ORIGINAL ARTICLE

Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

In the EMPA-KIDNEY trial, empagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, had positive cardiorenal effects in patients with chronic kidney disease who were at risk for disease progression. Post-trial follow-up was designed to assess how the effects of empagliflozin would evolve after the discontinuation of the trial drug.

METHODS

In the active trial, patients with chronic kidney disease were randomly assigned to receive either empagliflozin (10 mg once daily) or matching placebo and were followed for a median of 2 years. All the patients 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 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. Subsequently, surviving patients who consented were observed for 2 additional years. No trial empagliflozin or placebo was administered during the post-trial period, but local practitioners could prescribe open-label SGLT2 inhibitors, including open-label empagliflozin. The primary composite outcome was kidney disease progression or cardiovascular death as assessed from the start of the active-trial period to the end of the post-trial period.

RESULTS

Of the 6609 patients who had undergone randomization in the active trial, 4891 (74%) were enrolled in the post-trial period. During this period, the use of open-label SGLT2 inhibitors was similar in the two groups (43% in the empagliflozin group and 40% in the placebo group). During the combined active- and post-trial periods, a primary-outcome event occurred in 865 of 3304 patients (26.2%) in the empagliflozin group and in 1001 of 3305 patients (30.3%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.72 to 0.87). During the post-trial period only, the hazard ratio for a primary-outcome event was 0.87 (95% CI, 0.76 to 0.99). During the combined periods, the risk of kidney disease progression was 23.5% in the empagliflozin group and 27.1% in the placebo group; the risk of the composite of death or end-stage kidney disease was 16.9% and 19.6%, respectively; and the risk of cardiovascular death was 3.8% and 4.9%, respectively. There was no effect of empagliflozin on death from noncardiovascular causes (5.3% in both groups).

CONCLUSIONS

In a broad range of patients with chronic kidney disease at risk for progression, empagliflozin continued to have additional cardiorenal benefits for up to 12 months after it was discontinued. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EuDRACT number, 2017-002971-24.)

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CME

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Slowing of the progression of chronic kidney disease and avoidance of end-stage kidney disease (i.e., the need for maintenance dialysis or kidney transplantation) is highly desirable, given the associated adverse effects on quality of life, cardiovascular morbidity and mortality, and high economic costs.[1,2] The EMPA-KIDNEY trial was established to assess the efficacy and safety of the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin in a broad range of patients with chronic kidney disease at risk for progression. Findings from the active part of this trial and other large trials provided compelling evidence that SGLT2 inhibitors substantially slowed kidney disease progression and reduced cardiovascular risk.[3-6] SGLT2 inhibitors also reduced the risk of hospitalization for heart failure and acute kidney injury in patients with chronic kidney disease and other high-risk conditions, including diabetes and heart failure.[4]

Post-trial follow-up studies test how effects evolve after patients stop taking a trial drug, because additional benefits or harms may emerge after such discontinuation. The EMPA-KIDNEY trial was relatively short, because it was stopped early for efficacy after a median of 2 years of follow-up. Consequently, among patients who had slower progression of chronic kidney disease, the number of primary-outcome events — a composite of progression of kidney disease or death from cardiovascular causes — was low.[3] Post-trial follow-up provides particular value through prospectively collecting more outcomes regarding end-stage kidney disease, because these outcomes take longer to accrue than surrogates of progression (e.g., the percentage reduction in the estimated glomerular filtration rate [eGFR]). We now report the effects of empagliflozin during the active trial plus 2 years of post-trial observation.

METHODS

TRIAL DESIGN AND OVERSIGHT

The EMPA-KIDNEY trial was designed and conducted by the University of Oxford in collaboration with a steering committee (see the Supplementary Appendix and protocol, available with the full text of this article at NEJM.org). The rationale of the active trial, including its double-blind, placebo-controlled design and main results, have been reported previously.[3,7,8] The relevant regulatory authority and ethics committee at each participating center approved the trial and its post-trial follow-up. Post-trial follow-up was an optional substudy conducted at 185 of the 241 trial centers (77%) in seven of the original eight countries. All surviving patients from these participating centers were eligible for post-trial follow-up. The trial was funded by Boehringer Ingelheim, which along with Eli Lilly provided grant funding to the University of Oxford.

The first two and last two authors wrote the first draft of the manuscript and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were adults with a race-adjusted eGFR (calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula[9]) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, 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 mg of albumin per gram of creatinine at the screening visit for the active trial. Patients were required to be taking a clinically appropriate dose of a single-agent renin–angiotensin system (RAS) inhibitor, unless the investigator had determined that such medication either was not indicated or had an unacceptable side-effect profile.

PROCEDURES

At the final follow-up visit of the active trial, all unused doses of trial empagliflozin or placebo were retrieved from the patients and local doctors were informed about the conclusions of the trial. Investigators and patients remained unaware of their trial-group assignment, and no additional supplies of trial empagliflozin or placebo were provided to the patients. Local practitioners were free to prescribe open-label SGLT2 inhibitors (including open-label empagliflozin) when the drugs were considered to be indicated and were available; these practitioners were responsible for routine follow-up of kidney function according to local practice. Post-trial follow-up was designed to collect additional efficacy and cause-specific

outcome data with respect to mortality. The main method of follow-up was medical-record review, which was supplemented with registry data in the United Kingdom and Malaysia. If medical records were unavailable, information was collected by contacting the patients, a relative or caregiver, or local doctors. At reviews performed every 6 months, investigators obtained details regarding the patients' vital status, current kidney-replacement status, latest blood creatinine measurement, and any current use of relevant medications (limited to SGLT2 inhibitors, RAS inhibitors, and mineralocorticoid receptor antagonists) by means of a custom-made information technology system. Over 99% of reported cases of end-stage kidney disease were confirmed by local investigators, and reported deaths underwent central review and categorization by clinician adjudicators in a blinded manner, according to the prespecified definitions that had been developed for the active trial.[3]

OUTCOMES

The prespecified primary post-trial assessment was the effect of assignment to the empagliflozin group during the active trial on the time until the development of a composite of kidney disease progression or cardiovascular death occurring at any time during the active- and post-trial periods combined (i.e., the entirety of follow-up). Kidney disease progression was defined as a sustained reduction from randomization in the eGFR of at least 40%, the development of end-stage kidney disease, a sustained eGFR of less than 10 ml per minute per 1.73 m^2, or death from kidney failure.[3] Confirmation of a sustained eGFR required the evaluation of values on two consecutive measurements performed at least 30 days apart or was assumed if the measure was the last eGFR value obtained before death, withdrawal of consent, or completion of follow-up. In primary analyses, previously reported primary-outcome events from the active-trial period were carried over regardless of later eGFR results collected during the post-trial period. Because central samples were not collected during the post-trial period, all eGFR-based post-trial measurements were relative to the local eGFR measurement at baseline (see the Supplementary Methods for details).

The post-trial follow-up protocol prespecified key secondary outcomes: kidney disease progression alone and a composite of end-stage kidney disease or death from any cause. The other secondary outcome was end-stage kidney disease. Tertiary outcomes were death from any cause and, separately, death from cardiovascular and noncardiovascular causes (the latter being the safety outcome for post-trial follow-up); and the primary outcome assessed by key subgroups of interest. These subgroups were evaluated according to diabetes status, eGFR, urinary albumin-to-creatinine ratio, and primary kidney disease at randomization with the use of prespecified categories for the active-trial report.[3] Analyses explored the effect of empagliflozin on the primary and secondary outcomes according to year and eGFR values in different follow-up windows.

STATISTICAL ANALYSIS

The analyses were performed on the original full database developed and held by the University of Oxford. We used prespecified Cox proportional-hazards regression models that included adjustment for categorized baseline variables specified in the minimization algorithm (age, sex, previously diagnosed diabetes, eGFR, urinary albumin-to-creatinine ratio, and geographic region) to estimate hazard ratios and 95% confidence intervals for empagliflozin, as compared with placebo, in time-to-event analyses.[10] Data for surviving patients who did not enter the post-trial follow-up (e.g., because of enrollment at a nonparticipating site or unwillingness to be included) were censored at the end of follow-up in the active trial. We calculated Kaplan–Meier estimates for the time until each of the primary- and secondary-outcome events. We also calculated the absolute benefit per 1000 patients who had been assigned to receive empagliflozin on the basis of between-group differences in Kaplan–Meier curves. The eGFR-based explorations used analysis of covariance to estimate the baseline-adjusted absolute between-group difference in the mean eGFR at the last local measurement overall and for the four key subgroups. Mixed-model repeated-measures approaches were used to estimate the mean eGFR at each follow-up time point throughout the entire follow-up period on the basis of local laboratory measurements. Additional details regarding the statistical analysis are provided in the Supplementary Appendix and protocol. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.3.2.

Table 1. Characteristics of the Post-Trial Study Patients at Randomization.*

Characteristic	Empagliflozin (N=2472)	Placebo (N=2419)
Demographic		
Age — yr	63±14	63±14
Sex		
Men	1632 (66.0)	1595 (65.9)
Women	840 (34.0)	824 (34.1)
Race†		
White	1552 (62.8)	1503 (62.1)
Black	91 (3.7)	87 (3.6)
Asian	791 (32.0)	791 (32.7)
Mixed	14 (0.6)	6 (0.2)
Other	24 (1.0)	32 (1.3)
Medical history		
Diabetes‡	1087 (44.0)	1020 (42.2)
Cardiovascular disease§	639 (25.8)	641 (26.5)
Blood pressure — mm Hg		
Systolic	136.9±18.3	136.9±18.3
Diastolic	78.6±11.6	78.6±11.8
Body-mass index¶	29.9±6.6	30.0±6.7
eGFR (ml/min/1.73 m^2)‖		
Mean	36.9±14.1	36.9±14.1
Distribution — no. (%)		
<30	854 (34.5)	857 (35.4)
30 to <45	1128 (45.6)	1082 (44.7)
≥45	490 (19.8)	480 (19.8)
Urinary albumin-to-creatinine ratio**		
Geometric mean (±SE)	212±9	214±9
Median (IQR)	324 (44–1045)	313 (45–1079)
Distribution — no. (%)		
<30	515 (20.8)	515 (21.3)
30 to 300	686 (27.8)	677 (28.0)
>300	1271 (51.4)	1227 (50.7)
Concomitant medication use — no. (%)		
RAS inhibitor	2142 (86.7)	2066 (85.4)
Any diuretic	1028 (41.6)	1052 (43.5)
Any lipid-lowering medication	1638 (66.3)	1582 (65.4)
Cause of kidney disease — no. (%)		
Diabetes	727 (29.4)	677 (28.0)
Hypertensive or renovascular disease	553 (22.4)	572 (23.6)
Glomerular disease	670 (27.1)	636 (26.3)
Other or unknown	522 (21.1)	534 (22.1)

Table 1. (Continued.)

Characteristic	Empagliflozin (N = 2472)	Placebo (N = 2419)
Median 5-year predicted risk of kidney failure (IQR) — %	10 (3–29)	10 (3–30)

* Plus–minus values are means ±SD unless otherwise indicated. IQR denotes interquartile range, and RAS renin–angiotensin system.
† Race was reported by the patient.
‡ Previous diabetes mellitus was defined as a patient-reported history of diabetes of any type, use of glucose-lowering medication, or a baseline glycated hemoglobin value of at least 48 mmol per mol (6.5%) at the randomization visit.
§ Previous cardiovascular disease was defined as a patient-reported history of myocardial infarction, heart failure, stroke, transient ischemic attack, or peripheral arterial disease.
¶ Data regarding body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 12 patients in the two groups.
‖ The estimated glomerular filtration rate (eGFR) is the measurement obtained at the randomization visit or most recent local laboratory result before randomization.
** In this ratio, albumin is provided in milligrams and creatinine in grams.

RESULTS

RECRUITMENT AND FOLLOW-UP

From May 2019 through April 2021, a total of 6609 patients underwent randomization and entered the active-trial period, which lasted for a median of 2.0 years (interquartile range, 1.5 to 2.4). Of the 6253 patients with data at the end of the active trial, 1362 (21.8%) did not provide consent for post-trial follow-up or were attending sites that could not participate for logistic reasons (including all sites in Japan). Thus, 4891 patients were enrolled in the post-trial follow-up. These patients were followed for a median of 2.0 years (interquartile range, 2.0 to 2.1). By the end of post-trial follow-up, data regarding vital status were missing for 86 patients (1.8%), and 7 (0.1%) had withdrawn consent during the post-trial follow-up (Fig. S1 in the Supplementary Appendix).

The patients who were included in the post-trial follow-up were broadly representative of the population of patients with chronic kidney disease who are at risk for disease progression (Table S1), and baseline characteristics at randomization were similar in the empagliflozin and placebo groups (Table 1). The mean (±SD) age of these patients at randomization was 63±14 years, 1664 (34.0%) were women, and 2784 of 4891 (56.9%) did not have diabetes. The mean eGFR was 36.9±14.1 ml per minute per 1.73 m^2. The median urinary albumin-to-creatinine ratio was 317 mg of albumin per gram of creatinine (interquartile range, 44 to 1063); 2393 patients (48.9%) had a ratio of 300 or less; 3487 (71.3%) had a nondiabetic cause of chronic kidney disease. The patients who were enrolled in the post-trial follow-up were less likely to be Asian, were slightly younger, had a slightly lower eGFR and urinary albumin-to-creatinine ratio, and had a slightly higher risk of kidney failure than those who did not enter the post-trial period (Table S2).

During the combined active- and post-trial periods, blinding of trial-group assignments among both patients and investigators was maintained in 6578 of 6609 patients (99.5%). Trial empagliflozin (or an open-label SGLT2 inhibitor) was used during the active-trial period by 90% of the patients in the empagliflozin group, and 2% of those in the placebo group received an open-label SGLT2 inhibitor; during the post-trial period, the use of open-label SGLT2 inhibitors was similar in the two groups (43% and 40%, respectively) (Table 2). Patients who did not start an open-label SGLT2 inhibitor during the post-trial period were more likely to be from Asia, were less likely to have previously diagnosed diabetes, had a lower eGFR, had a notably higher risk of kidney failure, and were less likely to be receiving a RAS inhibitor (Table S3). During post-trial follow-up, the average use of RAS inhibitors declined over time but remained similar in both groups (68% in both groups) (Table S4).

PRIMARY AND SECONDARY OUTCOMES

During the combined active- and post-trial periods, the progression of kidney disease or death from cardiovascular causes (the primary outcome) occurred in 865 of 3304 patients (26.2%) in the empagliflozin group and in 1001 of 3305 (30.3%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.72 to 0.87) (Fig. 1A and Table 3). This hazard ratio is a combination of the

Table 2. Use of SGLT2 Inhibitors.

Variable	Empagliflozin	Placebo
All patients during active-trial period*		
No. of patients	3304	3305
Distribution — no./total no. (%)		
12-mo visit	2920/3164 (92.3)	21/3159 (0.7)
24-mo visit	1661/1884 (88.2)	41/1875 (2.2)
36-mo visit	270/326 (82.8)	12/323 (3.7)
Patients who entered post-trial period†		
No. of patients	2472	2419
Active-trial period — no./total no. (%)		
12-mo visit	2264/2423 (93.4)	13/2363 (0.6)
24-mo visit	1319/1483 (88.9)	30/1417 (2.1)
36-mo visit	254/297 (85.5)	10/289 (3.5)
Post-trial period — no./total no. (%)		
12-mo visit	885/2186 (40.5)	804/2147 (37.4)
24-mo visit	1078/2376 (45.4)	972/2312 (42.0)

* During the active-trial period, data were obtained at visit windows of 12, 24, and 36 months. During this period, the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors was defined as the receipt of at least 80% of doses that had been prescribed. The denominators are the number of patients who were known to be alive at each visit.

† During the post-trial period, data were obtained at time points defined as those nearest to 12 and 24 months since completion of active-trial follow-up. Post-trial use of open-label SGLT2 inhibitors was determined from review of the patient's medical records or direct contact with patients. The denominators are the number of patients who were enrolled in the post-trial follow-up, had a follow-up visit during the study period, and were known to be alive in the relevant period. During the post-trial period, open-label SGLT2 inhibitors were prescribed for 880 of 2032 patients (43.3%) in the empagliflozin group and 797 of 1960 patients (40.7%) in the placebo group at 12 months and for 1069 of 2129 patients (50.2%) in the empagliflozin group and 961 of 2015 patients (47.7%) in the placebo group at 24 months, after the exclusion of patients receiving kidney-replacement therapy.

hazard ratio for the active-trial period (0.72; 95% CI, 0.64 to 0.82, with 990 outcomes) and the hazard ratio for the post-trial period (0.87; 95% CI, 0.76 to 0.99, with 876 additional first primary-outcome events). Much of the post-trial benefit regarding the primary-outcome event occurred early, with a hazard ratio for the first 6 months of the post-trial period of 0.60 (95% CI, 0.38 to 0.93), a hazard ratio for the first year of 0.76 (95% CI, 0.60 to 0.96), and a hazard ratio for the second year of 0.90 (95% CI, 0.75 to 1.07) (Fig. 1B). The sensitivity analyses had results that were similar to those of the primary analysis (Fig. S2 and Table S5).

The effect on the primary outcome during the combined periods included a risk of kidney disease progression (a secondary outcome) that was 21% lower in the empagliflozin group than in the placebo group (23.5% and 27.1%, respectively), with a hazard ratio of 0.79 (95% CI, 0.72 to 0.87) (Table 3 and Fig. S3). The risk of end-stage kidney disease was 9.0% in the empagliflozin group and 11.3% in the placebo group (hazard ratio, 0.74; 95% CI, 0.64 to 0.87) (Table S5). During the post-trial period, the hazard ratios for kidney disease progression and end-stage kidney disease were 0.89 (95% CI, 0.77 to 1.02) and 0.80 (95% CI, 0.66 to 0.98), respectively (Fig. S3). During the combined active- and post-trial periods, the risk of end-stage kidney disease or death from any cause was 16.9% in the empagliflozin group and 19.6% in the placebo group (hazard ratio, 0.81; 95% CI, 0.72 to 0.90), including a hazard ratio of 0.82 (95% CI, 0.70 to 0.96) during the post-trial period.

On the basis of the absolute between-group difference (±SE) in Kaplan–Meier curves, a primary-outcome event had occurred in 57±14 fewer patients per 1000 population in the empagliflozin group than in the placebo group at the end of the active-trial period and in 45±14 fewer patients per 1000 population at the end of the combined active- and post-trial periods; end-stage kidney disease had occurred in 26±8 fewer patients per 1000 population in the empagliflozin group at the end of the active-trial period and in 25±10 fewer patients per 1000 population at the end of the combined period; and death or end-stage kidney disease had occurred in 25±11 and 32±12 fewer patients per 1000 population, respectively, at the end of the two periods (Table S6).

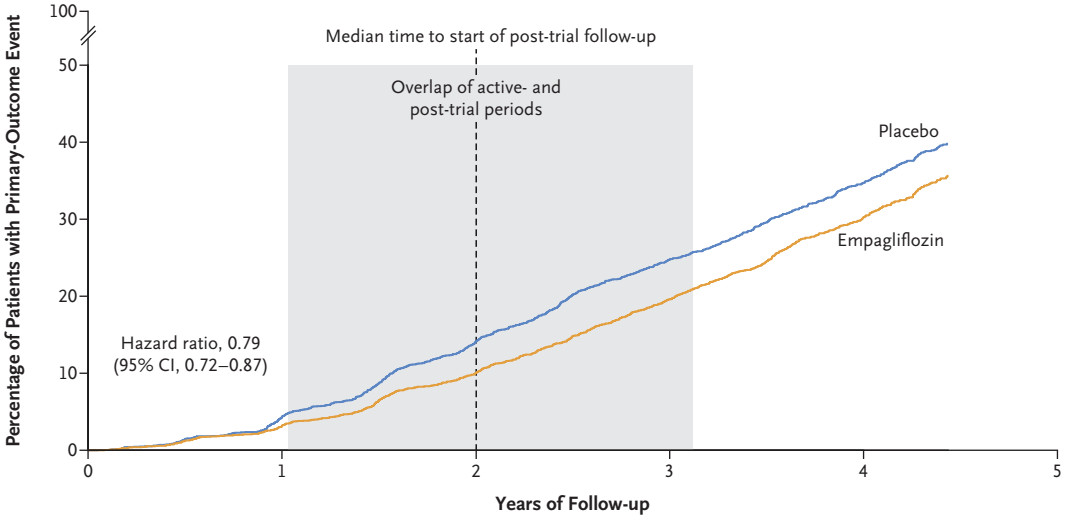
SUBGROUP ANALYSIS

The relative effects on the primary outcome were similar in subgroup analyses according to baseline diabetes status, eGFR, urinary albumin-to-creatinine ratio, and primary cause of kidney disease (Fig. 2). Findings were similar in post hoc exploratory analyses assessing effects on kidney disease progression alone according to key subgroups (Fig. S4).

TERTIARY ANALYSIS

During the combined active- and post-trial periods, the risk of death from a cardiovascular cause was 3.8% in the empagliflozin group and 4.9% in the placebo group (hazard ratio, 0.75; 95% CI,

A Primary-Outcome Events for Combined Active and Post-Trial Periods



No. at Risk					
Placebo	3305	3131	2484	1874	905
Empagliflozin	3304	3170	2596	2014	977
Absolute benefit		12±5	41±8	52±11	45±14

B Combined Active- and Post-Trial Periods, According to Year

Subgroup	Use of SGLT2 Inhibitor: Empagliflozin (percent)	Use of SGLT2 Inhibitor: Placebo (percent)	Primary Outcome: Empagliflozin (no. of events/total no. (%))	Primary Outcome: Placebo (no. of events/total no. (%))	Hazard Ratio (95% CI)
Active trial					
Yr 1	92	1	105/3304 (3.2)	144/3305 (4.4)	0.73 (0.57–0.94)
Yr 2	88	2	194/3163 (6.1)	271/3129 (8.7)	0.68 (0.57–0.82)
Yr ≥3	83	4	133/1543 (8.6)	143/1501 (9.5)	0.80 (0.63–1.02)
All active-trial period	90	2	432/3304 (13.1)	558/3305 (16.9)	0.72 (0.64–0.82)
Post trial					
Yr 1	40	37	125/2184 (5.7)	148/2073 (7.1)	0.76 (0.60–0.96)
Yr 2	45	42	258/2029 (12.7)	258/1899 (13.6)	0.90 (0.75–1.07)
Yr 3 (median, 0.8 mo)	45	42	50/1032 (4.8)	37/912 (4.1)	1.08 (0.70–1.65)
All post-trial period	43	40	433/2184 (19.8)	443/2073 (21.4)	0.87 (0.76–0.99)
All active- and post-trial period	71	16	865/3304 (26.2)	1001/3305 (30.3)	0.79 (0.72–0.87)

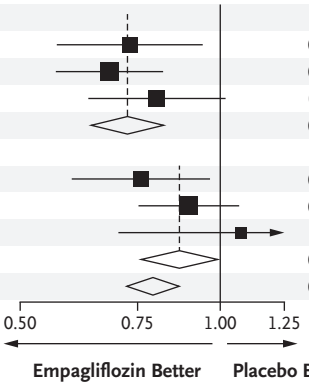


Figure 1. Progression of Kidney Disease or Death from Cardiovascular Causes.

Panel A shows a Kaplan–Meier plot of progression of kidney disease or death from cardiovascular causes (composite primary outcome) in the empagliflozin group and the placebo group during the combined active- and post-trial periods. The shaded area is wide because the median follow-up in the active-trial period was 2.0 years, with a range of 0.3 to 3.1 years owing to prolonged recruitment during the coronavirus 2019 disease pandemic. The absolute benefit (±SE) is the difference in the number of events per 1000 patients assigned to receive empagliflozin during the active-trial period, as calculated from the between-group difference in Kaplan–Meier curves. Panel B shows hazard ratios for a primary-outcome event among patients in the two groups during the active- and post-trial periods. During the post-trial period, no additional doses of empagliflozin or placebo were provided to the patients, but practitioners were free to prescribe open-label sodium–glucose cotransporter 2 (SGLT2) inhibitors (including open-label empagliflozin) if such use was indicated. The average use of SGLT2 inhibitors was calculated with the use of weights proportional to the total person-years at risk in each year. Denominators are the number of patients who were still at risk of a first primary-outcome event at the start of the risk period. The area of each box is proportional to the inverse of the variance of the log hazard ratio.

Table 3. Primary, Secondary, and Tertiary Outcomes during the Combined Active- and Post-Trial Periods.*

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)
	Patients with Event	Rate	Patients with Event	Rate	
	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	865 (26.2)	8.4	1001 (30.3)	10.0	0.79 (0.72–0.87)
Secondary outcome					
Kidney disease progression	778 (23.5)	7.5	897 (27.1)	9.0	0.79 (0.72–0.87)
Death from any cause or end-stage kidney disease	559 (16.9)	5.1	648 (19.6)	6.1	0.81 (0.72–0.90)
End-stage kidney disease	296 (9.0)	2.7	372 (11.3)	3.5	0.74 (0.64–0.87)
Tertiary outcome					
Death from any cause	301 (9.1)	2.7	336 (10.2)	3.0	0.86 (0.74–1.01)
Death from cardiovascular cause	126 (3.8)	1.1	162 (4.9)	1.5	0.75 (0.59–0.95)
Death from noncardiovascular cause	175 (5.3)	1.5	174 (5.3)	1.6	0.97 (0.79–1.20)

* No serious adverse events were attributed to trial empagliflozin during the post-trial follow-up period.

0.59 to 0.95); no material effect on the risk of death from noncardiovascular causes was observed, with 5.3% in both groups (hazard ratio, 0.97; 95% CI, 0.79 to 1.20). There were 301 deaths (9.1%) and 336 deaths (10.2%), respectively, from any cause (hazard ratio, 0.86; 95% CI, 0.74 to 1.01) (Table 3 and Fig. S5).

EXPLORATORY ANALYSIS

The mean (±SE) eGFR at the last local measurement during the combined active- and post-trial periods among patients without end-stage kidney disease was 31.4±0.2 ml per minute per 1.73 m^2 in the empagliflozin group and 30.6±0.2 ml per minute per 1.73 m^2 in the placebo group, for an absolute difference of 0.8 ml per minute per 1.73 m^2 (95% CI, 0.1 to 1.4) (Fig. S6). This absolute difference did not differ materially in any of the key subgroups (Fig. S7).

DISCUSSION

As we reported previously in the active period of the EMPA-KIDNEY trial, empagliflozin reduced the risk of the progression of kidney disease or cardiovascular death (the primary outcome) during a 2-year period in a population of patients with a wide range of causes of chronic kidney disease and levels of kidney function and albuminuria, with no major safety concerns.[3] In our current report on the results of a 2-year post-trial observation period in which the original group-assignment blinding was maintained, we found that similar percentages of patients in the two groups received open-label SGLT2 inhibitors and that there were important residual cardiorenal benefits from assignment to the empagliflozin group after the trial drug was discontinued.

If there had been no off-treatment effect of empagliflozin post-trial (i.e., if the hazard ratio had been 1.0 after discontinuation of the trial drug), absolute benefits would be observed to diminish from the end of the active-trial period (see details in the Methods section of the Supplementary Appendix). Instead, we observed that absolute benefits both for a composite primary-outcome event and for death or end-stage kidney disease were initially maintained. In relative terms, the carryover effect on the primary-outcome event was less than the effect of receiving empagliflozin during the active-trial period and appeared to last for up to 12 months, with most additional benefit seen in the first 6 months after the active trial

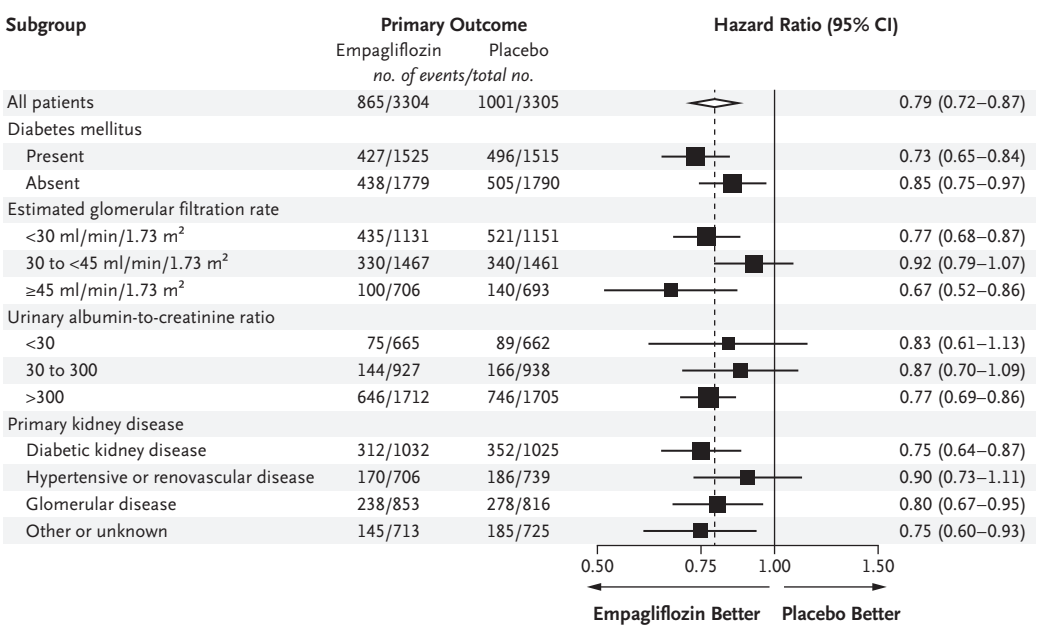


Figure 2. Subgroup Analysis of the Primary Outcome.

Shown is the risk of progression of kidney disease or death from cardiovascular causes (composite primary outcome) in the empagliflozin group and the placebo group in prespecified subgroups during the combined active- and post-trial periods. The urinary albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

ended. This finding suggests that the maximization of cardiorenal clinical benefits of SGLT2 inhibitors in chronic kidney disease requires long-term treatment.

The mechanisms for any persisting effects of SGLT2 inhibitors still need to be elucidated. Preservation of the number of nephrons during the active-trial period may have reduced hyperfiltration and the risk of end-stage kidney disease, and preservation of kidney function may have mediated some of the post-trial observed benefits on cardiovascular death.[11] Short-term decreases in the eGFR with SGLT2 inhibition are reversed within 4 weeks after discontinuation,[12,13] so some of the observed post-trial benefit on eGFR components of kidney disease progression could have resulted from such reversals. However, this hypothesis does not explain the continuing benefits of empagliflozin on end-stage kidney disease.

The patients who did not start an open-label SGLT2 inhibitor had twice the predicted risk of kidney failure as those who started an SGLT2 inhibitor post-trial. This phenomenon may reflect some uncertainty about the efficacy of SGLT2 inhibition in patients with more severe chronic kidney disease and inertia in changes in practice owing to the time taken for regulatory or payer approvals. This prognostic imbalance implies, in particular, that any comparison of outcomes between the patients in the empagliflozin group who started an SGLT2 inhibitor post-trial and those in the placebo group who did not will be confounded and hence unreliable.

Current international guidance regarding the use of SGLT2 inhibitors in chronic kidney disease provide recommendations of different strengths for patients who were eligible for the EMPA-KIDNEY trial on the basis of different levels of albuminuria.[14] The longer follow-up and almost doubling in the number of first primary-outcome events from 990 in the active-trial period to 1866 in the combined periods may help us to address uncertainties resulting from the active-trial period.[3] Benefits of empagliflozin with respect to primary-outcome events, kidney disease progression, and difference in eGFR on the last measurement

at the end of follow-up were similar regardless of the level of albuminuria, as well as diabetes status, level of kidney function, and primary kidney diagnosis. Analyses of the long-term eGFR slope from the active-trial period have also shown that empagliflozin slowed progression in all albuminuria subgroups.[12,15]

Our trial was designed to ensure that findings would be widely generalizable. Other key strengths of the trial were its large size and broad eligibility criteria, good adherence to trial empagliflozin and placebo, the high volunteer rate for post-trial follow-up, and high levels of complete follow-up.[3] Post-trial follow-up addresses some of the limitations of the active trial, including its low number of cardiovascular deaths.

Limitations of the post-trial study include the exclusion of patients from Japan (where the effects of active-trial treatment were similar to those in other regions[16]). Such exclusion did not bias the presented hazard ratios. In addition, post-trial follow-up relied on locally measured creatinine levels. We do not consider this factor to be a key limitation, because the results of the active trial were similar regardless of whether central or local creatinine values were used.[12] The lack of additional data regarding hospitalization — which was a deliberate decision to streamline post-trial follow-up as much as possible — prevented an assessment of any effects on hospitalization during the post-trial period.[3,17]

Post-trial follow-up of our active-trial patients provided more complete quantification of the total effects of a short period of 2 years of empagliflozin treatment, including any carryover effect after stopping the trial drug. In a broad range of patients with chronic kidney disease, empagliflozin continued to have additional cardiorenal benefits for up to 12 months after it was discontinued.

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

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