ORIGINAL ARTICLE

Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

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ABSTRACT

BACKGROUND

Limited evidence exists to support the simultaneous initiation of sodium–glucose cotransporter-2 inhibitors and finerenone, a nonsteroidal mineralocorticoid receptor antagonist, in persons with chronic kidney disease and type 2 diabetes.

METHODS

We randomly assigned participants with chronic kidney disease (estimated glomerular filtration rate [eGFR], 30 to 90 ml per minute per 1.73 m^2 of body-surface area), albuminuria (a urinary albumin-to-creatinine ratio of 100 to ≤5000 [with albumin measured in milligrams and creatinine measured in grams]), and type 2 diabetes, who were already taking a renin–angiotensin system inhibitor, in a 1:1:1 ratio to receive finerenone (with empagliflozin-matching placebo) at a dose of 10 or 20 mg per day, empagliflozin at a dose of 10 mg per day (with finerenone-matching placebo), or a combination of finerenone and empagliflozin. The primary outcome was the relative change in the log-transformed mean urinary albumin-to-creatinine ratio from baseline to 180 days. Safety was assessed.

RESULTS

At baseline, the urinary albumin-to-creatinine ratio was similar among the participants in the three groups; the median value was 579 (interquartile range, 292 to 1092) among those with available data (265 in the combination-therapy group, 258 in the finerenone group, and 261 participants in the empagliflozin group). At day 180, the reduction in the urinary albumin-to-creatinine ratio with combination therapy was 29% greater than that with finerenone alone (least-squares mean ratio of the difference in the change from baseline, 0.71; 95% confidence interval [CI], 0.61 to 0.82; P<0.001) and 32% greater than that with empagliflozin alone (least-squares mean ratio of the difference in the change from baseline, 0.68; 95% CI, 0.59 to 0.79; P<0.001). Neither agent, alone or in combination, led to unexpected adverse events. Symptomatic hypotension, acute kidney injury, and hyperkalemia leading to drug discontinuation were uncommon.

CONCLUSIONS

Among persons with both chronic kidney disease and type 2 diabetes, initial therapy with finerenone plus empagliflozin led to a greater reduction in the urinary albumin-to-creatinine ratio than either treatment alone. (Funded by Bayer; CONFIDENCE ClinicalTrials.gov number, NCT05254002.)

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Persons with both chronic kidney disease and type 2 diabetes face increased risks of cardiovascular disease and kidney failure.[1,2] Current medical management in persons with chronic kidney disease and type 2 diabetes includes the use of renin–angiotensin system blockers, sodium–glucose cotransporter-2 (SGLT2) inhibitors, finerenone (a nonsteroidal mineralocorticoid receptor antagonist), and glucagon-like peptide-1 receptor agonists. All these therapies aim to reduce the risk of chronic kidney disease progression and cardiovascular complications.[3] Secondary analyses of clinical trials of finerenone have shown that reductions in the urinary albumin-to-creatinine ratio with finerenone were not modified according to background use of SGLT2 inhibitors, which suggests that finerenone may have potential additive effects for reducing the urinary albumin-to-creatinine ratio and related outcomes.[4] Because post hoc analyses have limitations and do not address the clinical effects of the simultaneous initiation of both drugs, rigorous randomized trials to evaluate the efficacy and safety of this combination would be useful.[5] Although a step-up combination approach is practiced, the basis of current guidance rests on expert opinion.

We hypothesized that among participants with both chronic kidney disease and type 2 diabetes, a combination of finerenone and empagliflozin would decrease the urinary albumin-to-creatinine ratio more than either treatment alone. We also tested the safety of simultaneous initiation of these two drugs by measuring the blood pressure, serum potassium level, and estimated glomerular filtration rate (eGFR) at frequent predefined intervals and by monitoring adverse events.

Methods

Trial Design and Oversight

The CONFIDENCE (Combination Effect of Finerenone and Empagliflozin in Participants with Chronic Kidney Disease and Type 2 Diabetes Using a Urinary Albumin-to-Creatinine Ratio Endpoint) trial was a double-blind, randomized, active-controlled trial of finerenone alone, empagliflozin alone, or the combination of the two therapies in persons with chronic kidney disease with albuminuria and type 2 diabetes. The trial design and baseline characteristics have been previously published.[6,7] The trial protocol with the statistical analysis plan is available with the full text of this article at NEJM.org.

The trial was approved by the institutional review board at each participating site. All the participants provided written informed consent. An independent data and safety monitoring committee oversaw participant safety. The first author wrote the initial draft of the manuscript, had full access to the data, and analyzed and confirmed the data independently. All the authors reviewed subsequent drafts, including the version submitted for publication. Earlier versions of the manuscript were developed with editorial and medical writing assistance that was financially supported by Bayer (the sponsor). All the authors and the sponsor participated in the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data, and the sponsor and investigators vouch for the fidelity of the trial to the protocol.

Participants

Eligible participants had type 2 diabetes with glycated hemoglobin levels of less than 11%, an eGFR between 30 and 90 ml per minute per 1.73 m^2 of body surface area, and albuminuria, defined as a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) between 100 and 5000, as determined according to the mean value of the first urine specimens on three consecutive mornings. We excluded patients who had chronic heart failure with a reduced ejection fraction and persistent symptoms, those who had a serum potassium level above 4.8 mmol per liter, and those who had had a stroke or myocardial infarction or had been hospitalized for worsening heart failure within 90 days before the screening visit. Participants with type 1 diabetes were excluded, as were those who had undergone or were scheduled to undergo kidney transplantation. All the participants were required to have been receiving an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker (at the maximum labeled dose that has not been found to cause unacceptable side effects) for more than 1 month at the screening visit and must not have taken an SGLT2 inhibitor or potassium-binding agent within the 8 weeks before screening.

TRIAL VISITS

There were seven prespecified trial visits (Fig. S1 in the Supplementary Appendix, available at NEJM .org). Urine specimens that were collected on three consecutive mornings for the screening visit and two consecutive mornings for subsequent visits were used for the assessment of the urinary albumin-to-creatinine ratio, and blood was drawn for measurement of the serum potassium level and eGFR (derived from the serum creatinine level) at each visit. The urinary albumin-to-creatinine ratio and serum potassium and creatinine levels were analyzed at a central laboratory. At every visit, consistent, seated blood-pressure measurements (after ≥5 minutes of rest) were obtained three times. The assigned trial regimen was stopped at 180 days after randomization, and 30 days later, the urinary albumin-to-creatinine ratio, blood pressure, eGFR, and serum potassium level were again measured.

RANDOMIZATION

Participants were randomly assigned in a 1:1:1 ratio to receive finerenone at a dose of 10 or 20 mg per day (and empagliflozin-matching placebo), empagliflozin at a dose of 10 mg per day (and finerenone-matching placebo), or a combination of the two therapies. Randomization was performed with the use of an interactive Web-response system. Finerenone was initiated at 20 mg per day when the eGFR was 60 ml per minute per 1.73 m^2 or greater and at 10 mg per day when the baseline eGFR was less than 60 ml per minute per 1.73 m^2. Randomization was stratified according to the eGFR (<60 and ≥60 ml per minute per 1.73 m^2) and urinary albumin-to-creatinine ratio (≤850 and >850) measurements at screening. The trial-group assignments were concealed from the investigators, the treating physicians, the participants, and the outcome assessors.

TRIAL OUTCOMES

The primary efficacy outcome was the relative change in the log-transformed mean urinary albumin-to-creatinine ratio from baseline to 180 days. Secondary efficacy outcomes were the relative change in the urinary albumin-to-creatinine ratio between the end-of-treatment visit and 30 days after the end-of-treatment visit; the relative change in the urinary albumin-to-creatinine ratio between baseline and 30 days after the end-of-treatment visit; and the relative reduction in the urinary albumin-to-creatinine ratio according to prespecified thresholds (>30%, >40%, or >50%) at 180 days. Secondary safety outcomes included the change in the eGFR from baseline to day 30 and its reversibility with stopping the drug therapy, acute kidney injury, hyperkalemia, the change from baseline in the serum potassium level, symptomatic hypotension, ketoacidosis, severe hypoglycemia, and genital mycotic infections. Subgroup analyses were planned for the primary efficacy outcome on the basis of the following baseline variables: geographic region, screening eGFR category, screening urinary albumin-to-creatinine ratio category, history of atherosclerotic cardiovascular disease, serum potassium level, systolic blood pressure, sex, and age.

STATISTICAL ANALYSIS

Assuming that a maximum of 15% of participants would discontinue the trial, we calculated that a total of 807 participants would provide the trial with at least 80% power to detect a reduction from baseline in the urinary albumin-to-creatinine ratio that was at least 20% greater with combination therapy than with either therapy alone. We applied a two-sided, two-sample t-test, assuming equal variance, with an overall two-sided alpha level of 0.05. To adjust for the multiple testing of two hypotheses, the Holm–Bonferroni method was applied. The two-sided P values were first arranged in ascending order. If the lower P value (for the comparison between combination therapy and finerenone alone or empagliflozin alone, whichever was lower) was lower than 0.025, the corresponding null hypothesis could be rejected, and the comparison between combination therapy and the other therapy alone could be performed at the 0.05 alpha level. If the higher P value was lower than 0.05, the second null hypothesis could also be rejected.

All efficacy analyses were performed in the full analysis population (all the participants who had undergone randomization, with the exclusion of those who had not received at least one dose of a trial drug and those with critical violations of Good Clinical Practice guidelines). The primary analysis was performed with a mixed model for repeated measures that included the log-transformed urinary albumin-to-creatinine ratio measured throughout the trial as the dependent

variable; further details are provided in the Supplementary Appendix. Changes in the serum potassium level and blood pressure were summarized with the use of descriptive statistics. Changes in the eGFR were estimated with the use of a mixed model (see the Supplementary Appendix). The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation,[8] which was modified for Japanese participants.[9]

Multiple imputation was used to account for missing data in the primary analysis, with the assumption that data were missing at random. In the prespecified tipping-point analysis it was assumed that data were not missing at random.

RESULTS

TRIAL POPULATION

From June 23, 2022, to August 14, 2024, a total of 1664 participants underwent screening, among whom 818 were randomly assigned to a treatment group and entered the double-blind treatment period (Fig. S2). The date of the last participant visit was March 14, 2025, and the database was locked on April 8, 2025. Four participants underwent randomization in error and had not taken at least one dose of a trial drug, and 14 participants from one site were excluded because of violations of the Good Clinical Practice guidelines that were not related to the conduct of this trial; the data from these participants were not included in the analyses. Therefore, 800 participants were included in the full analysis population for the efficacy analyses (269 were assigned to the combination-therapy group, 264 to the finerenone group, and 267 to the empagliflozin group). A total of 798 participants received at least one dose of a trial drug and were included in the safety analyses (268 in the combination-therapy group, 264 in the finerenone group, and 266 in the empagliflozin group). A total of 746 participants completed the 30-day follow-up period.

Selected baseline characteristics of the participants who had undergone randomization are provided in Table 1 (a detailed list of baseline characteristics is provided in Table S1). At baseline, 787 of 800 participants (98.4%) were receiving an angiotensin-converting–enzyme inhibitor or an angiotensin-receptor blocker, the mean (±SD) eGFR was 54.2±17.1 ml per minute per 1.73 m^2, and the median urinary albumin-to-creatinine ratio was 579 (interquartile range, 292 to 1092). The mean glycated hemoglobin level at baseline was 7.3±1.2%. A diverse population of participants representative of persons with both chronic kidney disease and type 2 diabetes were enrolled in the trial (Table S2).

PRIMARY OUTCOME

At day 180, the reduction in the urinary albumin-to-creatinine ratio with combination therapy was 29% greater than that with finerenone alone (least-squares mean ratio of the difference in the change from baseline, 0.71; 95% confidence interval [CI], 0.61 to 0.82; P<0.001) and 32% greater than that with empagliflozin alone (least-squares mean ratio of the difference in the change from baseline, 0.68; 95% CI, 0.59 to 0.79; P<0.001). At baseline, the median urinary albumin-to-creatinine ratio was 574 (interquartile range, 274 to 999) in the combination-therapy group, 578 (292 to 1289) in the finerenone group, and 583 (301 to 1114) in the empagliflozin group. At 180 days after randomization, data on the urinary albumin-to-creatinine ratio were available for 714 participants (Table 2).

The change in urinary albumin-to-creatinine ratio over time is shown in Figure 1A. After 14 days, the urinary albumin-to-creatinine ratio among the participants in the combination-therapy group was reduced by more than 30% from baseline, and after 90 days, it was reduced by more than 40% from baseline. The least-squares mean ratio of the change in the urinary albumin-to-creatinine ratio (comparing baseline with day 180) was 0.48 (95% CI, 0.44 to 0.54) in the combination-therapy group, 0.68 (95% CI, 0.61 to 0.76) in the finerenone group, and 0.71 (95% CI, 0.64 to 0.79) in the empagliflozin group. The urinary albumin-to-creatinine ratio was measured 30 days after stopping the trial medication at 180 days after randomization. The urinary albumin-to-creatinine ratio increased from the end of treatment to the end of follow-up, with least-squares mean ratios (comparing day 180 with day 210) of 1.63 (95% CI, 1.49 to 1.78) in the combination-therapy group, 1.45 (95% CI, 1.32 to 1.59) in the finerenone group, and 1.44 (95% CI, 1.32 to 1.58) in the empagliflozin group. At day 180, more participants in the combination-therapy group than those in the finerenone group or the empagliflozin

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

Characteristic	Finerenone plus Empagliflozin (N=269)	Finerenone (N=264)	Empagliflozin (N=267)	Total (N=800)
Age — yr	67.7±10.0	65.5±10.7	66.2±10.1	66.5±10.3
Female sex — no. (%)	67 (24.9)	61 (23.1)	70 (26.2)	198 (24.8)
Race or ethnic group — no. (%)†				
White	130 (48.3)	105 (39.8)	116 (43.4)	351 (43.9)
Asian	114 (42.4)	132 (50.0)	125 (46.8)	371 (46.4)
Asian Indian	34 (12.6)	54 (20.5)	45 (16.9)	133 (16.6)
Black	22 (8.2)	21 (8.0)	24 (9.0)	67 (8.4)
Other	2 (0.7)	2 (0.8)	1 (0.4)	5 (0.6)
Geographic region — no. (%)				
Europe	81 (30.1)	62 (23.5)	72 (27.0)	215 (26.9)
North America	75 (27.9)	79 (29.9)	71 (26.6)	225 (28.1)
Asia	113 (42.0)	123 (46.6)	124 (46.4)	360 (45.0)
Glycated hemoglobin — %‡	7.3±1.2	7.3±1.2	7.3±1.2	7.3±1.2
Body weight — kg	83.0±21.7	81.9±20.3	80.8±19.5	81.9±20.5
Body-mass index§	29.8±6.7	29.1±5.7	29.0±5.7	29.3±6.1
eGFR — ml/min/1.73 m^2¶	53.9±16.9	54.3±17.8	54.2±16.6	54.2±17.1
Median urinary albumin-to-creatinine ratio (IQR)‖	574 (274–999)	578 (292–1289)	583 (301–1114)	579 (292–1092)
Urinary albumin-to-creatinine ratio category — no. (%)**				
≤850	184 (68.4)	166 (62.9)	170 (63.7)	520 (65.0)
>850	81 (30.1)	92 (34.8)	91 (34.1)	264 (33.0)
Systolic blood pressure — mm Hg	135.0±13.7	135.1±13.7	135.4±12.6	135.2±13.3
Serum potassium — mmol/liter††	4.4±0.4	4.5±0.5	4.5±0.4	4.5±0.4
History of atherosclerotic cardiovascular disease — no. (%)‡‡	75 (27.9)	71 (26.9)	78 (29.2)	224 (28.0)
Concomitant medications — no. (%)				
ACE inhibitor or ARB§§	267 (99.3)	260 (98.5)	260 (97.4)	787 (98.4)
Statins	209 (77.7)	197 (74.6)	191 (71.5)	597 (74.6)
Diuretics	108 (40.1)	97 (36.7)	84 (31.5)	289 (36.1)
Antihyperglycemic agents — no. (%)				
Insulin	108 (40.1)	96 (36.4)	113 (42.3)	317 (39.6)
GLP-1 RA	68 (25.3)	52 (19.7)	62 (23.2)	182 (22.8)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GLP-1 RA denotes glucagon-like peptide-1 receptor agonist, and IQR interquartile range.

† Race or ethnic group was reported by the participant. "Other" includes American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander.

‡ Data on the glycated hemoglobin level were missing for 19 participants (9 [3.3%] in the combination-therapy [finerenone plus empagliflozin] group, 7 [2.7%] in the finerenone group, and 3 [1.1%] in the empagliflozin group).

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

¶ The estimated glomerular filtration rate (eGFR) was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation,[8] which was modified for the Japanese participants.[9] Data were missing for 4 participants (2 [0.8%] in the finerenone group and 2 [0.7%] in the empagliflozin group).

‖ The urinary albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. Data were missing for 16 participants (4 [1.5%] in the combination-therapy group, 6 [2.3%] in the finerenone group, and 6 [2.2%] in the empagliflozin group).

** Albuminuria was defined as a urinary albumin-to-creatinine ratio between 100 and 5000, as determined according to the mean value of the first urine specimens on three consecutive mornings.

†† Data on the serum potassium level were missing for 5 participants (2 [0.7%] in the combination-therapy group, 1 [0.4%] in the finerenone group, and 2 [0.7%] in the empagliflozin group).

‡‡ A history of atherosclerotic cardiovascular disease was based on a group of preferred terms for coronary artery disease, cerebral infarction, and stroke (a transient ischemic attack alone is not sufficient), as well as for peripheral artery disease and carotid revascularization, in the *Medical Dictionary for Regulatory Activities*, version 27.1.

§§ According to the protocol, all the participants were required to be taking an angiotensin-converting–enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) at the clinically maximum tolerated dose.

Table 2. Primary and Secondary Outcomes for the Change in Urinary Albumin-to-Creatinine Ratio.

Variable	Finerenone plus Empagliflozin (N=269)		Finerenone (N=264)		Empagliflozin (N=267)	
	No. of Participants	Least-Squares Mean Ratio (95% CI)*	No. of Participants	Least-Squares Mean Ratio or Odds Ratio (95% CI)*	No. of Participants	Least-Squares Mean Ratio or Odds Ratio (95% CI)*
Change in urinary albumin-to-creatinine ratio						
Primary outcome: change from baseline to day 180	240	0.48 (0.44–0.54)	236	0.68 (0.61–0.76)	238	0.71 (0.64–0.79)
Difference in change, combination vs. monotherapy				0.71 (0.61–0.82)†		0.68 (0.59–0.79)†
Change from baseline to day 210	238	0.82 (0.73–0.91)	227	0.85 (0.76–0.96)	232	0.90 (0.80–1.00)
Difference in change, combination vs. monotherapy				0.96 (0.82–1.12)		0.91 (0.79–1.06)
Change from day 180 to day 210	239	1.63 (1.49–1.78)	234	1.45 (1.32–1.59)	238	1.44 (1.32–1.58)
Difference in change, combination vs. monotherapy				1.13 (1.00–1.27)		1.13 (1.00–1.28)
	No. with Reduction/ Total No. (%)		No. with Reduction/ Total No. (%)		No. with Reduction/ Total No. (%)	
Reduction in urinary albumin-to-creatinine ratio according to prespecified thresholds						
Reduction from baseline to day 180						
>30%	168/240 (70.0)		123/236 (52.1)	2.17 (1.49–3.17)	123/238 (51.7)	2.21 (1.52–3.22)
>40%	154/240 (64.2)		104/236 (44.1)	2.31 (1.59–3.34)	103/238 (43.3)	2.38 (1.64–3.44)
>50%	131/240 (54.6)		84/236 (35.6)	2.20 (1.52–3.19)	76/238 (31.9)	2.59 (1.78–3.77)
Reduction from baseline to day 210						
>30%	111/238 (46.6)		78/227 (34.4)		92/232 (39.7)	
>40%	85/238 (35.7)		62/227 (27.3)		69/232 (29.7)	
>50%	65/238 (27.3)		50/227 (22.0)		47/232 (20.3)	

* Least-squares mean ratios are shown for the changes in the urinary albumin-to-creatinine ratio, and odds ratios (combination vs. monotherapy) are shown for the reductions in the urinary albumin-to-creatinine ratio according to prespecified thresholds. The widths of the 95% confidence intervals for outcomes other than the primary outcome have not been adjusted for multiplicity and should not be used to test for efficacy.

† P<0.001.

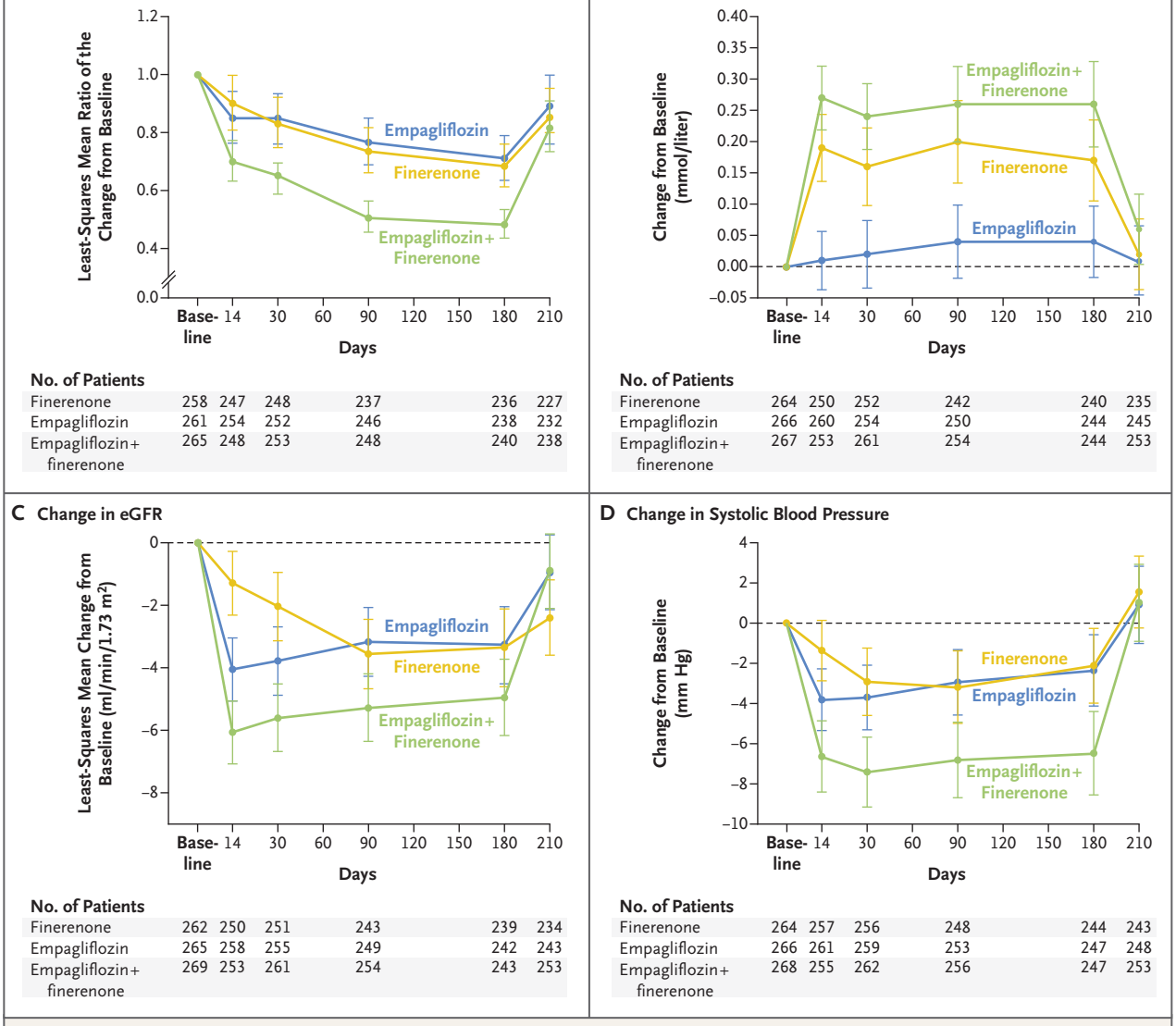

Figure 1. Urinary Albumin-to-Creatinine Ratio, Serum Potassium Level, Estimated Glomerular Filtration Rate, and Systolic Blood Pressure over Time.

Panel A shows the least-squares mean ratio of the change from baseline in the urinary albumin-to-creatinine ratio in the full analysis population (all the participants who had undergone randomization, with the exclusion of those who had not received at least one dose of a trial drug and those with critical violations of Good Clinical Practice guidelines). Multiple imputation was used to account for missing data, with the assumption that data were missing at random. Panel B shows the mean serum potassium level at each visit in the safety analysis population (all the participants who had undergone randomization and received at least one dose of a trial medication). Panel C shows the least-squares mean change in the estimated glomerular filtration rate (eGFR) in the safety analysis population. The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation,[8] which was modified for the Japanese participants,[9] and the analysis was performed with the use of a mixed model for repeated measures. Panel D shows the mean systolic blood pressure at each visit in the safety analysis population. Summary statistics for systolic blood pressure were derived from the mean value of all assessments (i.e., three assessments per visit per participant).

group had reductions in the urinary albumin-to-creatinine ratio from baseline of greater than 30%, 40%, and 50% (Table 2).

The results of prespecified subgroup analyses were consistent with those of the findings for the primary outcome (Fig. S3). The number of participants with missing data was low, and a prespecified tipping-point analysis of the primary

Table 3. Adverse Events and Safety Assessments after Treatment Initiation (Safety Analysis Population).*

Event or Assessment	Finerenone plus Empagliflozin (N=268)	Finerenone (N=264)	Empagliflozin (N=266)	Total (N=798)
	number (percent)			
Investigator-reported adverse events†				
Any adverse event	144 (53.7)	136 (51.5)	135 (50.8)	415 (52.0)
Adverse event leading to treatment discontinuation	12 (4.5)	9 (3.4)	9 (3.4)	30 (3.8)
Any serious adverse event	19 (7.1)	16 (6.1)	17 (6.4)	52 (6.5)
Serious adverse event leading to treatment discontinuation	3 (1.1)	3 (1.1)	2 (0.8)	8 (1.0)
Adverse event with death as the outcome	3 (1.1)	0	3 (1.1)	6 (0.8)
Hyperkalemia‡	25 (9.3)	30 (11.4)	10 (3.8)	65 (8.1)
Safety assessments				
>30% Decline in eGFR from baseline to 30 days§	17 (6.3)	10 (3.8)	3 (1.1)	30 (3.8)
Serum potassium level — no./total no.(%)¶				
>5.5 mmol/liter	40/262 (15.3)	48/258 (18.6)	25/257 (9.7)	113/777 (14.5)
>5.5 to ≤6.0 mmol/liter	34/262 (13.0)	43/258 (16.7)	21/257 (8.2)	98/777 (12.6)
>6.0 mmol/liter	12/263 (4.6)	12/262 (4.6)	7/262 (2.7)	31/787 (3.9)

* The safety analysis population comprised all the participants who had undergone randomization and received at least one dose of a trial drug.

† The participants with an adverse event reported here were those who had received at least one dose of a trial drug and had an adverse event that had started or worsened after the first dose and up to 3 days after any temporary or permanent interruption of the trial treatment.

‡ In the assessment of hyperkalemia, the investigators used the preferred terms "hyperkalemia" and "blood potassium increased" in the *Medical Dictionary for Regulatory Activities*, version 27.1..

§ The eGFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation,[8] which was modified for the Japanese participants.[9]

¶ The denominator represents all the participants at risk for an abnormal laboratory result. Participants must have had both a baseline and postbaseline (after the first dose and up to 3 days after any temporary or permanent interruption of the trial treatment) value, with the baseline value not exceeding the displayed threshold. The numerator represents the number of participants at risk who had at least one postbaseline laboratory assessment that met the criterion.

outcome supported the robustness of the results (Table S3).

SAFETY AND OTHER EFFICACY VARIABLES

Changes from baseline in the serum potassium level over time are shown in Figure 1B and Table S4. The mean increase from baseline in the serum potassium level was 0.27 mmol per liter (95% CI, 0.22 to 0.32) after 14 days in the combination-therapy group, and the levels declined to near baseline levels 30 days after the trial treatment was stopped (day 210). The mean serum potassium level increased from baseline by 0.19 mmol per liter (95% CI, 0.14 to 0.24) after 14 days in the finerenone group; this increase declined to near baseline levels 30 days after the trial treatment was stopped. Empagliflozin therapy was not associated with changes in the serum potassium level from baseline.

The least-squares mean change from baseline in the eGFR over time is shown in Figure 1C and Table S5. Most of the early decline in the eGFR was reversible with drug discontinuation at 180 days.

The pattern of change from baseline in systolic blood pressure is shown in Figure 1D. The systolic blood pressure initially decreased, with the most pronounced reduction occurring in the

combination-therapy group, before returning to baseline levels after discontinuation of the trial treatment at 180 days. Table S6 shows that combination therapy resulted in a 7.4–mm Hg reduction from baseline within 30 days and a 7.5–mm Hg increase in the 30-day follow-up period after treatment discontinuation (from day 180 to day 210). Both monotherapies were associated with changes in the systolic blood pressure during the treatment period of generally less than half the magnitude observed with combination therapy. The change from baseline in the glycated hemoglobin level is shown in Figure S4; no meaningful differences between the treatment groups at 180 days after randomization were observed.

ADVERSE EVENTS AND SAFETY ASSESSMENT

Adverse events that led to discontinuation of the trial treatment were recorded in less than 5% of the participants in each group (Table 3). Serious adverse events occurred in 19 of 268 participants (7.1%) in the combination-therapy group, in 16 of 264 participants (6.1%) in the finerenone group, and in 17 of 266 participants (6.4%) in the empagliflozin group. Serious adverse events leading to treatment discontinuation occurred in less than 2% of the participants in each group. Six participants died after treatment initiation (3 in the combination-therapy group and 3 in the empagliflozin group) (Table S7).

A decrease in the eGFR of greater than 30% at day 30 occurred in 17 participants (6.3%) in the combination-therapy group, 10 participants (3.8%) in the finerenone group, and 3 participants (1.1%) in the empagliflozin group (Table 3). Three participants (1 in each treatment group) permanently discontinued the trial treatment owing to hyperkalemia. Increases in serum potassium level according to prespecified thresholds are shown in Table 3.

Acute kidney injury was reported in 8 participants (5 in the combination therapy group and 3 in the finerenone group) (Table S8). Symptomatic hypotension was reported in 3 participants in the combination-therapy group. Genital mycotic infections were reported in 4 participants each in the combination-therapy group and the empagliflozin group; urosepsis–pyelonephritis occurred in 1 participant in each of these two groups. Disease-related events were few and were balanced among the treatment groups (Table S9).

DISCUSSION

In this double-blind, randomized, international, multicenter trial involving persons with both chronic kidney disease and type 2 diabetes who were receiving an angiotensin-converting–enzyme inhibitor or an angiotensin-receptor blocker at baseline, simultaneous initiation of the nonsteroidal mineralocorticoid receptor antagonist finerenone and the SGLT2 inhibitor empagliflozin led to a reduction in the urinary albumin-to-creatinine ratio that was 32% greater than that with empagliflozin alone and 29% greater than that with finerenone alone. After 180 days, the urinary albumin-to-creatinine ratio was reduced by 52% with combination therapy, which is in line with the full additive effect that was expected on the basis of the reductions observed with finerenone alone (32%) and empagliflozin alone (29%). After the therapy was stopped, urinary albumin-to-creatinine ratio levels increased but remained below baseline in the combination and finerenone treatment groups.

The time course of the changes in the urinary albumin-to-creatinine ratio suggests that most of the reduction occurred within 4 weeks after the initiation of therapy. The change in the urinary albumin-to-creatinine ratio over a 6-month period has been considered to be a valid surrogate for progression of chronic kidney disease, potentially predicting a reduction in the incidence of adverse kidney and cardiovascular events.[10,11] A reduction in the urinary albumin-to-creatinine ratio has been considered to be a key mediator of the effects of SGLT2 inhibitors on composite kidney outcomes and as a principal mediator of the effects of finerenone on composite kidney outcomes.[12-14] We speculate that, taken together, these data suggest that the reductions observed with combination therapy with empagliflozin and finerenone will probably correlate with meaningful reductions in the risk of progression of chronic kidney disease. Trial-level meta-analyses have shown that every 30% reduction in the urinary albumin-to-creatinine ratio was associated with a 27% reduction in a composite kidney end point comprising end-stage kidney disease, a doubling of the serum creatinine concentration, or an eGFR lower than 15 ml per minute per 1.73 m^2.[10]

The current trial provides clinically important information regarding both the efficacy and safety of combination therapy with empagliflozin and

finerenone. We observed that 30 days after the simultaneous initiation of empagliflozin and finerenone, the incidence of a decline in the eGFR of more than 30% was greater than that with either finerenone or empagliflozin alone. However, the eGFR stabilized after the initial decline, and the incidence of acute kidney injury was uncommon in the combination-therapy group (1.9%) in this trial. Although the increase in the mean serum potassium level was similar with combination therapy and finerenone alone, the frequency of hyperkalemia, as reported by the site investigators or assessed by the central laboratory (serum potassium level of >5.5 mmol per liter or >5.5 and ≤6.0 mmol per liter), was relatively lower by approximately 15 to 20% with combination therapy. This finding is consistent with those from a meta-analysis of randomized, controlled trials that showed a reduced risk of severe hyperkalemia with SGLT2 inhibitors, including in persons who were receiving a mineralocorticoid receptor antagonist at baseline.[15] Combination therapy resulted in a greater reduction in blood pressure than either therapy alone, which was generally reversible with drug discontinuation in all treatment groups. The incidence of symptomatic hypotension was low in this trial.

Stepwise therapy may prolong the time to effective treatment and can lead to clinical inertia. Current guidelines suggest serial measurement of the urinary albumin-to-creatinine ratio to guide treatment adjustments for effectiveness and inform decisions regarding the need for additional therapies.[16] However, in clinical practice, follow-up testing to assess the urinary albumin-to-creatinine ratio is infrequently performed, which may in turn underestimate the ongoing risk and add to clinical inertia.[17] In contrast, initial combination therapy may provide a greater and a more rapid reduction in urinary albumin-to-creatinine ratio than monotherapy with either an SGLT2 inhibitor or finerenone.

Our trial has certain limitations. The trial used a surrogate end point, and we did not follow the participants long enough to adequately measure differences among groups in cardiovascular outcomes or clinical kidney disease progression. The strengths of our trial include the high percentage of participants who completed the trial and the inclusion of persons from many countries, which improved the generalizability of the findings. The reduction in the urinary albumin-to-creatinine ratio as a valid biomarker of risk[10,11] also supports the use of this outcome to potentially predict cardiovascular and kidney protection in persons with both chronic kidney disease and type 2 diabetes.

In this trial involving persons with chronic kidney disease, albuminuria, and type 2 diabetes, combination therapy with finerenone and empagliflozin was more effective in rapidly reducing the urinary albumin-to-creatinine ratio over 180 days than either of the two drugs alone.

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