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# Supplemental data

## **Detailed methods**

## Patients and study design

The SONAR trial was a double-blind, randomized, placebo-controlled trial that assessed the effect of the endothelin receptor antagonist atrasentan on kidney outcomes in patients with type 2 diabetes and CKD. Details about this trial including design and results have been published previously.[1-3] In short, the SONAR trial included patients with type 2 diabetes, who were 18-85 year old, had an eGFR of 25-75 ml/min/1.73m2 and a urine albumin to creatinine ratio (UACR) of 300-5000 mg/g. All participants were required to receive a stable or recommended dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Information on concomitant diseases was collected including serum creatinine values before trial commencement.

Between May 2013 and June 2017 5117 patients from 689 sites in 41 countries were enrolled. All eligible participants received 6 weeks open label treatment with atrasentan 0.75 mg/day. The goal of the open-label active run-in period, termed enrichment period, was to select patients who responded to atrasentan without known side effects, particularly edema and heart failure. Because endothelin receptor antagonists including atrasentan may induce fluid retention potentially leading to heart failure, patients who developed signs of fluid retention, defined as at least 3 kg increase in bodyweight or an increase in brain natriuretic peptide (BNP) to 300 pg/ml or more during enrichment were excluded from the trial.[1-3] Patients who tolerated atrasentan and experienced at least 30% decrease in UACR during the enrichment period were defined as responders, the other patients as non-responders. Of the 5117 patients that entered the enrichment period, 2648 responders and 1020 non-responders were randomly assigned to continue atrasentan or transition to placebo in the double-blind treatment period. Because atrasentan reduced the primary kidney outcome in responders and non-responders, we combined the two groups for the purpose of the current study.[1] The trial protocol was approved by a central or local ethics committee at all trial sites, and each participant provided written consent. The trial was conducted in accordance with the Declaration of Helsinki (version amended October 2000). SONAR is registered on clinicaltrials.gov (NCT01858532). This study is conducted as a secondary analysis of the SONAR trial and was not pre-specified in the statistical analysis plan.

## Pre-trial eGFR slope

Towards the end of the SONAR trial, participating investigator were asked to participate in a voluntary sub-study to record pre-trial eGFR data if available. Pre-trial eGFR data was obtained from 79 sites (11.5% of total). Patients with at least three serum creatinine values before the trial were selected for this study. eGFR was calculated from the serum creatinine measurements using the CKD-EPI equation.[4] Each individual’s pre-trial eGFR slope was estimated using within individual linear regression analysis which mimics clinical practice if physicians calculate eGFR slope to establish clinical trial eligibility. These pre-intervention eGFR slopes were stratified into three groups based on previously defined cut-offs[5], i.e. fast progression (eGFR decline ≥5 ml/min/1.73m2/year), moderate progression (eGFR decline between 1 and 5 ml/min/1.73m2/year), and stable disease (eGFR decline <1 ml/min/1.73m2/year). In addition, we stratified the groups into thirds of the pre-intervention eGFR slope.

## Statistical analysis

Baseline characteristics are presented as mean and their standard deviation or median and the 25th and 75th percentile (the interquartile range, IQR) for variables with a nonparametric distribution. Categorical variables are presented as percentages of observations. In all analyses, we log-transformed UACR and BNP because of their skewed distributions. We did not perform statistical tests to compare baseline characteristics in the SONAR overall population and subgroup with pre-intervention eGFR slope since the large number of individuals would have meant that almost all were statistically different even when differences were clinically not meaningful.

We tested differences in baseline characteristics across the three pre-trial eGFR slope groups with one-way ANOVA or chi-squared test where appropriate. We used regression analysis to determine the association between pre-trial eGFR slope and baseline UACR and eGFR.

We assessed the event rates for the primary kidney outcome per 100 patients years. The primary kidney outcome was defined as a composite of time to doubling of serum creatinine, ESKD or renal death. ESKD was defined as chronic dialysis for >90 days, kidney transplantation or sustained eGFR<15 ml/min/1.73m2 for >90 days. We assessed frequency of hospitalizations for heart failure and severe edema by pre-trial eGFR slope categories.

We used linear mixed effects models with a random intercept and slope to assess the effect of atrasentan compared to placebo on eGFR slope during the clinical trial. Serum creatinine measurements during the enrichment period of the SONAR trial were excluded as these values may have been influenced by atrasentan treatment. Categories of pre-trial eGFR decline (≥5, between 1 and 5, and <1 ml/min/1.73m2/year), baseline UACR (≤1000 mg/g and <1000 mg/g) and baseline eGFR (≤45 ml/min/1.73m2 and >45 ml/min/1.73m2) were added as factors. The model included treatment allocation and time as factor, and an interaction term between treatment allocation and time. The variance-covariance matrix was assumed to be unstructured, i.e., purely data dependent. Heterogeneity of treatment effects by pre-trial eGFR slope, UACR, and eGFR was tested by adding interaction terms of all combinations of treatment, time and pre-trial eGFR slope, baseline UACR or eGFR, all fitted as a continuous variable, to the relevant linear mixed model. Two-sided p-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata 14.2 SE (StataCorp. 2015. College Station, TX: StataCorp LP) and SAS (SAS Institute Inc. NC, USA.)

*References*

1 Heerspink HJL, Parving H-H, Andress DL, Bakris G, Correa-Rotter R, Hou F-F, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet. 2019 May;393(10184):1937–47.

2 Heerspink HJL, Andress DL, Bakris G, Brennan JJ, Correa-Rotter R, Dey J, et al. Rationale and protocol of the Study Of diabetic Nephropathy with AtRasentan (SONAR) trial: A clinical trial design novel to diabetic nephropathy. Diabetes, Obes Metab. 2018;20(6):1369–76.

3 Heerspink HJL, Andress DL, Bakris G, Brennan JJ, Correa-Rotter R, Hou FF, et al. Baseline characteristics and enrichment results from the SONAR trial. Diabetes, Obes Metab. 2018;20(8):1829–35.

4 Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009;150(9):604.

5 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group; KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3(1):1–150.

## **Supplemental Table 1:** Baseline characteristics of the included pre-trial population and the enrichment population in the SONAR trial.

|  |  |  |
| --- | --- | --- |
|  | **Participants with pre-trial eGFR slope** | **SONAR**  **(overall)** |
| Number of patients | 630 | 5107 |
| Age, years | 64.8 (8.6) | 64.4 (8.8) |
| Gender, n (%) |  |  |
| Male | 490 (77.8) | 3713 (72.7) |
| Female | 140 (22.2) | 1394 (27.3) |
| Race, n (%) |  |  |
| White | 377 (59.8) | 3010 (58.9) |
| Black | 14 (2.2) | 352 (6.9) |
| Asian | 225 (35.7) | 1556 (30.5) |
| Other | 14 (2.2) | 189 (3.7) |
| Weight, kg | 86.2 (19.3) | 86.1 (19.9) |
| Blood pressure |  |  |
| Systolic, mmHg | 137.7 (15.3) | 137.5 (15.2) |
| Diastolic, mmHg | 74.5 (10.1) | 75.3 (9.9) |
| Serum creatinine, mg/dL | 1.7 (0.5) | 1.7 (0.5) |
| eGFR, mL/min/1.73 m2 | 43.0 (13.6) | 41.5 (12.8) |
| Hemoglobin, g/dL | 13.0 (1.7) | 12.8 (1.7) |
| HbA1c1, % | 7.5 (1.4) | 7.6 (1.5) |
| BNP, (pg/mL) | 47.5 [26 - 86] | 50 [27 - 91] |
| UACR, mg/g | 849.1 [481 - 1609] | 871 [463 - 1673] |
| Diabetes duration, years | 16.9 (8.4) | 16.4 (8.9) |
| History of retinopathy, n (%) | 213 (33.8) | 1676 (32.8) |
| Medications, n (%) |  |  |
| Diuretics | 535 (84.9) | 4125 (80.8) |
| Insulin | 398 (63.2) | 3244 (63.5) |

Data are n (%), mean (SD), or median [25th to 75th Percentile].

1 Based on all patients who were randomized in the double-blind treatment period, measured at start of the double-blind period. Abbreviations: BNP = Brain natriuretic peptide; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatinine ratio.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre-trial eGFR decline** | | | |
| **≥5 ml/min/1.73 m2/year** | **1 to 5 ml/min/1.73 m2/year** | **<1 ml/min/1.73 m2/year** | **P value\*** |
|  | **Fast progression** | **Moderate progression** | **Stable disease** |  |
| Number of patients (%) | 259 (41.1) | 183 (29.1) | 188 (29.8) |  |
| **Pre-trial eGFR Slope** |  |  |  |  |
| Mean | 12.0 (9.6) | 3.0 (1.2) | -3.4 (6.2) |  |
| Median | 8.8 [6.6 to 14.1] | 3.0 [2.2 to 4.0] | -1.3 [-4.1 to 0.0] |  |
| N creatinine measurements | 7.6 (4.5) | 8.9 (5.4) | 8.0 (4.6) | 0.027\* |
| **Patient characteristics** |  |  |  |  |
| Age, years | 63.8 (8.9) | 65.4 (8.4) | 65.4 (8.3) | 0.076 |
| Gender, n (%) |  |  |  | 0.728 |
| Male | 205 (79.2) | 139 (76.0) | 146 (77.7) |  |
| Female | 54 (20.9) | 44 (24.0) | 42 (22.3) |  |
| Race, n (%) |  |  |  | 0.325 |
| White | 149 (57.5) | 113 (61.8) | 115 (61.2) |  |
| Black | 8 (3.1) | 1 (0.6) | 5 (2.7) |  |
| Asian | 99 (38.2) | 64 (35.0) | 62 (33.0) |  |
| Other | 3 (1.2) | 5 (2.7) | 6 (3.2) |  |
| Weight, kg | 86.2 (19.9) | 85.6 (18.2) | 86.6 (19.3) | 0.895 |
| Blood pressure |  |  |  |  |
| Systolic, mm Hg | 139.5 (16.1) | 137.6 (14.7) | 135.4 (14.5) | 0.022\* |
| Diastolic, mm Hg | 75.3 (10.0) | 74.2 (9.9) | 73.6 (10.4) | 0.161 |
| Serum creatinine, mg/dL | 1.73 (0.47) | 1.69 (0.45) | 1.67 (0.49) | 0.318 |
| eGFR, mL/min/1.73 m2 | 42.3 (12.9) | 42.6 (13.6) | 44.2 (14.7) | 0.307 |
| Hemoglobin, g/L | 128.9 (15.9) | 129.8 (17.0) | 132.8 (17.4) | 0.046\* |
| HbA1c1, % | 7.5 (1.5) | 7.5 (1.4) | 7.4 (1.4) | 0.666 |
| BNP, (pg/mL) | 48 [26 to 86] | 50 [26.2 to 90] | 43 [24.5 to 83] | 0.690 |
| UACR, mg/g creatinine | 1041.7 [625.7 to 1929.7] | 734  [464 to 1259] | 614.7 [377.5 to 1230.1] | <0.001\* |
| Diabetes duration, years | 15.8 (7.8) | 18.1 (8.7) | 17.2 (8.9) | 0.021\* |
| History of retinopathy, n (%) | 98 (37.8) | 54 (29.5) | 61 (32.5) | 0.170 |
| Medications, n (%) |  |  |  |  |
| Diuretics | 221 (85.3) | 160 (87.4) | 154 (81.9) | 0.323 |
| Insulin | 165 (63.7) | 112 (61.2) | 121 (64.4) | 0.798 |

Data are n (%), mean (SD), or median [IQR].

1 Based on all patients who were randomized in the double-blind treatment period, measured at start of the double-blind period. Abbreviations: BNP = Brain natriuretic peptide; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; UACR = urinary albumin-to-creatinine ratio. \*Statistically significant differences across the 3 strata of eGFR slope.

## **Supplement 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.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Pre-trial eGFR decline** | | | | | |
| **≥5 ml/min/1.73 m2/year** | | **1 to 5 ml/min/1.73 m2/year** | | **<1 ml/min/1.73 m2/year** | |
|  | **Fast progression** | | **Moderate progression** | | **Stable disease** | |
|  | **Atrasentan** | **Placebo** | **Atrasentan** | **Placebo** | **Atrasentan** | **Placebo** |
| Number of patients | 127 | 93 | 70 | 86 | 74 | 82 |
| Severe edema | 2 (1.6%) | 1 (1.1%) | 1 (1.4%) | 0 (0%) | 1 (1.4%) | 0 (0%) |
| Heart failure | 4 (3.2%)\* | 10 (10.8%) | 3 (4.3%) | 0 (0%) | 1 (1.4%) | 1 (1.2%) |

\*Hazard ratio: 0.34 (95% CI 0.10 to 1.14) based on Cox proportional hazard model as described before [1]. Due to the small number of events the hazard ratios for the other comparisons could not be calculated*.*

## **Supplemental Figure 1:** Large variation in rate of eGFR decline (pre-trial eGFR slope) before enrollment in the SONAR trial. The dashed lines represent a -5 and -1 slope in eGFR per year (ml/min/1.73m2/year). The numbers (%) of patients with pre-trial eGFR decline ≥5 ml/min/1.73m2/year (fast progression); between 1 and 5 ml/min/1.73m2/year (moderate progression) and <1ml/min/1.73m2/year (stable disease) are shown at the top of the graph.

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Histogram shows the pre-trial eGFR slopes truncated at -30 to 30 ml/min/1.73m2/year. eGFR = estimated glomerular filtration rate.

## **Supplemental Figure 2:** Correlation plots of UACR and eGFR at baseline and pre-trial eGFR slope.

The black solid line represents the regression line. The horizontal dotted line represents a pre-trial eGFR slope of -5 ml/min/1.73m2/year (i.e. decline of 5 ml/min/1.73m2/year). The vertical dotted line represents a baseline UACR of 1000 mg/g (Panel A) or a baseline eGFR of 45 ml/min/1.73m2 (Panel B). Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Y:\FAR\Medewerkers\AIO\Simke Waijer\2. Research\8. SONAR_2\Manuscript\Figure 2.emf