ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

METHODS

We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

RESULTS

A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

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Chronic kidney disease (CKD) is often progressive, with a decreased glomerular filtration rate (GFR) and the presence of albuminuria representing key risk factors for the subsequent development of kidney failure.[1] Slowing CKD progression and avoiding dialysis or kidney transplantation is highly desirable, given the effects of dialysis and kidney transplantation on quality of life and cardiovascular morbidity and mortality, as well as the substantial costs associated with kidney-replacement therapy.[2]

Large, placebo-controlled trials involving patients with diabetic kidney disease with increased albuminuria have shown that renin–angiotensin system (RAS) inhibitors,[3-5] sodium–glucose cotransporter 2 (SGLT2) inhibitors,[6,7] and the nonsteroidal mineralocorticoid receptor antagonist finerenone[8,9] all reduced the risk of progression to kidney failure. There is geographic variation, but worldwide, the majority of people with CKD have low levels of albuminuria (i.e., a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of <300) and do not have diabetes.[10,11] Therefore, studying a wide range of patients with CKD has particular importance for public health. The results of a prespecified subgroup analysis from a trial of the SGLT2 inhibitor dapagliflozin in patients with CKD and a urinary albumin-to-creatinine ratio of at least 200 showed that benefits with respect to kidney failure extended to patients without diabetes, but there were limited data regarding patients with an estimated GFR (eGFR) of less than 30 ml per minute per 1.73 m^2 of body-surface area and how these benefits might vary among the wider population of patients with CKD.[7,12,13]

The EMPA-KIDNEY trial (Study of Heart and Kidney Protection with Empagliflozin) — an international, randomized, parallel-group, double-blind, placebo-controlled, clinical trial of the SGLT2 inhibitor empagliflozin — was designed to assess the effect of once-daily empagliflozin treatment on the progression of kidney disease and cardiovascular disease and to examine the safety profile of the drug in a wide range of patients with CKD. The trial aimed to include large numbers of patients without diabetes, patients with an eGFR of less than 30 ml per minute per 1.73 m^2, and patients with low levels of proteinuria, as measured by the urinary albumin-to-creatinine ratio.[14]

Methods

Trial Design and Oversight

We conducted this trial at 241 centers in eight countries. Regulatory authorities, as well as ethics committees at each center, approved the trial. The details of the rationale and design of the trial have been reported previously.[14,15] The trial was designed and led by a steering committee that included representatives from the central coordinating office at the University of Oxford, each recruiting region, the sponsor (Boehringer Ingelheim), and other clinical and statistical experts. The steering committee was responsible for writing the first draft of the manuscript and made the decision to submit the manuscript for publication. The first and last members of the writing committee vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. An independent data and safety monitoring committee regularly reviewed unblinded data to ensure patient safety and conducted a protocol-specified formal interim efficacy analysis. The protocol is available with the full text of this article at NEJM.org. The protocol and the full statistical analysis plan are available at www.empakidney.org.

Patients

Eligible patients were adults with a race-adjusted eGFR (calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula[16]) of at least 20 but less than 45 ml per minute per 1.73 m^2, regardless of the level of albuminuria, or with an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio of at least 200 at the screening visit. Patients were required to be taking a clinically appropriate dose of a single-agent RAS inhibitor, but patients could be included, as specified in the protocol, if an investigator judged that a RAS inhibitor was not indicated or would not be not tolerated. Patients with or without diabetes were eligible. Patients with polycystic kidney disease and those who had received a kidney transplant were excluded. Full details regarding the eligibility criteria are provided in the protocol. All the patients provided written informed consent.

Trial Procedures

All eligible patients entered a prerandomization run-in phase and were provided with a 15-week

supply of once-daily placebo tablets. During this time, local investigators reviewed screening data, assessed current RAS inhibitor use, and approved potential patients for later randomization. Throughout the trial, clinical responsibility for patients remained with their local doctors.

After patients had completed at least 6 weeks of the run-in phase, blood and urine specimens were obtained for central analysis and storage from those who agreed to participate. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. Randomization was performed with the use of a minimization process with a 10% stochastic element.[17] At each follow-up visit, patients provided information on their kidney status (i.e., any dialysis treatment or receipt of a kidney transplant), adherence to the assigned trial regimen (including reasons for stopping), and details of concomitant medication use. They were also asked, in a structured interview, about any serious adverse events (and protocol-specified nonserious adverse events), and they underwent clinical assessment of blood pressure and weight and had blood specimens obtained for local safety assessments of creatinine levels, liver function, and potassium. Urine specimens (obtained at selected visits) and blood specimens were sent to the central laboratory to be assessed for efficacy analyses and for archiving. The assay methods and adaptations that were made to the trial as a result of the coronavirus disease 2019 pandemic are provided in the Supplementary Appendix (available at NEJM.org).

OUTCOMES

The prespecified primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes. Progression of kidney disease was defined as end-stage kidney disease (ESKD; the initiation of maintenance dialysis or receipt of a kidney transplant), a sustained decrease in the eGFR to less than 10 ml per minute per 1.73 m^2, a sustained decrease from baseline in the eGFR of at least 40%, or death from renal causes. The assessment of a sustained decrease used either the values measured at two consecutive scheduled follow-up visits at least 30 days apart or the values measured at the final follow-up visit or the last scheduled visit before death (or withdrawal of consent or loss to follow-up). Central laboratory measurements of serum creatinine were used to estimate the GFR, with measurements from the local laboratory being used when central results were missing.

The prespecified key secondary outcomes were a composite of hospitalization for heart failure or death from cardiovascular causes, hospitalization for any cause (including the first and any subsequent hospitalizations), and death from any cause. Other secondary outcomes were progression of kidney disease, death from cardiovascular causes, and a composite of ESKD or death from cardiovascular causes. Details regarding the tertiary, safety, and laboratory assessments and planned exploratory assessments are provided in the statistical analysis plan.

Prespecified key subgroup analyses of the primary outcome were stratified according to diabetes status, eGFR, and urinary albumin-to-creatinine ratio at baseline. All events of death, potential hospitalizations for heart failure, myocardial infarction, stroke, liver injury, ketoacidosis, lower-limb amputation, acute kidney injury, and serious genital infections were adjudicated by clinicians who were unaware of trial-group assignments, with the use of prespecified definitions and source documents collected from trial sites. Definitions of the clinical outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that a first occurrence of a primary-outcome event among 1070 patients would provide the trial with 90% power (at a two-sided P value of 0.05) to detect a risk of a primary-outcome event that was 18% lower in the empagliflozin group than in the placebo group.[14] The protocol specified that a single formal interim analysis for efficacy would be conducted when 150 patients had had a first occurrence of ESKD. On the basis of the number of primary-outcome events at the time of the interim analysis (624 events), the two conditions for recommending an early stop for efficacy were prespecified as a hazard ratio of less than 0.778 for the primary outcome and the secondary outcome of ESKD or death from cardiovascular causes, with two-sided P values of less than 0.0017 and less than 0.05, respectively. (Details are provided in the protocol.)

All the analyses were performed according to the intention-to-treat principle and included data

from all patients who had undergone randomization, including data collected from the time of the formal interim analysis to the final follow-up visits.[18-20] A Cox proportional-hazards regression model with adjustment for baseline variables specified in the minimization algorithm (age, sex, history of diabetes, eGFR, urinary albumin-to-creatinine ratio, and geographic region) was used to estimate the hazard ratio and 95% confidence intervals for empagliflozin as compared with placebo for time-to-event analyses.[21] The key secondary outcomes were prespecified to be adjusted for multiple testing with the use of the Hochberg step-up procedure, with a familywise error rate of 0.029. A semiparametric joint frailty model was used for the analysis of the outcome of the first and subsequent hospitalizations for any cause.[22] For the tertiary and exploratory outcomes based on the annual rate of change in the eGFR, the effects of emplagliflozin treatment were analyzed with the use of shared-parameter models.[23] Further statistical details are provided in the Supplementary Statistical Methods section in the Supplementary Appendix and in the statistical analysis plan. The Nuffield Department of Population Health at the University of Oxford performed the analyses with the use of SAS software, version 9.4 (SAS Institute), and holds the original full database.

RESULTS

RECRUITMENT AND FOLLOW-UP

From February 2019 through April 2021, a total of 8544 potential participants attended a screening visit; 8184 patients (95.8%) entered the prerandomization run-in phase, and 6609 underwent randomization (Fig. S1 in the Supplementary Appendix). At the time of randomization, the mean age of the patients was 63.8 years, 33.2% of the patients were women, and 54.0% did not have diabetes (Table 1). The patients were broadly representative of the population of patients with CKD who are at risk for disease progression (Table S1). The mean (±SD) eGFR was 37.3±14.5 ml per minute per 1.73 m^2, and 34.5% of the patients had an eGFR of less than 30 ml per minute per 1.73 m^2. The median urinary albumin-to-creatinine ratio was 329, and 48.3% of the patients had a urinary albumin-to-creatinine ratio of 300 or less (Table 1 and Table S2).

On March 7, 2022, the independent data and safety monitoring committee reported that on the basis of 624 first primary-outcome events, both conditions for stopping early for efficacy were met at the time of the formal interim analysis. Follow-up was completed on July 5, 2022, at which time the median follow-up was 2.0 years (interquartile range, 1.5 to 2.4). In total, 6552 patients (99.1%) were alive and completed final follow-up or had died during follow-up. Vital status was missing for 18 patients (0.3%), and 39 patients (0.6%) withdrew consent. All the eligible events were adjudicated.

At 12 months of follow-up (the approximate midpoint of the trial), 2909 of 3245 patients (89.6%) in the empagliflozin group and 2924 of 3239 (90.3%) in the placebo group reported that they had taken most (i.e., >80%) of the empagliflozin or placebo tablets. At the time of the final follow-up visit, 557 surviving patients (16.9%) in the empagliflozin group and 640 (19.4%) in the placebo group had discontinued the assigned trial regimen, including 18 patients (0.5%) in the empagliflozin group and 31 (0.9%) in the placebo group who had started treatment with an open-label SGLT2 inhibitor during the trial. Details regarding the reasons for discontinuation are provided in Table S3.

PRIMARY AND SECONDARY OUTCOMES

Progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001) (Fig. 1). After we controlled the familywise error rate for the three key secondary outcomes, the rate of first and subsequent hospitalizations from any cause was lower in the empagliflozin group than in the placebo group (24.8 vs. 29.2 hospitalizations per 100 patient-years; hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003) (Table 2 and Table S4). No significant effect was observed with respect to hospitalization for heart failure or death from cardiovascular causes (composite outcome) (which occurred in 4.0% of the patients in the empagliflozin group and in 4.6% of those in the placebo group; hazard ratio, 0.84; 95% CI, 0.67 to 1.07; P=0.15) or with respect to death from any cause (in 4.5% and 5.1%, respectively; hazard ratio, 0.87; 95% CI, 0.70 to 1.08; P=0.21) (Table 2).

The hazard ratio for the comparison of empagliflozin with placebo with respect to progression of kidney disease was 0.71 (95% CI, 0.62 to 0.81) (Table 2, Table S5, and Fig. S2A). The hazard ratio for death from cardiovascular causes was 0.84 (95% CI, 0.60 to 1.19) (Figs. S2B and S3), and the hazard ratio for the composite outcome of ESKD or death from cardiovascular causes was 0.73 (95% CI, 0.59 to 0.89) (Table 2).

TERTIARY AND EXPLORATORY OUTCOMES

The effect of empagliflozin treatment with respect to the primary outcome was generally consistent across prespecified key subgroups and other prespecified subgroups. In particular, the benefits of empagliflozin treatment were consistent among patients with or without diabetes and regardless of the eGFR at randomization. There was some evidence that the proportional risk reduction may have been larger among patients with higher urinary albumin-to-creatinine ratios (Fig. 2 and Fig. S4). Results were similar in prespecified exploratory subgroup analyses of the outcome of progression of kidney disease (Fig. S5).

The rate of annual decrease in the eGFR in the placebo group was constant. In the empagliflozin group, there was an acute decrease in the eGFR when the trial regimen was started; the rate of annual decline slowed after this initial decrease. Overall, the between-group difference in the eGFR slope from randomization to the final follow-up visit was 0.75 ml per minute per 1.73 m^2 (95% CI, 0.54 to 0.96) per year, favoring empagliflozin. With respect to the decline in eGFR from 2 months to the time of the final follow-up visit, there was a between-group difference of 1.37 ml per minute per 1.73 m^2 (95% CI, 1.16 to 1.59) per year (Fig. 3 and Fig. S6). Prespecified exploratory analyses in subgroups showed that the rate of decline after the initial decrease was slower in the empagliflozin group than in the placebo group in all key subgroups, including in the subgroup of patients with a low urinary albumin-to-creatinine ratio. Between-group differences in the rate of eGFR decline were larger in the subgroups of patients with faster rates of annual decline (i.e., patients with a higher eGFR or a higher baseline urinary albumin-to-creatinine ratio) (Fig. S7). No significant effects of empagliflozin were observed with respect to any specific cause of death, major cardiovascular events (hazard ratio, 0.93; 95% CI, 0.76 to 1.12), patient-reported episodes of gout, or development of new-onset diabetes (Tables S5 and S6).

SAFETY OUTCOMES AND ADVERSE EVENTS

Ketoacidosis occurred in 6 patients in the empagliflozin group and in 1 patient in the placebo group (0.09 and 0.02 events per 100 patient-years, respectively). Lower-limb amputations occurred in 28 patients in the empagliflozin group and in 19 patients in the placebo group (0.43 and 0.29 events per 100 patient-years, respectively). The incidences of serious urinary tract infection, hyperkalemia, acute kidney injury, serious or symptomatic dehydration, liver injury, and bone fracture were broadly similar in the two groups (Table 2 and Table S7). There was no apparent evidence that empagliflozin treatment increased the incidence of serious adverse events overall or increased serious adverse events in any particular system organ class in the *Medical Dictionary for Regulatory Activities*, version 20.1 (Table S8).

CLINICAL MEASUREMENTS AND LABORATORY ASSESSMENTS

The weighted-average difference between the empagliflozin group and the placebo group in mean (±SE) body weight was −0.9±0.1 kg; in systolic blood pressure, −2.6±0.3 mm Hg; in diastolic blood pressure, −0.5±0.2 mm Hg; and in glycated hemoglobin level, −0.39 mmol per mole (95% CI, −0.77 to −0.01 [−0.04%; 95% CI, −0.07 to 0.00]) (Table S9). The geometric mean urinary albumin-to-creatinine ratio was 19% lower in the empagliflozin group than in the placebo group (95% CI, 15 to 23). Table S10 provides details of the observed between-group differences in hematocrit and hemoglobin levels and the absence of clinically relevant differences in blood calcium, phosphate, and sodium levels, as assessed in a subgroup of patients at 18 months.

DISCUSSION

In this population of patients with a wide range of GFRs, levels of albuminuria, and causes of CKD, empagliflozin led to a risk of progression of kidney disease or death from cardiovascular causes that was 28% lower than that with placebo, with no major safety concerns. Treatment with empagliflozin was effective regardless of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=3304)	Placebo (N=3305)
Age — yr	63.9±13.9	63.8±13.9
Female sex — no. (%)	1097 (33.2)	1095 (33.1)
Race — no. (%)†		
White	1939 (58.7)	1920 (58.1)
Black	128 (3.9)	134 (4.1)
Asian	1194 (36.1)	1199 (36.3)
Multiple	14 (0.4)	7 (0.2)
Other	29 (0.9)	45 (1.4)
History of diabetes — no. (%)‡		
Yes	1525 (46.2)	1515 (45.8)
No	1779 (53.8)	1790 (54.2)
Diabetes type — no./total no. (%)		
Type 1	34/1525 (2.2)	34/1515 (2.2)
Type 2	1470/1525 (96.4)	1466/1515 (96.8)
Other or unknown	21/1525 (1.4)	15/1515 (1.0)
History of cardiovascular disease — no. (%)§		
Yes	861 (26.1)	904 (27.4)
No	2443 (73.9)	2401 (72.6)
Blood pressure — mm Hg		
Systolic	136.4±18.1	136.7±18.4
Diastolic	78.1±11.7	78.1±11.9
Body-mass index¶	29.7±6.7	29.8±6.8
Estimated GFR‖		
Mean — ml/min/1.73 m^2	37.4±14.5	37.3±14.4
Distribution — no. (%)		
<30 ml/min/1.73 m^2	1131 (34.2)	1151 (34.8)
≥30 to <45 ml/min/1.73 m^2	1467 (44.4)	1461 (44.2)
≥45 ml/min/1.73 m^2	706 (21.4)	693 (21.0)
Urinary albumin-to-creatinine ratio‖**		
Geometric mean (95% CI)	219 (205–234)	226 (211–242)
Median (IQR)	331 (46–1061)	327 (54–1074)
Distribution — no. (%)		
<30	665 (20.1)	663 (20.1)
≥30 to ≤300	927 (28.1)	937 (28.4)
>300	1712 (51.8)	1705 (51.6)
Median NT-proBNP (IQR) — ng/liter	162 (70–421)	159 (68–417)
Baseline medications — no. (%)		
Renin–angiotensin system inhibitor	2831 (85.7)	2797 (84.6)
Any diuretic	1362 (41.2)	1453 (44.0)
Any lipid-lowering medication	2190 (66.3)	2188 (66.2)

Table 1. (Continued.)

Characteristic	Empagliflozin (N=3304)	Placebo (N=3305)
Cause of kidney disease — no. (%)		
Diabetic kidney disease	1032 (31.2)	1025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CI denotes confidence interval, IQR interquartile range, and NT-proBNP N-terminal pro–B-type natriuretic peptide.
† Race was reported by the patients. The "other" category indicates that the race was not specified or the patient preferred not to answer.
‡ History of diabetes was defined as a patient-reported history of diabetes of any type, use of glucose-lowering medication, or a glycated hemoglobin level of at least 48 mmol per mole (6.5%) at the randomization visit.
§ History of cardiovascular disease was defined as a patient-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ The values represent the measurement recorded at the randomization visit or the most recent local laboratory result recorded before randomization.
** For the urinary albumin-to-creatinine ratio, albumin was measured in milligrams and creatinine was measured in grams.

diabetes status and was effective in patients with a broad range of eGFRs, down to approximately 20 ml per minute per 1.73 m^2. The risk of hospitalization for any cause was 14% lower in the empagliflozin group than in the placebo group.

The effect of SGLT2 inhibition on the progression of kidney disease or death from cardiovascular causes that was seen in the current trial is quantitatively similar to that seen in two other large, placebo-controlled trials involving patients with CKD.[6,7] The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial of canagliflozin required all participants to have type 2 diabetes and a urinary albumin-to-creatinine ratio of at least 300 and excluded patients with an eGFR of less than 30 ml per minute per 1.73 m^2.[6] The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial of dapagliflozin required participants to have a urinary albumin-to-creatinine ratio of at least 200 and an eGFR of 25 to 75 ml per minute per 1.73 m^2. The DAPA-CKD trial included 1398 participants without diabetes and 624 participants with an eGFR of less than 30 ml per minute per 1.73 m^2.[7] The EMPA-KIDNEY trial adds substantially to the existing evidence

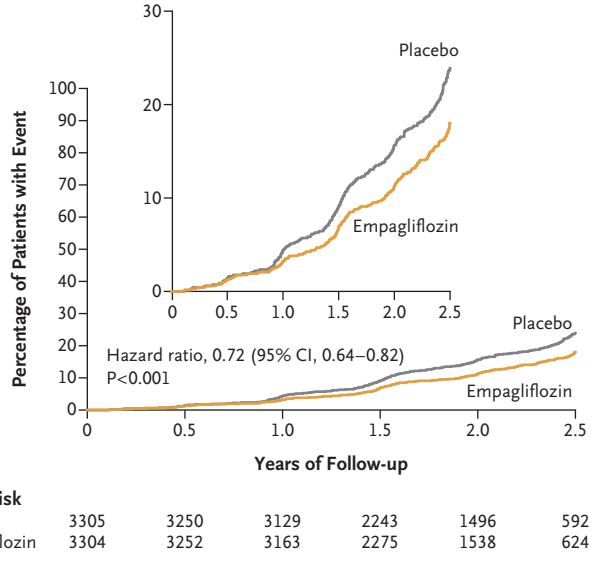

Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.
Shown are the results of the primary composite outcome of progression of kidney disease or death from cardiovascular causes. Over a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 patients (13.1%) in the empagliflozin group and in 558 patients (16.9%) in the placebo group, representing 42 fewer primary-outcome events per 1000 patients in the empagliflozin group than in the placebo group over 2 years. The inset shows the same data on an enlarged y axis.

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21
Other secondary outcomes						
Progression of kidney disease	384 (11.6)	6.09	504 (15.2)	8.09	0.71 (0.62–0.81)	
Death from cardiovascular causes	59 (1.8)	0.91	69 (2.1)	1.06	0.84 (0.60–1.19)	
End-stage kidney disease or death from cardiovascular causes§	163 (4.9)	2.54	217 (6.6)	3.40	0.73 (0.59–0.89)	
Safety outcomes						
Serious urinary tract infection	52 (1.6)	0.81	54 (1.6)	0.84	0.94 (0.64–1.37)	
Serious genital infection	1 (<0.1)	0.02	1 (<0.1)	0.02	—	
Serious hyperkalemia	92 (2.8)	1.44	109 (3.3)	1.72	0.83 (0.63–1.09)	
Serious acute kidney injury	107 (3.2)	1.67	135 (4.1)	2.11	0.78 (0.60–1.00)	
Serious dehydration	30 (0.9)	0.46	24 (0.7)	0.37	1.25 (0.73–2.14)	
Liver injury	13 (0.4)	0.20	12 (0.4)	0.19	1.09 (0.50–2.38)	
Ketoacidosis¶	6 (0.2)	0.09	1 (<0.1)	0.02	—	
Lower-limb amputation	28 (0.8)	0.43	19 (0.6)	0.29	1.43 (0.80–2.57)	
Bone fracture	133 (4.0)	2.09	123 (3.7)	1.93	1.08 (0.84–1.38)	
Severe hypoglycemia‖	77 (2.3)	1.20	77 (2.3)	1.21	1.00 (0.73–1.37)	
Symptomatic dehydration**	83 (2.5)	1.30	76 (2.3)	1.19	1.10 (0.81–1.51)	

* Hazard ratios were not calculated for outcomes with fewer than 10 events.
† Key secondary outcomes were prespecified to be adjusted for multiple testing with the use of the Hochberg step-up procedure with a family-wise error rate of 0.029.
‡ The analysis of hospitalizations for any cause included the first and all subsequent events, so only the rates are shown; 1611 hospitalizations occurred among 960 patients in the empagliflozin group, and 1895 hospitalizations occurred among 1035 patients in the placebo group.
§ End-stage kidney disease was defined as the initiation of maintenance dialysis or receipt of a kidney transplant.
¶ Ketoacidosis occurred in one patient (in the empagliflozin group) without diabetes at baseline.
‖ Severe hypoglycemia was defined as a low blood glucose level causing severe cognitive impairment and warranting assistance from another person for recovery.
** Symptomatic dehydration was defined as symptoms attributed by patients to dehydration, such as feeling faint or fainting.

by showing consistent benefits among 3569 patients (54.0%) without diabetes and, separately, among 2282 patients (34.5%) with an eGFR of less than 30 ml per minute per 1.73 m^2. Despite the enrollment of 3192 patients (48.3%) with a urinary albumin-to-creatinine ratio of less than 300, there was a limited number of primary-outcome events among these patients, since CKD was progressing at a slower rate in these patients than in those with a urinary albumin-to-creatinine ratio of 300 or more. Prespecified exploratory analyses of the annual rate of change in the eGFR — an accepted surrogate for progression of kidney disease[24] — showed that empa-

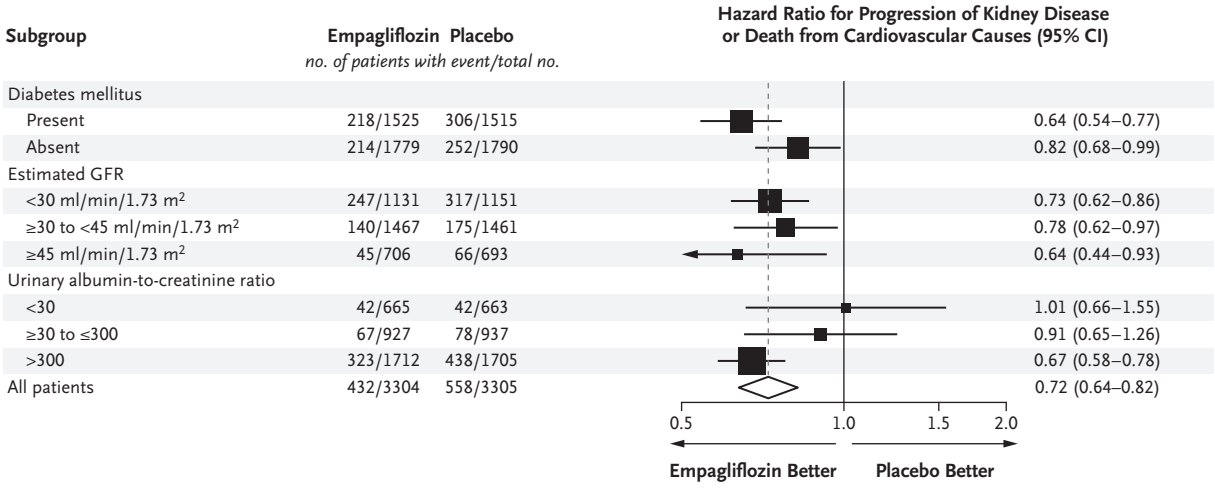

Figure 2. Primary Outcome in Key Prespecified Subgroups.

Shown are the hazard ratios for the primary outcome in key prespecified subgroups defined according to baseline characteristics. Hazard ratios and confidence intervals were estimated with the use of Cox proportional-hazards regression models, with adjustment for age, sex, history of diabetes, estimated glomerular filtration rate (GFR), urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams), and geographic region. The area of each box is proportional to the inverse of the variance of the log hazard ratios. The arrow indicates that the boundary of the 95% confidence interval is outside the graphed area. The diamond represents the result of the primary analysis, with the width of the diamond indicating the 95% confidence interval. The dashed line indicates the hazard ratio in the overall population.

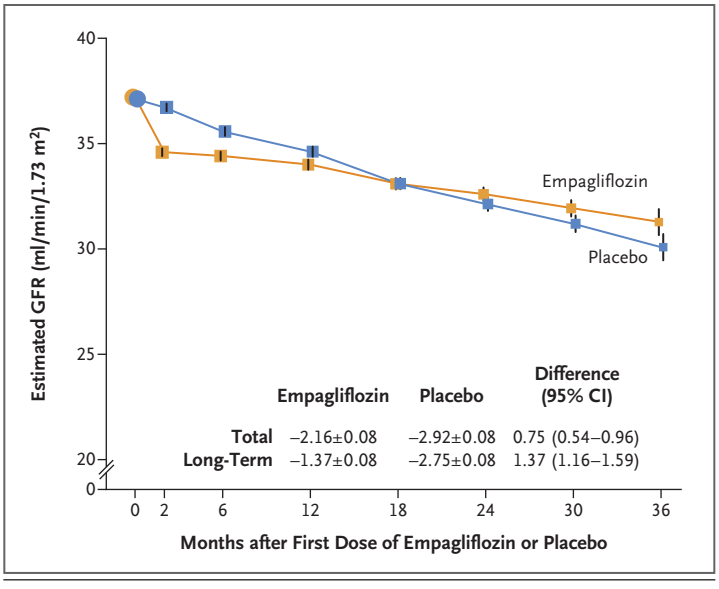

Figure 3. Change from Baseline in the Estimated GFR.

The values shown as "Total" represent the mean (±SE) changes from randomization to the final follow-up visit. The values shown as "Long-Term" represent the mean (±SE) changes from 2 months after the first dose of empagliflozin or placebo to the final follow-up visit. The mean changes in each trial group were estimated with the use of shared parameter models. For the plot, linear mixed models for repeated measures analyses were used to estimate the mean estimated GFR in each group at each scheduled follow-up visit (prespecified exploratory assessment). The vertical lines indicate the 95% confidence intervals for the estimated means. The coordinates of the boxes are shifted slightly on the x axis to avoid overlap. Additional details regarding statistical approaches are provided in the Supplementary Statistical Methods section in the Supplementary Appendix (available at NEJM.org).

gliflozin slowed the rate of long-term eGFR decline among patients with a urinary albumin-to-creatinine ratio of less than 300 at baseline (including patients with a urinary albumin-to-creatinine ratio of <30).

Key strengths of this trial were its large size and broad eligibility criteria, the high level of adherence to the trial regimen, and the almost complete follow-up of all patients. The trial has certain limitations, including the lower-than-expected number of cardiovascular events, which reduced the statistical power for the assessment

of the secondary and tertiary cardiovascular outcomes. Nevertheless, the hazard ratios for the cardiovascular outcomes were consistent with the totality of the evidence to date: a meta-analysis showed that SGLT2 inhibitors lowered the risk of death from cardiovascular causes by 14% (relative risk, 0.86; 95% CI, 0.81 to 0.92) and lowered the risk of hospitalization for heart failure or death from cardiovascular causes by 23% (relative risk, 0.77; 95% CI, 0.74 to 0.81).[13]

Among a broad range of patients with CKD who were at risk for disease progression, including a large number of patients without diabetes, with an eGFR of less than 30 ml per minute per 1.73 m^2, and with a low urinary albumin-to-creatinine ratio, empagliflozin treatment led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.

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APPENDIX

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