Renin-angiotensin system inhibition in advanced chronic kidney disease

STOP ACEi Trial Investigators

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22-10639.R2 **Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease**

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Abstract

Background

Renin-angiotensin system inhibitors (RASi), both angiotensin converting-enzyme inhibitors (ACEi) and receptor blockers (ARB), slow progression of mild and moderate chronic kidney disease (CKD). However, some suggest that discontinuation of RASi in patients with advanced CKD might increase estimated glomerular filtration (eGFR) or slow its decline.

Methods

This investigator-initiated, multi-center, open-label trial randomly assigned patients with advanced and progressive CKD (eGFR less than 30 mL/min/1.73m^2) to stop or to continue RASi. The primary outcome was the difference in eGFR at three years, excluding measurements of eGFR after starting kidney replacement therapy (KRT). Secondary outcomes included development of end-stage kidney disease (ESKD), a composite of either a >50% decline in eGFR or KRT (including ESKD), hospitalizations, blood pressure, exercise capacity and quality of life. Cardiovascular events and deaths were recorded. Pre-specified subgroups included age, eGFR, diabetes-type, mean arterial pressure and proteinuria**.**

Results

We randomized 411 patients. At three years, mean difference in eGFR between groups was -0.7 mL/min/1.73m^2 (95% confidence interval [CI], -2.5 to 1.0; P=0.42) with no heterogeneity

in pre-specified subgroups. ESKD or KRT occurred in 128 (62%) and 115 (56%) patients randomized to stop or to continue RASi, respectively (hazard ratio, 1.28; 95% CI, 0.99 to 1.65). Cardiovascular events (108 versus 88) and deaths (20 versus 22) were similar for participants randomized to stop and continue RASi, respectively. There were 409 adverse events recorded.

Conclusions

Stopping RASi in advanced and progressive CKD did not lead to clinically relevant changes in eGFR or difference in the long-term rate of decline in eGFR.

Trial Registration: STOP ACEi EudraCT Number, 2013-003798-82; ISTRCTN 62869767)

Keywords: Angiotensin converting-enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), chronic kidney disease (CKD), eGFR, proteinuria, randomized controlled trial, End Stage Kidney Disease.

For patients with mild or moderate chronic kidney disease (CKD), renin-angiotensin system inhibitors (RASi), including angiotensin converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), reduce blood pressure (BP), slow decline in estimated glomerular filtration rate (eGFR), reduce proteinuria[1-5] and delay progression to advanced CKD (Stage-4 or Stage-5), which is associated with impaired quality of life,[6] greater need for kidney replacement therapy (KRT) and a higher risk of cardiovascular events and mortality.[7-11] However, there is little evidence that RASi benefit patients with advanced CKD. An observational study suggested that stopping RASi in this setting may increase eGFR[12] and current guidelines do not provide specific advice on whether to continue or stop ACEi/ARBs for advanced CKD.[13]

Accordingly, we conducted the STOP-ACEi trial in patients with advanced and progressive CKD to assess whether or not stopping RASi would improve or stabilize eGFR.[14]

METHODS

Trial Design and Oversight

This was an investigator-initiated, multi-center, randomized, open-label trial that compared stopping or continuing RASi for patients with advanced and progressive stage-4 or stage-5 CKD. Details of its objectives, design, and methods have been published.[14]

The protocol (see Supplementary Appendix, available at NEJM.org) was approved by relevant health authorities and institutional review boards. The Birmingham Clinical Trials Unit (BCTU) co-ordinated the trial. The management group was chaired by the Chief Investigator (SB). An independent blinded steering committee oversaw the trial's conduct, and an unblinded data and safety monitoring committee monitored patient safety.

SB, NI and PC designed and obtained funding for the trial. JGFC provided advice on cardiovascular outcomes and helped design the trial. NI and SM provided statistical oversight and oversaw the final data analyses. SB, AK, PC, JGFC, NI, SM contributed to data interpretation. SB was the chief investigator and wrote the first draft of the manuscript that was edited by all co-authors; 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) with stage-4 or stage-5 CKD (eGFR less than 30 mL/min/1.73m^2, using the four-variable modification of diet in renal disease (MDRD) equation ($MDRD_{175}$), who were not receiving dialysis and had not received a kidney transplant were eligible for participation, provided eGFR had declined by more than 2 mL/min/1.73m^2 per year over the previous two years and they were receiving treatment with either an ACEi, ARB or their combination, for more than six months. Exclusion criteria included uncontrolled hypertension or a history of myocardial infarction or stroke within the previous three months. Full inclusion and exclusion criteria are provided in the protocol. All participants provided written informed consent.

Trial Procedures—Randomization, Treatment and Follow-Up

Patients were randomly assigned in a 1:1 ratio to either discontinue or continue RASi using a centralized internet-based system hosted at BCTU. Minimization was used to ensure balance between groups for the following variables: age (<65 years or ≥65 years), eGFR (<15 mL/min/1.73m^2 or ≥15 mL/min/1.73m^2), diabetes (type I diabetes, type II diabetes or no diabetes), mean arterial pressure (MAP; <100 or ≥100 mmHg), and proteinuria (protein:creatinine ratio <100 or ≥100 mg/mmol). BP was measured as typically done in each practice; measurement was not standardized.

Trial Treatment

For those randomized to stopping RASi, any guideline-recommended antihypertensive agent other than RASi could be used to control blood pressure (BP).[15] Re-initiation of RASi was permitted only as a last resort if other agents had failed or were not tolerated. For those randomized to continue RASi, the responsible clinician chose the agent and dose and could combine it with any other guideline-recommended anti-hypertensive agent.[15] For both groups, the protocol target BP was ≤140/85 mmHg with monitoring as recommended by UK National Institute for Health and Care Excellence (NICE) Hypertension and CKD guidelines.[13, 15]

Follow-Up

Patient follow-up took place every three months from randomization to three years. Censoring was then at three years, allowing for the three-month window of follow-up. The schedule of assessments is detailed in the protocol.

Outcomes

The primary outcome was the difference in eGFR at three years using the $MDRD_{175}$ four-variable equation.[16] The primary outcome was censored at KRT. Secondary outcome measures included the time taken to reach end-stage kidney disease (ESKD) (as defined by the local investigator, including terminal palliative care or KRT), a composite of either a >50% decline in eGFR or reaching ESKD or starting KRT (wherever it occurs), hospitalization for any cause, cystatin-C, BP, quality of life (using the KDQoL-SF^{TM}v1.3 questionnaire), exercise capacity (assessed by a 6-minute walk test), cardiovascular events, and mortality. The transfer and processing of samples for cystatin-C has not yet occurred, therefore these results are not reported. We also measured blood hemoglobin concentrations and urinary protein excretion.

Statistical Considerations

To detect a minimum relevant difference (MRD) in eGFR between groups of 5 mL/min/1.73m^2 (i.e., an effect size of 0.31, assuming a standard deviation of 16 mL/min/1.73m^2) with 80% power and alpha = 0.05, required 410 participants (205 per group) including a 20% attrition rate.

Analyses were based on the intention-to-treat (ITT) principle and were adjusted for the minimization variables and baseline value (where available). The ITT population included all participants analyzed according to the group to which they were originally assigned, regardless of what treatment (if any) they received. All available data for participants that were lost to follow-up or withdrew or had died prior to completing the final trial follow-up, were included in the analysis. The reference group for all analyses was those who continued RASi. The statistical analysis plan did not provide correction for multiplicity, therefore secondary outcomes are reported as point estimates and 95% confidence intervals. Further, confidence interval widths were not adjusted for multiplicity and may not be used for hypothesis testing.

Analyses were performed with SAS software version 9.4 (SAS Institute) and Stata software version 17 (Stata-Corp).

Full details of the analysis methods are provided in the Statistical Analysis Plan (Supplementary Appendix, available at NEJM.org). The primary outcome was analyzed using a repeated measures, mixed-effects linear regression model (which included a time-by- treatment-group interaction term) to estimate the difference in eGFR at three years. A compound symmetry covariance structure was assumed. Any measurements of eGFR made after starting dialysis or receiving a kidney transplant were excluded. To examine the impact of data missing not at random, sensitivity analyses (fitting pattern mixture and joint models) were performed for the primary outcome. We also repeated analyses for the primary outcome using the CKD-EPI 2009 and $MDRD_{186}$ four-variable equations for eGFR (see Box for formulas in the Supplementary Appendix).

Continuously distributed secondary outcomes, such as BP, were analyzed using the same methods as for the primary outcome but were not censored when KRT was started. Categorical (dichotomous) secondary outcomes were analyzed using a Poisson regression model with robust standard errors to estimate the relative risk and 95% confidence interval, as the log-binomial model failed to converge. Time-to-event outcomes, such as ESKD, were analyzed using a Cox proportional-hazards model to obtain a hazard ratio and 95% confidence interval. Categorical (dichotomous) safety outcome measures (hospitalizations, serious adverse events [SAEs]) were summarized as the proportion of participants and percentages using a chi-squared test with these events.

Data collection for kidney outcomes did not distinguish between ESKD and KRT outcomes (i.e., they were coded the same, apart from the free text entry). Pre-specified 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 by subgroup and the three-way interaction between treatment, time and subgroup were included in the model. Although all data were included in the regression models for the subgroup analyses, estimates of differences are only presented at three years.

RESULTS

Patient Characteristics

Between July 11th, 2014 and June 19th, 2018, 17,290 patients were screened at 39 centers in the UK and 1,210 invited to participate in the trial (**Fig. 1**), of whom 411 patients at 37 centers were randomized; 206 to stop and 205 to continue RASi. Follow up continued until June 19th 2021. The median follow-up was 3 years (mean (SD) 2.7 (0.8) years).

Patient characteristics at baseline are shown in **Tables 1 and S1**. Median age was 63 years, 281 (68.4%) were men and 60 (14.6%) were non-white. Median eGFR at baseline was 18 mL/min/1.73m^2; 118 (28.7%) had an eGFR of less than 15mL/min/1.73m^2. The median level of proteinuria was 115 mg/mmol (interquartile range 28 to 248) and median hemoglobin 11.6 g/dL (interquartile range, 10.7 to 12.5). Diabetes (87; 21.2%), hypertensive/renovascular nephropathy (68; 16.5%), genetic diseases (81; 19.7%), and glomerulonephritis (76; 18.5%) accounted for most cases of CKD (**Table 1**). Clinically overt cardiovascular disease was not common (**Table S2**). Most patients (58%) were on three or more antihypertensive medicines; 268 (65.5%) were on a statin (**Tables S3 and S4**). Forty percent (163/411) were on bicarbonate supplements.

Treatment Adherence

In the first three months, 180 (94.2%) of participants who were randomized to stop RASi and 179 (94.2%) of those randomized to continue RASi did so. At three years, of those who did not withdraw from the trial, commence dialysis, receive a kidney transplant or die, 50 (87.7%) of those randomized to stop remained off RASi and 53 (76.8%) of those randomized to continue remained on RASi (**Table S5**).

Primary Outcome

At three years, changes in eGFR were similar for those randomized to stop compared to continue RASi (estimated adjusted mean difference: -0.7 mL/min/1.73m^2 [95% CI, -2.5 to +1.0]; p=0.42; negative values indicate an advantage to continuing RASi). (**Fig. 2a, Tables 2 and S6**), There was no heterogeneity of treatment effect in pre-specified subgroups (**Fig 2b**). Sensitivity analyses using pattern mixture models and a joint model gave similar results as did analyses using CKD-EPI 2009 and MDRD$_{186}$ 4-variable equations. (**Tables S7-10, Figs. S1-17**).

Secondary Outcomes

Of patients randomized to stop RASi, 128 (68% cumulative incidence at three years) developed ESKD or had KRT (dialysis or transplantation) compared to 115 (63%) randomized to continue RASi (adjusted hazard ratio [HR] 1.28 [95% CI, 0.99 to 1.65]) (**Fig. 2c**). The number of participants with a >50% decline in eGFR or starting KRT including ESKD was also similar (140 (68%) if RASi was stopped versus 127 (63%) if RASi was continued (adjusted relative risk [RR] 1.07 [95% CI, 0.94 to1.22])) (**Table 2**). The number of hospitalizations for any reason (414 versus 413) and cardiovascular (CV) events (108 versus 88) were similar for the stop and continue groups respectively (**Table 2**). Twenty patients randomized to stop and 22 randomized to continue RASi died (HR 0.85 (95% CI, 0.46 to 1.57) (**Table 2, Fig. S18**).

In the first 15 months both systolic and diastolic BP were higher in those randomized to stop rather than continue RASi. After this point, BP was similar in each group (**Fig. S19a and 19b**).

The number of anti-hypertensive medicines prescribed during the trial were similar between groups (**Table S11**).

At three years, the mean distance covered during a 6-minute walk test for those randomized to stop RASi was 383 meters (SD 180) compared to 431 meters (SD 115) in those randomized to continue RASi (estimated adjusted mean difference -18 [95% CI, -57 to 22]) (**Table 2 and S12**). There was no difference in quality of life between groups as measured by various domains of KDQOL-SF™v1.3. (**Table S13**).

There was a transient increase in proteinuria over the first year in those randomized to stop RASi (estimated mean difference 108 mg/mmol (95% CI, 72 to 145) but little difference thereafter (estimated mean difference at three years -0.9 (95% CI, -76 to 74) mg/mmol (**Tables 2 and S14, and Fig. S20**). Mean hemoglobin concentration was similar for each group at three years (**Tables 2 and S15**).

Adverse Events and Safety

Overall, there were 490 serious adverse events, of which 21 may have been related to the trial intervention, with similar numbers for each group (**Tables 2, and S16 to S18**). Serious adverse cardiovascular, vascular and heart failure events were also similar for each group. One suspected unexpected serious adverse reaction, a possible transient ischaemic attack, was reported approximately 15 months after the patient was randomized to stop RASi. The early changes in BP as a result of stopping RASi were recorded as recognized adverse events (Supplementary Appendix).

DISCUSSION

The present trial evaluated discontinuation of RASi in patients with advanced and progressive CKD. The trial excluded a clinically relevant improvement in eGFR after stopping RASi for such patients, overall or in pre-specified subgroups by age, severity of CKD, diabetes, proteinuria, or BP. The number of patients developing ESKD or receiving KRT and the rate of cardiovascular events and death during three years of follow-up was similar for those who stopped or continued RASi. Systolic and diastolic BP and proteinuria were greater over the first year of follow-up in those randomized to stop RASi but there was little difference thereafter, reflecting initiation of anti-hypertensive agents other than RASi. No differences in quality of life or exercise capacity were observed for those who stopped or continued RASi.

There are conflicting data about whether RASi is nephro-protective in advanced CKD. Two earlier post-hoc analyses of randomized trials comparing RASi to placebo included a small proportion of patients with advanced CKD and suggested that RASi were beneficial in advanced CKD.[17, 18] A small (n=52) observational study reported that withdrawing RASi from patients with advanced CKD led to a mean increase in eGFR of 10 (16 to 27) mL/min/1.7 3m^2 over 12 months, and an increase or stabilization in eGFR in all but four patients[12]. Analysis of a large observational registry also suggested that stopping RASi reduced progression to ESKD.[19] Our trial suggests that stopping RASi in patients with advanced and progressive CKD does not improve kidney function, quality of life or exercise capacity.

For patients with CKD, the rate of decline in eGFR is a good predictor of developing ESKD[20]. Preservation of eGFR slope by >0.75 mL/min/1.73m^2 per year over three years predicts a clinically relevant delay of CKD progression.[21] This measure has been used as a surrogate

outcome in several recent randomized trials.[22-25] Although, RASi slow the decline in eGFR for patients with mild or moderate CKD[17, 18, 26] our trial was consistent with the possibility that they might not do so for patients with advanced and progressing CKD. Of note, BP control was similar for each group during follow-up. Assuming that control of BP is important for this population, our trial js consistent with the concept that choice of guideline-recommended anti-hypertensive agent may not be important.

Randomized trials that have specifically assessed the effect of RASi on cardiovascular risk in patients with advanced non-dialysis CKD have been lacking. However, in a large observational registry, Fu et al. reported an increase in major CV events and mortality for patients who stopped RASi.[19] In a separate retrospective cohort study, Qiao et al. also found that stopping RASi increased the risk of CV events and mortality and did not reduce the need for KRT.[27] Our trial lacked sufficient power to investigate the effect of withdrawing RASi on CV events or mortality. However, because our trial is consistent with lack of advantage in stopping RASi from the perspective of kidney function, there is little rationale to conduct a larger randomized trial to investigate cardiovascular safety.

Our trial has several limitations. Participants were demographically similar to those included in the UK National Renal Registry[28] but ethnicities other than white are poorly represented, limiting generalisability to other 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 endpoints including quality of life and exercise capacity. We only included patients on RASi 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., uPCR >300mg/mmol). The median baseline value was 115 mg/mmol suggesting few cases had nephrotic syndrome.

Numerically more patients who stopped RASi progressed to ESKD; a larger trial might have demonstrated an advantage to continuing with RASi.

In summary our trial found that discontinuing RASi for patients with advanced and progressive CKD did not lead to a clinically relevant change in eGFR or difference in the rate of long-term decline in eGFR.

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Conflicts of Interest

There are no conflicts of interest related to this research with any of the authors.

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Figure Legends

Figure 1: Consort Diagram.

Details the screening, potential eligibility, randomized allocation and disposition of participants.

Expected and Received refer to the number of eGFR evaluations for the primary endpoint analysis.

* 3 participants died but completed the 36 months assessment prior to death and so are not included in the consort diagram; this explains the difference in the total deaths reported in the trial.

RASi = renin angiotensin inhibitors. A detailed explanation for the screening and potentially eligible patients can be found in the supplementary appendix.

Figure 2a: Primary Outcome plot of the Least Squares Means ± 95% Confidence intervals (CI) over time for Revised $MDRD_{175}$ 4-variable Equation.

Difference in estimated glomerular filtration rate over three years (analyzed by least squares means using the revised $MDRD_{175}$ 4-variable equation)

Figure 2b: Pre-specified Subgroup Analysis for the Primary Outcome at Three Years

Pre-specified 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 by subgroup and the three-way interaction between treatment, time and subgroup were included in the model. Although all data were included in the regression models for the subgroup analyses, estimates of differences are only presented at three years. Numbers in each subgroup are shown in Table 1.

MAP = mean arterial pressure, eGFR = estimated glomerular filtration rate

Figure 2c: Time to Kidney Replacement Therapy or End-Stage Kidney Disease

Kaplan-Meier curves show time to end stage kidney disease for each randomized group.

Table 1 Baseline Characteristics

Baseline Characteristics *(*Minimization variables)*		**Stop RASi (N=206)**	**Continue RASi (N=205)**
Age group*	<65 years	116(56%)	110 (54%)
	≥65 years	90 (44%)	95 (46%)
Gender	Male	140(68%)	141 (69%)
Ethnicity	White	171 (83%)	180 (88%)
	Black	16 (8%)	7 (3%)
	Asian	14 (7%)	16 (8%)
	Any other	5 (2%)	2 (1%)
Smoking status	Never smoked	86 (42%)	100 (49%)
	Ex-smoker	97 (47%)	80 (39%)
	Current smoker	23 (11%)	23 (11%)
	Missing	0 (0%)	2 (1%)
Diabetes*	Type 1	9 (4%)	11 (5%)
	Type 2	66 (32%)	67 (33%)
	No diabetes	131(64%)	127 (62%)
Etiology of CKD[$]			
Glomerulonephritis (primary/secondary/multisystem)		45	31
Tubulointerstitial Disease		3	3
Hereditary (including ADPKD)		42	39
Renal vascular disease and/or Hypertension		32	36
Diabetic nephropathy		44	43
Other cause of CKD		21	30
Unknown		37	34
Systolic BP	Median [IQR]	138 [126 to 147]	136 [129 to 147]
Diastolic BP	Median [IQR]	77 [70 to 82]	77 [70 to 82]
MAP	Median [IQR]	97 [92 to 103]	97 [91 to 102]
MAP group*	>100	132(64%)	129 (63%)
	≥100	74 (36%)	76 (37%)
Hemoglobin (Hb) (g/dL)	Median [IQR]	11.6 [10.8 to 12.7]	11.5 [10.7 to 12.4]
Serum Creatinine (mg/dl)	Median [IQR]	3.4 [2.7 to 4.2]	3.4 [2.7 to 4.2]
eGFR mL/min/1.73m^2	Median [IQR]	18 [14 to 21]	18 [14 to 22]
eGFR group*	<15ml/min	58 (28%)	60 (29%)
	≥15ml/min	148(72%)	145 (71%)
Rate of decline eGFR	Median [IQR]	-4.7 [-7.3 to -3.5]	-4.8 [-7.6 to -3.3]
Potassium (mmol/L)	Median [IQR]	5 [4.6 to 5.4]	5 [4.6 to 5.4]
Proteinuria (mg/mmol)	Median [IQR]	117 [30 to 252]	108.5 [26 to 236.3]
Proteinuria group*	<100	97 (47%)	98 (48%)
	≥100	109(53%)	107 (52%)

$Not mutually exclusive. Full baseline data available in Table S1 in supplementary appendix
BP = blood pressure; MAP = mean arterial pressure; eGFR = estimated glomerular filtration rate.
ADPKD = autosomal dominant polycystic kidney disease; CKD = chronic kidney disease

Table 2: Primary Outcome, Sensitivity Analysis and Secondary Outcomes

Outcomes	Stop RASi	Continue RASi	Mean difference or Relative Risk or Hazard ratio (95% CI)[1]
Primary outcome – LS-Mean ± [SE] at 3 years			-0.7 (-2.5, 1.0)
eGFR using revised $MDRD_{175}$ 4-variable	12.6 ± [0.7]	13.3 ± [0.6]	P=0.42
Primary outcome sensitivity analysis – LS-Mean ± [SE] at 3 years			
eGFR using CKD-EPI Creatinine Equation	12.0 ± [0.7]	12.8 ± [0.6]	-0.8 (-2.5, 1.0)
eGFR using original $MDRD_{186}$ 4-variable	13.4 ± [0.7]	14.1 ± [0.6]	-0.8 (-2.6, 1.1)
Primary outcome sensitivity analysis – Pattern Mixture Models			
eGFR using revised $MDRD_{175}$ 4-variable with:			
Flat value 5 imputation for MNAR eGFR values	-	-	-0.5 (-1.7, 0.7)
Flat value 7 imputation for MNAR eGFR values	-	-	-0.4 (-1.5, 0.7)
LOCF imputation for MNAR eGFR values	-	-	-0.4 (-1.5, 0.6)
Primary outcome sensitivity analysis – Joint Model			
eGFR using revised $MDRD_{175}$ 4-variable	-	-	-0.8 (-2.0, 0.4)
Secondary clinical outcomes and adverse events			
Time to ESKD or KRT – no. with outcome/total no. (%)	128/206 (62%)	115/205 (56%)	1.28 (0.99, 1.65)
KRT or >50% decline in eGFR – no. with outcome/total no. (%)	140/206 (68%)	127/202 (63%)	1.07 (0.94, 1.22)
Mortality – no. with outcome/total no. (%)	20/206 (10%)	22/205 (11%)	0.85 (0.46, 1.57)
Number with any hospitalization – no. with outcome/total no. (%)	135/206 (66%)	147/205 (72%)	-
Total hospitalizations – total events	*414*	*413*	-
N with any SAE – no. with outcome/total no. (%)	107/206 (52%)	101/205 (49%)	-
Total SAE's – total events	*237*	*253*	-
Total Cardiovascular events – total events	108	88	-
Systolic BP (mmHg) – LS-Mean ± [SE] at 3 years	140 ± [2]	140 ± [2]	0 (-4, 5)
Diastolic BP (mmHg) – LS-Mean ± [SE] at 3 years	76 ± [1]	76 ± [1]	0 (-2, 3)
Distance (in meters) from six-minute walk test – LS-Mean ± [SE] at 3 years	394 ± [19]	412 ± [9]	-18 (-57, 22)
Secondary mechanistic outcomes			
Hemoglobin (g/dL) – LS-Mean ± [SE] at 3 years	11.9 ± [0.1]	11.9 ± [0.1]	0 (-0.3, 0.4)
Urine protein excretion (mg/mmol) – LS-Mean ± [SE] at 3 years	192 ± [31]	193 ± [22]	-1 (-76, 74)
N with ESA treatment – no. with outcome/total no. (%)	114/206 (55%)	112/202 (55%)	0.96 (0.81, 1.13)

*all treatment effects are shown as mean difference except for "Time taken to reach ESKD (KRT or terminal palliative care)" and "Mortality" which is reported as hazard ratio, and "KRT or >50% decline in eGFR" and "N with ESA treatment" which is reported as a relative risk.
1-all analysis were adjusted for minimization variables and baseline value (where available). For any outcomes that was continuous data and collected at multiple time-point, time-point and treatment by time interaction were also included in the model.
MNAR=Missing Not at Random; LOCF=Last Observation Carried Forward; KRT=Kidney Replacement Therapy; ESKD=End Stage Kidney Disease; LS-Mean=Least squares mean; SE=Standard Error; eGFR = Estimated Glomerular Filtration Rate; BP = Blood Pressure; ESA = Erythropoetin Stimulating Agent; SAE = Serious Adverse Event.
CV=Cardiovascular Events which included those reported during safety and included the following (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.
Note:

- Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
- In the secondary clinical analysis seven patients designated with ESKD did not have KRT and were likely conservative therapy.