updated and approved by the appropriate institutional review boards. The description of statistical methods herein reflects this change (additional details are provided in Section B in the Supplementary Appendix). Investigators and participants were informed of the positive results of the EMPA-REG OUTCOME trial, and participants signed a revised informed consent document to continue participation.

Trial Population

Eligible patients were 40 years of age or older and had type 2 diabetes, a glycated hemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 ml or more per min-

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ute. Eligible patients also had multiple risk factors for atherosclerotic cardiovascular disease or had established atherosclerotic cardiovascular disease (defined as clinically evident ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease). Participants with multiple risk factors were men 55 years of age or older or women 60 years of age or older who had one or more traditional risk factors, including hypertension, dyslipidemia (defined as a low-density lipoprotein cholesterol level >130 mg per deciliter [3.36 mmol per liter] or the use of lipid-lowering therapies), or use of tobacco. A complete list of eligibility criteria is provided in Section C in the Supplementary Appendix.[20]

TRIAL PROCEDURES

Eligible patients were enrolled in a 4-to-8-week, single-blind run-in period during which all patients received placebo, and blood and urine testing was performed. Patients who remained eligible after the run-in period were randomly assigned in a 1:1 ratio, in a double-blind fashion, to receive 10 mg of dapagliflozin daily or matching placebo. The use of other glucose-lowering agents (other than an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone) was at the discretion of the treating physician. Patients were to return for in-person follow-up every 6 months until trial completion for laboratory testing and assessment of clinical and safety events and adherence to the trial regimen. Patients were contacted by telephone every 3 months between in-person visits.

OUTCOMES

The primary safety outcome was MACE (defined as cardiovascular death, myocardial infarction, or ischemic stroke). The two primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Two secondary efficacy outcomes were prespecified. The first was a renal composite outcome, defined as a sustained decrease of 40% or more in estimated glomerular filtration rate (eGFR) — calculated by means of the Chronic Kidney Disease Epidemiology Collaboration equation[22] — to less than 60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes. The other secondary outcome was death from any cause. A prespecified additional renal composite outcome included all the criteria described for the secondary renal outcome except for cardiovascular death. Serious adverse events and adverse events leading to discontinuation of dapagliflozin or placebo were collected comprehensively, as described in Section B in the Supplementary Appendix. The clinical-events committee of the TIMI Study Group adjudicated all components of the primary outcomes and key components of other safety and efficacy outcomes (Section D in the Supplementary Appendix).[23]

STATISTICAL ANALYSIS

Safety was assessed first in an analysis of the noninferiority of dapagliflozin to placebo with respect to MACE. In accordance with FDA guidelines,[10] noninferiority would be shown if the upper boundary of the two-sided 95% confidence interval of the hazard ratio for MACE was less than 1.3, at a one-sided alpha level of 0.023 (after adjustment for two interim analyses). If noninferiority of dapagliflozin to placebo was confirmed, then the two efficacy outcomes of MACE and the composite of cardiovascular death or hospitalization for heart failure were to be tested in parallel, each at a two-sided alpha level of 0.023. If either was significant, the alpha value could be recycled[24] to test the other efficacy outcome at a two-sided alpha level of 0.046. If after this procedure both efficacy outcomes were significant, the secondary outcomes were to be tested, at a two-sided alpha level of 0.046, in a hierarchical fashion.[20]

In the original design of the trial, we determined that approximately 17,150 patients would need to be enrolled to accrue at least 1390 events, with a minimum follow-up period of 3 years. This event number was calculated to provide the trial with 85% power to show a 15% lower rate of MACE in the dapagliflozin group than in the placebo group, at a two-sided alpha level of 0.046, and to provide more than 99% power to show the noninferiority of dapagliflozin to placebo with respect to MACE. Details about the effects on the power calculation of the addition of cardiovascular death or hospitalization for heart failure as a primary efficacy outcome are provided in Section B in the Supplementary Appendix.

The primary analyses of cardiovascular safety and efficacy were performed with data from 17,160 patients who underwent randomization, with the exclusion of 30 participants from one site; data from patients at that site were excluded because

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of serious Good Clinical Practice violations in another trial that created uncertainty about the integrity of the data. Analyses were performed according to the intention-to-treat principle with the use of adjudicated events. Hazard ratios, 95% confidence intervals, and P values for time-to-event analyses are reported for the primary outcomes and were derived from a Cox proportional-hazards model in the overall population; all analyses were stratified according to baseline atherosclerotic cardiovascular disease category (established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease) and the presence or absence of hematuria at baseline. After the MACE safety analysis, other safety assessments were performed in a safety analysis population (which consisted of patients who received at least one dose of dapagliflozin or placebo). Safety events are reported with P values without adjustment for multiple testing.

RESULTS

PATIENTS, TRIAL REGIMEN, AND FOLLOW-UP

During the run-in phase, we enrolled 25,698 patients. A total of 17,160 participants completed the run-in phase and were eligible to undergo randomization, including 6974 patients (40.6%) with established atherosclerotic cardiovascular disease and 10,186 (59.4%) with multiple risk factors for atherosclerotic cardiovascular disease. Patients were followed for a median of 4.2 years (interquartile range, 3.9 to 4.4), for a total of 69,547 patient-years of follow-up. A total of 3962 patients discontinued the trial regimen prematurely, at a rate of 5.7% per year, including 1811 of 8574 patients (21.1%) in the dapagliflozin group and 2151 of 8569 (25.1%) in the placebo group. Rates of withdrawal of consent (224 patients, at a rate of 0.3% per year) and loss to follow-up (30 patients, at a rate of <0.1% per year) were low and did not differ between the two groups (Fig. S1 in the Supplementary Appendix).

Baseline characteristics of the patients were balanced between the groups (Table 1). The mean (±SD) glycated hemoglobin level was 8.3±1.2%, and the median duration of diabetes was 11.0 years (interquartile range, 6.0 to 16.0). The mean eGFR was 85.2 ml per minute per 1.73 m^2; 45% of patients had an eGFR between 60 and 90 ml per minute per 1.73 m^2. As a result of the exclusion criterion for creatinine clearance at screening, only a small percentage (7%) of patients had an eGFR of less than 60 ml per minute per 1.73 m^2 at randomization. Before trial entry, 10% of patients had a history of heart failure.

EFFECT ON CARDIOVASCULAR RISK FACTORS

Dapagliflozin had favorable effects on several cardiovascular risk factors (Fig. S2 in the Supplementary Appendix). Patients in the dapagliflozin group had lower glycated hemoglobin levels throughout the trial than patients in the placebo group (average least-squares mean absolute difference between the groups, 0.42%; 95% confidence interval [CI], 0.40 to 0.45). During the trial, 9.5% of the patients in the dapagliflozin group and 11.4% in the placebo group received treatment with glucagon-like protein receptor agonists, and 3.4% and 6.1%, respectively, received treatment with open-label SGLT2 inhibitors. The least-squares mean difference between the groups in the reduction in weight during the trial was 1.8 kg (95% CI, 1.7 to 2.0), the difference in the reduction in systolic blood pressure was 2.7 mm Hg (95% CI, 2.4 to 3.0), and the difference in the reduction in diastolic blood pressure was 0.7 mm Hg (95% CI, 0.6 to 0.9). All reductions were greater with dapagliflozin.

CARDIOVASCULAR AND RENAL OUTCOMES

Dapagliflozin met the prespecified criterion for noninferiority with respect to MACE (upper boundary of the 95% CI, <1.3; P<0.001 for noninferiority). With respect to efficacy, dapagliflozin resulted in a lower rate of cardiovascular death or hospitalization for heart failure than placebo (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005) (Fig. 1). It should be noted that the lower rate of the composite outcome of cardiovascular death or hospitalization for heart failure in the dapagliflozin group than in the placebo group was due to a lower rate of hospitalization for heart failure in the dapagliflozin group (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no difference between the groups in the rate of cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17) (Fig. 2). In addition, this efficacy of dapagliflozin with respect to the rate of cardiovascular death or hospitalization for heart failure was similar in the subgroup of patients with established atherosclerotic cardiovascular disease (7.8% in the dapagliflozin group and 9.3% in the

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dapagliflozin (N=8582)	Placebo (N=8578)
Age — yr	63.9±6.8	64.0±6.8
Female sex — no. (%)	3171 (36.9)	3251 (37.9)
Race — no. (%)†		
White	6843 (79.7)	6810 (79.4)
Black	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
Other	296 (3.4)	305 (3.6)
Region — no. (%)		
North America	2737 (31.9)	2731 (31.8)
Europe	3806 (44.3)	3823 (44.6)
Latin America	946 (11.0)	931 (10.9)
Asia–Pacific	1093 (12.7)	1093 (12.7)
Body-mass index‡	32.1±6.0	32.0±6.1
Median duration of type 2 diabetes (IQR) — yr	11.0 (6.0–16.0)	10.0 (6.0–16.0)
Glycated hemoglobin — %	8.3±1.2	8.3±1.2
Systolic blood pressure — mm Hg	135.1±15.3	134.8±15.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	85.4±15.8	85.1±16.0
Established atherosclerotic cardiovascular disease — no. (%)	3474 (40.5)	3500 (40.8)
History of coronary artery disease — no. (%)	2824 (32.9)	2834 (33.0)
History of peripheral artery disease — no. (%)	522 (6.1)	503 (5.9)
History of cerebrovascular disease — no. (%)	653 (7.6)	648 (7.6)
History of heart failure — no. (%)	852 (9.9)	872 (10.2)
Glucose-lowering therapies — no. (%)		
Insulin	3567 (41.6)	3446 (40.2)
Metformin	7020 (81.8)	7048 (82.2)
Sulfonylurea	3615 (42.1)	3707 (43.2)
DPP-4	1418 (16.5)	1470 (17.1)
GLP-1 receptor agonist	397 (4.6)	353 (4.1)
Cardiovascular therapies — no. (%)		
Antiplatelet agents	5245 (61.1)	5242 (61.1)
ACE inhibitor or ARB	6977 (81.3)	6973 (81.3)
Beta-blocker	4498 (52.4)	4532 (52.8)
Statin or ezetimibe	6432 (74.9)	6436 (75.0)
Diuretics	3488 (40.6)	3479 (40.6)

* Plus–minus values are means ±SD. There were no significant differences between the groups in the characteristics at baseline. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DPP-4 dipeptidyl peptidase 4, GLP-1 glucagon-like peptide 1, and IQR interquartile range.
† Race was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

placebo group; hazard ratio, 0.83; 95% CI, 0.71 to 0.98) and in the subgroup of patients with multiple risk factors (2.8% in the dapagliflozin group and 3.4% in the placebo group; hazard ratio, 0.84; 95% CI, 0.67 to 1.04; P=0.99 for interaction) (Fig. 3). Dapagliflozin did not result in a lower rate of MACE than placebo (8.8% and 9.4% in the two groups, respectively; hazard ra-

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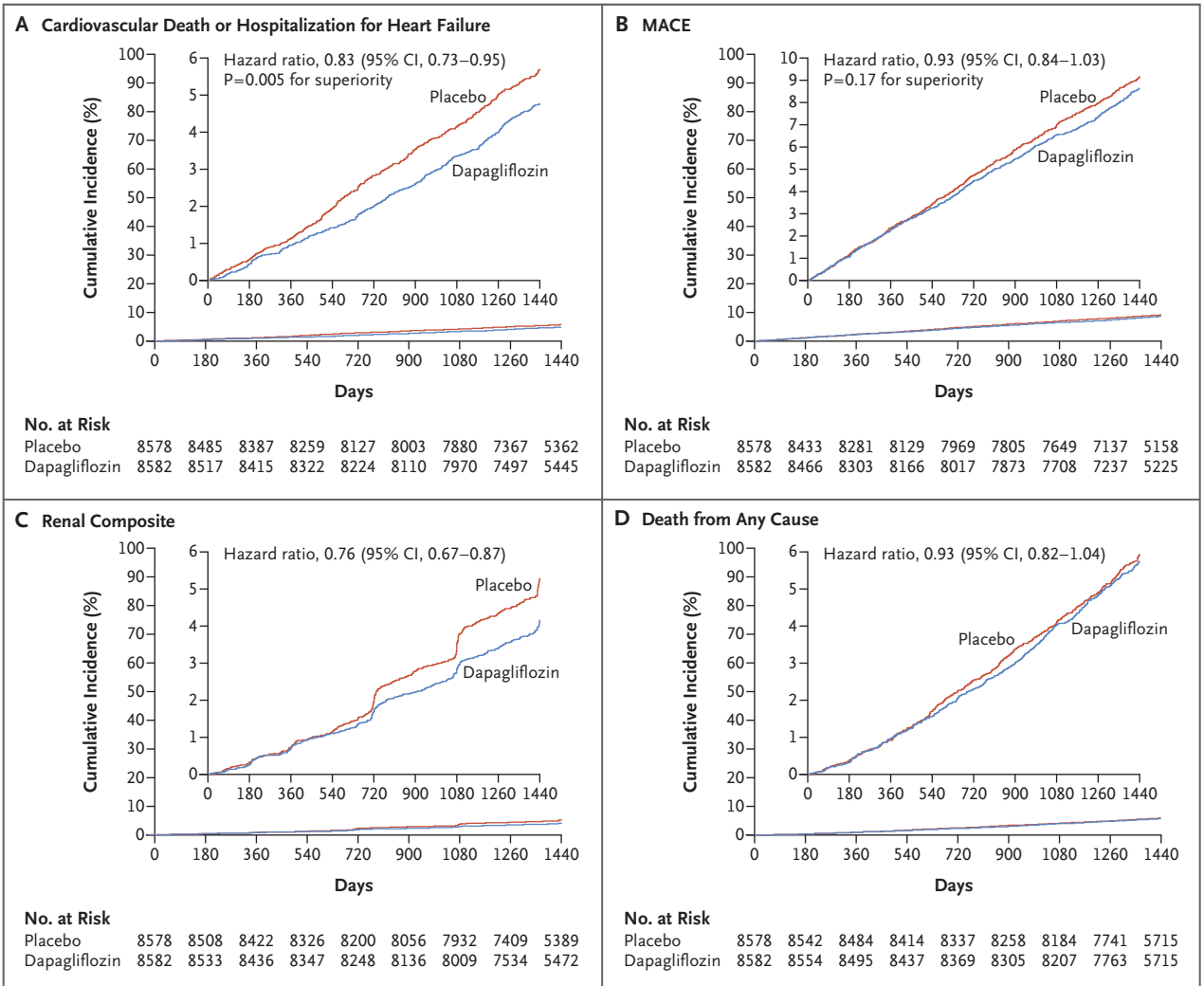


Figure 1. Major Cardiovascular and Renal Outcomes and Death from Any Cause.

Shown is the cumulative incidence of the two primary efficacy outcomes of cardiovascular death or hospitalization for heart failure (Panel A) and major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke (Panel B). Dapagliflozin was noninferior to placebo with respect to the primary safety outcome of MACE (upper boundary of the 95% CI, <1.3; P<0.001 for noninferiority). Also shown is the cumulative incidence of the secondary efficacy outcomes of a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) (Panel C) and death from any cause (Panel D). The inset in each panel shows the same data on an enlarged y axis.

tio, 0.93; 95% CI, 0.84 to 1.03; P=0.17) (Fig. 1). Among patients with established atherosclerotic cardiovascular disease, the rate of MACE was 13.9% in the dapagliflozin group and 15.3% in the placebo group (hazard ratio, 0.90; 95% CI, 0.79 to 1.02); among patients with multiple risk factors, the rate was 5.3% and 5.2%, respectively (hazard ratio, 1.01; 95% CI, 0.86 to 1.20; P=0.25 for interaction). Comparisons of individual components of the composite outcomes are shown in Figure 2. Sensitivity analyses of the primary safety and efficacy outcomes with the use of competing-risk and per-protocol approaches did not materially affect any of the estimates (Table S2 in the Supplementary Appendix).

Because dapagliflozin resulted in a significantly lower rate of cardiovascular death and hospitalization for heart failure than placebo but did not result in a significantly lower rate of MACE, analyses of additional outcomes are hypothesis-gener-

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Outcome	Dapagliflozin (N=8582) no. (%)	Dapagliflozin (N=8582) rate/1000 patient-yr	Placebo (N=8578) no. (%)	Placebo (N=8578) rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Cardiovascular death or hospitalization for heart failure	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73–0.95)	0.005
MACE	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84–1.03)	0.17
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause	370 (4.3)	10.8	480 (5.6)	14.1	0.76 (0.67–0.87)	
Death from any cause	529 (6.2)	15.1	570 (6.6)	16.4	0.93 (0.82–1.04)	
Hospitalization for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61–0.88)	
Myocardial infarction	393 (4.6)	11.7	441 (5.1)	13.2	0.89 (0.77–1.01)	
Ischemic stroke	235 (2.7)	6.9	231 (2.7)	6.8	1.01 (0.84–1.21)	
Death from cardiovascular cause	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82–1.17)	
Death from noncardiovascular cause	211 (2.5)	6.0	238 (2.8)	6.8	0.88 (0.73–1.06)	
≥40% decrease in eGFR to <60 ml/min/1.73 m^2, ESRD, or death from renal cause	127 (1.5)	3.7	238 (2.8)	7.0	0.53 (0.43–0.66)	

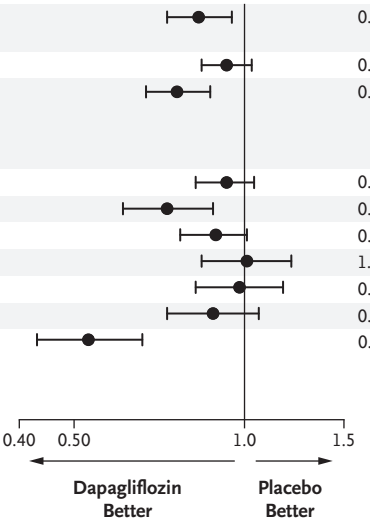


Figure 2. Key Efficacy Outcomes and Their Components.

Two-sided P values are shown for the two primary efficacy outcomes of cardiovascular death or hospitalization for heart failure and MACE. The abbreviation eGFR denotes estimated glomerular filtration rate, and ESRD end-stage renal disease.

ating. In the overall population, the incidence of the renal composite outcome was 4.3% in the dapagliflozin group and 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87). The rate of death from any cause did not differ significantly between the groups (6.2% in the dapagliflozin group and 6.6% in the placebo group; hazard ratio, 0.93; 95% CI, 0.82 to 1.04) (Fig. 1).

Major subgroup analyses were performed according to risk group (established atherosclerotic cardiovascular disease or risk factors for atherosclerotic cardiovascular disease), history of heart failure (yes or no), and eGFR (≥90, ≥60 to <90, and <60 ml per minute per 1.73 m^2) (Fig. 3). Other subgroups of interest are shown in Figure S3 in the Supplementary Appendix. The benefit of dapagliflozin with respect to cardiovascular death or hospitalization for heart failure tended to be similar across subgroups. Additional component outcomes in key subgroups are shown in Figures S4 through S6 in the Supplementary Appendix.

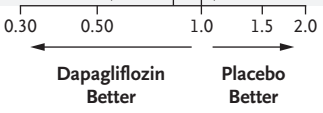
ADDITIONAL SAFETY ASSESSMENTS

Key safety results are provided in Table 2, and in Table S3 in the Supplementary Appendix. Fewer patients in the dapagliflozin group than in the placebo group discontinued the assigned regimen during the course of the trial, and fewer patients in the dapagliflozin group reported a serious adverse event or had major hypoglycemia (see the Supplementary Appendix), acute kidney injury, or bladder cancer. The rates of amputation, fracture, volume depletion, and hypersensitivity were balanced between the groups. Diabetic ketoacidosis was more common in the dapagliflozin group than in the placebo group (0.3% vs. 0.1%; hazard ratio, 2.18; 95% CI, 1.10 to 4.30; P=0.02). More than 80% of patients with diabetic ketoacidosis were using insulin at baseline. Genital infections that led to discontinuation of the trial regimen or were considered to be serious adverse events were more common in the dapagliflozin group than in the placebo group (0.9% vs. 0.1%; hazard ratio, 8.36; 95% CI, 4.19 to 16.68; P<0.001), both in men and in women, although genital infections reported as serious adverse events were rare (two events in each group). Six cases of Fournier's gangrene were reported, one in the dapagliflozin group and five in the placebo group.

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A Cardiovascular Death or Hospitalization for Heart Failure

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Total cohort	417/8582	496/8578	0.83 (0.73–0.95)	
Risk group				0.99
ASCVD	272/3474	325/3500	0.83 (0.71–0.98)	
MRF	145/5108	171/5078	0.84 (0.67–1.04)	
History of heart failure				0.60
Yes	142/852	172/872	0.79 (0.63–0.99)	
No	275/7730	324/7706	0.84 (0.72–0.99)	
eGFR				0.37
≥90 ml/min/1.73 m^2	163/4137	163/4025	0.96 (0.77–1.19)	
60 to <90 ml/min/1.73 m^2	199/3838	252/3894	0.79 (0.66–0.95)	
<60 ml/min/1.73 m^2	55/606	81/659	0.78 (0.55–1.09)	



B MACE

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Total cohort	756/8582	803/8578	0.93 (0.84–1.03)	
Risk group				0.25
ASCVD	483/3474	537/3500	0.90 (0.79–1.02)	
MRF	273/5108	266/5078	1.01 (0.86–1.20)	
History of heart failure				0.46
Yes	153/852	151/872	1.01 (0.81–1.27)	
No	603/7730	652/7706	0.92 (0.82–1.02)	
eGFR				0.99
≥90 ml/min/1.73 m^2	304/4137	309/4025	0.94 (0.80–1.10)	
60 to <90 ml/min/1.73 m^2	367/3838	390/3894	0.95 (0.82–1.09)	
<60 ml/min/1.73 m^2	85/606	104/659	0.92 (0.69–1.23)	

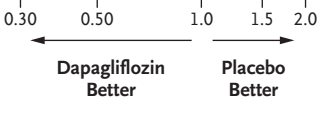


Figure 3. Major Subgroup Analyses of the Primary Efficacy Outcomes.

The two primary efficacy outcomes were a composite of cardiovascular death or hospitalization for heart failure and MACE. ASCVD denotes atherosclerotic cardiovascular disease, and MRF multiple risk factors with no evidence of ASCVD.

DISCUSSION

DECLARE–TIMI 58 was a large trial that assessed cardiovascular outcomes with the SGLT2 inhibitor dapagliflozin. It involved more than 17,000 patients who were followed for a median of 4.2 years; over the course of the trial, more than 1500 patients had MACE and 900 died from cardiovascular causes or were hospitalized for heart failure. This trial included more than 10,000 patients without evident atherosclerotic cardiovascular disease, a population for which definitive data on the effects of SGLT2 inhibitors were previously lacking.

There are several key findings from the DECLARE–TIMI 58 trial. In a broad population of patients with type 2 diabetes who were at high risk for cardiovascular events, dapagliflozin was noninferior to placebo with respect to the composite safety outcome of cardiovascular death, myocardial infarction, or ischemic stroke (MACE), but it did not result in a significantly lower rate of MACE than placebo. Dapagliflozin did result in a lower rate of the other prespecified primary

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Table 2. Safety Events.*

Event	Dapagliflozin (N=8574)	Placebo (N=8569)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Serious adverse event	2925 (34.1)	3100 (36.2)	0.91 (0.87–0.96)	<0.001
Adverse event leading to discontinuation of trial regimen	693 (8.1)	592 (6.9)	1.15 (1.03–1.28)	0.01
Major hypoglycemic event	58 (0.7)	83 (1.0)	0.68 (0.49–0.95)	0.02
Diabetic ketoacidosis	27 (0.3)	12 (0.1)	2.18 (1.10–4.30)	0.02
Amputation	123 (1.4)	113 (1.3)	1.09 (0.84–1.40)	0.53
Fracture	457 (5.3)	440 (5.1)	1.04 (0.91–1.18)	0.59
Symptoms of volume depletion	213 (2.5)	207 (2.4)	1.00 (0.83–1.21)	0.99
Acute kidney injury	125 (1.5)	175 (2.0)	0.69 (0.55–0.87)	0.002
Genital infection	76 (0.9)	9 (0.1)	8.36 (4.19–16.68)	<0.001
Urinary tract infection	127 (1.5)	133 (1.6)	0.93 (0.73–1.18)	0.54
Cancer	481 (5.6)	486 (5.7)	0.99 (0.87–1.12)	0.83
Bladder cancer	26 (0.3)	45 (0.5)	0.57 (0.35–0.93)	0.02
Breast cancer	36 (0.4)	35 (0.4)	1.02 (0.64–1.63)	0.92
Hypersensitivity	32 (0.4)	36 (0.4)	0.87 (0.54–1.40)	0.57
Hepatic event	82 (1.0)	87 (1.0)	0.92 (0.68–1.25)	0.60

* Additional details, data sources, and a complete list of serious adverse events are provided in the Supplementary Appendix. P values and 95% confidence intervals have not been adjusted for multiple comparisons.

efficacy outcome (the composite of cardiovascular death or hospitalization for heart failure), which reflected a lower rate of hospitalization for heart failure.

The lower rate of cardiovascular death or hospitalization for heart failure in the dapagliflozin group than in the placebo group was consistent across multiple subgroups, which shows that dapagliflozin prevented cardiovascular events, particularly hospitalization for heart failure, in a broad range of patients, regardless of a history of atherosclerotic cardiovascular disease or heart failure. The majority of patients did not have a history of heart failure, so the prevention of new clinical heart failure is notable. Ongoing trials will assess the effects of dapagliflozin in dedicated populations of patients with heart failure. Likewise, a consistent pattern of lower rates of progression of renal disease was seen among patients with and those without established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease at baseline.

On the basis of results from previous trials,[8,9,25,26] current international guidelines for the management of diabetes[25] have focused on the use of SGLT2 inhibitors in patients with atherosclerotic cardiovascular disease. These new data suggest that in patients without established atherosclerotic cardiovascular disease, SGLT2 inhibition can prevent serious clinical events, particularly hospitalization for heart failure, and possibly reduce the likelihood of progression of renal disease.

The DECLARE–TIMI 58 trial also adds substantially to the literature on current safety concerns for this class of drugs, which are based on relatively sparse previous data. There have been conflicting reports of a possible increased risk of stroke, amputation, and fractures with various SGLT2 inhibitors.[14,15,27,28] We saw no evidence, despite focused collection of events, of a higher risk of stroke, amputations, or fractures with dapagliflozin than with placebo. Likewise, despite the observation of an excess of cases of bladder cancer in earlier, smaller studies of dapagliflozin, we observed a lower rate of bladder cancer with dapagliflozin than with placebo. The rate of diabetic ketoacidosis was higher in the dapagliflozin group than in the placebo group, a finding consistent with observations in

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studies of other SGLT2 inhibitors[15,29]; the excess rate was less than 0.1% per year. The rate of genital infections was higher with dapagliflozin than with placebo, but the rate of Fournier's gangrene was not.

In the context of previous cardiovascular outcomes trials with empagliflozin and canagliflozin, the DECLARE–TIMI 58 trial supports clear patterns of effect. First, SGLT2 inhibitors have a more robust and consistent effect on the prevention of heart failure and renal outcomes than on atherosclerotic cardiovascular events. These observations fit with the mechanism of action of SGLT2 inhibitors on the kidney and the well-documented downstream effects, including natriuresis, blood-pressure reduction, improved tubular glomerular feedback, vascular compliance, and endothelial function.[15,30-33] Second, although treatment with SGLT2 inhibitors appears to result in a moderate reduction in the risk of MACE in patients with atherosclerotic cardiovascular disease, no effect has been observed in patients with multiple risk factors for atherosclerotic cardiovascular disease.[15] This observation is distinct from the robust data from multiple trials that show reductions in the risk of heart failure and renal outcomes regardless of patient characteristics.

We did not find that SGLT2 inhibition with dapagliflozin resulted in a lower rate of cardiovascular death or death from any cause than placebo, a finding that contrasts with that in the EMPA-REG OUTCOME trial. Although we cannot discount that there are differences among the specific drugs in the class, there are other possible explanations. There were important differences in the design of the trials, including a more restrictive exclusion of patients according to creatinine clearance in our trial (patients with a creatinine clearance <60 ml per minute were not eligible), which could have contributed to this distinction. Because SGLT2 inhibitors act in the kidney, and because in other trials patients with chronic kidney disease are a population that seemed to have greater benefits with SGLT2 inhibitors than other populations, it is possible that excluding these patients may have limited a mortality benefit.[34,35] Overall mortality rates in the placebo group were lower in the current trial than in the EMPA-REG OUTCOME trial, which highlights possible differences among populations. Finally, it is possible that the lack of benefit with respect to cardiovascular death was due to chance, since the confidence intervals around the estimate are wide.

The trial outcomes were modified in response to external data that pointed to the prevention of hospitalization for heart failure as a major benefit of SGLT2 inhibitors. These adaptations, which were made in accordance with the principles of adaptive trial design,[36] were not based on knowledge of any blinded or unblinded comparative data on MACE in the trial. They were made before the data and safety monitoring board performed efficacy analyses, and trial participants, ethics committees, and regulators were appropriately notified. Although the change resulted in a positive result for the primary outcome of cardiovascular death or hospitalization for heart failure, splitting the alpha without increasing the sample size could have resulted in lower statistical power for the trial.

This trial included a broad population of patients with and those without atherosclerotic cardiovascular disease. It is possible that some patients may have had undiagnosed atherosclerotic cardiovascular disease or heart failure. Given the adherence requirement in the placebo run-in period, patients who found it difficult to adhere to the regimen may have withdrawn from the trial before randomization.

The DECLARE–TIMI 58 trial showed that the SGLT2 inhibitor dapagliflozin was noninferior to placebo with respect to the primary safety outcome of MACE. Dapagliflozin did not result in a significantly lower rate of MACE, but in a broad population of patients with type 2 diabetes it did result in a significantly lower rate of cardiovascular death or hospitalization for heart failure than placebo, with additional findings supporting a possible lower rate of adverse renal outcomes.

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

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APPENDIX

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