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Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

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ABSTRACT

BACKGROUND

Renin–angiotensin system (RAS) inhibitors — including angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) — slow the progression of mild or moderate chronic kidney disease. However, the results of some studies have suggested that the discontinuation of RAS inhibitors in patients with advanced chronic kidney disease may increase the estimated glomerular filtration rate (eGFR) or slow its decline.

METHODS

In this multicenter, open-label trial, we randomly assigned patients with advanced and progressive chronic kidney disease (eGFR, <30 ml per minute per 1.73 m^2 of body-surface area) either to discontinue or to continue therapy with RAS inhibitors. The primary outcome was the eGFR at 3 years; eGFR values that were obtained after the initiation of renal-replacement therapy were excluded. Secondary outcomes included the development of end-stage kidney disease (ESKD); a composite of a decrease of more than 50% in the eGFR or the initiation of renal-replacement therapy, including ESKD; hospitalization; blood pressure; exercise capacity; and quality of life. Prespecified subgroups were defined according to age, eGFR, type of diabetes, mean arterial pressure, and proteinuria.

RESULTS

At 3 years, among the 411 patients who were enrolled, the least-squares mean (±SE) eGFR was 12.6±0.7 ml per minute per 1.73 m^2 in the discontinuation group and 13.3±0.6 ml per minute per 1.73 m^2 in the continuation group (difference, −0.7; 95% confidence interval [CI], −2.5 to 1.0; P=0.42), with a negative value favoring the outcome in the continuation group. No heterogeneity in outcome according to the prespecified subgroups was observed. ESKD or the initiation of renal-replacement therapy occurred in 128 patients (62%) in the discontinuation group and in 115 patients (56%) in the continuation group (hazard ratio, 1.28; 95% CI, 0.99 to 1.65). Adverse events were similar in the discontinuation group and continuation group with respect to cardiovascular events (108 vs. 88) and deaths (20 vs. 22).

CONCLUSIONS

Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of decrease in the eGFR. (Funded by the National Institute for Health Research and the Medical Research Council; STOP ACEi EudraCT number, 2013-003798-82; ISRCTN number, 62869767.)

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A Quick Take is available at NEJM.org

In patients with mild or moderate chronic kidney disease, the use of renin–angiotensin system (RAS) inhibitors — including angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers — reduces blood pressure, slows decline in the estimated glomerular filtration rate (eGFR), reduces proteinuria,[1-5] and delays progression to advanced chronic kidney disease (stage 4 or 5). Among such patients, the progression to advanced chronic kidney disease has been associated with an impaired quality of life[6] and an increased risk of renal-replacement therapy, cardiovascular events, and death.[7-11] However, there is little evidence that the use of RAS inhibitors benefits patients with advanced chronic kidney disease. An observational study suggested that the discontinuation of RAS inhibitors in such patients may increase the eGFR.[12] Current guidelines do not provide specific advice on whether to continue or stop ACE inhibitors or angiotensin-receptor blockers for advanced chronic kidney disease.[13]

Accordingly, we conducted the multicenter, randomized, open-label STOP-ACEi trial involving patients with advanced and progressive chronic kidney disease to assess whether the discontinuation of RAS inhibitors would increase or stabilize the eGFR.[14]

Methods

Trial Design and Oversight

Patients underwent screening at 39 centers in the United Kingdom. Details regarding the objectives, design, and methods of the trial have been published previously.[14] The trial protocol (available with the full text of this article at NEJM.org) was approved by the relevant health authorities and institutional review boards.

The trial was funded by the National Institute for Health Research and the Medical Research Council; no industry support was provided. The Birmingham Clinical Trials Unit coordinated the trial. An independent steering committee whose members were unaware of trial-group assignments oversaw the conduct of the trial. A data and safety monitoring committee monitored patient safety in an unblinded manner.

The trial was designed by the first, fifth, and last authors, with assistance on the adoption of cardiovascular outcomes by the fourth author. The first author wrote the first draft of the manuscript, which was then edited by all the coauthors; no other medical writing assistance was provided. The authors had access to the results and take responsibility for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the decision to submit the manuscript for publication.

Patients

Adults (≥18 years of age) with stage 4 or 5 chronic kidney disease (eGFR, <30 ml per minute per 1.73 m^2 of body-surface area) were eligible to participate in the trial if they were not receiving dialysis and had not undergone kidney transplantation. All eligible patients were required to have had a decrease of more than 2 ml per minute per 1.73 m^2 per year in the eGFR during the previous 2 years and to have been receiving treatment with an ACE inhibitor, an angiotensin-receptor blocker, or both for more than 6 months.

We calculated the eGFR using the four-variable equation used in the Modification of Diet in Renal Disease (MDRD) study, as updated in 2005 (MDRD175). Exclusion criteria included uncontrolled hypertension or a history of myocardial infarction or stroke within the previous 3 months. Full inclusion and exclusion criteria are provided in the protocol. All the patients provided written informed consent.

Randomization

Patients were randomly assigned in a 1:1 ratio either to discontinue or to continue RAS inhibitors. Randomization was performed with the use of a centralized internet-based system. Minimization was used to ensure balance between the two groups for the following variables: age (<65 years or ≥65 years), eGFR (<15 or ≥15 ml per minute per 1.73 m^2), diabetes (type 1, type 2, or none), mean arterial pressure (<100 or ≥100 mm Hg), and proteinuria (protein:creatinine ratio, <885 or ≥885). (For the calculation of the ratio of protein to creatinine, urinary protein was measured in milligrams and urinary creatinine in grams. To convert these measures to milligrams per millimole, multiply by 0.113.) Blood pressure was measured according to usual care in each practice; measurement was not standardized.

Treatment

In the group that discontinued RAS inhibitors, any guideline-recommended antihypertensive agent other than a RAS inhibitor could be used

to control blood pressure.[15] Reinitiation of RAS inhibitors was permitted only as a last resort if other agents had failed or were associated with unacceptable side effects. In the continuation group, the responsible clinician chose the agent and dose of the RAS inhibitor and could combine it with any other guideline-recommended antihypertensive agent.[15] In the two groups, the protocol-mandated target blood pressure was 140/85 mm Hg or less, with monitoring as recommended by the U.K. National Institute for Health and Care Excellence in its hypertension guidelines for patients with chronic kidney disease.[13,15]

FOLLOW-UP

The follow-up of all patients took place every 3 months after randomization for 3 years. Data censoring was performed at 3 years, after allowance for the 3-month window of follow-up. The schedule of assessments is detailed in the protocol.

OUTCOMES

The primary outcome was the eGFR at 3 years as calculated according to the MDRD175 four-variable equation.[16] Data for the primary analysis were censored at the initiation of renal-replacement therapy (dialysis or transplantation). Secondary outcome measures included the time until the development of end-stage kidney disease (ESKD) (as defined by the local investigator according to criteria that included terminal palliative care or renal-replacement therapy); a composite of a decrease of more than 50% in the eGFR, the development of ESKD, or the initiation of renal-replacement therapy; hospitalization for any cause; measures of cystatin C and blood pressure; quality of life (as measured on the Kidney Disease Quality of Life 36-Item Short Form Survey, version 1.3); exercise capacity (as assessed by the 6-minute walk test); and cardiovascular events and death. At the time of this report, the transfer and processing of samples for cystatin C measurement had not yet occurred, so the results are not provided here. Secondary mechanistic outcomes included measures of hemoglobin and urinary protein excretion (protein:creatinine ratio).

STATISTICAL ANALYSIS

We determined that the enrollment of 410 patients (205 per trial group) would provide a power of 80% to determine a minimum relevant between-group difference in the eGFR of 5 ml per minute per 1.73 m^2 at an alpha level of 0.05, assuming a loss to follow-up of 20%. This difference would represent an effect size of 0.31, with a standard deviation of 16 ml per minute per 1.73 m^2.

Analyses were based on the intention-to-treat principle and were adjusted for the minimization variables and baseline values (where available). The intention-to-treat population included all the patients who had undergone randomization, regardless of what treatment (if any) they had received. All available data for patients who had been lost to follow-up, had withdrawn from the trial, or had died before trial completion were included in the analysis. The statistical analysis plan did not include a provision for correction for multiplicity, so secondary outcomes are reported as point estimates and 95% confidence intervals. The widths of confidence intervals have not been adjusted for multiple comparisons and may not be used for hypothesis testing. Full details regarding the analysis methods are provided in the statistical analysis plan, available with the protocol.

We used a repeated-measures, mixed-effects linear regression model (which included a term for the interaction of the time with treatment group) to estimate the between-group difference in eGFR at 3 years. A compound symmetry covariance structure was assumed. Any measurements of eGFR that were made after patients had initiated dialysis or undergone kidney transplantation were excluded. To examine the effect of data that were not missing at random, we performed sensitivity analyses by fitting pattern-mixture and joint models for the primary outcome. We also repeated analyses for the primary outcome with the use of two other four-variable equations for the eGFR calculation: the Chronic Kidney Disease Epidemiology Collaboration 2009 (CKD-EPI 2009) equation and the MDRD186 equation. Details regarding these analyses are provided in the Supplementary Appendix, available at NEJM.org.

Continuously distributed secondary outcomes, such as blood pressure, were analyzed with the use of the same methods that were used in the primary analysis, but data were not censored at the time of initiation of renal-replacement therapy. Categorical (dichotomous) secondary outcomes were analyzed with the use of a Poisson regression model with robust standard errors to

estimate the relative risk and 95% confidence interval, because the log-binomial model did not converge. We used a Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals for time-to-event outcomes, such as the development of ESKD or the initiation of renal-replacement therapy. Categorical safety outcome measures (i.e., hospitalization and serious adverse events) were summarized as the percentage of patients with these events.

Data collection for kidney outcomes did not distinguish between ESKD and renal-replacement outcomes (i.e., both outcomes used the same end-point code), although investigators could note the specific outcome. Prespecified subgroup analyses were performed only for the primary outcome according to the minimization variables. Time and subgroup were included in the model to allow for the possibility of differential changes over time within subgroups, time according to subgroup, and the three-way interaction among the variables of treatment, time, and subgroup. Although all data were included in the regression models for the subgroup analyses, only estimates of differences at 3 years are presented. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and Stata software, version 17 (StataCorp).

RESULTS

PATIENTS

From July 11, 2014, to June 19, 2018, a total of 17,290 patients were screened at the 39 participating centers, among whom 1210 patients were invited to participate in the trial (Fig. 1). Of these patients, 411 at 37 centers underwent randomization to a trial group (with 206 assigned to the discontinuation group and 205 assigned to the continuation group). Follow-up continued until June 19, 2021. The median follow-up was 3 years (mean [±SD], 2.7±0.8 years).

The characteristics of the patients at baseline are shown in Table 1 and Table S1 in the Supplementary Appendix. The median age was 63 years; 281 patients (68%) were men, and 60 (15%) were non-White. The median eGFR at baseline was 18 ml per minute per 1.73 m^2; 118 patients (29%) had an eGFR of less than 15 ml per minute per 1.73 m^2. The median protein:creatinine ratio was 1018 (interquartile range, 248 to 2195), and the median hemoglobin level was 11.6 g per deciliter (interquartile range, 10.7 to 12.5). Diabetes (either type 1 or type 2) had been diagnosed in 153 patients (37%), diabetic nephropathy in 87 (21%), hypertensive or renovascular nephropathy in 68 (17%), genetic diseases in 81 (20%), and glomerulonephritis in 76 (18%). Clinically overt cardiovascular disease was not common (Table S2). Most patients (58%) were taking three or more antihypertensive medicines; 268 (65%) were receiving a statin (Tables S3 and S4). Of the 411 patients, 163 (40%) were taking a bicarbonate supplement.

TREATMENT ADHERENCE

During the first 3 months, treatment adherence was reported in 180 patients (94.2%) in the discontinuation group and in 179 patients (94.2%) in the continuation group. At 3 years, treatment adherence was reported in 50 of 57 patients (88%) in the discontinuation group and in 53 of 69 patients (77%) in the continuation group (Table S5).

PRIMARY OUTCOME

At 3 years, among the 411 patients who had undergone randomization, the least-squares mean (±SE) eGFR was 12.6±0.7 ml per minute per 1.73 m^2 in the discontinuation group and 13.3±0.6 ml per minute per 1.73 m^2 in the continuation group (difference, −0.7; 95% confidence interval [CI], −2.5 to 1.0; P=0.42), with a negative value favoring the outcome in the continuation group (Fig. 2A, Table 2, and Table S6). No heterogeneity in outcome according to the prespecified subgroups was observed (Fig. 2B). The results of sensitivity analyses that were performed with pattern-mixture models and a joint model were similar to the primary-outcome results, as were those obtained with the use of the CKD-EPI 2009 and MDRD186 four-variable equations (Tables S7 through S10 and Figs. S1 through S17).

SECONDARY OUTCOMES

At 3 years, ESKD or renal-replacement therapy had occurred in 128 of 206 patients (62%) in the discontinuation group and in 115 of 205 patients (56%) in the continuation group (adjusted hazard ratio, 1.28; 95% CI, 0.99 to 1.65) (Fig. 2C). The number of patients who underwent renal-replacement therapy (including those with ESKD) or had a decrease of more than 50% in

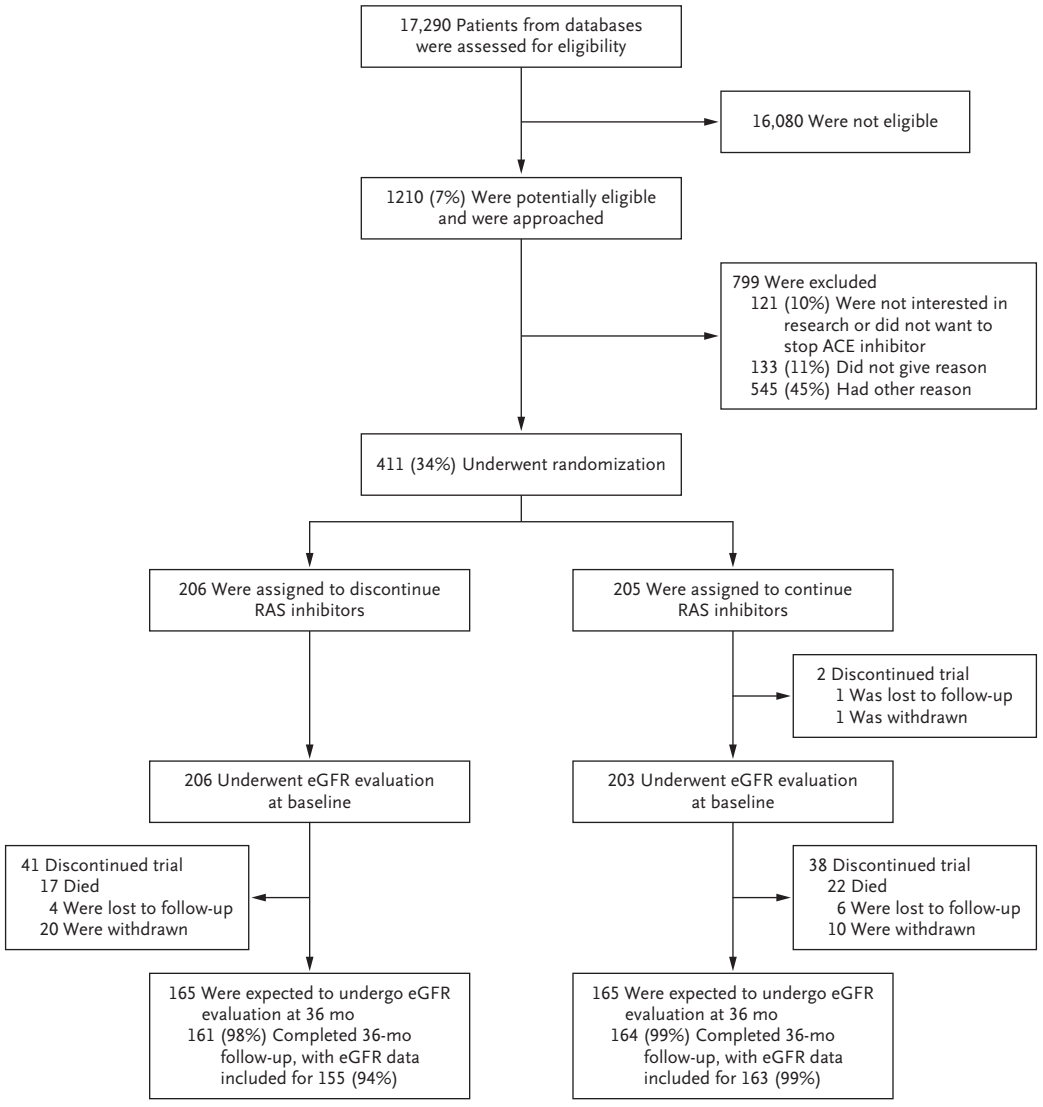


Figure 1. Randomization and Outcomes.

Details are shown regarding the screening, potential eligibility, randomized assignments, and disposition of the trial patients. Among the patients who died during the trial, three had completed the 3-year assessment before death, so their data were included in the analysis. This factor explains the difference in the total number of deaths that were reported in the trial. ACE denotes angiotensin-converting enzyme, and RAS renin–angiotensin system. Details regarding the methods that were used for screening and the determining of eligibility are provided in the Supplementary Appendix.

the eGFR was 140 of 206 (68%) in the discontinuation group and 127 of 202 (63%) in the continuation group (adjusted relative risk, 1.07; 95% CI, 0.94 to 1.22) (Table 2). The numbers of hospitalizations for any reason were similar in the discontinuation group and the continuation group (414 and 413, respectively), as were the numbers of cardiovascular events (108 and 88, respectively). Death was reported in 20 patients in the discontinuation group and in 22 patients in the continuation group (hazard ratio, 0.85; 95% CI, 0.46 to 1.57) (Fig. S18).

In the first 15 months after randomization, both systolic and diastolic blood-pressure values were higher in the discontinuation group than in the continuation group. After that point,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	RAS Inhibitor Discontinuation Group (N=206)	RAS Inhibitor Continuation Group (N=205)
Demographic		
Age group		
<65 yr	116 (56)	110 (54)
≥65 yr	90 (44)	95 (46)
Male sex — no. (%)	140 (68)	141 (69)
Race — no. (%)†		
White	171 (83)	180 (88)
Black	16 (8)	7 (3)
Asian	14 (7)	16 (8)
Other	5 (2)	2 (1)
Medical history		
Smoking status — no. (%)		
Never smoked	86 (42)	100 (49)
Ex-smoker	97 (47)	80 (39)
Current smoker	23 (11)	23 (11)
Missing data	0	2 (1)
Diabetes — no. (%)		
Yes		
Type 1	9 (4)	11 (5)
Type 2	66 (32)	67 (33)
No	131 (64)	127 (62)
Source of chronic kidney disease — no. (%)‡		
Glomerulonephritis: primary, secondary, or multisystem	45 (22)	31 (15)
Tubulointerstitial disease	3 (1)	3 (1)
Hereditary including ADPKD	42 (20)	39 (19)
Renal vascular disease or hypertension	32 (16)	36 (18)
Diabetic nephropathy	43 (21)	44 (21)
Other cause	21 (10)	30 (15)
Unknown	37 (18)	34 (17)
Blood pressure — mm Hg		
Median systolic (IQR)	136 (129 to 147)	138 (126 to 147)
Median diastolic (IQR)	77 (70 to 82)	77 (70 to 82)
Mean arterial pressure — mm Hg		
Median (IQR) — mm Hg	97 (91 to 102)	97 (92 to 103)
Distribution — no. (%)		
<100 — mm Hg	132 (64)	129 (63)
≥100 — mm Hg	74 (36)	76 (37)

Table 1. (Continued.)

Characteristic	RAS Inhibitor Discontinuation Group (N=206)	RAS Inhibitor Continuation Group (N=205)
Laboratory values		
Median hemoglobin (IQR) — g/dl	11.6 (10.8 to 12.7)	11.5 (10.7 to 12.4)
Median serum creatinine (IQR) — mg/dl	3.4 (2.7 to 4.2)	3.4 (2.7 to 4.2)
Estimated glomerular filtration rate		
Median (IQR) — ml/min/1.73 m^2	18 (14 to 22)	18 (14 to 21)
Distribution — no. (%)		
<15 ml/min/1.73 m^2	58 (28)	60 (29)
≥15 ml/min/1.73 m^2	148 (72)	145 (71)
Median rate of decrease over 24 mo (IQR) — ml/min/yr	–4.8 (–7.6 to –3.3)	–4.7 (–7.3 to –3.5)
Median potassium (IQR) — mmol/liter	5 (4.6 to 5.4)	5 (4.6 to 5.4)
Protein:creatinine ratio§		
Median (IQR)	960 (230 to 2089)	1035 (265 to 2230)
Distribution — no. of patients(%)		
<885	97 (47)	98 (48)
≥885	109 (53)	107 (52)

* Details regarding the patients' baseline data are provided in Table S1 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. ADPKD denotes autosomal dominant polycystic kidney disease, and IQR interquartile range.
† Race was reported by the patients.
‡ Patients could have more than one source of chronic kidney disease.
§ The protein:creatinine ratio was calculated with urinary protein measured in milligrams and urinary creatinine in grams. To convert these measures to milligrams per millimole, multiply by 0.113.

blood-pressure values were similar in the two groups (Fig. S19), as were the number of antihypertensive medicines that were prescribed during the trial (Table S11).

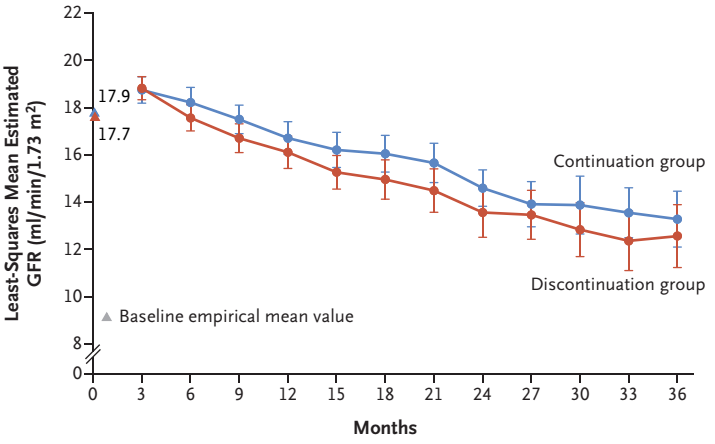
At 3 years, the least-squares mean (±SE) distance covered during a 6-minute walk test was 394±19 m in the discontinuation group and 412±9 m in the continuation group (estimated adjusted mean difference, –18 m; 95% CI, –57 to 22) (Table S12). There were no meaningful between-group differences in the various domains that were measured regarding quality of life (Table S13).

During the first year after randomization, the discontinuation group had a transient increase in the urinary protein:creatinine ratio, but little between-group difference was observed thereafter (estimated adjusted mean difference at 3 years, –9; 95% CI, –673 to 655) (Table S14 and Fig. S20). The mean hemoglobin level was similar in the two groups at 3 years (Table S15).

ADVERSE EVENTS

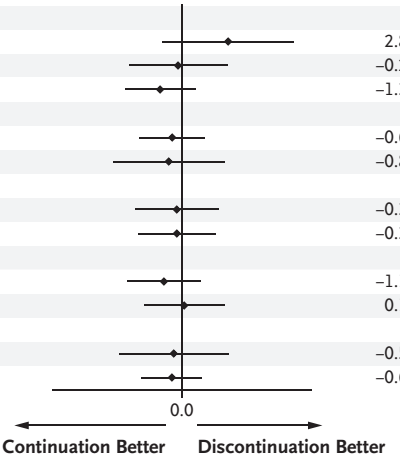
Overall, there were 490 serious adverse events, of which 21 may have been related to the trial-group assignment, as adjudicated by the investigator, with similar numbers of patients in each group (Table 2 and Tables S16 to S18). The numbers of serious adverse cardiovascular, vascular, and heart-failure events were also similar in the two groups. One suspected serious adverse reaction, a possible transient ischemic attack, was reported in the discontinuation group approximately 15 months after randomization. The early changes in blood pressure as a result of the discontinuation of RAS inhibitors were recorded as adverse events (Table S16).

A Primary Outcome

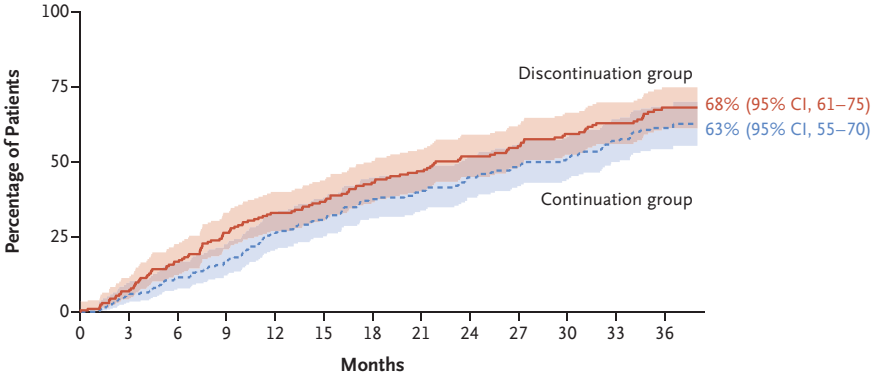


B Subgroup Analysis of the Primary Outcome at Yr 3

Subgroup	Discontinuation Group	Continuation Group	Mean Difference in Estimated GFR at 3 Yr (95% CI)
	no. of patients		
Diabetes			
Type 1	9	11	2.89 (−1.22 to 6.99)
Type 2	66	67	−0.24 (−3.33 to 2.84)
None	131	127	−1.36 (−3.57 to 0.84)
Mean arterial pressure			
<100 mm Hg	132	129	−0.61 (−2.65 to 1.43)
≥100 mm Hg	74	76	−0.82 (−4.30 to 2.65)
Age			
<65 yr	116	110	−0.32 (−2.92 to 2.28)
≥65 yr	90	95	−0.32 (−2.72 to 2.09)
Protein:creatinine ratio			
<885	97	98	−1.12 (−3.41 to 1.16)
≥885	109	107	0.14 (−2.37 to 2.65)
Estimated GFR			
<15 ml/min/1.73 m²	58	60	−0.51 (−3.92 to 2.91)
≥15 ml/min/1.73 m²	148	145	−0.62 (−2.52 to 1.27)



C Renal-Replacement Therapy or End-Stage Kidney Disease



No. at Risk

Discontinuation group	206	190	165	145	129	119	106	97	86	77	70	61	35
Continuation group	205	190	175	162	142	131	115	107	97	90	85	71	43

Figure 2 (facing page). Primary Outcome and Key Secondary Outcome.

Panel A shows the results of the primary analysis of the estimated glomerular filtration rate (GFR) over the 3-year follow-up period among the patients who discontinued RAS inhibitors and those who continued to receive them. I bars indicate 95% confidence intervals (CIs). Panel B shows the results of the prespecified subgroup analysis of the primary outcome, with the between-group difference in the estimated GFR expressed in milliliters per minute per 1.73^2 of body-surface area. The protein:creatinine ratio was calculated with protein measured in milligrams and creatinine in grams. Prespecified subgroup analyses were performed only for the primary outcome according to the minimization variables. To allow for the possibility of differential changes over time within subgroups, time according to subgroup and the three-way interaction among treatment, time, and subgroup were included in the model. Panel C shows Kaplan–Meier curves indicating the percentage of patients who underwent renal-replacement therapy or had end-stage kidney disease at 3 years. Shading indicates 95% CIs.

DISCUSSION

In this trial, we evaluated the effects of the discontinuation of RAS inhibitors in patients with advanced and progressive chronic kidney disease. We determined that patients in the discontinuation group did not have a clinically relevant increase in the eGFR (the primary outcome), either overall or in prespecified subgroups defined according to age, severity of chronic kidney disease, the presence or absence of diabetes or proteinuria, or blood pressure. During the 3 years of follow-up, the numbers of patients who had ESKD or had undergone renal-replacement therapy were similar in the two groups, as were the frequency of cardiovascular events and death. During the first year of follow-up, higher levels of systolic and diastolic blood pressures and proteinuria were observed in the discontinuation group, but there was little difference in these measures thereafter, which reflected the initiation of antihypertensive agents other than RAS inhibitors. No material differences in quality of life or exercise capacity were observed between the two groups.

Data from previous trials have been inconsistent regarding whether the use of RAS inhibitors is nephroprotective in patients with advanced chronic kidney disease. Two earlier post hoc analyses of randomized trials comparing RAS inhibitors with placebo, which included a small percentage of patients with advanced chronic kidney disease, suggested that the use of RAS inhibitors may be beneficial in such patients.[17,18] However, in a small observational study involving 52 patients, investigators found that the discontinuation of RAS inhibitors in patients with advanced chronic kidney disease led to a mean increase in the eGFR of 10 ml per minute per 1.73 m^2 from baseline to 12 months and an increase in or stabilization of the eGFR in all but 4 patients.[12] The analysis of a large observational registry also suggested that the discontinuation of RAS inhibitors reduced the risk of progression to ESKD.[19] Our findings do not support the hypothesis that the discontinuation of RAS inhibitors in patients with advanced and progressive chronic kidney disease would improve kidney function, quality of life, or exercise capacity.

In patients with chronic kidney disease, the rate of decline in the eGFR is a good predictor of the development of ESKD.[20] Over a 3-year period, preservation of the eGFR slope by more than 0.75 ml per minute per 1.73 m^2 per year predicts a clinically relevant delay in the progression of chronic kidney disease.[21] This measure has been used as a surrogate outcome in several randomized trials.[22-25] Although the use of RAS inhibitors has been found to slow the decline in eGFR in patients with mild or moderate chronic kidney disease,[17,18,26] our findings are consistent with the possibility that these drugs may not be as helpful in patients with advanced and progressive chronic kidney disease. In our trial, the level of blood-pressure control was similar in the two groups during follow-up. If we assume that blood-pressure control is important in this population, our findings are consistent with the concept that the choice of guideline-recommended antihypertensive agents may not be important in maintaining such control.

Data have been lacking from randomized trials that have specifically assessed the effect of RAS inhibitors on cardiovascular risk in patients with advanced chronic kidney disease who were not receiving dialysis. However, in a large observational trial, Fu et al. found an increase in the incidence of major cardiovascular events and death among patients who had discontinued RAS inhibitors.[19] In a separate retrospective cohort study, Qiao et al. also found that stopping

Table 2. Primary Outcome with Sensitivity Analyses, Secondary Outcomes, and Adverse Events.*

Outcomes	Discontinuation Group	Continuation Group	Treatment Effect (95% CI)†
Primary outcome			
Estimated glomerular filtration rate at 3 yr — ml/min/1.73²‡	12.6±0.7	13.3±0.6	−0.7 (−2.5 to 1.0)
Sensitivity analyses at 3 yr			
According to equation used§			
CKD-EPI creatinine	12.0±0.7	12.8±0.6	−0.8 (−2.5 to 1.0)
MDRD186	13.4±0.7	14.1±0.6	−0.8 (−2.6 to 1.1)
According to pattern-mixture models with use of MDRD175 equation¶			
Flat value 5 imputation for MNAR	9.4±0.4	9.9±0.4	−0.5 (−1.7 to 0.7)
Flat value 7 imputation for MNAR	10.6±0.4	11.0±0.4	−0.4 (−1.5 to 0.7)
LOCF imputation for MNAR	12.1±0.4	12.5±0.4	−0.4 (−1.5 to 0.6)
According to joint model with use of MDRD175	12.2±0.4	13.0±0.4	−0.8 (−2.0 to 0.4)
Secondary clinical outcomes			
ESKD or renal-replacement therapy — no./total no. (%)	128/206 (62)	115/205 (56)	1.28 (0.99 to 1.65)‖
Renal-replacement therapy (including patients with ESKD) or >50% decrease in estimated glomerular filtration rate — no./total no. (%)	140/206 (68)	127/202 (63)	1.07 (0.94 to 1.22)**
Death — no./total no. (%)	20/206 (10)	22/205 (11)	0.85 (0.46 to 1.57)‖
Hospitalization			
Patients — no./total no. (%)	135/206 (66)	147/205 (72)	—
No. of events	414	413	—
Blood pressure at 3 yr — mm Hg			
Systolic	140±2	140±2	0 (−4 to 5)
Diastolic	76±1	76±1	0 (−2 to 3)
Distance on 6-minute walk test at 3 yr — m	394±19	412±9	−18 (−57 to 22)
Adverse events			
Serious adverse events			
Patients — no./total no. (%)	107/206 (52)	101/205 (49)	—
No. of events	237	253	—
No. of cardiovascular events††	108	88	—
Secondary mechanistic outcomes			
Hemoglobin at 3 yr — g/dl	11.9±0.1	11.9±0.1	0 (−0.3 to 0.4)
Protein:creatinine ratio at 3 yr‡‡	1699±274	1708±195	−9 (−673 to 655)
Treatment with erythropoietin-stimulating agent — no./total no. (%)	114/206 (55)	112/202 (55)	0.96 (0.81 to 1.13)**

* Plus–minus values are least-squares means ±SE. ESKD denotes end-stage kidney disease.

† All treatment effects are shown as the mean between-group difference except as marked. All analyses were adjusted for minimization variables and baseline value (where available). For any outcomes that were continuous data and collected at multiple time points, the time point and treatment according to time interaction were also included in the model. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

‡ The estimated glomerular filtration rate was calculated with the use of the four-variable equation used in the Modification of Diet in Renal Disease (MDRD) study, as updated in 2005 (MDRD175). A negative value for the treatment effect in this category favors the outcome in the continuation group. P=0.42 for this comparison.

§ In this sensitivity analysis, the estimated glomerular filtration rate was calculated with equations used in the Chronic Kidney Disease Epidemiology Collaboration 2009 (CKD-EPI 2009) and the MDRD186.

¶ This sensitivity analysis was performed to examine the effect of data that were missing not at random (MNAR). LOCF denotes last observation carried forward.

‖ This treatment effect is reported as a hazard ratio.

** This treatment effect is reported as a relative risk.

†† Cardiovascular events included hospitalization for heart failure, myocardial infarction, stroke, heart-failure events, angina, coronary intervention, hypertension, atrial arrhythmias, venous thromboembolism, peripheral vascular disease, and other cardiac conditions.

‡‡ The protein:creatinine ratio was calculated with protein measured in milligrams and creatinine in grams. To convert these measures to milligrams per millimole, multiply by 0.113.

RAS inhibitors increased the risk of cardiovascular events and death and did not reduce the need for renal-replacement therapy.[27] Our trial did not have sufficient power to investigate the effect of the discontinuation of RAS inhibitors on cardiovascular events or mortality. However, because our findings are consistent with a lack of advantage for such discontinuation with respect to kidney function, there is little rationale to conduct a larger randomized trial to investigate cardiovascular safety.

Our trial has several limitations. The patients were demographically similar to those included in the U.K. National Renal Registry,[28] but patients with non-White ethnic backgrounds were poorly represented, which limits the generalizability of our results to other racial or ethnic groups (Table S19). Failure to adhere to the randomly assigned management strategy may have influenced the results. The open-label nature of the trial may have affected clinical care and subjective end points, including quality of life and exercise capacity. We included patients who were receiving RAS inhibitors at the time of randomization and hence excluded those who had already discontinued these agents. The findings may not generalize to patients with higher levels of proteinuria (e.g., ratio of urinary protein to creatinine, >2655 [with protein measured in milligrams and creatinine in grams]). The median baseline value for the urinary ratio was 1018, which suggests that few patients had nephrotic syndrome. Numerically more patients who discontinued RAS inhibitors had progression to ESKD, so a larger trial might have shown an advantage to continuing with RAS inhibition.

In this trial, the discontinuation of RAS inhibitors in patients with advanced and progressive chronic kidney disease did not lead to a clinically relevant change in the eGFR or a between-group difference in the long-term rate of decline in the eGFR.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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