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Early Response in Albuminuria and Long-Term Kidney Protection during Treatment with an Endothelin Receptor Antagonist: A Prespecified Analysis from the SONAR Trial

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ABSTRACT

Background Whether early reduction in albuminuria with atrasentan treatment predicts its long-term kidney-protective effect is unknown.

Methods To assess the long-term effects on kidney outcomes of atrasentan versus placebo in the SONAR trial, we enrolled patients who had type 2 diabetes and CKD (stage 2–4) and a urinary albumin creatinine ratio (UACR) of 300–5000 mg/g; participants were receiving maximum tolerated renin-angiotensin system inhibition. After 6 weeks exposure to 0.75 mg/day atrasentan (enrichment period), participants were randomized (stratified by UACR response during enrichment, ranging from ≤60% to >0%) to continue atrasentan or transition to placebo. Primary kidney outcome was a composite of sustained serum creatinine doubling or ESKD.

Results UACR response to atrasentan during enrichment persisted throughout the double-blind treatment phase and predicted the primary kidney outcome, whereas UACR levels with placebo remained below pre-enrichment values in the two highest UACR response strata, and exceeded pre-enrichment values in the two lowest strata. As a result, early UACR response to atrasentan during enrichment was also associated with the primary kidney outcome during placebo. Accordingly, the predictive effect of early albuminuria changes during atrasentan was eliminated after placebo correction, leading to a consistent relative risk reduction for the primary kidney outcome with atrasentan compared with placebo, irrespective of the initial UACR response. The difference between atrasentan and placebo in UACR during double-blind treatment was also consistent across UACR response strata.

Conclusions Our findings do not support UACR response as a causal predictor of atrasentan's treatment effect. However, the variable trajectory in UACR with placebo, aspects of the trial design, day-to-day variability in albuminuria, and potential long-lasting effects of atrasentan may have contributed.

CKD is recognized as a growing public health problem.[1,2] Clinical practice guidelines recommend early detection for CKD and appropriate treatment to slow progression of kidney function decline and reduce the risk of long-term complications.[3] Albuminuria is a strong risk marker of CKD progression and cardiovascular complications. Screening and monitoring of albuminuria is therefore an important component in the management of patients with CKD.

Various drugs such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) and the more recent sodium glucose cotransporter 2 inhibitors and mineralocorticoid receptor antagonists reduce albuminuria and the risk of kidney failure and cardiovascular events.[4,5] Observational analyses from clinical trials demonstrating the efficacy of these interventions have consistently shown the early reduction in albuminuria, achieved within the first months of treatment, is associated with long-term kidney protection.[6–9] On the basis of these studies, it has been recommended to monitor albuminuria after initiation of these drugs to guide clinical management.[10] However, these observational analyses from clinical trials are prone to selection bias and residual confounding. It is therefore possible that the lower risk of kidney failure among patients in whom albuminuria was reduced is caused by factors unrelated to the reduction in albuminuria. To overcome this bias, one should ideally design a clinical trial that first records albuminuria responses during exposure in an active run-in period, subsequently randomly assigns patients to continue the drug or transition to a placebo treatment, and analyzes the long-term drug effect relative to placebo in subgroups, according to the response in albuminuria during the run-in period.

The selective endothelin A receptor antagonist atrasentan has been demonstrated to reduce albuminuria in patients with type 2 diabetes and CKD.[11] Of note, the albuminuria-lowering effect varied considerably between patients.[11] This favorable effect of atrasentan on albuminuria led to the conduct of a confirmatory clinical trial, the Study of Diabetic Nephropathy with Atrasentan (SONAR) trial, to assess the long-term efficacy and safety of atrasentan. The primary results were reported previously and demonstrated that atrasentan significantly reduced the risk of kidney failure compared with placebo in patients with type 2 diabetes and CKD.[12] The design of the SONAR trial included an open-label active run-in period (termed a response enrichment period), during which all patients received atrasentan 0.75 mg once daily for 6 weeks. After the response-enrichment period, eligible patients were randomly assigned to placebo or atrasentan, stratified by the degree of albuminuria lowering during enrichment. This strategy offered the opportunity to investigate in a placebo-controlled design whether the early reduction in albuminuria to atrasentan predicts its long-term kidney protective effect. We therefore undertook a prespecified analysis of the effect of atrasentan according to the degree of albuminuria response achieved during the response-enrichment period of the SONAR trial.

METHODS

Study Design and Participants
The SONAR trial was a multicentre, double-blind, placebo-controlled, randomized trial evaluating the effects of

Significance Statement

This prespecified analysis of the SONAR trial in patients with type 2 diabetes and CKD demonstrated the early albuminuria reduction during an open-label, 6-week run-in period with atrasentan was associated with a reduced risk for long-term kidney outcomes in patients who continued atrasentan after randomization. But because the early albuminuria reduction also associated with long-term kidney outcomes in patients who transitioned from atrasentan to placebo at randomization, atrasentan's effect on the primary kidney outcome was consistent, regardless of the early albuminuria change, suggesting the early albuminuria response is not a causal predictor for atrasentan's nephroprotective effect. However, the variable UACR trajectory in the placebo arm, aspects of the SONAR trial design, day-to-day variability in albuminuria, and potential long-lasting effects of atrasentan may have contributed.

atrasentan on kidney outcomes in subjects who had type 2 diabetes and CKD. The SONAR trial is registered with ClinicalTrials.gov, number NCT01858532, and the trial protocol including a detailed description of the trial design and statistical analysis plans has been published previously, along with the primary SONAR trial article.[12,13] In brief, patients with type 2 diabetes mellitus and CKD, defined as eGFR of 25–75 ml/min per 1.73m^2 and urinary albumin-creatinine ratio (UACR) of 300–5000 mg/g, who were receiving a maximum tolerated dose of an ACE-inhibitor or ARB, were eligible. Patients prone to fluid retention, defined as B-type natriuretic peptide (BNP) > 200 pg/ml, prior hospital admission for heart failure, or a history of severe edema, could not participate in the trial. After screening, eligible patients received 0.75 mg atrasentan once daily during the 6 weeks response enrichment period, aimed to select patients that were likely to respond to atrasentan, defined as an UACR reduction of ≥30%, and to exclude patients that were prone to atrasentan-induced fluid retention, defined as an increase of ≥3 kg in body weight or an increase in BNP to ≥300 pg/ml.

All responder patients who tolerated atrasentan and a selection of patients who were nonresponders subsequently proceeded to the randomization visit and were assigned in a 1:1 ratio to continue atrasentan 0.75 mg/day or to transition to placebo. Randomization was performed centrally through an interactive voice response system on the basis of a computer-generated randomization schedule. A stratified randomization scheme was used to ensure balance in treatment allocation within geographic regions and with baseline UACR levels (≤ or >1000 mg/g). Additionally, randomization was stratified by UACR change during the response-enrichment period: ≤-60%; -60% to ≤-45%; -45% to ≤-30% (classified as UACR responders); and -30% to ≤-15%; -15% to ≤0%; >0% (classified as UACR nonresponders). This stratification by different UACR response levels was prespecified to assess if the effect of atrasentan compared with placebo on the primary kidney outcome depended on the UACR response during response enrichment.

The median total follow-up period was 2.2 years until the last trial visits (either in clinic or telephone), which occurred by March 29, 2018. Local institutional ethics committees approved the trial protocols at each site. All participants provided written informed consent. The trial was conducted according to the principles outlined in the Declaration of Helsinki.

Outcomes

The primary outcome used to evaluate the efficacy of atrasentan in delaying the progression of CKD was the time to the first occurrence of any of the following components of a composite end point consisting of: doubling of serum creatinine (confirmed by a second serum creatinine measurement ≥30 days later), onset of ESKD (defined as chronic dialysis for >90 days, kidney transplantation, or eGFR <15 ml/min per 1.73m^2, confirmed by a second measurement ≥90 days later), or death from kidney failure. An independent end point committee adjudicated all potential outcomes using rigorous end-point definitions.

Statistical Analysis

The analytical approach and power calculation have been published.[12] The trial was originally powered to capture 425 primary outcomes that provided 90% power to detect a hazard ratio (HR) of 0.73. As described previously, the sponsor decided to stop the trial prematurely due to a lower than expected event rate. At completion of the trial, 184 primary renal events had occurred, providing >80% power to detect an HR of 0.66.[12]

For this prespecified analysis, we performed Cox proportional hazard regression to estimate the HR and the 95% confidence interval (95% CI) for atrasentan, compared with placebo for the primary kidney outcomes in each UACR response stratum. For patients who experienced more than one event during follow-up, survival time to the first relevant end point was used. The treatment effect in the model was adjusted for log-transformed UACR values, serum albumin, age, and eGFR at randomization. To assess whether the treatment effect of atrasentan compared with placebo during double-blind treatment varied by different UACR response levels, we performed prespecified tests for heterogeneity by adding interaction terms between the UACR response stratum, as a categorical variable, and randomized treatment assignment to the relevant Cox models. We performed *post-hoc* Cox proportional hazard regression to assess the associations between changes in UACR during the response-enrichment period and the primary kidney outcome within the atrasentan and placebo treatment group separately. The model was adjusted for age, sex, race, baseline systolic and diastolic BP, body weight, HbA1c, eGFR, albumin, hemoglobin log-transformed UACR, cardiovascular disease history, diuretic and beta-blocker use at baseline, and change in systolic BP during the response-

enrichment period. We verified Cox proportional hazard assumptions by visual inspection of the log(-log[survival]) curve and by adding a time by treatment interaction to the Cox model. These analyses showed no violations of the model assumptions.

We calculated the difference of change in the geometric mean UACR between the atrasentan and placebo groups during double-blind treatment with a repeated mixed-effects models to determine the effect of atrasentan versus placebo on UACR. We determined the effect of atrasentan relative to placebo on UACR in the overall population and in each UACR response stratum. The mixed-effects model included treatment allocation and time as factor, and an interaction term between treatment allocation and time. The model also included UACR response stratum as factor and interaction terms between treatment assignment and UACR response stratum, time and UACR response stratum, and time, treatment assignment, and UACR response stratum. The model was adjusted for the log-transformed baseline UACR level and interaction term between time and baseline log-transformed UACR. The variance-covariance matrix was assumed to be unstructured, that is, purely data dependent. The same model was used to calculate systolic BP differences between atrasentan and placebo during double-blind treatment.

All analyses were conducted using SAS, version 9.4. A two-sided *P* value <0.05 was considered statistically significant and no adjustment was made for multiplicity.

RESULTS

Baseline Characteristics

The SONAR trial randomized 3668 participants, of whom 2648 were UACR responders (≥30% UACR reduction) and 1020 were nonresponders (<30% UACR reduction). At baseline the median UACR was 829 mg/g (25th to 75th percentile 457–1556). A total of 2055 (56.0%) participants had a UACR <1000 mg/g and 1613 (44.0%) a UACR ≥1000 mg/g. Nearly all participants (98.5%) were using an inhibitor of the renin-angiotensin-aldosterone system (RAAS) at baseline. Across progressively larger UACR response strata, participants were older, had a higher eGFR, serum albumin, and a lower body weight. Median UACR was progressively lower in higher UACR response strata (Table 1). eGFR values before screening were recorded in a random selection of 532 patients whose characteristics were similar to all randomized participants (Supplemental Table 1). The pretrial eGFR decline in these participants was similar between UACR responders with ≥30% UACR reduction during response enrichment compared with UACR nonresponders, with <30% UACR reduction during response enrichment (4.7 ml/min per 1.73m^2 per year, SD 10.3, versus 5.5 ml/min per 1.73m^2, SD 8.7; P=0.39). Baseline characteristics were balanced between atrasentan and placebo groups

Table 1. Patient characteristics at start of the enrichment period according to predefined UACR response strata

Characteristics	UACR ≥60%	UACR 45%–60%	UACR 30%–45%	UACR 15%–30%	UACR 0%–15%	UACR <0%	P for trend
N patients (%)	591	968	1089	479	286	255	
Age, yrs	65.6 (9)	64.6 (9)	64.6 (9)	64.5 (9)	63.1 (9)	62.9 (9)	<0.001
Sex							0.215
Male	420 (71.1)	716 (74.0)	829 (76.1)	356 (74.3)	219 (76.6)	182 (71.4)	
Female	171 (28.9)	252 (26.0)	260 (23.9)	123 (25.7)	67 (23.4)	73 (28.6)	
Body weight, kg	84.3 (19)	84.2 (20)	85.1 (19)	87.4 (20)	85.9 (19)	87.2 (21)	0.028
Systolic BP, mmHg	137.4 (15)	136.4 (15)	135.7 (15)	135.5 (15)	135.5 (15)	137.2 (16)	0.185
Diastolic BP, mmHg	75.0 (10)	74.8 (10)	75.0 (10)	74.3 (10)	75.1 (10)	75.8 (9)	0.482
Hba1c (%)	7.6 (1.5)	7.5 (1.4)	7.6 (1.4)	7.6 (1.5)	7.7 (1.6)	7.6 (1.5)	0.543
Serum creatinine, μmol/L	141 (42)	147 (42)	152 (42)	158 (48)	155 (45)	152 (42)	<0.001
eGFR, ml/min per 1.73m^2	45.6 (15)	44.2 (14)	42.6 (13)	41.2 (15)	42.4 (14)	42.3 (12)	<0.001
Serum albumin, g/L	39.9 (3.4)	39.3 (3.5)	39.1 (3.5)	38.7 (3.8)	38.3 (3.9)	38.7 (3.7)	<0.001
Hemoglobin, g/L	129 (17)	129 (17)	130 (17)	130(17)	128 (18)	128 (18)	0.103
BNP, pg/mL	56 (27–95)	49 (26–89)	46 (25–82)	46 (25–80)	45 (25–85)	47 (27–85)	0.099
UACR, mg/g	660 (389–1188)	806 (448–1431)	884 (496–1619)	955 (486–1879)	1070 (545–2176)	800 (406–1475)	<0.001
Medication use[a]							
Diuretics	500 (84.6)	817 (84.4)	903 (82.9)	396 (82.7)	234 (81.8)	215 (84.3)	0.806
Beta-blockers	271 (45.9)	419 (43.3)	428 (39.3)	189 (39.5)	121 (42.3)	103 (40.4)	0.110
Lipid-lowering drugs	453 (76.6)	761 (78.6)	879 (80.7)	399 (83.3)	221 (77.3)	200 (78.4)	0.086

Numeric variables are presented as mean (SD) or median (25th to 75th percentile) where appropriate. Categorical variables are presented as counts.
[a]All patients had to be on a maximum tolerated dose of an ACE-inhibitor or ARB. P for trend is test for trend across the UACR response strata.

within each enrichment UACR response stratum (Supplemental Table 2).

Greater reductions in BP and eGFR during enrichment were observed in higher UACR response strata, whereas changes in body weight and BNP were similar across UACR response strata (Supplemental Table 3). A total of 3104 participants completed the trial, of whom 2275 were UACR responders with a medium follow-up of 2.2 years, and 829 were UACR nonresponders with a median follow-up of 2.3 years.

Early UACR Change and Kidney Outcomes

To assess whether changes in UACR during atrasentan were associated with subsequent kidney outcomes, we first analyzed the atrasentan group. Among participants who were randomized to continue atrasentan, we observed that the change in UACR during the response enrichment period persisted during the double-blind treatment phase across all UACR response strata. For example, the geometric mean percentage UACR reduction among participants in the ≥60% UACR response stratum was -70.5% (95% CI, -71.6 to -69.4) during response enrichment and -61.4% (95% CI, -66.1 to -56.0) during the double-blind treatment phase (Table 2). In these participants, the incidence of the primary kidney outcome was lower in higher UACR response strata (Figure 1A). In a multivariable Cox model adjusting for differences in patient characteristics across UACR response strata, participants with a >60% decrease in UACR during enrichment had an multivariable adjusted 75% lower hazard for the composite kidney outcome (HR,

0.25; 95% CI, 0.11 to 0.59) compared with participants with a UACR increase <15% (Figure 1A).

To assess whether the association between UACR responses to atrasentan and the primary kidney outcome persisted after taking into account the placebo group, we analyzed the effect of atrasentan compared with placebo in each UACR response stratum. The primary kidney outcome occurred in 152 (8.3%) participants in the atrasentan group and 192 (10.5%) participants in the placebo group (HR, 0.72; 95% CI, 0.58 to 0.89). The relative effect of atrasentan compared with placebo on the primary kidney outcome was consistent across UACR enrichment response strata (P for heterogeneity 0.59; Figure 2). The same was true for the components of the primary kidney outcome: sustained doubling of serum creatinine (Figure 2, P for heterogeneity 0.12) and ESKD (Figure 2, P for heterogeneity 0.19). No heterogeneity was observed for any of these outcomes when interaction tests were undertaken using log-transformed UACR as a continuous variable. Atrasentan reduced the mean rate of change in eGFR compared with placebo by 0.65 ml/min per 1.73m^2 per year (95% CI, 0.28 to 1.01; $P<0.001$). This effect was consistent across UACR enrichment response strata (P for heterogeneity 0.91; Supplemental Figure 1). The effect of atrasentan compared with placebo on heart failure hospitalizations was also consistent across UACR response strata (P for heterogeneity 0.72; Supplemental Figure 2).

To examine why the association between UACR responses to atrasentan and kidney outcomes blunted after considering the placebo arm, we assessed UACR trajectories within the placebo group. Among participants who

A

Atrasentan group

UACR response stratum	n Events/ N Patients	Event Rate per 100 patient-yrs	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	P for trend
Composite Renal Outcome					<0.001
≥60%	8/297	1.4		0.25 (0.11−0.59)	
45−<60%	32/484	3.2		0.55 (0.31−0.97)	
30−<45%	39/544	3.5		0.58 (0.34−1.00)	
15−<30%	38/241	7.6		1.01 (0.58−1.76)	
0−<15%	21/142	7.0		Reference	
<0%	14/126	5.7		1.17 (0.59−2.34)	
Doubling Serum Creatinine					0.002
≥60%	2/297	0.3		0.10 (0.02−0.44)	
45−<60%	26/484	2.6		0.66 (0.34−1.29)	
30−<45%	28/544	2.5		0.60 (0.31−1.15)	
15−<30%	28/241	5.5		1.07 (0.55−2.06)	
0−<15%	15/142	5.0		Reference	
<0%	13/126	5.3		1.53 (0.71−3.30)	
ESRD					0.009
≥60%	8/297	1.4		0.29 (0.12−0.69)	
45−<60%	28/484	2.8		0.61 (0.33−1.14)	
30−<45%	31/544	2.8		0.59 (0.32−1.08)	
15−<30%	33/241	6.6		1.04 (0.56−1.91)	
0−<15%	17/142	5.6		Reference	
<0%	9/126	3.7		1.06 (0.46−2.41)	

0.13 0.25 0.5 1.0 2.0 4.0

Hazard ratio (95%CI)

B

Placebo group

UACR response stratum	n Events/ N Patients	Event Rate per 100 patient-yrs	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	P for trend
Composite Renal Outcome					0.012
≥60%	16/294	2.7		0.58 (0.30−1.14)	
45−<60%	38/484	3.8		0.62 (0.37−1.04)	
30−<45%	51/545	4.7		0.68 (0.41−1.11)	
15−<30%	40/238	7.8		1.09 (0.65−1.84)	
0−<15%	26/144	9.0		Reference	
<0%	21/129	8.8		1.33 (0.73−2.44)	
Doubling Serum Creatinine					0.057
≥60%	13/294	2.2		0.80 (0.37−1.72)	
45−<60%	28/484	2.8		0.74 (0.40−1.38)	
30−<45%	37/545	3.3		0.80 (0.44−1.45)	
15−<30%	27/238	5.2		1.32 (0.71−2.49)	
0−<15%	18/144	6.2		Reference	
<0%	16/129	6.6		1.71 (0.83-3.51)	
ESRD					<0.001
≥60%	9/294	1.5		0.27 (0.12−0.62)	
45−<60%	29/484	2.9		0.41 (0.24−0.72)	
30−<45%	43/545	3.9		0.50 (0.30−0.83)	
15−<30%	34/238)	6.6		0.76 (0.44−1.31)	
0−<15%	26/144	9.0		Reference	
<0%	20/129	8.3		1.19 (0.64−2.19)	

0.13 0.25 0.5 1.0 2.0 4.0
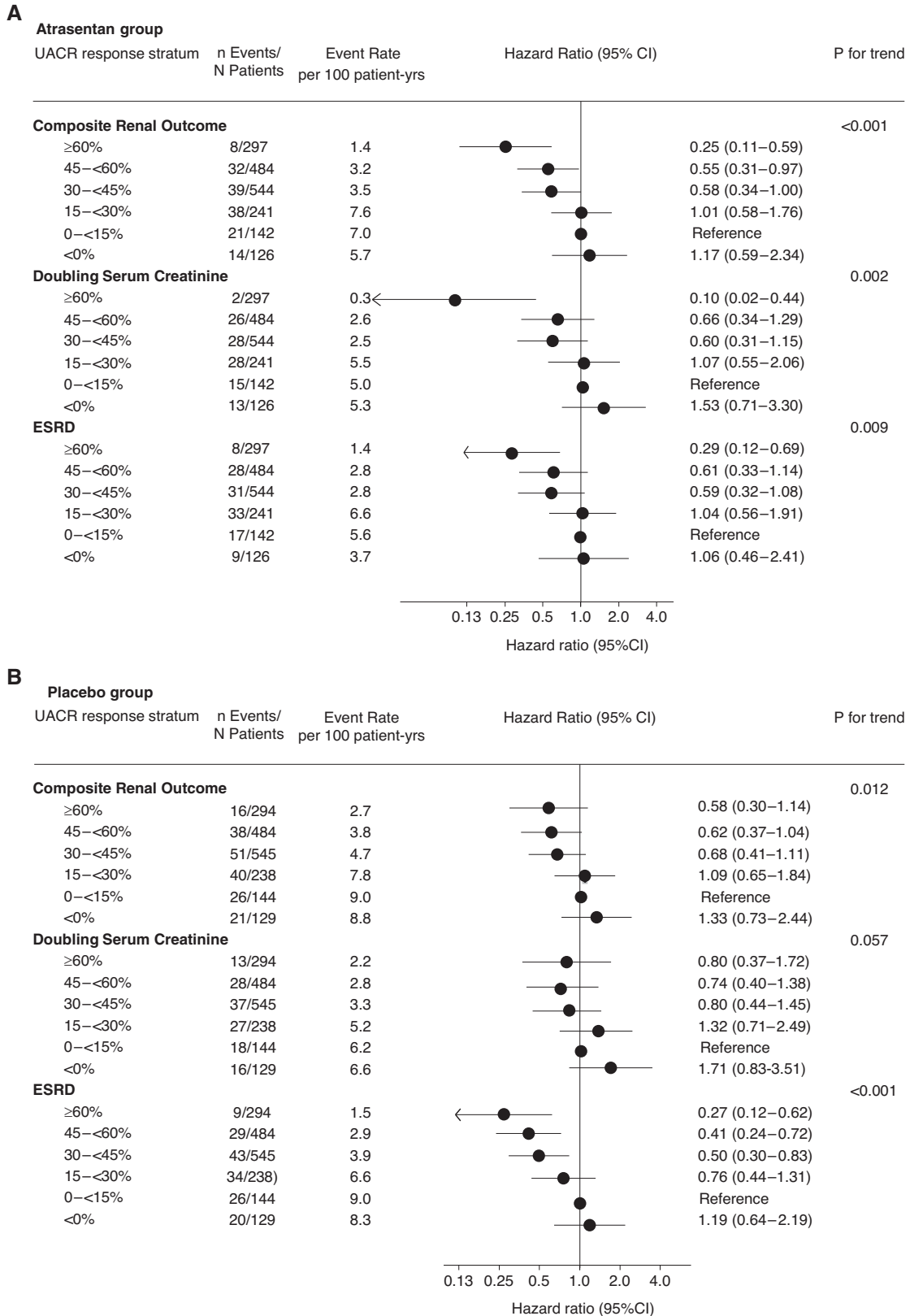
Hazard ratio (95%CI)

Figure 1. Association between changes in UACR during the 6-weeks response-enrichment period and subsequent kidney outcomes recorded during the double-blind treatment period. (A) The association in participants who continued atrasentan during the double-blind treatment period. (B) The association in participants who transitioned from atrasentan to placebo at randomization.

Table 2. Percent change (95%CI) in UACR in the atrasentan and placebo groups during response enrichment, double-blind treatment, and after discontinuation of atrasentan

UACR Response Strata	Atrasentan			Placebo		
	Δ UACR from Pre-enrichment to End of Enrichment	Δ UACR from Pre-enrichment to Double-blind Treatment	Δ UACR from Last On-treatment to Off-treatment	Δ UACR from Pre-enrichment to End of Enrichment	Δ UACR from Pre-enrichment to Double-blind Treatment[a]	Δ UACR from Last On-treatment to Off-treatment
≥60% reduction	−70.5 (−71.6, −69.4)	−61.4 (−66.1, −56.0)	49.0 (43.6, 53.9)	−71.6 (−72.7, −70.6)	−28.1 (−36.8, −18.3)	53.2 (49.7, 56.5)
45–60% reduction	−52.9 (−54.3, −51.5)	−44.8 (−50.0, −39.1)	48.1 (43.8, 52.0)	−52.2 (−53.6, −50.8)	−15.6 (−23.5, −7.0)	38.8 (34.1, 41.2)
30–45% reduction	−38.6 (−40.3, −36.9)	−36.6 (−42.4, −30.2)	42.0 (37.4, 46.2)	−39.1 (−40.8, −37.4)	10.6 (0.8, 21.4)	35.4 (31.8, 38.8)
15–30% reduction	−23.9 (−26.9, −20.7)	−30.7 (−39.5, −20.7)	38.2 (30.5, 45.0)	−23.9 (−27.0, −20.7)	26.7 (11.2, 44.4)	26.2 (19.9, 31.9)
0–15% reduction	−6.5 (−11.4, −1.3)	−0.2 (−16.5, 19.3)	36.5 (26.1, 45.4)	−11.4 (−16.0, −6.5)	40.8 (17.5, 68.8)	29.9 (22.0, 36.9)
≥0% increase	23.7 (16.9, 31.0)	18.4 (−4.1, 46.1)	36.0 (24.1, 46.1)	36.3 (28.8, 44.2)	48.3 (20.8, 81.9)	−0.9 (−13.1, 9.9)

[a]We had expected UACR levels in the placebo group would return to baseline pre-enrichment values and the change in UACR from pre-enrichment to double-blind treatment would be 0%. However, UACR levels stayed low in the responder strata (indicated by the negative signs) and increased to values above pre-enrichment in the nonresponder strata.

were transitioned to placebo at randomization, the change in UACR observed during the response-enrichment phase was similar compared with participants who continued atrasentan after randomization (Table 2, Figure 3 and 4A). However, during the double-blind treatment phase, UACR levels did not return to pre-enrichment values. Specifically, in the ≥60% UACR reduction and 45 to <60% UACR reduction strata, UACR levels remained below pre-enrichment values (Table 2, Figure 3 and 4B). In contrast, in the <15% UACR reduction and >0% UACR increase strata, UACR values increased to levels above pre-enrichment values (Table 2 and Figure 3). Thus, in the

placebo group, where we expected that UACR would return to pre-enrichment values during double-blind treatment, we observed that the geometric mean change in UACR from pre-enrichment to the double-blind treatment phase decreased in the UACR responder strata, whereas it increased in UACR nonresponder strata (Table 2 and Figure 4B). Accordingly, the higher UACR response strata had lower UACR values and a lower incidence rate of the primary kidney outcome than the poor response strata (Supplemental Figure 3). The lower risk of the primary kidney outcomes persisted after adjustment for differences in patient characteristics (Figure 1B). Because the UACR
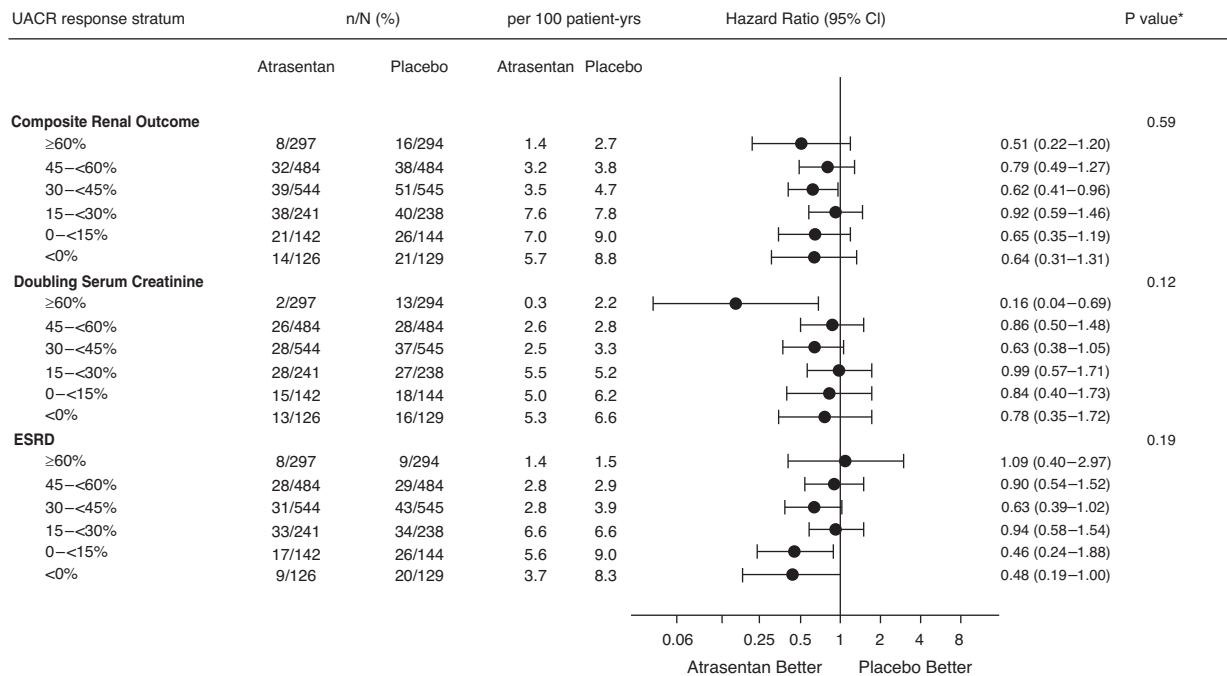
UACR response stratum	n/N (%)		per 100 patient-yrs		Hazard Ratio (95% CI)		P value*
	Atrasentan	Placebo	Atrasentan	Placebo			
Composite Renal Outcome							0.59
≥60%	8/297	16/294	1.4	2.7		0.51 (0.22–1.20)	
45−<60%	32/484	38/484	3.2	3.8		0.79 (0.49–1.27)	
30−<45%	39/544	51/545	3.5	4.7		0.62 (0.41–0.96)	
15−<30%	38/241	40/238	7.6	7.8		0.92 (0.59–1.46)	
0−<15%	21/142	26/144	7.0	9.0		0.65 (0.35–1.19)	
<0%	14/126	21/129	5.7	8.8		0.64 (0.31–1.31)	
Doubling Serum Creatinine							0.12
≥60%	2/297	13/294	0.3	2.2		0.16 (0.04–0.69)	
45−<60%	26/484	28/484	2.6	2.8		0.86 (0.50–1.48)	
30−<45%	28/544	37/545	2.5	3.3		0.63 (0.38–1.05)	
15−<30%	28/241	27/238	5.5	5.2		0.99 (0.57–1.71)	
0−<15%	15/142	18/144	5.0	6.2		0.84 (0.40–1.73)	
<0%	13/126	16/129	5.3	6.6		0.78 (0.35–1.72)	
ESRD							0.19
≥60%	8/297	9/294	1.4	1.5		1.09 (0.40–2.97)	
45−<60%	28/484	29/484	2.8	2.9		0.90 (0.54–1.52)	
30−<45%	31/544	43/545	2.8	3.9		0.63 (0.39–1.02)	
15−<30%	33/241	34/238	6.6	6.6		0.94 (0.58–1.54)	
0−<15%	17/142	26/144	5.6	9.0		0.46 (0.24–1.88)	
<0%	9/126	20/129	3.7	8.3		0.48 (0.19–1.00)	

0.06 0.25 0.5 1 2 4 8
Atrasentan Better   Placebo Better

Figure 2. Effects of atrasentan compared with placebo on the primary kidney end point and its components during the double-blind treatment period according to UACR response during the response enrichment period.
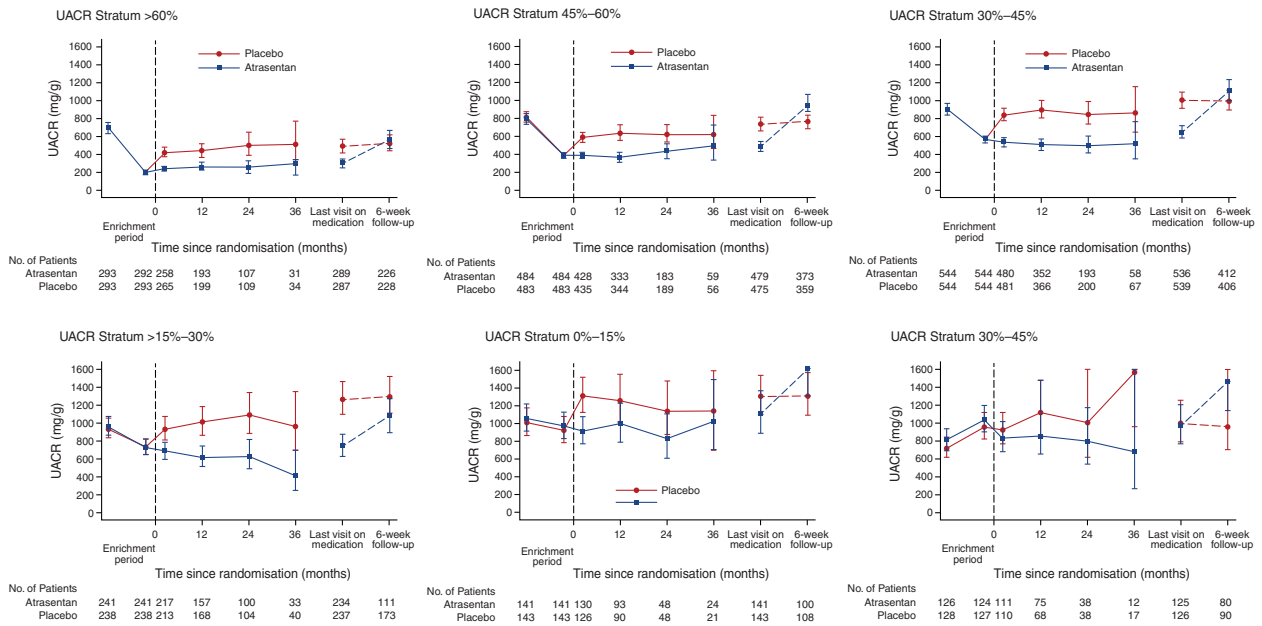
Figure 3. Changes in UACR during response enrichment and double-blind treatment in each UACR response stratum.

values did not reverse to pre-enrichment values during double-blind treatment, the overall difference in UACR of 39.6% (95% CI, 35.0% to 43.8%) between atrasentan and placebo during double-blind treatment was consistent irrespective of the UACR response strata (P for heterogeneity 0.18; Figure 4C). Additional analyses also demonstrated no clear heterogeneity in placebo-subtracted effects of atrasentan on systolic BP across UACR response strata, although the largest UACR response stratum showed a greater BP difference (Supplemental Table 4).

UACR Changes During Wash-out
During the 6-week wash-out phase at the end of the trial, there was no change in UACR among placebo participants

in any UACR response strata. Among atrasentan-assigned participants in the $\geq 60\%$ UACR response stratum, the increase in UACR during wash-out was significantly less than the decrease during enrichment ($P<0.001$; Table 2 and Figure 3). In contrast, in the 15%–30% and <15% UACR response strata, the increase in UACR during wash-out was significantly larger than the reduction during enrichment (both $P<0.001$), whereas in the >0% UACR strata, UACR further increased after atrasentan discontinuation at the end of the trial ($P<0.001$; Figure 3).

Diuretic Treatment
Analyses to assess whether escalation of concomitant therapies during enrichment could have led to misclassification
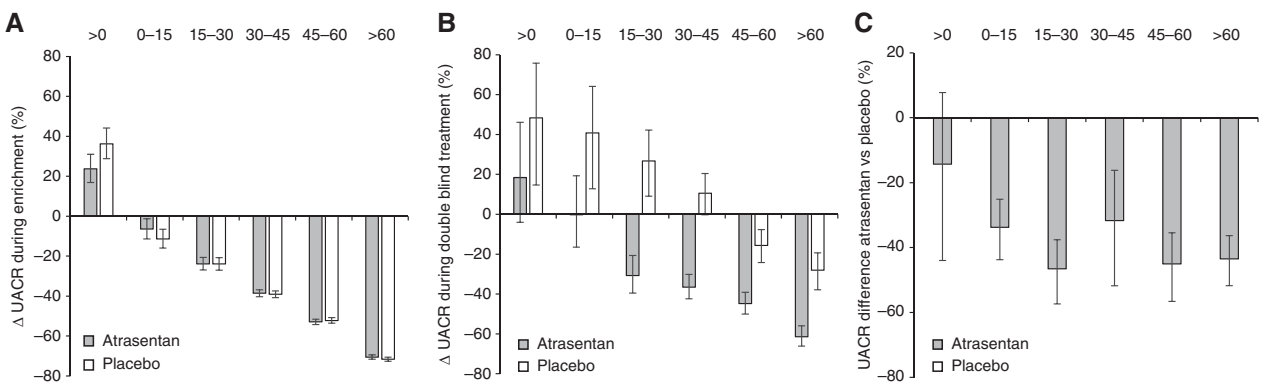
Figure 4. Changes in UACR from (A) pre-enrichment to end-enrichment, and (B) pre-enrichment to double-blind treatment in the atrasentan and placebo group. (C) The difference in UACR between atrasentan and placebo during double-blind treatment.

Table 3. Number of patients (percentages) in whom diuretic treatment was escalated during enrichment in each UACR response stratum

UACR Response Stratum	All Participants (n=3668)	Atrasentan (n=1834)	Placebo (n=1834)
≥60% reduction	156 (26.4)	76 (25.6)	80 (27.2)
45%–60% reduction	233 (24.1)	116 (24.0)	117 (24.2)
30%–45% reduction	207 (19.0)	110 (20.2)	97 (17.8)
15%–30% reduction	104 (21.7)	53 (22.0)	51 (21.4)
0%–15% reduction	59 (20.6)	28 (19.7)	31 (21.5)
≥0% increase	46 (18.1)	14 (11.1)	32 (25.0)
P value	0.0039	0.019	0.033

Diuretic treatment could be initiated regardless whether patients were already using diuretics at start of enrichment. In combination with Table 1, the total number of patients using a diuretic can exceed 100%. Escalation of diuretic treatment was defined as an increase in the dose of the diuretic or initiation of an additional diuretic (e.g., initiation of a loop diuretic in a patient already using a thiazide diuretic).

of the UACR response during the response enrichment phase showed that escalation of diuretics, defined as an increase of the dose or initiation of an additional diuretic, occurred in a greater proportion of patients in the higher UACR response strata (Table 3). Loop diuretics were most frequently escalated (Supplemental Table 5).

DISCUSSION

The design of the SONAR trial included an enrichment-response period, which enabled us to assess whether early changes in albuminuria predict long-term kidney outcomes in a placebo-controlled design. Within the atrasentan group, larger reductions in albuminuria were statistically significantly associated with a lower risk of kidney outcomes. In participants who transitioned to placebo treatment at randomization, we observed that the early reduction in albuminuria during response enrichment was associated with a lower risk of the kidney outcome. Accordingly, the predictive effect of UACR in the atrasentan group was eliminated after placebo correction. This resulted in a consistent relative risk reduction in kidney outcomes with atrasentan compared with placebo across all UACR strata. Because albuminuria levels after transitioning from atrasentan to placebo did not return to pre-enrichment values during double-blind treatment, the difference in UACR between atrasentan and placebo during double-blind treatment was also similar across all albuminuria response strata.

Earlier trials have shown that early reductions in albuminuria achieved with ACE inhibitors, ARBs, or sodium glucose cotransporter 2 inhibitors are significantly associated with long-term risk reductions for kidney end points.[6,7,14,15] Furthermore, meta-analyses have demonstrated that early treatment effects on albuminuria of

25%–30% are strongly associated with significant benefits on clinical kidney end points.[16] These data support a role for early change in albuminuria as a surrogate for clinical end points in CKD clinical trials. In accord with these studies, we observed within the atrasentan treatment group that a greater reduction in albuminuria in each responder stratum persisted during long-term atrasentan treatment, and was associated with a larger relative risk reduction for the primary kidney outcome. The current data are thus in accordance with those previously observed with ACE inhibitors or ARBs, but were achieved with an intervention that does not directly interfere in the renin-angiotensin system.

However, the previous post-hoc analysis are potentially biased because they correlate changes in albuminuria with outcomes, rather than compare outcomes between randomized groups. Therefore, the possibility that the lower risk of kidney outcomes across progressively higher albuminuria response strata was caused by factors unrelated to the albuminuria lowering effect of atrasentan cannot be excluded. We therefore adjusted the association between albuminuria changes and kidney outcomes for placebo effects. Within the placebo group, a larger reduction in albuminuria observed during atrasentan treatment in the enrichment period was, unexpectedly, associated with a lower incidence of kidney outcomes, so the predictive effect of early albuminuria changes during atrasentan was eliminated after placebo correction. This resulted in a consistent reduction in the risk of kidney outcomes with atrasentan compared with placebo across all UACR response strata, and consistent differences in albuminuria between atrasentan and placebo. Why was the association between albuminuria changes during enrichment and kidney outcomes observed in the atrasentan group eliminated after placebo correction? It is possible albuminuria change is not a causal predictor for the long-term effect of atrasentan and factors unrelated to the early albuminuria response to atrasentan explain the lower risk of kidney outcomes. However, it is also possible the early albuminuria change predicts the long-term benefit of atrasentan, but issues with respect to the imprecise assessment of albuminuria, regression-to-the-mean and introduction of concomitant medication during enrichment, did not enable us to ascertain this predictive effect.

To assess whether albuminuria responders comprised a selected subgroup with a genuinely lower risk of CKD progression, we compared the pretrial rate of eGFR decline in a random selection of SONAR participants. The similar rates of eGFR declines between albuminuria responders and nonresponders before response enrichment makes it less likely intrinsic differences in patient characteristics not accounted for in the analyses explain the observed association in the placebo group.

An alternative explanation for why we failed to identify atrasentan responders with optimal kidney protection compared with placebo may be attributed to methodological aspects relevant for future biomarker-based enrichment

clinical trials. After randomization, the effect of atrasentan on UACR persisted during double-blind treatment in the atrasentan group, yet in the placebo group UACR levels did not return to baseline so differences in UACR between atrasentan and placebo were comparable during double-blind treatment in all response strata. These similar between-group differences in albuminuria would also explain the consistent long-term kidney protective effect of atrasentan. Why did albuminuria not return to baseline in the placebo group? There are several potential explanations for this unexpected finding. First, the observed albuminuria changes during the double-blind treatment phase could be affected by regression to the mean.[17] This explanation is supported by the finding that the albuminuria levels in the placebo group in the highest response strata (>60% and 45%–60% UACR response) remained below pre-enrichment albuminuria values during double-blind treatment, whereas in the lowest UACR response strata (0%–15% and ≥0%) they exceeded pre-enrichment levels. This suggests the measured albuminuria values at baseline may be higher than the actual values in some responders, whereas in nonresponders the measured values may be lower than the actual values. This may have resulted in an overestimation or underestimation of the response in responders and nonresponders, respectively. An alternative explanation for why albuminuria did not return to baseline is that atrasentan may have longer-lasting effects than expected, and these persisted throughout the double-blind treatment phase in the placebo group. This legacy effect may explain the incomplete reversal and the lower than expected albuminuria levels in the placebo arm during double-blind treatment.

Second, albuminuria fluctuates within individuals over time. This complicates determination of the true change in albuminuria for an individual and thereby hampers separation between responders and nonresponders. In the SONAR trial, albuminuria varied substantially within an individual. The median within individual coefficient of variation in albuminuria during treatment with atrasentan was 26.6%. This magnitude is consistent with prior studies.[18,19]

A third explanation is that during the enrichment period, more patients in higher albuminuria response strata initiated diuretic treatment. Diuretic initiation was allowed per protocol to manage sodium and fluid retention. However, diuretics can also potentiate the effects of RAAS inhibition on BP and albuminuria lowering.[20–22] Because all patients were using an inhibitor of the RAAS, the initiation of diuretic treatment added to RAAS inhibition may have potentiated the albuminuria lowering effect of RAAS inhibitors and obscured proper assessment of response to atrasentan.

The SONAR trial was terminated early by the sponsor because of a lower event rate than planned.[12] This study shows albuminuria levels were lower than expected in patients randomized to placebo who responded to atrasentan during enrichment due to incomplete reversal of albuminuria after randomization. The lower-than-anticipated event rate may be attributable to the lower albuminuria levels because the average albuminuria levels during the double-blind treatment phase were associated with the primary kidney end point.

Four specific lessons learned from the SONAR trial will help inform design of future trials. First, when using an enrichment period to select trial participants, a wash-out period between the enrichment and randomization visit might minimize potential long-lasting effects and confirm reversibility of the initial drug response. Second, a crossover enrichment period can be considered to assess the individual drug response to a placebo response although this increases complexity and feasibility. Third, the magnitude of the within-individual variation in the biomarker to identify treatment responders should be carefully considered because a large variability hampers necessary precision to separate responders and nonresponders. Finally, initiation of concomitant medication should be avoided and carefully monitored to properly assess the individual response to the study medication.

This study has some limitations. First, SONAR was terminated early and was not designed or powered to assess the effect of atrasentan according the degree of albuminuria reduction during enrichment. However, the marked consistency in the effect of atrasentan compared with placebo on clinical end points makes it unlikely the results would be different if more end points were collected. Secondly, during follow-up, 20.7% of randomized participants discontinued study drug, which may have affected the estimation of the long-term efficacy of atrasentan. SONAR recruited patients with type 2 diabetes and CKD. All participants had severely increased albuminuria, which limits the generalizability of the results to the broader population of patients with type 2 diabetes and CKD.

In conclusion, the UACR change during open-label treatment with atrasentan predicted the primary kidney outcome. However, this association diminished after considering UACR changes during placebo treatment. These data indicate that, despite the careful assessment of albuminuria in the SONAR trial, we did not identify a greater kidney-protective effect of atrasentan compared with placebo in patients who experienced a larger albuminuria reduction during open-label treatment with atrasentan. Intrinsic patient factors associated with a lower risk of kidney failure, methodologic issues inherent to biomarker-based enrichment clinical trials, and aspects of the SONAR trial design and conduct may have contributed to the consistent effects of atrasentan compared with placebo on albuminuria and kidney outcomes during the double-blind treatment phase of the trial. Until we find a better way to randomize albuminuria responders to active and placebo treatment, the question remains whether the predictive performance of albuminuria response for kidney outcomes can be attributed to the albuminuria change alone.

DISCLOSURES

FUNDING

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021030391/-/DCSupplemental.

Supplemental Table 1. Baseline characteristics according predefined UACR response strata.

Supplemental Table 2. Baseline characteristics of participants with available eGFR data before enrollment in the SONAR trial.

Supplemental Table 3. Changes in risk markers of cardiovascular and kidney disease progression in predefined UACR response strata during the response-enrichment period.

Supplemental Table 4. Effects of atrasentan compared with placebo on systolic BP during double-blind treatment in UACR response strata.

Supplemental Table 5. Number of patients (percentages) in whom thiazide, loop, and potassium sparing diuretic treatment was escalated during enrichment in each UACR response stratum.

Supplemental Figure 1. Effect of atrasentan compared with placebo on rate of eGFR decline during the double-blind treatment period according to UACR response during the response enrichment period.

Supplemental Figure 2. Effect of atrasentan compared with placebo on hospitalizations for heart failure during the double-blind treatment period according to UACR response during the response-enrichment period.

Supplemental Figure 3. Association between the geometric mean UACR level achieved during double-blind treatment and event rate for the primary kidney outcome according to the UACR response recorded during the response-enrichment period.

Supplemental Summary 1. Full member list of the SONAR investigators.

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Supplement to Early response in albuminuria and long-term kidney protection during treatment with an endothelin receptor antagonist– a pre-specified analysis from the SONAR trial

Supplement to Early response in albuminuria and long-term kidney protection during treatment with an endothelin receptor antagonist– a pre-specified analysis from the SONAR trial

Supplement table 1: Baseline characteristics according pre-defined UACR response strata

	UACR ≥ 60%		UACR 45 – 60%		UACR 30-45%		UACR 15- 30%		UACR 0 – 15%		UACR<0%	
	Atrasentan	Placebo	Atrasentan	Placebo	Atrasentan	Placebo	Atrasentan	Placebo	Atrasentan	Placebo	Atrasentan	Placebo
N patients (%)	297	294	484	484	544	545	241	238	142	144	126	129
Age, years*	65.5 (8.5)	65.6 (8.6)	64.9 (8.2)	64.2 (8.6)	64.5 (9.0)	64.7 (8.7)	64.0 (9.6)	65.0 (8.7)	63.3 (9.0)	62.8 (9.1)	63.8 (8.3)	62.0 (8.9)
Sex												
Male	214 (72.1)	206 (70.1)	365 (75.4)	351 (72.5)	415 (76.3)	414 (76.0)	181 (75.1)	175 (73.5)	107 (75.4)	112 (77.7)	94 (74.6)	88 (68.2)
Female	83 (27.9)	88 (29.9)	119 (24.6)	133 (27.5)	129 (23.7)	131 (24.0)	60 (24.9)	63 (26.5)	35 (24.6)	32 (22.2)	32 (25.4)	41 (31.8)
Body Weight, (kg)	83.8 (20)	84.8 (18)	83.8 (21)	84.7 (20)	85.8 (19)	84.5 (18)	88.5 (22)	86.2 (18)	86.0 (19)	85.8 (19)	87.3 (20)	87.1 (22)
Systolic BP, mmHg	136.9 (15)	137.8 (15)	136.8 (14)	136.0 (15)	135.9 (16)	135.5 (15)	135.8 (15)	135.2 (16)	135.7 (16)	135.3 (17)	138.4 (15)	136.1 (17)
Diastolic BP, mmhg	75.2 (10)	74.9 (10)	74.7 (10)	74.9 (10)	75.2 (10)	74.8 (10)	74.3 (11)	74.2 (10)	75.2 (10)	75.0 (10)	76.2 (10)	75.4 (9)
Hba1c, (mmol/mol)	7.5 (1.4)	7.7 (1.6)	7.6 (1.4)	7.5 (1.3)	7.6 (1.4)	7.6 (1.5)	7.5 (1.3)	7.7 (1.6)	7.6 (1.5)	7.8 (1.7)	7.7 (1.6)	7.5 (1.5)
S. creatinine, (µmol/L)*	150.3 (40)	152.8 (44)	147.8 (43)	145.5 (41)	151.0 (43)	152.2 (42)	159.7 (49)	156.3 (47)	149.9 (44)	159.9 (45)	140.7 (44)	141.6 (40)
eGFR, ml/min/1.73m^{2*}	46.1 (14)	45.1 (15)	44.0 (14)	44.3 (14)	42.8 (13)	42.4 (13)	40.9 (15)	41.5 (14)	43.9 (15)	41.0 (13)	42.8 (12)	41.8 (12)
Serum Albumin, g/L*	40.0 (3.4)	39.7 (3.4)	39.5 (3.6)	39.1 (3.3)	38.9 (3.5)	39.2 (3.5)	38.7 (3.7)	38.6 (3.9)	38.4 (3.8)	38.3 (3.9)	39.0 (3.7)	38.4 (3.6)
Hemoglobin, g/L	129.9 (17)	127.3 (17)	129.8 (17)	128.3 (17)	129.9 (17)	130.0 (17)	130.5 (18)	130.3 (17)	129.8 (18)	126.5 (17)	128.8 (19)	126.1 (17)
BNP, pg/Ml	53.0 [27, 91]	58.0 [29, 101]	49.5 [27, 89]	48.0 [25, 87]	47.0 [25, 82]	45.0 [25, 82]	48.0 [26, 84]	42.5 [23, 78]	49.0 [26, 82]	41.0 [25, 87]	45.5 [27, 73]	56.0 [27, 95]
UACR, mg/g*	662 [399, 1180]	652 [373, 1188]	820 [469, 1415]	781 [442, 1435]	877 [486,1671]	887 [512, 1582]	955 [529, 1858]	926 [447, 1879]	1161 [520, 2284]	1048 [554, 2142]	808.0 [436, 1475]	756.5 [395, 1467]
Medication use‡												
Diuretics	247 (83.2)	253 (86.1)	408 (84.3)	409 (84.5)	453 (83.3)	450 (82.6)	204 (84.6)	192 (80.7)	117 (82.4)	117 (81.3)	106 (84.1)	109 (84.5)
Beta-blockers	144 (48.5)	127 (43.2)	216 (44.6)	203 (41.9)	206 (37.9)	222 (40.7)	98 (40.7)	91 (38.2)	53 (37.3)	68 (47.2)	57 (45.2)	46 (35.7)
Lipid lowering drugs	225 (75.8)	228 (77.6)	381 (78.7)	380 (78.5)	427 (78.5)	452 (82.9)	198 (82.2)	201 (84.5)	107 (75.4)	114 (79.2)	99 (78.6)	101 (78.3)

‡All patients had to be on a maximum tolerated dose of an ACE-inhibitor or ARB. Abbreviations: BP, blood pressure; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; UACR, urine protein: urine creatinine ratio. Numeric variables are presented as mean (SD) or median [25th to 75th Percentile] where appropriate. Categorical variables are presented as counts (%).*p-value across UACR response strata <0.001; ‡p-value across UACR response strata 0.0284

Supplement Table 2: Baseline characteristics of participants with available eGFR data prior to enrollment in the SONAR trial

Characteristics	Participants with pre-intervention eGFR slope	SONAR (overall)
Number of patients	532	3668
Age, years	64.7 (8.5)	64.5 (8.8)
Gender		
Male	419 (78.8%)	2722 (74.2%)
Female	113 (21.2%)	946 (25.8%)
Race, n (%)		
White	317 (59.6%)	2110 (57.5%)
Black	10 (1.9%)	224 (6.1%)
Asian	191 (35.9%)	1198 (32.7%)
Other	14 (2.6%)	136 (3.7%)
Blood pressure		
Systolic, mm Hg	136.5 (14.9)	136.2 (15.2)
Diastolic, mm Hg	74.4 (10.1)	74.9 (9.9)
Serum creatinine, µmol/L	148.9 (41.6)	149.7 (43.2)
eGFR, mL/min/1.73 m^2	43.7 (13.8)	43.3 (13.8)
Hemoglobin, g/L	131.0 (16.5)	129.3 (17.1)
HbA1c, %	7.5 (1.4)	7.6 (1.5)
Serum Albumin, g/L	39.7 (3.5)	39.1 (3.6)
UACR, mg/g	820 [475 - 1553]	829 [457 - 1556]
Medications		
Diuretics, n (%)	465 (87.4)	3055 (83.6)
Beta-blockers, n (%)	273 (51.3)	1531 (41.7)
Lipid-lowering, n (%)	460 (86.5)	2913 (79.4)

Data are n (%), mean (SD), or median [25th to 75th Percentile].
eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatinine ratio.

Supplement table 3: Changes in risk markers of cardiovascular and kidney disease progression in predefined UACR response strata during the response enrichment period. Shown are mean (SD) except for B-type Natriuretic Peptide which is presented as percentage geometric mean change (95%CI).

	UACR ≥ 60%	UACR 45 – 60%	UACR 30-45%	UACR 15- 30%	UACR 0 – 15%	UACR<0%
Blood pressure						
Systolic	-6.6 (15)	-6.5 (14)	-5.5 (15)	-2.9 (15)	-1.7 (16)	-1.0 (16)
Diastolic	-5.2 (9)	-5.3 (9)	-4.8 (9)	-3.0 (9)	-2.7 (10)	-2.4 (9)
eGFR	-2.3 (7.4)	-1.7 (6.3)	-0.8 (6.2)	-0.3 (5.9)	-0.1 (5.4)	1.4 (7.4)
Body weight	0.4 (1.5)	0.5 (1.7)	0.6 (1.5)	0.6 (1.5)	0.7 (1.5)	0.6 (1.8)
B-type Natriuretic Peptide	1.1 (-4.3, 6.7)	6.0 (1.7, 10.5)	9.0 (5.0, 13.1)	8.8 (2.9, 15.0)	9.2 (1.9, 16.9)	11.9 (2.9, 21.7)

Supplement table 4: Effects of atrasentan compared to placebo on systolic blood pressure during double blind treatment in UACR response strata.

UACR response stratum	Least square mean systolic blood pressure during double blind treatment (95%CI)		
	Atrasentan (N=1834)	Placebo (N=1834)	Difference Atrasentan vs Placebo
≥ 60% reduction	135.6 (134.1, 137.0)	139.0, (137.6, 140.4)	-3.37 (-5.39, -1.34)
45 to 60% reduction	137.4 (136.3, 138.5)	138.6 (137.5, 139.7)	-1.15 (-2.69, 0.40)
30 to 45% reduction	137.3 (136.2, 138.4)	138.8 (137.8, 139.9)	-1.54 (-3.02, -0.05)
15 to 30% reduction	138.5 (137.0, 140.0)	138.4 (136.9, 139.9)	0.10 (-2.04, 2.25)
0 to 15% reduction	138.7 (136.7, 140.7)	139.8 (137.8, 142.8)	-1.11 (-3.96, 1.73)
≥0% increase	139.0 (136.7, 141.3)	138.2 (136.0, 140.5)	0.77 (-2.44, 3.98)

Supplement table 5: Number of patients (percentages) in whom thiazide, loop, and potassium sparing diuretic treatment was escalated during enrichment in each UACR response stratum.

UACR response stratum	Thiazide-diuretics	Loop-diuretics	Potassium-sparing diuretics
≥ 60% reduction	36 (6.1)	130 (22.0)	0 (0.0)
45 to 60% reduction	64 (6.6)	177 (18.3)	2 (0.2)
30 to 45% reduction	58 (5.3)	157 (14.4)	2 (0.2)
15 to 30% reduction	22 (4.6)	89 (18.6)	0 (0.0)
0 to 15% reduction	13 (4.6)	47 (16.4)	0 (0.0)
≥0% increase	15 (5.9)	31 (12.2)	0 (0.0)

Some patients started both thiazide and loop-diuretics and therefore the total numbers exceed those in table 3 for a couple of subgroups. Thiazide diuretics initiated during enrichment include hydrochlorothiazide, chlorthalidone, indapamide, metolazone; Loop diuretics include furosemide and torazemide; Potassium sparing diuretic is spironolactone

Supplement figure 1: Effect of atrasentan compared to placebo on rate of eGFR decline during the double blind treatment period according to UACR response during the response enrichment period

UACR response strata: >60, 45-60, 30-45, 15-30, 0-15, >0

Placebo subtracted difference (95%CI) (ml/min/1.73m^2/year): -0.2(-1.0, 0.7), -0.7(-1.4, 0.0), -0.8(-1.4, -0.2), -0.7(-1.7, 0.3), -0.1(-1.6, 1.4), -0.9(-2.5, 0.7)

eGFR slope (ml/min/1.73m^2/year)

■ Placebo
☐ Atrasentan
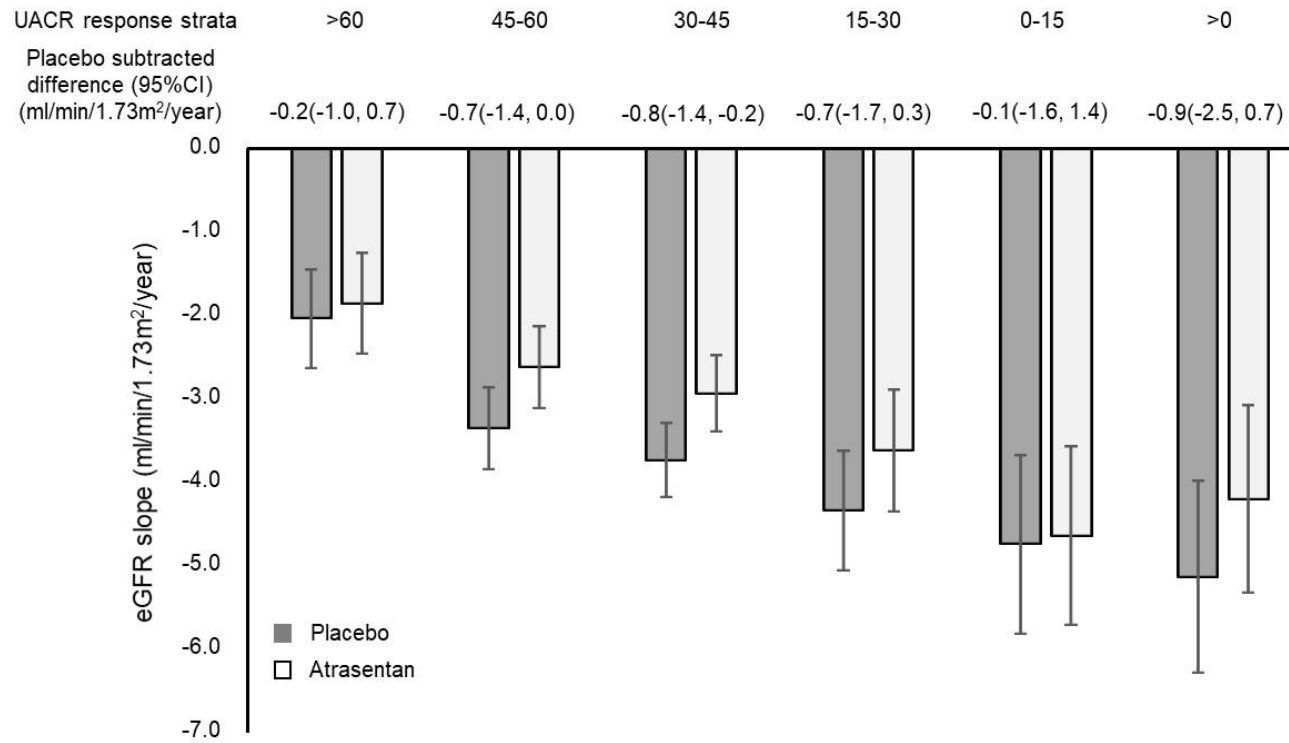
Supplement figure 2: Effect of atrasentan compared to placebo on hospitalizations for heart failure during the double blind treatment period according to UACR response during the response enrichment period

UACR response stratum	n/N (%)		per 100 patient-yrs		Hazard Ratio (95% CI)	P value
	Atrasentan	Placebo	Atrasentan	Placebo		
Congestive Heart Failure						0.72
≥60%	10/297	8/294	1.7	1.3	1.54 (0.59-4.01)	
45 - <60%	20/484	13/484	1,9	1.3	1.46 (0.72-2.94)	
30 - <45%	17/544	13/545	1.5	1.1	1.09 (0.52-2.30)	
15 - <30%	11/241	6/238	2.0	1.1	2.03 (0.73-5.62)	
0 - <15%	9/142	3/144	2.9	0.9	2.84 (0.76-10.66)	
<0%	6/126	8/129	2.3	3.1	0.65 (0.21-1.99)	

0.13 0.25 0.5 1 2 4 8

Atrasentan Better   Placebo Better
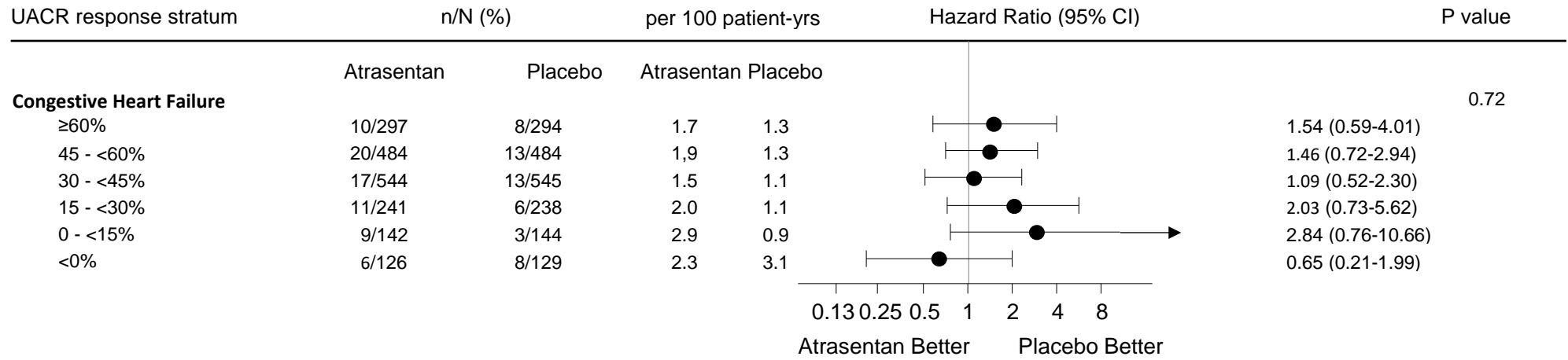
Supplement Figure 3: Association between the geometric mean UACR level achieved during double blind treatment and event rate for the primary kidney outcome according to the UACR response recorded during the response enrichment period. The association is displayed for participants who were randomized to continue atrasentan (blue dots; R^2=0.76; p=0.024) and randomized to transition to placebo (red dots; R^2=0.88; p=0.006). Numbers in the figure indicate the UACR response strata: 1, ≤-60%; 2, -60% to ≤-45%; 3, -45% to ≤-30%; 4, -30% to ≤-15%; 5, -15% to ≤0%; 6, >0%
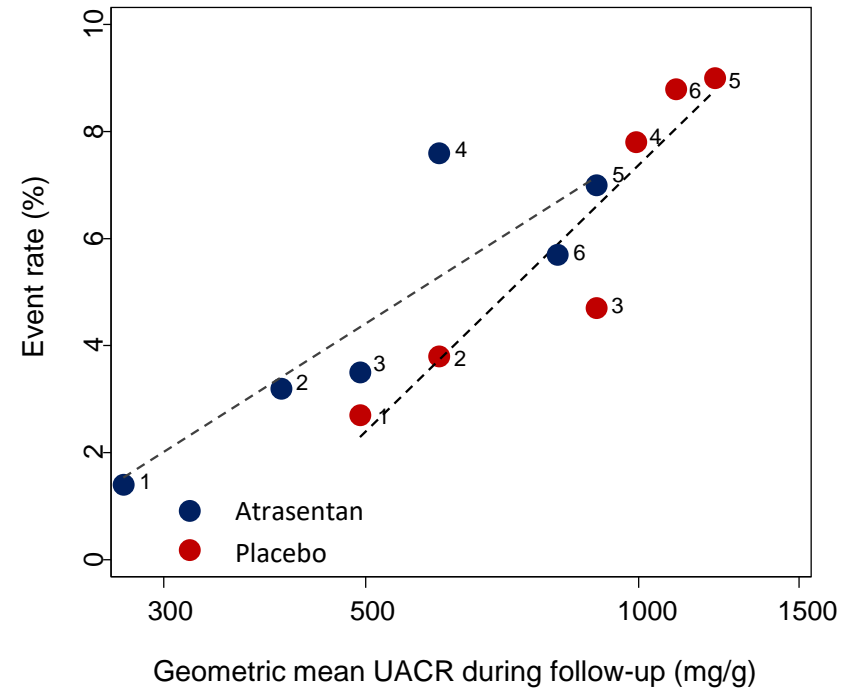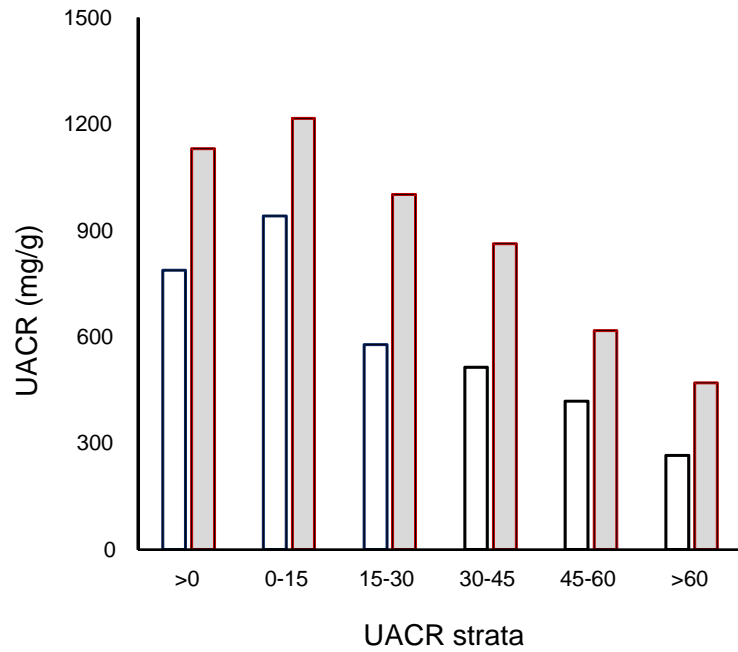
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Malaysia	Hospital Universiti Kebangsaan, Kuala Lumpur	Norlela Sukor
Malaysia	Hospital Tuanku Ja afar, Seremban	Noor Adam
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United States of America	East Texas Nephrology Associates, Lufkin	Imran Nazeer
United States of America	AKDHC Medical Research Service, Peoria	Liqun Bai
United States of America	Thomas Jefferson University, Philadelphia	Serge Jabbour
United States of America	Texas Health Physicians Group, Dallas	Carlos Arauz-Pacheco
United States of America	Diagnostic Clinic Of Houston, Houston	Freemu Varghese
United States of America	Janett DelaCruz FNP, a Professional Nursing Corporation., Downey	Michael Fang
United States of America	Palm Research Center, Inc., Las Vegas	Samer Nakhle
United States of America	Seacoast Kidney and Hypertension, Portsmouth	Sucharit Joshi
United States of America	Eastern Nephrology Associates, Kinston	Rekha John
United States of America	University of California San Francisco, San Francisco	Sam James
United States of America	Hanson Clinical Research Center, Port Charlotte	Lenita Hanson
United States of America	Houston Nephrology Group, Cypress	Rupi Chatha
United States of America	Nephrology Associates P.C., Birmingham	Roman Brantley
United States of America	California Institute Renal Res, San Diego	Mark Boiskin
United States of America	Lee County Internal Medicine A, Fort Myers	Guillermo Bohm
United States of America	Iowa Diabetes & Endocrinology Research Center, Des Moines	Anuj Bhargava
United States of America	Nephrology Associates Northern VA, Fairfax	Ali Assefi
United States of America	West Virginia University School Med, Morgantown	Rebecca Schmidt

United States of America	Knoxville Kidney Center, PLLC, Knoxville	George Newman
United States of America	Lucita M. Cruz MD, Norwalk	Lucita Cruz
United States of America	University of Utah, Salt Lake City	Srinivasan Beddhu
United States of America	Alta Pharmaceutical Research, Dunwoody	Alan Miller
United States of America	Apex Medical Research, MI, Inc., Flint	Ahmed Arif
United States of America	Columbia Nephrology Associates, Columbia	Thomas Powell
United States of America	The Medical Group of Texas, Forth Worth	Odilon Alvarado
United States of America	Alvarado, Fort Worth, TX	Odilon Alvarado
United States of America	Cooper Nephrology, Camden	Christopher McFadden
United States of America	National Research Institute, Los Angeles	Juan Frias
United States of America	Stamford Nephrology, Stamford	Eric Brown
United States of America	Sierra Nevada Nephro Consult, Reno	Steven Vicks
United States of America	Jersey Shore University Medical Center, Neptune	Judith Slover
United States of America	My Kidney Center, LLC, Manhattan	Fadi Bedros
United States of America	Boice-Willis Clinic, P.A., Rocky Mount	Charles Jere
United States of America	East Carolina University, Greenville	Melanie Hames
United States of America	Capital Nephrology Medical Group, Sacramento	Naveen Atray
United States of America	Clinical Research Development Associates, Rosedale	David Scott
United States of America	Louisiana State University HSC, New Orleans	Efrain Reisin
United States of America	Endocrinology Associates, Inc., Columbus	Elena Christofides
United States of America	Hypertension and Nephrology, Eatontown	Kenneth Liss
United States of America	MultiCare Institute for Research & Innovation, Tacoma	Ronald Graf
United States of America	University of Tennessee Health Sciences Center, Memphis	Csaba Kovesdy
United States of America	Providence Clinical Research, North Hollywood	Teresa Sligh
United States of America	North America Research Institute, San Dimas	Ramon Guadiz
United States of America	Emory University Hospital, Atlanta	Antonio Guasch
United States of America	University of Chicago, Chicago	George Bakris
United States of America	St. Jude Hospital, Fullerton	John Gilbert
United States of America	Eastern Nephrology Associates, New Bern	Manuel Montero
United States of America	Green Clinic LLC, Ruston	Michael Nammour
United States of America	PrimeCare Medical Group, Houston	Ankur Doshi