

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

RESULTS

The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; $P < 0.001$; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; $P < 0.001$), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; $P = 0.009$). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; $P = 0.004$). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by Astra-Zeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

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*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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WORLDWIDE ESTIMATES INDICATE that nearly 700 million persons have chronic kidney disease.¹ Chronic kidney disease is an important contributor to illness and is associated with a diminished quality of life and a reduced life expectancy. Despite the widespread availability of simple laboratory tests to identify patients with impaired kidney function, fewer clinical trials have been conducted for kidney diseases than for other common medical conditions.² Until recently, the only classes of medication that have been shown to slow a decline in kidney function were angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs); however, most of the evidence was generated in patients with type 2 diabetes.³⁻⁶

Sodium-glucose cotransporter 2 (SGLT2) inhibitors decrease glycated hemoglobin levels and have shown favorable effects on kidney and cardiovascular outcomes in large clinical trials involving patients with type 2 diabetes.⁷⁻⁹ The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed that long-term administration of canagliflozin conferred renal and cardiovascular protection in patients with type 2 diabetes with chronic kidney disease.¹⁰ Although the underlying mechanisms are not completely understood, the benefits of SGLT2 inhibitors appear to be independent of their blood glucose-lowering effects and may be mediated by natriuresis and glucose-induced osmotic diuresis, leading to a reduction in intraglomerular pressure.¹¹⁻¹³ This favorable hemodynamic effect may also preserve kidney function in persons with kidney diseases due to causes other than type 2 diabetes. We designed the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial to assess the long-term efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes.

METHODS

TRIAL DESIGN AND OVERSIGHT

Our trial was a randomized, double-blind, placebo-controlled, multicenter clinical trial; details regarding the trial design and baseline characteristics of the participants have been published previously.^{14,15} The trial was sponsored by AstraZeneca and conducted at 386 sites in 21 coun-

tries from February 2, 2017, through June 12, 2020. An executive committee consisting of nine academic members and two nonvoting employees of the sponsor was responsible for the design and oversight of the trial and the reporting of the results. The trial protocol (available with the full text of this article at NEJM.org) was approved by a central or local ethics committee at each trial site. All the participants provided written informed consent before any trial-specific procedure commenced. The safety of the participants was overseen by an independent data monitoring committee. The analyses that were conducted by the sponsor were replicated by an independent academic group at the University Medical Center Groningen. The first draft of the manuscript was written by the first and last authors and was revised by the coauthors. The decision to submit the manuscript for publication was made jointly by all the authors. The first and last authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Adults with or without type 2 diabetes who had an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m² of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 were eligible for participation. All the participants were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks before screening. However, participants who were documented to be unable to take ACE inhibitors or ARBs were allowed to participate. Key exclusion criteria were a documented diagnosis of type 1 diabetes, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis. Participants who had received immunotherapy for primary or secondary kidney disease within 6 months before enrollment were also excluded. The full inclusion and exclusion criteria are listed in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES

Participants were randomly assigned to receive dapagliflozin (10 mg once daily) or matching placebo, in accordance with the sequestered, fixed-randomization schedule, with the use of balanced

blocks to ensure an approximate 1:1 ratio of the two regimens. Randomization was stratified according to the diagnosis of type 2 diabetes (yes or no) and the urinary albumin-to-creatinine ratio (≤ 1000 or >1000). Investigators used an interactive voice-response or Web-response system to determine trial-group assignments. Randomization was monitored to ensure that a minimum of 30% of the participants were recruited to either the population with type 2 diabetes or the population without diabetes. Recruitment of participants with an estimated GFR of 60 to 75 ml per minute per 1.73 m^2 was halted on November 27, 2017, to ensure that no more than 10% of the trial participants had stage 2 chronic kidney disease. Participants and all trial personnel (except the members of the independent data monitoring committee) were unaware of the trial-group assignments. Dapagliflozin and placebo were packaged identically, with uniform tablet appearance, labeling, and administration schedules.

After randomization, in-person trial visits were performed at 2 weeks, at 2, 4, and 8 months, and at 4-month intervals thereafter (Fig. S1 in the Supplementary Appendix). At each follow-up visit, vital signs were recorded, blood and urine samples were sent for laboratory assessment, and information on potential trial outcomes, adverse events, concomitant therapies, and adherence to the trial regimen was collected. Dapagliflozin or placebo was to be discontinued if pregnancy or diabetic ketoacidosis occurred. Before trial completion, each participant underwent a final trial visit.

OUTCOMES

The primary composite outcome, assessed in a time-to-event analysis, was the first occurrence of any of the following: a decline of at least 50% in the estimated GFR (confirmed by a second serum creatinine measurement after ≥ 28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for ≥ 28 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 confirmed by a second measurement after ≥ 28 days), or death from renal or cardiovascular causes. Secondary outcomes (also assessed in time-to-event analyses) were, in hierarchical order, the composite kidney outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes; a composite cardiovascular outcome

defined as hospitalization for heart failure or death from cardiovascular causes; and death from any cause. An independent committee whose members were unaware of the trial-group assignments adjudicated all primary and secondary outcomes, except for a sustained decline in the estimated GFR of at least 50% and a sustained estimated GFR of less than 15 ml per minute per 1.73 m^2 , which were ascertained from central laboratory measurements. Members of the event-adjudication committee and the outcome definitions are reported in the Supplementary Appendix.

Selected adverse-event data were collected in the trial. These included serious adverse events, adverse events resulting in the discontinuation of dapagliflozin or placebo, and adverse events of interest (symptoms of volume depletion, renal events, major hypoglycemia, bone fractures, amputations, and potential diabetic ketoacidosis). Potential cases of diabetic ketoacidosis were adjudicated by the independent adjudication committee. All events suggestive of Fournier's gangrene were evaluated by an internal safety group consisting of representatives of the sponsor who were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

The analytical approach and power calculations have been published previously,¹⁴ and the complete prespecified statistical analysis plan is available with the protocol at NEJM.org. In brief, a formal interim analysis was originally planned when 75% of primary outcome events had occurred. However, during the conduct of the trial it became apparent that the interim analysis would occur close to the end of the trial. The executive committee therefore decided to remove the interim analysis from the protocol. We estimated that 681 primary outcome events would be needed to detect a 22% lower relative risk in the dapagliflozin group than in the placebo group (hazard ratio of 0.78), with 90% power using a two-sided alpha level of 0.05 and assuming an annual event rate for the primary outcome of 7.5% in the placebo group. A closed testing procedure that included a prespecified hierarchical order of the primary and secondary outcomes was used to ensure control of type I error at a two-sided 0.05 level.

The primary efficacy analysis was based on the intention-to-treat population, which included all the participants who had undergone random-

ization. A Cox proportional-hazards regression model that was stratified according to the factors used at randomization (type 2 diabetes and urinary albumin-to-creatinine ratio) and that was adjusted for the baseline estimated GFR was used to estimate the hazard ratio and 95% confidence intervals for dapagliflozin as compared with placebo for the primary and secondary outcomes. Data were censored on April 3, 2020, or the date of the last central laboratory assessment, clinical assessment, or known contact, depending on the specific outcome. Prespecified subgroups were assessed with the use of the same stratified Cox proportional-hazards model without adjustment for multiple comparisons. A mixed model for repeated measurements was used to analyze changes in the estimated GFR in the on-treatment analysis population. The model was adjusted for the baseline value, trial-group assignment, visit, and the interaction between trial-group assignment and visit. All available on-treatment measurements were used with no distinction made for missing outcomes for participants who were alive and outcomes that were not observed because of death. The effect of dapagliflozin as compared with placebo on the rate of decline in the estimated GFR during the acute phase (baseline to week 2), chronic phase (week 2 until end of treatment), and total slope to month 30 was analyzed with the use of a two-slope model; details are provided in the Supplementary Appendix.

Safety data are summarized according to trial group with the use of the data set for all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo. Safety analyses were performed on all adverse events occurring before or at the trial closure visit. All analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS AND FOLLOW-UP

From February 2017 through October 2018, a total of 7517 participants were screened, of whom 4094 underwent randomization. Because of regulatory delays, enrollment in China did not commence until December 2019, after which 210 participants from China underwent randomization until March 2020. Details about the randomization and follow-up of the participants are

provided in Figure S2. The baseline characteristics, including medications for type 2 diabetes and kidney disease, were balanced between the dapagliflozin and placebo groups (Table 1). The mean (\pm SD) age was 61.8 ± 12.1 years, and 1425 participants (33.1%) were female. The mean estimated GFR was 43.1 ± 12.4 ml per minute per 1.73 m^2 , the median urinary albumin-to-creatinine ratio was 949, and 2906 participants (67.5%) had received a diagnosis of type 2 diabetes.

After a regular review meeting on March 26, 2020, the independent data monitoring committee recommended to the two coprincipal investigators (the first and last authors) that the trial be discontinued because of clear efficacy, on the basis of 408 primary outcome events. The trial leadership team accepted this recommendation and chose April 3, 2020, as the cutoff date for all efficacy analyses.

At the conclusion of the trial, the median follow-up was 2.4 years (interquartile range, 2.0 to 2.7). Dapagliflozin was discontinued for reasons other than death in 274 participants, and placebo was discontinued in 309 participants (12.7% and 14.4%, respectively). In all, 4289 participants (99.7%) completed the trial (i.e., were alive with follow-up data available at the trial completion visit or had died during follow-up). A total of 11 participants (0.3%) withdrew consent, and vital status was ascertained for all but 5 participants (0.1%).

EFFICACY OUTCOMES

The primary composite outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes occurred in 197 participants (9.2%) in the dapagliflozin group and 312 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; $P<0.001$) (Table 2 and Fig. 1A). The event rates for all components of the composite outcome favored dapagliflozin (Table 2). The number of participants who needed to be treated during the trial period to prevent one primary outcome event was 19 (95% CI, 15 to 27).

The effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups (Fig. 2). In participants with type 2 diabetes, the hazard ratio for the comparison of dapagliflozin and placebo for the primary outcome was 0.64 (95% CI, 0.52 to 0.79), as com-

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

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m ²	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m ²	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m ²	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m ²	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m ²	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

* Plus–minus values are mean ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and GFR glomerular filtration rate.

† Race was reported by the investigators; the designation “other” includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and other.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

¶ Cardiovascular disease was defined as a history of peripheral artery disease, angina pectoris, myocardial infarction, percutaneous coronary intervention, coronary-artery bypass grafting, heart failure, valvular heart disease, abdominal aorta aneurysm, atrial fibrillation, atrial flutter, ischemic stroke, transient ischemic attack, hemorrhagic stroke, carotid artery stenosis, cardiac-pacemaker insertion, vascular stent, coronary-artery stenosis, ventricular arrhythmia, implantable cardioverter-defibrillator, noncoronary revascularization, or surgical amputation.

Table 2. Primary and Secondary Outcomes and Adverse Events of Special Interest.*

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	events/100 patient-yr	no./total no. (%)	events/100 patient-yr		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	4.8	0.53 (0.42–0.67)	NA
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	3.8	0.64 (0.50–0.82)	NA
Estimated GFR of <15 ml/min/1.73 m ²	84/2152 (3.9)	1.9	120/2152 (5.6)	2.8	0.67 (0.51–0.88)	NA
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	2.2	0.66 (0.48–0.90)	NA
Kidney transplantation‡	3/2152 (0.1)	0.1	8/2152 (0.4)	0.2	—	NA
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	0.1	—	NA
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	1.7	0.81 (0.58–1.12)	NA
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004
Safety outcomes ‡						
Discontinuation of regimen due to adverse event	118/2149 (5.5)	—	123/2149 (5.7)	—	—	0.79
Any serious adverse event	633/2149 (29.5)	—	729/2149 (33.9)	—	—	0.002
Adverse events of interest						
Amputation§	35/2149 (1.6)	—	39/2149 (1.8)	—	—	0.73
Any definite or probable diabetic ketoacidosis	0/2149	—	2/2149 (<0.1)	—	—	0.50
Fracture¶	85/2149 (4.0)	—	69/2149 (3.2)	—	—	0.22
Renal-related adverse event¶¶	155/2149 (7.2)	—	188/2149 (8.7)	—	—	0.07
Major hypoglycemia¶¶¶	14/2149 (0.7)	—	28/2149 (1.3)	—	—	0.04
Volume depletion¶¶¶¶	127/2149 (5.9)	—	90/2149 (4.2)	—	—	0.01

* NA denotes not applicable because P values for efficacy outcomes are reported only for outcomes that were included in the hierarchical testing strategy.
 † For the composite of long-term dialysis or kidney transplantation, there were 69 outcome events in the dapagliflozin group and 100 outcome events in the placebo group (hazard ratio, 0.66; 95% CI, 0.49 to 0.90).
 ‡ Safety analyses included all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo.
 § Shown are cases of surgical amputation or spontaneous or nonsurgical amputation, excluding amputation due to trauma.
 ¶ These outcomes are based on a predefined list of preferred terms.
 ¶¶ The following criteria were confirmed by the investigator: symptoms of severe impairment in consciousness or behavior, need of external assistance, intervention to treat hypoglycemia, and prompt recovery from acute symptoms after the intervention.

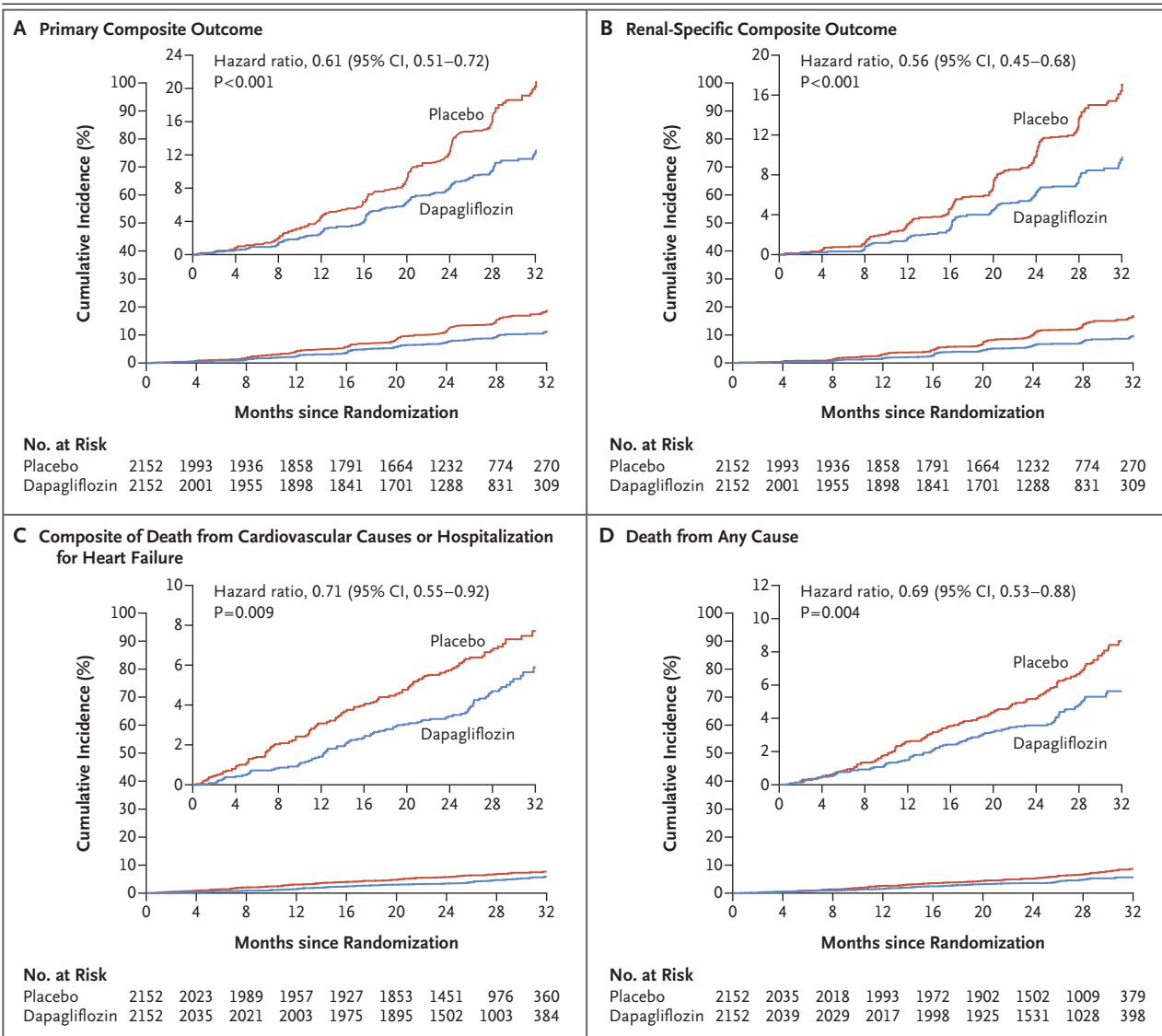


Figure 1. Primary and Secondary Outcomes.

The primary outcome was a composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes (Panel A). The primary outcome and the secondary outcomes of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes (Panel B), a composite of death from cardiovascular causes or hospitalization for heart failure (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method. Hazard ratios, confidence intervals, and P values were estimated with the use of Cox proportional-hazards regression models, stratified according to randomization factors (diabetes diagnosis and urinary albumin-to-creatinine ratio) and adjusted for baseline estimated GFR. Included in these analyses are all the participants who had undergone randomization and received at least one dose of dapagliflozin or placebo. The graphs are truncated at 32 months (the point at which <15% of participants remained at risk). The insets show the same data on an expanded y axis.

pared with 0.50 (95% CI, 0.35 to 0.72) in participants without type 2 diabetes.

The incidence of each secondary outcome was lower in the dapagliflozin group than in the placebo group (Table 2). The hazard ratio for the kidney composite of a sustained decline in

the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001) (Table 2 and Fig. 1B). The hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to

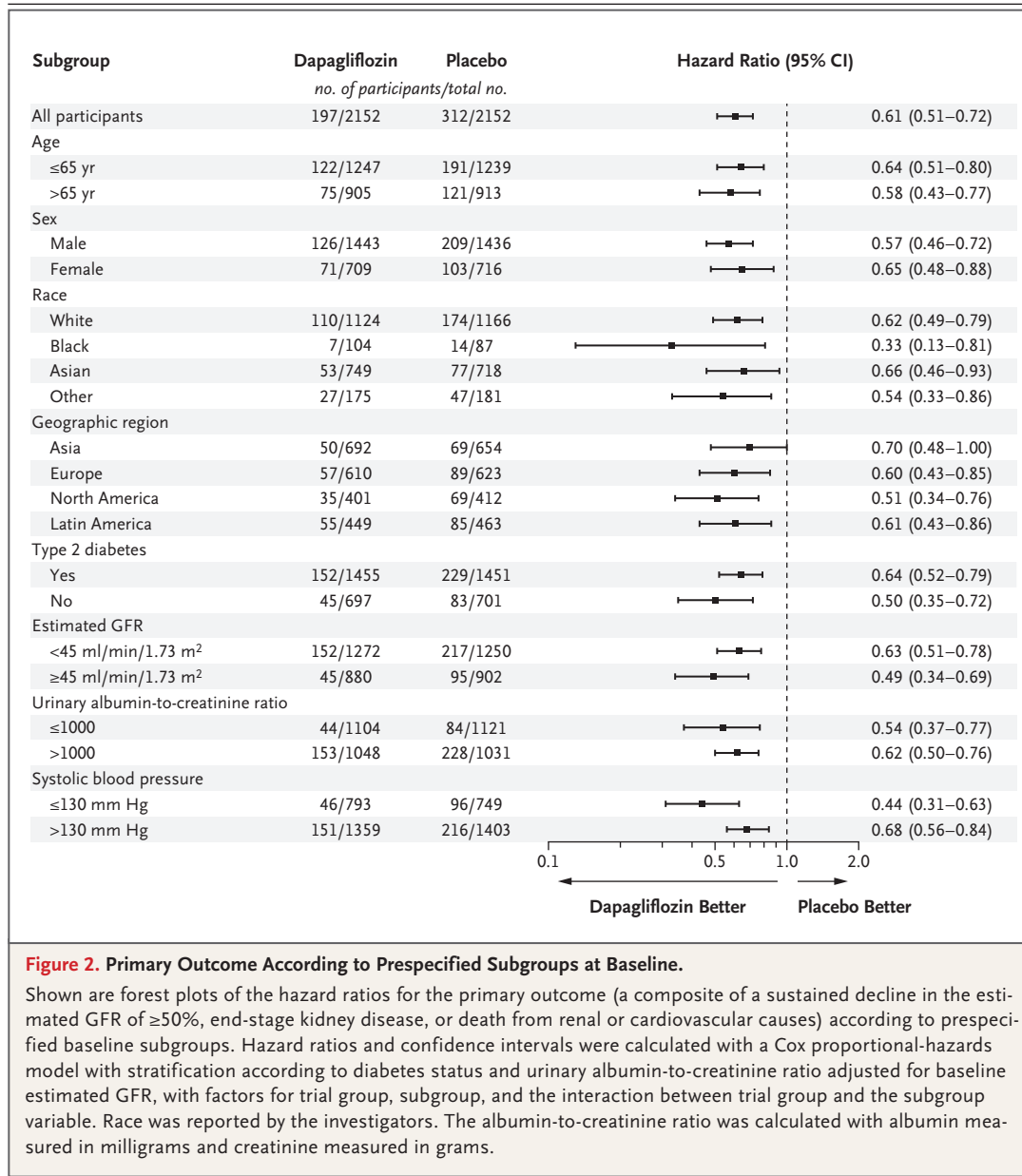


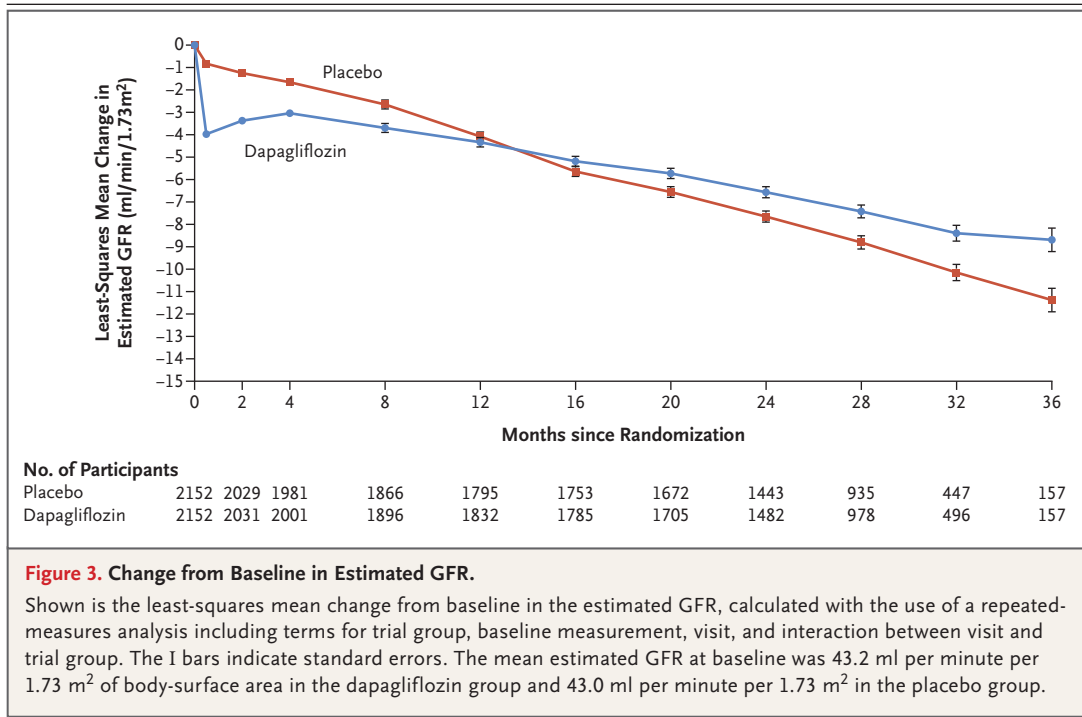
Figure 2. Primary Outcome According to Prespecified Subgroups at Baseline.

Shown are forest plots of the hazard ratios for the primary outcome (a composite of a sustained decline in the estimated GFR of ≥50%, end-stage kidney disease, or death from renal or cardiovascular causes) according to prespecified baseline subgroups. Hazard ratios and confidence intervals were calculated with a Cox proportional-hazards model with stratification according to diabetes status and urinary albumin-to-creatinine ratio adjusted for baseline estimated GFR, with factors for trial group, subgroup, and the interaction between trial group and the subgroup variable. Race was reported by the investigators. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

0.92; P=0.009) (Table 2 and Fig. 1C). There were 101 deaths (4.7%) from any cause in the dapagliflozin group and 146 (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004) (Table 2 and Fig. 1D).

The least-squares mean (±SE) estimated GFR slopes from baseline to 30 months in the dapagliflozin and placebo groups were -2.86 ± 0.11 and -3.79 ± 0.11 ml per minute per 1.73 m² per year, respectively, resulting in a between-group difference of 0.93 ml per minute per 1.73 m² per year

(95% CI, 0.61 to 1.25) (Fig. 3). During the first 2 weeks, there was a greater reduction in the estimated GFR in the dapagliflozin group than in the placebo group (-3.97 ± 0.15 vs. -0.82 ± 0.15 ml per minute per 1.73 m²). Thereafter, the annual change in the mean estimated GFR was smaller with dapagliflozin than with placebo (-1.67 ± 0.11 and -3.59 ± 0.11 ml per minute per 1.73 m², respectively), for a between-group difference of 1.92 ml per minute per 1.73 m² per year (95% CI, 1.61 to 2.24).



SAFETY OUTCOMES AND ADVERSE EVENTS

The incidences of adverse events and serious adverse events were similar overall in the dapagliflozin and placebo groups (Table 2). Diabetic ketoacidosis was not reported in any participants who received dapagliflozin and in two participants who received placebo. Neither diabetic ketoacidosis nor severe hypoglycemia was observed in participants without type 2 diabetes. There was one confirmed case of Fournier's gangrene in the placebo group and none in the dapagliflozin group.

DISCUSSION

We found that participants with chronic kidney disease, with or without type 2 diabetes, who were randomly assigned to receive dapagliflozin had a lower risk of the primary composite outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes than participants who were assigned to receive placebo. Each of the components of the composite outcome occurred less frequently in the dapagliflozin group, with results that were similar for the occurrence of death from cardiovascular causes or hospital-

ization for heart failure and death from any cause. Our trial adds to the literature by examining the effect of an SGLT2 inhibitor, added to background therapy including an ACE inhibitor or ARB, in participants with chronic kidney disease, with or without type 2 diabetes.

The kidney-protective effects of SGLT2 inhibitors have previously been shown in patients with type 2 diabetes and chronic kidney disease in the CREDENCE trial.¹⁰ In that trial, as in most previous cardiovascular outcome trials of SGLT2 inhibitors, the lower estimated GFR cutoff for inclusion was 30 ml per minute per 1.73 m².¹⁶ In contrast to the CREDENCE trial, the present trial examined the effects of an SGLT2 inhibitor in patients with chronic kidney disease of whom 32.5% did not have type 2 diabetes and 14.5% had an estimated GFR below 30 ml per minute per 1.73 m². Our trial confirms that the kidney-protective effects of SGLT2 inhibitors extend to the broader population of persons with chronic kidney disease without type 2 diabetes, for whom ACE inhibitors are the only pharmacologic treatments that have been shown to prevent kidney failure.^{3,4}

Life expectancy is markedly reduced when kidney function declines or albuminuria devel-

ops. Global estimates indicate that 1.2 million deaths were attributable to chronic kidney disease in 2017.¹⁷ The findings from the present trial confirm the high mortality among patients with impaired kidney function. The markedly lower mortality in the dapagliflozin group than in the placebo group supports the use of dapagliflozin as an addition to the therapeutic management of chronic kidney disease.

Participants in our trial also had a high risk of hospitalization for heart failure or death from cardiovascular causes. The lower risk of hospitalization for heart failure or death from cardiovascular causes in the dapagliflozin group than in the placebo group is consistent with the results of two previous trials of dapagliflozin, the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58) and DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trials.^{9,18} Clinical trials of other SGLT2 inhibitors have shown similar results.^{8,10,19}

Dapagliflozin had an acceptable safety profile in this population, which included participants with an estimated GFR as low as 25 ml per minute per 1.73 m². Overall, the present trial confirmed the beneficial safety profile of dapagliflozin. In particular, there were no cases of diabetic ketoacidosis with dapagliflozin, and hypoglycemic episodes did not occur in participants without diabetes.

Our trial has some limitations. First, the trial was stopped on the basis of a recommendation from the independent data monitoring committee. This may have reduced the power of some

secondary outcomes. However, the strong internal and external validity of the treatment effect suggests that this limitation is unlikely to have had a major influence on the findings. As in other trials of SGLT2 inhibitors, there was an initial dip in the estimated GFR, followed by a stabilization of kidney-function decline.^{7,8,10} This dip in the estimated GFR reflects favorable hemodynamic changes in the glomerulus. We did not collect estimated GFR values after the completion of the trial and are unable to ascertain whether the initial dip in the estimated GFR is reversible after the discontinuation of dapagliflozin, as observed in other dapagliflozin studies.²⁰

The present trial showed that persons with chronic kidney disease who received dapagliflozin had a significantly lower risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes than those who received placebo, independent of the presence or absence of type 2 diabetes. In addition, those who received dapagliflozin had a lower risk of death from cardiovascular causes or hospitalization for heart failure and had longer survival.

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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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REFERENCES

1. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet* 2017;389:1238-52.
2. Chatzimanouil MKT, Wilkens L, Anders H-J. Quantity and reporting quality of kidney research. *J Am Soc Nephrol* 2019;30:13-22.
3. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354:359-64.

4. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;354:131-40.
5. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
6. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
7. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323-34.
8. 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.
9. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347-57.
10. 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.
11. Cherney DZI, Dekkers CCJ, Barbour SJ, et al. Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *Lancet Diabetes Endocrinol* 2020;8:582-93.
12. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int* 2018;94:26-39.
13. van Bommel EJM, Muskiet MHA, van Baar MJB, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. *Kidney Int* 2020;97:202-12.
14. Heerspink HJL, Stefánsson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant* 2020;35:274-82.
15. Wheeler DC, Stefánsson BV, Batiushin M, et al. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial: baseline characteristics. *Nephrol Dial Transplant* 2020 August 30 (Epub ahead of print).
16. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2019;7:845-54.
17. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;395:709-33.
18. 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.
19. 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.
20. Pollock C, Stefánsson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019;7:429-41.

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