Large Between-Patient Variability in eGFR Decline Before Clinical Trial Enrollment and Impact on Atrasentan's Efficacy - A Post-Hoc Analysis From the SONAR Trial

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Large Between-Patient Variability in eGFR Decline before Clinical Trial Enrollment and Impact on Atrasentan's Efficacy: A *Post Hoc* Analysis from the SONAR Trial

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Patients with high albuminuria and low eGFR levels are usually enrolled in clinical trials to enrich the population at risk of ESKD in order to accrue sufficient clinical end points. However, the relatively low event rates in recent nephrology trials suggest that this approach does not completely rule out enrollment of patients without progressive kidney function loss.[1–3] The rate of eGFR decline before trial entry (pretrial eGFR slope) is a more direct determinant of ESKD risk and could be a more appropriate approach to select high-risk clinical trial participants, but it has not been used, most likely because of logistical challenges to obtain pretrial eGFR data. However, with the introduction of electronic medical records, obtaining historical eGFR data has become easier and practically more feasible. Using electronic medical record data, we determined pretrial eGFR slope in participants of the Study of Diabetic Nephropathy with Atrasentan (SONAR) trial with high albuminuria and low eGFR. We subsequently determined whether the effect of atrasentan in slowing progressive kidney function loss is higher among participants with a steeper pretrial eGFR slope.

We performed a *post hoc* analysis of the SONAR trial, which determined the effect of the endothelin receptor antagonist atrasentan in patients with type 2 diabetes and CKD on kidney outcomes. The SONAR trial included adult patients with type 2 diabetes who had an eGFR of 25–75 ml/min per 1.73 m^2 and a urine albumin-creatinine ratio (UACR) of 300–5000 mg/g.[3–5] Participating investigators were asked to participate in a voluntary substudy to record pretrial eGFR data from medical records if available. Each individual's pretrial eGFR slope was estimated using within individual linear regression. We used linear mixed effects models with a random intercept and slope to assess the effect of atrasentan compared with placebo on eGFR slope during the clinical trial. Detailed methods are described in the Supplemental Material.

A total of 630 patients (12.3% of total cohort) with at least three serum creatinine values before the start of the trial were included. Over a median pretrial duration of 1.8 years, a mean of 8.1 (SD 4.8) pretrial serum creatinine measurements were collected. Baseline characteristics of the 630 included participants were similar with the overall SONAR cohort (Supplemental Table 1).

The mean rate of pretrial eGFR decline was 4.8 (SD 9.6) ml/min per 1.73 m^2 per year. We observed a large between-individual variation in pretrial eGFR slopes (Supplemental Figure 1). The annual rate of decline in eGFR prior to the SONAR trial was ≥5 ml/min per 1.73 m^2 per year in 259 (41.1%) patients, between 1 and 5 ml/min per 1.73 m^2 per year in 183 (29.1%) patients, and <1 ml/min per 1.73 m^2 per year in 188 (29.8%) patients (Supplemental Table 2). The event rate for the primary kidney outcome in placebo-treated patients with a fast progression was two-fold higher compared with patients with a stable disease: 6.9 (95% confidence interval [CI], 4.0 to 11.9) versus 3.3 (95% CI, 1.5 to 7.4) events per 100 patients-years. Although patients with a baseline UACR >1000 mg/g had a statistically significantly steeper pretrial eGFR decline than patients with a baseline UACR of ≤1000 mg/g (P=0.001), UACR only explained a modest proportion of the variation in pretrial eGFR slope (R^2=2.9%). There was no association between pretrial eGFR slope and baseline eGFR (Supplemental Figure 2, Supplemental Table 2).

The effect of atrasentan versus placebo on clinical trial eGFR slope depended on the pretrial eGFR slope. In patients with a pretrial eGFR decline ≥5 ml/min per 1.73 m^2 per year, the

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mean rates of eGFR decline during the double-blind treatment phase of the trial in the atrasentan and placebo groups were 3.3 and 4.9 ml/min per 1.73 m^2 per year, respectively, resulting in a between-group difference of 1.6 (95% CI, 0.0 to 3.2) ml/min per 1.73 m^2 per year. In contrast, in patients with a pretrial eGFR decline between 1 and 5 ml/min per 1.73 m^2 per year and of <1 ml/min per 1.73 m^2 per year, the between-group differences in rate of eGFR decline were −0.1 and −0.2 ml/min per 1.73 m^2 per year, respectively (*P* value for interaction of 0.005). Baseline UACR and eGFR did not modify the effect of atrasentan on eGFR decline during the trial (Figure 1).

Endothelin receptor antagonists, including atrasentan, can increase the risk of edema and heart failure in patients with type 2 diabetes and CKD who are at risk of fluid retention.[3] Heart failure hospitalizations occurred more frequently in patients with a fast eGFR decline compared with those with a slower decline. However, within fast progressors, these events occurred more frequently in the placebo group (10.8%) compared with the atrasentan group (3.2%; hazard ratio, 0.34; 95% CI, 0.10 to 1.14) (Supplemental Table 3).

In this *post hoc* analysis of 630 SONAR participants with type 2 diabetes, increased albuminuria, and decreased eGFR who were selected for their high risk of kidney failure, our study showed that only 41% had a rapid eGFR decline of at least 5 ml/min per 1.73 m^2 per year prior to enrollment into the trial. In other words, despite enriching the SONAR trial for patients with a high UACR, still more than half of the selected patients included had a relatively stable eGFR trajectory and thus, were unlikely to reach kidney failure within the duration of the trial.

We also demonstrated that the therapeutic effect of atrasentan on slowing kidney function decline varied by the pretrial eGFR slope, whereas the effect was consistent in subgroups defined by baseline UACR and eGFR as reported previously.[3] These data suggest that the pretrial eGFR slope may be a suitable tool to identify patients more likely to benefit from atrasentan. We recognize, however, that the statistical power for these analyses was low, and the results should be considered hypothesis generating. Ongoing prospective clinical trials, such as the Atrasentan in Patients With IgA Nephropathy (ALIGN) trial (NCT04573478), are warranted to confirm if atrasentan more effectively reduces the rate of kidney failure in patients with more progressive kidney function loss. Future research is also required to define the time period and minimal number of eGFR assessments to optimally estimate the pretrial eGFR slope for prognostic enrichment. We also acknowledge that the pretrial eGFR data are not perfectly structured but derived from electronic medical records, which means varying laboratory techniques for serum creatinine measurements per patient or even within one patient, varying numbers and intervals between the creatinine measurements, and potential variation in medications and comorbidities. These variations may have introduced random noise and increased variation in pretrial eGFR slope.

In conclusion, the efficacy of atrasentan in slowing progressive kidney function loss was larger in participants with a steeper pretrial eGFR decline, suggesting that the preintervention eGFR slope may be a better tool than UACR or eGFR to select clinical trial participants.

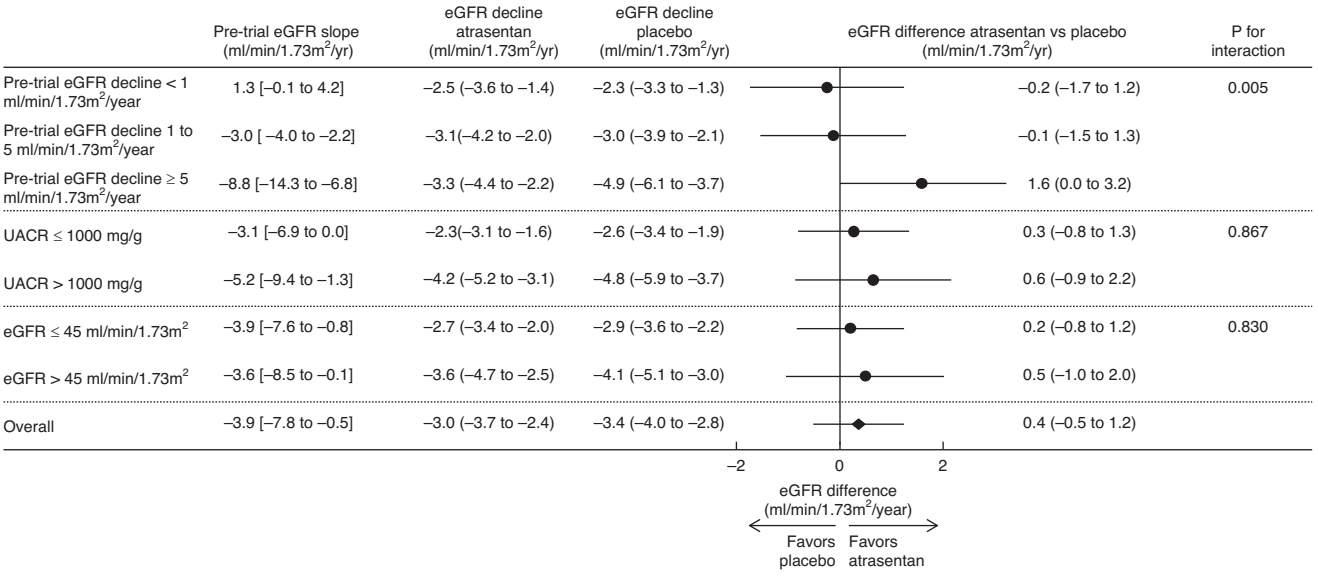

Figure 1. The effect of atrasentan versus placebo on clinical trial eGFR slope depends on the pretrial eGFR slope, but not on baseline UACR or eGFR. Figure shows the effect of atrasentan compared with placebo on clinical trial eGFR slope stratified by pretrial eGFR decline (<1, between 1 and 5, and ≥5 ml/min per 1.73 m^2 per year), baseline UACR (UACR≤1000 and >1000 mg/g), and baseline eGFR (eGFR≤45 and >45 ml/min per 1.73 m^2). The circles in the figure represent the hazard ratio and the horizontal line the 95% CI.

DISCLOSURES

R. Busch has received research support from AstraZeneca, Kowa, Lilly, and Novo Nordisk and has served on the speaker bureau for Amarin, AstraZeneca, Boehringer-Ingelheim, Lilly, and Novo. L. De Nicola reports consultancy agreements and/or lecturer fees from Astellas, AstraZeneca, Mundipharma, Novo Nordisk, and Vifor Fresenius; and scientific advisor or membership with Abbvie, Astellas, AstraZeneca, *Italian Journal of Nephrology*, Janssen, and Vifor Fresenius. S.T. de Vries reports funding from the Dutch Medicines Evaluation Board, the European Union's Horizon 2020 Research and Innovation Programme under Marie Sklodowska-Curie grant 754425, and ZonMW–The Netherlands Organization for Health Research and Development project 849100006. 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All authors were involved in data collection; S.T. de Vries, D. de Zeeuw, H.J.L. Heerspink, and S.W. Waijer analyzed and interpreted the data; S.T. de Vries, H.J.L. Heerspink, and S.W. Waijer wrote the first draft of the manuscript; all authors were involved in data interpretation and contributed to revisions for important intellectual content; and all authors read and approved the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2021040498/-/DCSupplemental.

Supplemental Material. Detailed methods.

Supplemental Table 1. Baseline characteristics of the included pretrial population and the enrichment population in the SONAR trial.

Supplemental Table 2. Baseline characteristics of the 630 included patients stratified by the annual decline in eGFR prior to the SONAR trial.

Supplemental Table 3. Heart failure and severe edema in atrasentan- and placebo-treated patients stratified by the annual decline in eGFR prior to the SONAR trial.

Supplemental Figure 1. Large variation in rate of eGFR decline (pretrial eGFR slope) before enrollment in the SONAR trial.

Supplemental Figure 2. Correlation plots of UACR and eGFR at baseline and pretrial eGFR slope.

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