Original Investigation

Effect of Finerenone on Albuminuria in Patients With Diabetic Nephropathy
A Randomized Clinical Trial

George L. Bakris, MD; Rajiv Agarwal, MD; Juliana C. Chan, MD; Mark E. Cooper, MD, PhD; Ron T. Gansevoort, MD, PhD; Hermann Haller, MD, PhD; Giuseppe Remuzzi, MD; Peter Rossing, MD; Roland E. Schmieder, MD; Christina Nowack, MD; Peter Kolkhof, PhD; Amer Joseph, MBBS; Alexander Pieper, DiplStat; Nina Kimmeskamp-Kirschbaum, PhD; Luis M. Ruilope, MD, PhD; for the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group

IMPORTANCE Steroidal mineralocorticoid receptor antagonists, when added to a renin-angiotensin system blocker, further reduce proteinuria in patients with chronic kidney disease but may be underused because of a high risk of adverse events.

OBJECTIVE To evaluate the safety and efficacy of different oral doses of the nonsteroidal mineralocorticoid receptor antagonist finerenone, given for 90 days to patients with diabetes and high or very high albuminuria who are receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled, parallel-group study conducted at 148 sites in 23 countries. Patients were recruited from June 2013 to February 2014 and the study was completed in August 2014. Of 1501 screened patients, 823 were randomized and 821 received study drug.

INTERVENTIONS Participants were randomly assigned to receive oral, once-daily finerenone (1.25 mg/d, n = 96; 2.5 mg/d, n = 92; 5 mg/d, n = 100; 7.5 mg/d, n = 97; 10 mg/d, n = 98; 15 mg/d, n = 125; and 25 mg/d, n = 119) or matching placebo (n = 94) for 90 days.

MAIN OUTCOMES AND MEASURES The primary outcome was the ratio of the urinary albumin-creatinine ratio (UACR) at day 90 vs at baseline. Safety end points were changes from baseline in serum potassium and estimated glomerular filtration rate.

RESULTS The mean age of the participants was 64.2 years; 78% were male. At baseline, 36.7% of patients treated had very high albuminuria (UACR ≥300 mg/g) and 40.0% had an estimated glomerular filtration rate of 60 mL/min/1.73 m² or lower. Finerenone demonstrated a dose-dependent reduction in UACR. The primary outcome, the placebo-corrected mean ratio of the UACR at day 90 relative to baseline, was reduced in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups (for 7.5 mg/d, 0.79 [90% CI, 0.68-0.91; P = .004]; for 10 mg/d, 0.76 [90% CI, 0.65-0.88; P = .001]; for 15 mg/d, 0.67 [90% CI, 0.58-0.77; P<.001]; for 20 mg/d, 0.62 [90% CI, 0.54-0.72; P < .001]). The prespecified secondary outcome of hyperkalemia leading to discontinuation was not observed in the placebo and finerenone 10-mg/d groups; incidences in the finerenone 7.5-, 15-, and 20-mg/d groups were 2.1%, 3.2%, and 1.7%, respectively. There were no differences in the incidence of the prespecified secondary outcome of an estimated glomerular filtration rate decrease of 30% or more or in incidences of adverse events and serious adverse events between the placebo and finerenone groups.

CONCLUSIONS AND RELEVANCE Among patients with diabetic nephropathy, most receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, the addition of finerenone compared with placebo resulted in improvement in the urinary albumin-creatinine ratio. Further trials are needed to compare finerenone with other active medications.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT1874431

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ARTS-DN Study Group investigators are listed at the end of this article.

Corresponding Author: George L. Bakris, MD, ASH Comprehensive Hypertension Center, University of Chicago Medicine and Biological Sciences, 5841 S Maryland Ave, MC 1027, Chicago, IL 60637 (gbakris@gmail.com).

Reviews of randomized studies demonstrate that mineralocorticoid receptor antagonists (MRAs), when added to a renin-angiotensin system (RAS) blocker, further reduce proteinuria in patients with chronic kidney disease (CKD) from either diabetes or nondiabetic causes.[1-5] However, eplerenone and spironolactone increase the risk of hyperkalemia in patients with stage 3 or higher CKD by as much as 3- to 8-fold.[5,6]

Finerenone (BAY 94-8862) is a novel nonsteroidal MRA that has greater receptor selectivity than spironolactone and better receptor affinity than eplerenone in vitro.[7] In preclinical studies, equinatriuretic doses of finerenone provided a greater reduction in proteinuria and end organ damage than eplerenone.[8] In the Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS), finerenone doses of 2.5 to 10 mg/d reduced albuminuria from baseline in patients with CKD and heart failure, with a lower incidence of hyperkalemia than spironolactone.[9] Thus, finerenone may be able to address the unmet medical need of safely managing albuminuria without adversely affecting serum potassium in patients with type 2 diabetes mellitus who have clinical diagnosis of diabetic kidney disease.

ARTS-Diabetic Nephropathy (ARTS-DN) was designed to compare the efficacy and safety of different once-daily oral doses of finerenone and placebo in patients with type 2 diabetes mellitus and persistent albuminuria (urinary albumin-creatinine ratio [UACR] ≥30 mg/g) who were receiving an RAS blocker.

ACE *angiotensin-converting enzyme*

CKD *chronic kidney disease*

eGFR *estimated glomerular filtration rate*

MRA *mineralocorticoid receptor antagonist*

RAS *renin-angiotensin system*

UACR *urinary albumin-creatinine ratio*

Methods

Study Design

ARTS-DN was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2B study designed to compare the effects of finerenone, 1.25 to 20 mg once daily, with placebo, added to standard of care with an RAS blocker (**Figure 1**). The study started in June 2013 and was clinically completed in August 2014. The trial conformed to the Declaration of Helsinki and to Good Clinical Practice guidelines. It was conducted in keeping with applicable local law(s) and regulation(s). Documented approval from appropriate independent ethics committee(s) or institutional review board(s) was obtained for all participating centers/countries before the start of the study. All individuals provided written informed consent for participation. The study protocol and statistical analysis plan are available in Supplement 1.

Initially, eligible patients were randomized in equal proportions to treatment with oral once-daily finerenone, 1.25 to 10 mg/d, or placebo in combination with an RAS blocker for 90 days. Randomization was done centrally by an interactive voice/web response system using computer-generated randomization lists, and participants, investigators, and the sponsor's clini-

cal team were blinded to treatment allocation. Treatment groups of once-daily finerenone, 15 mg/d and 20 mg/d, were added on the recommendation of an independent data monitoring committee after review of the safety data from the ongoing study, and randomization was adapted accordingly to reach approximately balanced treatment ratios. It was planned to have approximately 75 patients valid for the full analysis set (modified intention to treat) in each treatment group, with a possible increase to 90 patients per treatment group to increase the amount of safety data for patients with very high albuminuria. Randomization was stratified by region and severity of albuminuria (high [UACR 30 to <300 mg/g] or very high [≥300 mg/g]).

Patients

The eligibility criteria and methods for ARTS-DN are described in detail elsewhere[10] and in the eAppendix in Supplement 2. Briefly, patients were included if they had type 2 diabetes, albuminuria (UACR ≥30 mg/g), and an estimated glomerular filtration rate (eGFR) higher than 30 mL/min/1.73 m^2; were being treated with at least the minimum recommended dosage of an RAS blocker prior to the screening visit; and had a serum potassium concentration less than or equal to 4.8 mmol/L at screening. Patients with an eGFR of 30 to 45 mL/min/1.73 m^2 must have been receiving treatment with a non–potassium-sparing diuretic at the screening visit and without any adjustments for 4 weeks or longer beforehand. Patients were excluded if they received concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or a potassium-sparing diuretic that could not be discontinued for the run-in and treatment periods.
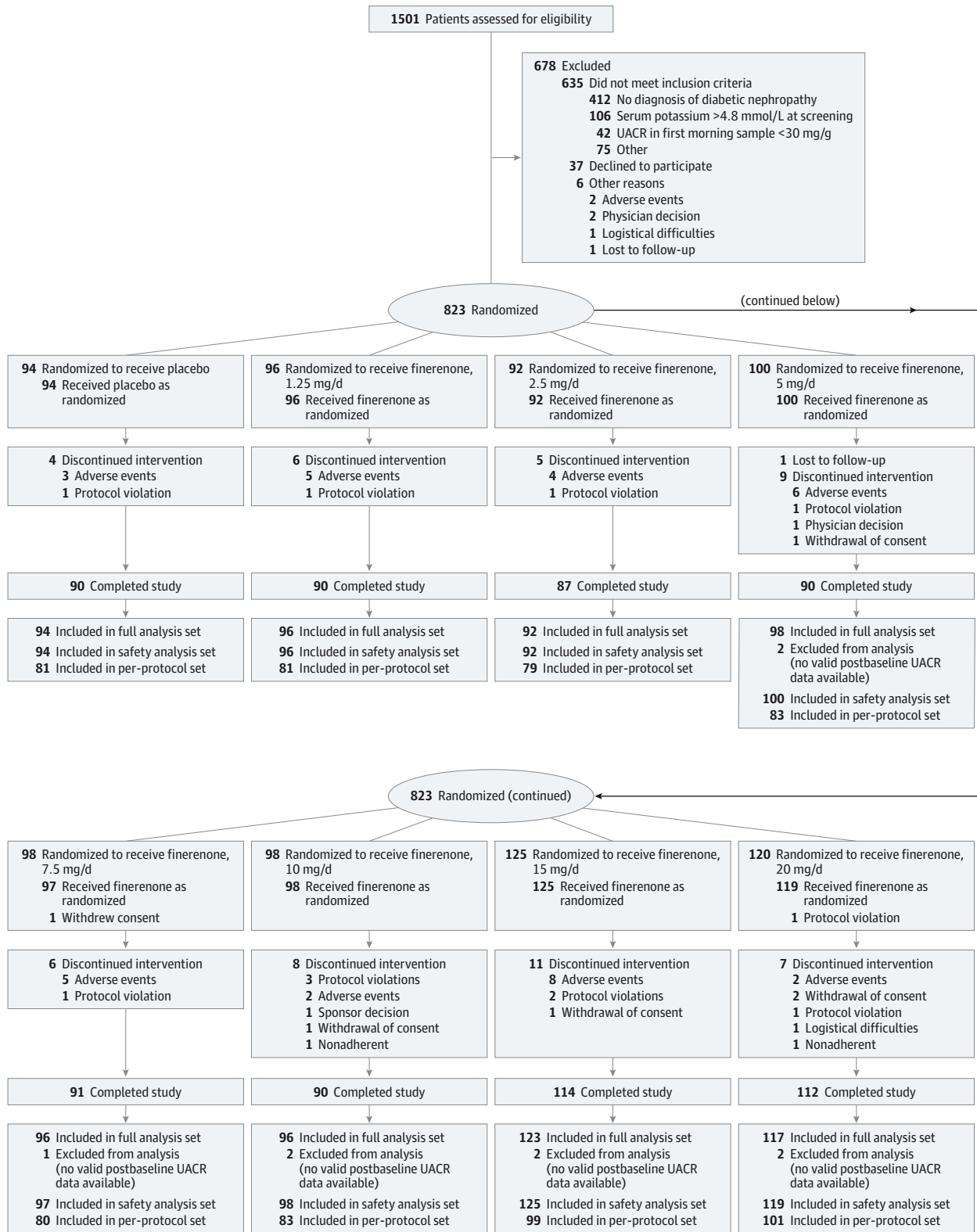
It was intended that at least 35% of patients should have very high albuminuria (UACR ≥300 mg/g). Screening visits took place during the run-in period within 14 days of the planned randomization to confirm eligibility for randomization.

Participant race and ethnicity were reported by investigators, with race categorized as white, black, Asian, American Indian/Alaskan Native, Native Hawaiian/other Pacific Islander, or not reported, and ethnicity as Hispanic/Latino or not Hispanic/Latino. The categories were defined based on US Food and Drug Administration guidance on the collection of race and ethnicity data in clinical trials, and subgroup analyses using race were performed to assess for any racial differences in safety or treatment response.

Serum Potassium Monitoring

No advice on dietary sodium or potassium restrictions was given during the study, and patients maintained their normal diet. With the exception of non–potassium-sparing diuretics, starting treatment with potassium-lowering agents (eg, sodium polystyrene sulfonate, calcium polystyrene sulfonate, insulin, and glucose infusion) was not permitted during treatment with study drug. If hyperkalemia occurred during study treatment, the treatment was discontinued prior to starting a potassium-lowering agent. Any potassium supplementation was stopped prior to randomization if potassium levels were within the normal range. If potassium levels were low at randomization or at any of the following visits, potassium supplementation was continued or restarted until potassium values were within the normal range again.

Figure 1. Flow of Participants in the Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy

```
                    ┌──────────────────────────────────────────┐
                    │ 1501  Patients assessed for eligibility   │
                    └──────────────────────────────────────────┘
                                        │
                                        │    ┌──────────────────────────────────────────────────────────────┐
                                        ├───▶│ 678  Excluded                                                │
                                        │    │    635  Did not meet inclusion criteria                      │
                                        │    │         412  No diagnosis of diabetic nephropathy            │
                                        │    │         106  Serum potassium >4.8 mmol/L at screening        │
                                        │    │          42  UACR in first morning sample <30 mg/g           │
                                        │    │          75  Other                                           │
                                        │    │     37  Declined to participate                              │
                                        │    │      6  Other reasons                                        │
                                        │    │         2  Adverse events                                    │
                                        │    │         2  Physician decision                                │
                                        │    │         1  Logistical difficulties                           │
                                        │    │         1  Lost to follow-up                                 │
                                        │    └──────────────────────────────────────────────────────────────┘
                                        ▼
                            ┌──────────────────────┐                      (continued below)
                            │  823  Randomized     │───────────────────────────────────────────────▶
                            └──────────────────────┘
```

94 Randomized to receive placebo 94 Received placebo as randomized	96 Randomized to receive finerenone, 1.25 mg/d 96 Received finerenone as randomized	92 Randomized to receive finerenone, 2.5 mg/d 92 Received finerenone as randomized	100 Randomized to receive finerenone, 5 mg/d 100 Received finerenone as randomized
4 Discontinued intervention 3 Adverse events 1 Protocol violation	6 Discontinued intervention 5 Adverse events 1 Protocol violation	5 Discontinued intervention 4 Adverse events 1 Protocol violation	1 Lost to follow-up 9 Discontinued intervention 6 Adverse events 1 Protocol violation 1 Physician decision 1 Withdrawal of consent
90 Completed study	90 Completed study	87 Completed study	90 Completed study
94 Included in full analysis set 94 Included in safety analysis set 81 Included in per-protocol set	96 Included in full analysis set 96 Included in safety analysis set 81 Included in per-protocol set	92 Included in full analysis set 92 Included in safety analysis set 79 Included in per-protocol set	98 Included in full analysis set 2 Excluded from analysis (no valid postbaseline UACR data available) 100 Included in safety analysis set 83 Included in per-protocol set

```
                            ┌────────────────────────────────┐
        ◀───────────────────│  823  Randomized (continued)   │
                            └────────────────────────────────┘
```

98 Randomized to receive finerenone, 7.5 mg/d 97 Received finerenone as randomized 1 Withdrew consent	98 Randomized to receive finerenone, 10 mg/d 98 Received finerenone as randomized	125 Randomized to receive finerenone, 15 mg/d 125 Received finerenone as randomized	120 Randomized to receive finerenone, 20 mg/d 119 Received finerenone as randomized 1 Protocol violation
6 Discontinued intervention 5 Adverse events 1 Protocol violation	8 Discontinued intervention 3 Protocol violations 2 Adverse events 1 Sponsor decision 1 Withdrawal of consent 1 Nonadherent	11 Discontinued intervention 8 Adverse events 2 Protocol violations 1 Withdrawal of consent	7 Discontinued intervention 2 Adverse events 2 Withdrawal of consent 1 Protocol violation 1 Logistical difficulties 1 Nonadherent
91 Completed study	90 Completed study	114 Completed study	112 Completed study
96 Included in full analysis set 1 Excluded from analysis (no valid postbaseline UACR data available) 97 Included in safety analysis set 80 Included in per-protocol set	96 Included in full analysis set 2 Excluded from analysis (no valid postbaseline UACR data available) 98 Included in safety analysis set 83 Included in per-protocol set	123 Included in full analysis set 2 Excluded from analysis (no valid postbaseline UACR data available) 125 Included in safety analysis set 99 Included in per-protocol set	117 Included in full analysis set 2 Excluded from analysis (no valid postbaseline UACR data available) 119 Included in safety analysis set 101 Included in per-protocol set

Full reasons for not meeting inclusion criteria are shown in eTable 1 in Supplement 2. UACR indicates urinary albumin-creatinine ratio.

Procedures

All assessments of urine and blood were performed in central laboratories in Europe, Asia, and the United States. The urinary albumin concentration was determined by immunonephelometry and the urine creatinine concentration was determined by means of the Jaffe reaction. The Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation was used to estimate the glomerular filtration rate. Glycated hemoglobin was measured by means of high-performance liquid chromatography. All other laboratory variables were measured centrally using conventional laboratory techniques.

Primary End Point

The primary outcome variable was the ratio of UACR at day 90 vs at baseline.

Further Efficacy and Safety Variables

Further efficacy and safety variables included the proportion of patients with adverse and serious adverse events, change in serum potassium levels, the incidence of serum potassium levels of 5.6 mmol/L or higher and higher than 6.0 mmol/L, the incidence of a decrease in eGFR of 30% or more, 40% or more, and 57% or more (equivalent to a doubling in serum creatinine level), and the change in UACR at day 30 and day 60 relative to baseline.

Statistical Analysis

The safety analysis set was defined as all randomized patients who had taken at least 1 dose of study drug and for whom there were posttreatment data. The full analysis set included all patients in the safety population who had baseline and at least 1 postbaseline UACR value. The per-protocol analysis set was defined as all patients in the full analysis set who had a valid UACR value at day 90 and no major protocol deviation. The primary and supportive analyses were performed on the full analysis set. Safety data were assessed in the safety analysis set. All analyses were performed using the actual treatment, which was the same as the planned treatment for each patient. The study was powered adequately to demonstrate a dose-dependent effect for the primary end point. Sample size calculations were performed with Query Advisor 7.0 (Statistical Solutions). A ratio of UACR at visit 5 to UACR at baseline of 0.91 or 0.95 is assumed for placebo, whereas UACR ratios are expected to decrease with an increasing dose of finerenone until a ratio of 0.64 to 0.46 for finerenone, 15 mg/d, is achieved in different scenarios. A sample size of 75 patients who were valid for the full analysis set in each treatment group would provide a power of at least 83% to demonstrate a dose-dependent effect on the primary variable for 7 treatment groups (dosages up to 15 mg/d) using the linear contrast L7' = (4.714, 3.714, 2.714, 0.716, –1.286, –3.286, –7.286) at a significance level of .05 (1-sided), assuming a common standard deviation of 1.25 on the log scale and a true contrast of the log-transformed UACR ratios of at least 3.937. It was expected that the power would increase in the case of 8 treatment groups (dosages up to 20 mg/d). Taking into account that the 15-mg/d and 20-mg/d finerenone treatment groups were added, 600 patients were required in total. To achieve this, approximately 1500 pa-

tients were enrolled into ARTS-DN (assuming a screening failure rate of up to 50%) and 823 were randomized among treatment groups (assuming a dropout rate of 10%). It was planned to increase the sample size in the case that less than 35% of randomized patients were diagnosed as having very high albuminuria. As a result, more than 670 patients were actually randomized.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc). Because the log of UACR is assumed to be normally distributed, the treatment effect regarding UACR change is evaluated in terms of ratios to baseline. For the primary analysis, dose dependency was assessed by fitting an analysis-of-covariance model to the log-transformed ratios of UACR at day 90 to UACR at baseline (eAppendix in Supplement 2), including the factors treatment group, region, and type of albuminuria and the log-transformed baseline UACR as a covariate nested within type of albuminuria, and testing a prespecified linear contrast at a 1-sided significance level of .05. Subsequent hierarchical pairwise comparisons with placebo were performed. A last-observation-carried-forward (LOCF) method was applied, whereby the higher UACR value from the premature discontinuation measurement and the follow-up measurement was used to impute missing UACR values at day 90. Sensitivity analyses for the LOCF method were performed for the primary efficacy variable by repeating the primary analyses for several other imputation methods, including an observed case analysis (only patients with a UACR value at day 90 available), an on-treatment LOCF approach (similar to that of the primary analysis but including only data before the premature discontinuation visit), a baseline-observation-carried-forward analysis (imputing the baseline value for missing data; ie, including all patients in the full analysis set with missing data at day 90 with a value of 1 for the primary efficacy variable), a mean value imputation (imputing the value of the primary efficacy variable by the least squares mean value of the primary efficacy analysis), a random imputation (imputing the value of the primary efficacy variable by a random number from a normal distribution with least squares mean and variance [from descriptive statistics]), and a post hoc multiple imputation. The distributional model assumptions were checked by inspection of residual plots of Studentized residuals vs normal-order scores to check normality and Studentized residuals vs predicted values to check homogeneity of variance.

An analysis-of-covariance model for the log-transformed ratio of UACR at day 90 with the same factors as for the primary analysis plus factors for the interaction between treatment group and region and between treatment group and type of albuminuria was calculated. The ratios of UACRs at days 30, 60, and 90 to those at baseline were assessed by fitting a mixed-effects repeated-measures model to the log-transformed ratios, with the same factors as for the primary analysis plus the factor of time and the interaction between treatment and time. Further exploratory analyses have been detailed previously.[10]

The results of the analyses of covariance are presented as point estimates (least squares means) and corresponding confidence intervals. *P* values are reported only for the primary analysis, for which the prespecified significance level is kept,

as no adjustment for multiple testing was performed for the other exploratory analyses.

As a post hoc analysis, Pearson correlation coefficients between the ratio of UACR at day 90 vs at baseline and both the change in systolic blood pressure from baseline to day 90 and the change in eGFR from baseline to day 90 were calculated across all treatment groups. A further post hoc analysis examined the proportion of patients with a UACR decrease of at least 30%, at least 40%, and at least 50% from baseline at each visit. The subgroup of patients with CKD stage 3 at baseline was also analyzed for changes in serum potassium and eGFR. Additionally, a post hoc analysis of RAS inhibition at baseline was reviewed and the dosages of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers were categorized.

Results

Demographic Characteristics
As planned, the sample size was increased to enlarge the amount of safety data for patients with very high albuminuria. Of 1501 patients screened, 823 patients were randomized (Figure 1 and eTable 1 in Supplement 2); 764 patients (93%) completed treatment.[10] Mean age was 64.2 years; 78% were male. One patient in each of the 7.5-mg/d and 20-mg/d groups did not take any study medication. Nine patients did not have a postbaseline UACR measurement, leaving data from 812 patients in the primary analysis. At baseline, 301 patients (36.7%) treated had very high albuminuria (UACR ≥300 mg/g) and 328 (40.0%) had an eGFR of 60 mL/min/1.73 m^2 or less. The demographics and cardiovascular and diabetic medical history of patients in ARTS-DN are shown in **Table 1** and **Table 2**.

A post hoc analysis showed that at baseline, approximately 45% of patients were receiving an ACE inhibitor (Table 2) and one-quarter of all patients received RAS inhibition below (2.6%) or at (24.8%) the minimal recommended dosage (eTable 2 in Supplement 2).[11] The minimum recommended and maximum dosages used in outcome trials were obtained from the Kidney Disease Outcomes Quality Initiative clinical practice guidelines on hypertension and antihypertensive agents in CKD.[11] Among patients receiving an ACE inhibitor, approximately half were receiving a dosage at baseline between the minimum recommended and maximum dosages used in outcome trials, and approximately 16% and 6% received the maximum or more than the maximum dosage used in outcome trials, respectively. Approximately 17% of patients receiving an angiotensin receptor blocker at baseline were receiving a dosage between the minimum and maximum dosage used in outcome trials, whereas approximately 54% and 3% received the maximum or above maximum dosage used in trials, respectively (eTable 2 in Supplement 2).

Primary End Point
A dose-dependent relationship across all dosages studied for the primary end point was demonstrated by analysis of covariance (1-sided F test for linear contrast, $P<.001$). The least squares mean changes from baseline in UACR at day 90 for the placebo and finerenone groups are shown in **Figure 2**. The mean placebo-corrected ratios of UACR at day 90 vs baseline in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups were 0.79 (90% CI, 0.68-0.91; $P = .004$), 0.76 (90% CI, 0.65-0.88; $P = .001$), 0.67 (90% CI, 0.58-0.77; $P<.001$), and 0.62 (90% CI, 0.54-0.72; $P<.001$), respectively. The placebo-corrected ratio of UACR to baseline (derived from a mixed-model analysis) decreased over time for the 7.5-, 15-, and 20-mg/d groups, whereas the lowest ratio was observed at day 60 and was slightly increased at day 90 in the 10-mg group (eTable 3 in Supplement 2). Results of a post hoc analysis by multiple imputation were not different from those from the LOCF method (eTable 4 in Supplement 2).

The prespecified secondary end point of the placebo-corrected ratio of UACR at baseline vs at day 30, day 60, and day 90 (derived from a mixed-model analysis) decreased for the 7.5-, 15-, and 20-mg/d groups, whereas the lowest ratio was observed at day 60 and was slightly increased at day 90 for the other groups (eTable 5 in Supplement 2).

The exploratory test for an interaction between region ($P = .30$) or severity of albuminuria ($P = .80$) at screening and treatment group regarding changes in UACR did not indicate an interaction. Nevertheless, a smaller treatment effect within the very high albuminuria group compared with the high albuminuria group was observed. In patients with high albuminuria, the 90% CIs for the placebo-corrected ratios of UACR at day 90 vs baseline were less than 1 for the finerenone 10-, 15-, and 20-mg/d groups (eTable 6 in Supplement 2). In patients with very high albuminuria, the 90% CIs for the placebo-corrected ratios of UACR at day 90 vs baseline spanned unity for all finerenone dosage groups (eTable 5 in Supplement 2).

The post hoc analysis of the proportions of patients who experienced a decrease in UACR of at least 30%, 40%, and 50% from baseline to day 90 are shown in eTable 7 in Supplement 2. A UACR decrease of at least 50% from baseline to day 90 was observed in 13.6% of patients in the placebo group and in 17.2%, 17.2%, 33.6%, and 40.2% in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups, respectively.

Other Efficacy and Safety Variables
Estimated Glomerular Filtration Rate
Figure 3A shows mean eGFR values over time in the finerenone and placebo groups. Absolute mean change in eGFR from baseline to day 90 is shown in eTable 8 in Supplement 2. The placebo-corrected least squares mean differences in eGFR were −1.8 (95% CI, −4.4 to 0.8) mL/min/1.73 m^2, −2.6 (95% CI, −5.1 to −0.04) mL/min/1.73 m^2, −2.2 (95% CI, −4.6 to 0.2) mL/min/1.73 m^2, and −2.4 (95% CI, −4.9 to 0.0) mL/min/1.73 m^2 in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups, respectively (eFigure 1 in Supplement 2). Changes in the finerenone groups were reversible 30 days after completion of treatment at the follow-up assessment (day 120). The incidences of an eGFR decrease of at least 40% at any time postbaseline were similar in the placebo and finerenone 1.25-, 7.5-, 10-, 15-, and 20-mg/d groups (eTable 9 in Supplement 2), with no cases observed in the 2.5- and 5-mg/d groups. There were no occurrences of eGFR decreases of at least 57%.

Table 1. Demographic Characteristics of Patients Treated With Placebo or Finerenone, 1.25-20 mg/d (Safety Analysis Set)

Characteristics	Placebo (n = 94)	Finerenone, mg/d						
		1.25 (n = 96)	2.5 (n = 92)	5 (n = 100)	7.5 (n = 97)	10 (n = 98)	15 (n = 125)	20 (n = 119)
Age, mean (SD), y	63.26 (8.68)	64.91 (9.57)	64.86 (9.09)	63.31 (8.79)	63.73 (10.04)	64.94 (9.62)	63.95 (8.34)	64.70 (9.26)
Male, No. (%)	69 (73.4)	78 (81.3)	78 (84.8)	71 (71.0)	79 (81.4)	77 (78.6)	98 (78.4)	89 (74.8)
Race/ethnicity, No. (%)								
White	83 (88.3)	79 (82.3)	79 (85.9)	83 (83.0)	81 (83.5)	82 (83.7)	105 (84.0)	99 (83.2)
Black or African American	3 (3.2)	2 (2.1)	3 (3.3)	5 (5.0)	4 (4.1)	3 (3.1)	6 (4.8)	2 (1.7)
Asian	8 (8.5)	11 (11.5)	8 (8.7)	11 (11.0)	8 (8.2)	12 (12.2)	10 (8.0)	16 (13.4)
Multiple	0	0	1 (1.1)	0	4 (4.1)	1 (1.0)	4 (3.2)	1 (0.8)
Not reported	0	4 (4.2)	1 (1.1)	1 (1.0)	0	0	0	1 (0.8)
Hispanic or Latino	2 (2.1)	3 (3.1)	3 (3.3)	2 (2.0)	3 (3.1)	1 (1.0)	2 (1.6)	2 (1.7)
Region, No. (%)								
Europe	68 (72.3)	69 (71.9)	67 (72.8)	68 (68.0)	66 (68.0)	70 (71.4)	81 (64.8)	78 (65.5)
North America	10 (10.6)	8 (8.3)	8 (8.7)	11 (11.0)	11 (11.3)	10 (10.2)	12 (9.6)	11 (9.2)
Asia	4 (4.3)	6 (6.3)	5 (5.4)	7 (7.0)	4 (4.1)	4 (4.1)	5 (4.0)	6 (5.0)
Australia, Israel, South Africa	12 (12.8)	13 (13.5)	12 (13.0)	14 (14.0)	16 (16.5)	14 (14.3)	27 (21.6)	24 (20.2)
Smoking history, No. (%)								
Never	40 (42.6)	42 (43.8)	39 (42.4)	39 (39.0)	36 (37.1)	39 (39.8)	42 (33.6)	43 (36.1)
Former	36 (38.3)	41 (42.7)	38 (41.3)	49 (49.0)	41 (42.3)	41 (41.8)	46 (36.8)	53 (44.5)
Current	18 (19.1)	13 (13.5)	15 (16.3)	12 (12.0)	20 (20.6)	18 (18.4)	37 (29.6)	23 (19.3)
BMI, mean (SD)[a]	32.49 (5.27)	32.19 (6.67)	31.54 (5.42)	31.85 (5.44)	31.60 (5.81)	31.70 (5.39)	31.97 (5.66)	31.39 (4.72)
Hemoglobin A_{1c}, mean (SD), %	7.6 (1.3)	7.6 (1.3)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)	7.7 (1.2)	7.5 (1.2)	7.7 (1.3)
Systolic BP, mean (SD), mm Hg	139.9 (14.3)	138.9 (13.7)	137.3 (14.2)	138.2 (15.2)	137.8 (14.6)	137.6 (14.0)	137.6 (14.7)	138.1 (14.3)
Diastolic BP, mean (SD), mm Hg	78.2 (9.7)	77.8 (9.6)	77.4 (8.5)	76.4 (9.8)	77.5 (10.3)	76.5 (10.0)	76.2 (10.1)	77.2 (9.9)
UACR								
Median (range), mg/g	182.9 (15.0-3056)	216.8 (14.1-2707)	158.9 (21.2-4020)	174.8 (27.9-2649)	166.4 (10.7-4948)	249.5 (30.4-3917)	161.1 (21.2-4144)	202.7 (4.4-2298)
Geometric mean (CV%), mg/g	188.4 (169.8)	227.1 (162.6)	196.1 (192.0)	191.2 (189.0)	180.3 (190.1)	230.7 (171.0)	204.7 (193.1)	204.1 (171.9)
Albuminuria, No. (%)								
High (≥30-<300 mg/g)	58 (61.7)	54 (56.3)	62 (67.4)	64 (64.0)	63 (64.9)	56 (57.1)	74 (59.2)	66 (55.5)
Very high (≥300 mg/g)	34 (36.2)	38 (39.6)	28 (30.4)	34 (34.0)	31 (32.0)	42 (42.9)	46 (36.8)	48 (40.3)
Serum potassium, mean (SD), mmol/L	4.3 (0.48)	4.32 (0.43)	4.30 (0.43)	4.31 (0.33)	4.3 (0.44)	4.3 (0.42)	4.3 (0.46)	4.3 (0.44)
eGFR								
Mean (SD), mL/min/1.73 m²	72.2 (20.4)	66.1 (21.9)	67.4 (20.2)	67.1 (22.2)	67.5 (21.9)	67.0 (20.9)	67.5 (23.6)	66.0 (22.2)
≤60 mL/min/1.73 m², No. (%)	26 (27.7)	41 (42.7)	35 (38.0)	41 (41.0)	39 (40.2)	44 (44.9)	50 (40.0)	52 (43.7)
Serum creatinine, mean (SD), mg/dL	1.1 (0.3)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)	1.2 (0.4)

Abbreviations: BP, blood pressure; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio.

[a] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Table 2. Cardiovascular and Diabetic History of Patients Treated With Placebo or Finerenone, 1.25-20 mg/d (Safety Analysis Set)[a]

| | No. (%) of Participants | | | | | | | |
| | | Finerenone, mg/d | | | | | | |
Characteristics	Placebo (n = 94)	1.25 (n = 96)	2.5 (n = 92)	5 (n = 100)	7.5 (n = 97)	10 (n = 98)	15 (n = 125)	20 (n = 119)
Hypertension	89 (94.7)	90 (93.8)	86 (93.5)	97 (97.0)	92 (94.8)	96 (98.0)	112 (89.6)	112 (94.1)
Diabetic neuropathy	27 (28.7)	21 (21.9)	25 (27.2)	14 (14.0)	19 (19.6)	17 (17.3)	17 (13.6)	26 (21.8)
Diabetic retinopathy	19 (20.2)	18 (18.8)	26 (28.3)	15 (15.0)	23 (23.7)	21 (21.4)	17 (13.6)	29 (24.4)
Myocardial ischemia	7 (7.4)	12 (12.5)	4 (4.3)	12 (12.0)	12 (12.4)	7 (7.1)	12 (9.6)	15 (12.6)
Atrial fibrillation	8 (8.5)	9 (9.4)	11 (12.0)	7 (7.0)	10 (10.3)	6 (6.1)	7 (5.6)	10 (8.4)
Coronary artery disease	4 (4.3)	7 (7.3)	1 (1.1)	12 (12.0)	6 (6.2)	12 (12.2)	11 (8.8)	14 (11.8)
Myocardial infarction	7 (7.4)	11 (11.5)	5 (5.4)	7 (7.0)	8 (8.2)	5 (5.1)	10 (8.0)	9 (7.6)
Coronary artery bypass graft surgery	1 (1.1)	5 (5.2)	4 (4.3)	6 (6.0)	5 (5.2)	6 (6.1)	11 (8.8)	8 (6.7)
Concomitant medications[b]								
Drugs used in diabetes[c]	92 (97.9)	93 (96.9)	92 (100.0)	96 (96.0)	94 (96.9)	98 (100.0)	124 (99.2)	117 (98.3)
Serum lipid-reducing agents[c]	67 (71.3)	70 (72.9)	69 (75.0)	78 (78.0)	75 (77.3)	73 (74.5)	103 (82.4)	90 (75.6)
Diuretics[d]	68 (72.3)	62 (64.6)	58 (63.0)	69 (69.0)	68 (70.1)	72 (73.5)	81 (64.8)	86 (72.3)
Thiazide diuretics[d]	54 (57.4)	46 (47.9)	40 (43.5)	55 (55.0)	50 (51.5)	55 (56.1)	57 (45.6)	65 (54.6)
Loop diuretics[d]	22 (23.4)	25 (26.0)	26 (28.3)	19 (19.0)	26 (26.8)	22 (22.4)	28 (22.4)	29 (24.4)
Calcium channel blockers[d]	62 (66.0)	48 (50.0)	50 (54.3)	58 (58.0)	74 (76.3)	59 (60.2)	69 (55.2)	66 (55.5)
RAS inhibitor therapy[d]								
ACE inhibitors	41 (43.6)	42 (43.8)	39 (42.4)	38 (38.0)	42 (43.3)	46 (46.9)	64 (51.2)	63 (52.9)
ARBs	55 (58.5)	53 (55.2)	53 (57.6)	62 (62.0)	56 (57.7)	56 (57.1)	61 (48.8)	56 (47.1)
β-blockers	51 (54.3)	52 (54.2)	42 (45.7)	46 (46.0)	38 (39.2)	44 (44.9)	60 (48.0)	59 (49.6)
Potassium supplements	3 (3.2)	3 (3.1)	6 (6.5)	5 (5.0)	3 (3.1)	5 (5.1)	4 (3.2)	8 (6.7)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system.

[a] *Medical Dictionary for Regulatory Activities* primary system organ class/preferred term; patients may have more than one comorbidity; only conditions occurring in more than 5% of patients are listed.

[b] Includes drugs ongoing at start of study drug, begun after start of study drug,

or started after end of study drug treatment; patients may have been taking more than 1 type of medication; only concomitant medications that are considered to be of most interest are listed.

[c] Based on *World Health Organization Drug Dictionary* classification.

[d] Based on Bayer drug grouping.

Figure 2. Change in Least Squares Mean UACR at Day 90 Relative to Baseline in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo
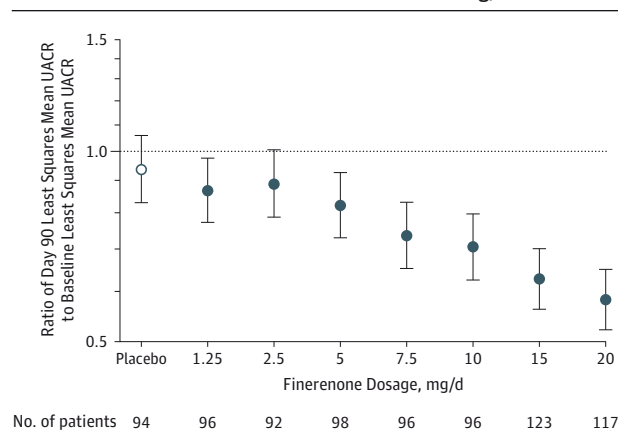
Error bars indicate 90% confidence intervals. UACR indicates urinary albumin-creatinine ratio. Data are from the full analysis set (n=812).

In a post hoc analysis in patients with CKD stage 3 at baseline, mean changes in eGFR to day 90 were analyzed (eTable 8 in Supplement 2). eFigure 2 in Supplement 2 shows mean eGFR values over time in this subgroup.

Adverse Events

There was no difference in the overall incidence of adverse events and serious adverse events between the finerenone groups and the placebo group (**Table 3**). There was no relevant increase in adverse events across finerenone dosages. Drug-related serious adverse events occurred in 1.5% of patients receiving finerenone.

Serum Potassium

Figure 3B shows mean serum potassium concentrations over time. Absolute mean changes in serum potassium from baseline to day 90 are shown in eTable 10 in Supplement 2. Placebo-corrected least squares mean changes in serum potassium from baseline to day 90 in the finerenone groups are shown in eFigure 3 in Supplement 2.

Twelve of 821 patients (1.5%), all of whom were receiving finerenone, experienced increases in serum potassium of at least 5.6 mmol/L, leading to subsequent discontinuation of study treatment. The incidences were 2.1%, 1.1%, 1.0%, 2.1%, 3.2%, and 1.7% in the finerenone 1.25-, 2.5-, 5-, 7.5-, 15-, and 20-mg/d groups, respectively, with no cases observed in the finerenone 10-mg/d group. The overall incidence for the 7.5- to 20-mg/d groups (the groups in which a significant change in the primary end point was observed) was 1.8%. A serum potassium level of more than 6.0 mmol/L was observed in the

Figure 3. Estimated Glomerular Filtration Rate and Serum Potassium Levels in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo
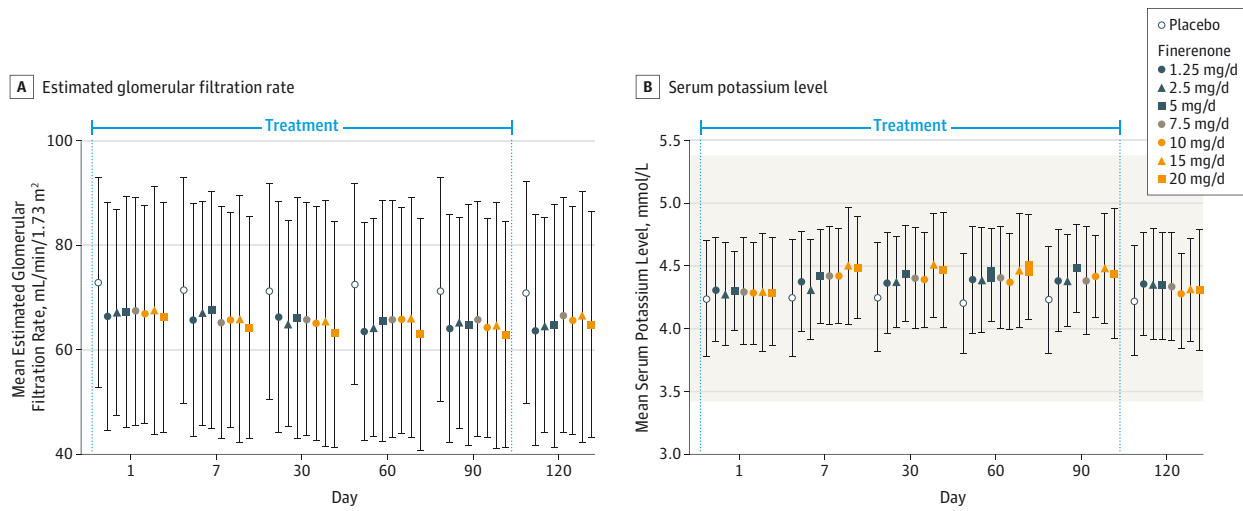
Error bars indicate standard deviations. Data are from the safety analysis set (n=821). Right panel, tinted area indicates the reference range for serum potassium.

Table 3. Adverse Events and Serious Adverse Events in Patients Treated With Placebo or Finerenone, 1.25-20 mg/d, by *Medical Dictionary for Regulatory Activities* Version 17.0 Preferred Term

Events	No. (%) of Participants								
	Placebo (n = 94)	Finerenone, mg/d							Total (n = 821)
		1.25 (n = 96)	2.5 (n = 92)	5 (n = 100)	7.5 (n = 97)	10 (n = 98)	15 (n = 125)	20 (n = 119)	
Any adverse event	47 (50.0)	48 (50.0)	51 (55.4)	50 (50.0)	54 (55.7)	58 (59.2)	61 (48.8)	64 (53.8)	433 (52.7)
Any serious adverse event	3 (3.2)	5 (5.2)	3 (3.3)	7 (7.0)	8 (8.2)	2 (2.0)	6 (4.8)	4 (3.4)	38 (4.6)
Any drug-related serious adverse event	1 (1.1)	2 (2.1)	1 (1.1)	1 (1.0)	2 (2.1)	0	3 (2.4)	2 (1.7)	12 (1.5)
Discontinuation of study medication due to adverse event	3 (3.2)	5 (5.2)	4 (4.3)	5 (5.0)	5 (5.2)	2 (2.0)	8 (6.4)	2 (1.7)	34 (4.1)
Discontinuation of study medication due to serious adverse event	1 (1.1)	2 (2.1)	1 (1.1)	4 (4.0)	4 (4.1)	0	4 (3.2)	2 (1.7)	18 (2.2)
Discontinuation of study medication due to serum potassium ≥5.6 mmol/L	0	2 (2.1)	1 (1.1)	1 (1.0)	2 (2.1)	0	4 (3.2)	2 (1.7)	12 (1.5)
Serious adverse events occurring in >1 patient									
Hyperkalemia	0	2 (2.1)	0	1 (1.0)	1 (1.0)	0	2 (1.6)	2 (1.7)	8 (1.0)
Blood potassium increased	0	0	2 (2.2)	0	1 (1.0)	0	2 (1.6)	1 (0.8)	6 (0.7)
Cerebrovascular accident	1 (1.1)	0	0	0	1 (1.0)	0	0	0	2 (0.2)
Coronary artery disease	0	0	0	0	1 (1.0)	1 (1.0)	0	0	2 (0.2)
Prostate cancer	0	1 (1.0)	0	0	1 (1.0)	0	0	0	2 (0.2)
Adverse events occurring in ≥2% patients overall									
Nasopharyngitis	5 (5.3)	7 (7.3)	4 (4.3)	8 (8.0)	9 (9.3)	5 (5.1)	4 (3.2)	8 (6.7)	50 (6.1)
Diarrhea	2 (2.1)	5 (5.2)	2 (2.2)	4 (4.0)	2 (2.1)	2 (2.0)	3 (2.4)	5 (4.2)	25 (3.0)
Blood creatine phosphokinase increased	1 (1.1)	2 (2.1)	3 (3.3)	1 (1.0)	3 (3.1)	3 (3.1)	2 (1.6)	3 (2.5)	18 (2.2)
Muscle spasms	2 (2.1)	0	2 (2.2)	1 (1.0)	4 (4.1)	1 (1.0)	5 (4.0)	3 (2.5)	18 (2.2)
Glomerular filtration rate decreased	2 (2.1)	2 (2.1)	3 (3.3)	4 (4.0)	2 (2.1)	2 (2.0)	2 (1.6)	1 (0.8)	18 (2.2)
Dizziness	2 (2.1)	6 (6.3)	1 (1.1)	3 (3.0)	1 (1.0)	3 (3.1)	5 (4.0)	1 (0.8)	22 (2.7)

finerenone 1.25-mg/d group (2.1%; n = 2) and 15-mg/d group (0.8%; n = 1) but not in the 7.5-, 10-, or 20-mg/d groups.

In a post hoc analysis in patients with CKD stage 3 at baseline, the incidences of a serum potassium level of at least 5.6 mmol/L were 2.7%, 5.4%, 4.1%, and 6.3% in the finerenone 1.25-, 7.5-, 15-, and 20-mg/d groups, respectively, with no cases in the placebo, 2.5-, 5-, and 10-mg groups. No cases of a serum potassium level of more than 6.0 mmol/L were observed

Figure 4. Systolic Blood Pressure and Diastolic Blood Pressure in Patients Treated With Finerenone, 1.25-20 mg/d, or Placebo
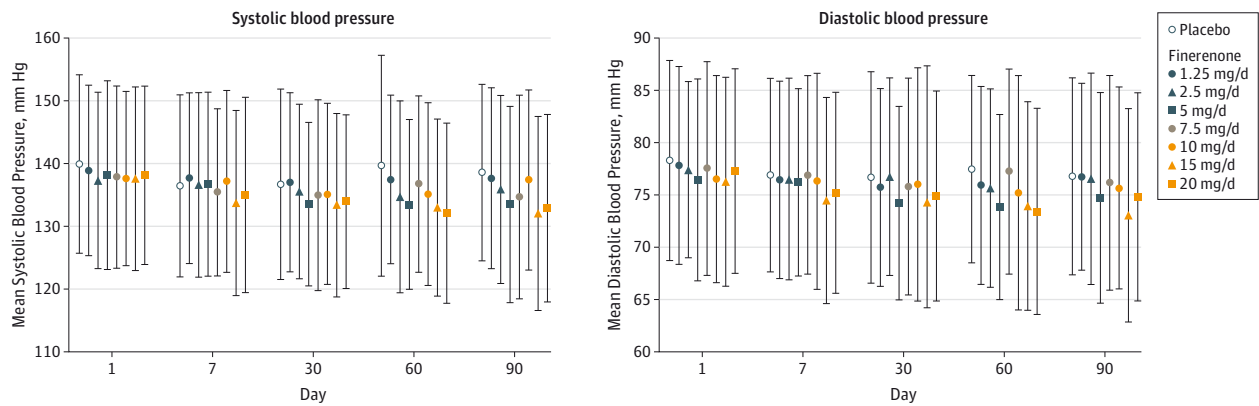
Error bars indicate standard deviation. Data are from the safety analysis set (n=821).

in any of the finerenone groups except the 1.25-mg/d group. Mean changes in serum potassium from baseline to day 90 in this subgroup are shown in eTable 10 in Supplement 2. eFigure 4 in Supplement 2 shows mean serum potassium concentrations over time in this subgroup.

Blood Pressure

Figure 4 shows mean systolic and diastolic blood pressure values in the placebo and finerenone groups over time. The placebo-corrected least squares mean differences in systolic blood pressure from baseline to day 90 in the finerenone 7.5-, 10-, 15-, and 20-mg/d groups were –2.8 (95% CI, –6.5 to 0.8) mm Hg, 0.1 (95% CI, –3.5 to 3.8) mm Hg, –5.1 (95% CI, –8.5 to –1.7) mm Hg, and –4.7 (95% CI, –8.2 to -1.3) mm Hg (eFigure 5 in Supplement 2).

Post hoc analysis showed that no meaningful correlation was observed across all treatment groups between the ratio of UACR and the change in systolic blood pressure or change in eGFR from baseline to day 90 (eFigures 6 and 7 in Supplement 2, respectively).

Discussion

Diabetes mellitus is the most common cause of end-stage renal disease in the developed world.[12] In outcome trials of patients with diabetic nephropathy, retrospective analyses demonstrate a robust relationship between magnitude of albuminuria reduction and slowing of CKD progression as well as reduced cardiovascular event rates.[13-18] Addition of steroidal MRAs is well documented to reduce albuminuria further when added to RAS blockers.[5,19,20] Large-scale outcome studies examining the long-term effects of MRAs on CKD progression in diabetic nephropathy are lacking, in large part because of safety issues regarding the risk of hyperkalemia and worsening kidney function.[5,19,20]

ARTS-DN examines the effects of finerenone, a novel nonsteroidal, highly selective MRA with a greater affinity for the mineralocorticoid receptor than eplerenone[7] and with improved cardiorenal protective properties at equiefficient na-

triuretic doses in animals compared with eplerenone.[8] To our knowledge, this is the first multicenter clinical trial of finerenone in combination with an RAS inhibitor in patients with diabetic nephropathy investigating an optimal dosage to use in an outcome study. At baseline, all patients were receiving RAS blockade, with 72.7% receiving a dosage above the minimum recommended dosage recommended by the *Physicians' Desk Reference*. Finerenone reduced the placebo-corrected UACR at day 90 in a dose-dependent manner, with a significant reduction in UACR ranging from 21% to 38% in the finerenone dosage groups of 7.5 to 20 mg/d compared with placebo.

Previous studies have shown conflicting results regarding the incidence of hyperkalemia in patients with diabetes receiving steroidal MRAs. A systematic review documented an increased incidence of hyperkalemia in patients with diabetic nephropathy receiving steroidal MRAs with RAS blockers compared with RAS blockade alone.[19] The dropout rates due to hyperkalemia in 2 of the 8 studies were 8% and 17%.[19] In one study evaluating spironolactone in patients with diabetic nephropathy, clinically significant hyperkalemia (serum potassium level >6.0 mmol/L) was noted in 52% of patients treated with high-dose ACE inhibitors plus low-dose spironolactone over 48 weeks.[20] In contrast, a randomized study of the more selective MRA eplerenone, 100 mg/d, demonstrated a 48% median reduction in UACR over 12 weeks (compared with a 7% reduction in the placebo group), with a low incidence of hyperkalemia that was similar between the eplerenone and placebo groups in patients with diabetic nephropathy.[3] It is noteworthy that 2 separate studies used an ACE inhibitor dosage higher than recommended by the US Food and Drug Administration. This higher dosage may have contributed to higher rates of hyperkalemia in these studies.[3,20]

Post hoc analyses of clinical trials show that reduction in UACR of at least 30% is associated with reduced progression of CKD and decreased overall mortality.[21,22] However, this is not true when using dual RAS blockade in advanced nephropathy. Both the VA NEPHRON-D and ALTITUDE studies demonstrated that combining 2 RAS inhibitors in patients with diabetic nephropathy while providing a greater reduction in

albuminuria compared with a single RAS blocker failed to meet their primary end points secondary to hyperkalemia and reduced kidney function.[23,24]

In ARTS-DN, hyperkalemia and subsequent discontinuation of study drug occurred in 1.8% of patients receiving finerenone, 7.5 to 20 mg/d, compared with no cases in the placebo group. Three cases of serum potassium more than 6.0 mmol/L were observed overall, 2 in the finerenone 1.25-mg/d group and 1 in the 15-mg/d group. The lack of a significant decrease in eGFR may be a contributing factor to the low risk of hyperkalemia in ARTS-DN. Furthermore, patients with a serum potassium concentration greater than 4.8 mmol/L at screening, a well-known risk marker for hyperkalemia, were excluded from ARTS-DN.[6] While the primary end point of ARTS-DN is CKD progression, and the study population was smaller with shorter follow-up than the previous trials,[23,24] the significant reduction in UACR in patients receiving finerenone, combined with a safety profile similar to that in the placebo group, suggests that longer-term studies investigating clinical end points are warranted.

There was only a modest reduction in blood pressure at the highest dosage of finerenone in both ARTS[9] and ARTS-DN. In contrast, other studies have shown clear reductions in blood pressure after 3 months with other, steroidal MRAs.[5] This differential effect on blood pressure may be related to steroidal MRAs

crossing the blood-brain barrier and acting centrally on mineralocorticoid receptors, which are believed to play a major role in the control of blood pressure.[25] [14C]-Finerenone was not found in the brain after oral application in preclinical studies.[9]

While the study has some strengths, including its randomized multicenter design, large numbers of patients, and very low dropout rate, it is a dose-finding study that lacks an active control group. Another limitation is that 60% of patients had an eGFR above 60 mL/min/1.73 m^2, thus putting them at lower risk of hyperkalemia. Moreover, while reductions in albuminuria are highly correlated with slowed progression of CKD, they are not a validated surrogate marker for renal outcomes such as time to dialysis. Additionally, the short duration of the study did not allow assessment of the long-term effects of finerenone on CKD progression or assessment of antifibrotic or anti-inflammatory effects.

Conclusions

Among patients with diabetic nephropathy, most receiving an ACE inhibitor or an angiotensin receptor blocker, the addition of finerenone compared with placebo resulted in improvement in the UACR. Further trials are needed to compare finerenone with other active medications.

REFERENCES

1. Bomback AS, Kshirsagar AV, Amamoo MA, et al. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD. *Am J Kidney Dis*. 2008;51(2):199-211.

2. Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. *N Engl J Med*. 2001;345(12):925-926.

3. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2006;1(5):940-951.

4. Rossing K, Schjoedt KJ, Smidt UM, et al. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy. *Diabetes Care*. 2005;28(9):2106-2112.

5. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014;4:CD007004.

6. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Semin Nephrol*. 2014;34(3):333-339.

7. Bärfacker L, Kuhl A, Hillisch A, et al. Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. *ChemMedChem*. 2012;7(8):1385-1403.

8. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64(1):69-78.

9. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel nonsteroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. *Eur Heart J*. 2013;34(31):2453-2463.

10. Ruilope LM, Agarwal R, Chan JC, et al. Rationale, design, and baseline characteristics of ARTS-DN: a randomized study to assess the safety and efficacy of finerenone in patients with type 2 diabetes mellitus and a clinical diagnosis of diabetic nephropathy. *Am J Nephrol*. 2014;40(6):572-581.

11. Kidney Disease Outcomes Quality Initiative. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43(5)(suppl 1):S1-S290.

12. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. *Diabetes Care*. 2014;37(10):2864-2883.

13. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*. 2004;110(8):921-927.

14. Holtkamp FA, de Zeeuw D, de Graeff PA, et al. Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy. *Eur Heart J*. 2011;32(12):1493-1499.

15. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol*. 2009;20(8):1813-1821.

16. Schmieder RE, Schutte R, Schumacher H, et al. Mortality and morbidity in relation to changes in albuminuria, glucose status and systolic blood pressure. *Diabetologia*. 2014;57(10):2019-2029.

17. Bakris GL. Recognition, pathogenesis, and treatment of different stages of nephropathy in patients with type 2 diabetes mellitus. *Mayo Clin Proc*. 2011;86(5):444-456.

18. Yamout H, Lazich I, Bakris GL. Blood pressure, hypertension, RAAS blockade, and drug therapy in diabetic kidney disease. *Adv Chronic Kidney Dis*. 2014;21(3):281-286.

19. Mavrakanas TA, Gariani K, Martin PY. Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: an emerging paradigm in diabetic nephropathy. *Eur J Intern Med*. 2014;25(2):173-176.

20. Mehdi UF, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol*. 2009;20(12):2641-2650.

21. Schmieder RE, Mann JF, Schumacher H, et al. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol*. 2011;22(7):1353-1364.

22. Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease. *Arch Intern Med*. 2005;165(8):947-953.

23. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369(20):1892-1903.

24. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367(23):2204-2213.

25. Gomez-Sanchez EP, Gomez-Sanchez CE. Central regulation of blood pressure by the mineralocorticoid receptor. *Mol Cell Endocrinol*. 2012;350(2):289-298.