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Published in:
Diabetes obesity & metabolism

DOI:
10.1111/dom.14252

Received: 20 September 2020 | Revised: 30 October 2020 | Accepted: 5 November 2020

DOI: 10.1111/dom.14252

ORIGINAL ARTICLE

WILEY

Inter-individual variability in atrasentan exposure partly explains variability in kidney protection and fluid retention responses: A post hoc analysis of the SONAR trial

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Funding information
Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Grant/Award Number: 917.15.306; Novo Nordisk UK Research Foundation, Grant/Award Number: NNF OC0013659; The SONAR trial was funded by AbbVie

Abstract

Aim: To evaluate whether atrasentan plasma exposure explains between-patient variability in urinary albumin-to-creatinine ratio (UACR) response, a surrogate for kidney protection, and B-type natriuretic peptide (BNP) response, a surrogate for fluid expansion.

Methods: Type 2 diabetic patients with chronic kidney disease (n = 4775) received 0.75 mg atrasentan for 6 weeks in the active run-in period. Individual area under the concentration-time-curve (AUC) was estimated using a population pharmacokinetic model. The association between atrasentan AUC, other clinical characteristics, and UACR and BNP response, was estimated using linear regression.

Results: The median atrasentan AUC was 43.8 ng.h/mL with a large variation among patients (2.5th-97.5th percentiles [P]: 12.6 to 197.5 ng.h/mL). Median UACR change at the end of enrichment was −36.0% and median BNP change was 8.7%, which also varied among patients (UACR, 2.5th-97.5th P: −76.2% to 44.5%; BNP, 2.5th-97.5th P: −71.5% to 300.0%). In the multivariable analysis, higher atrasentan AUC was

associated with greater UACR reduction (4.88% per doubling in ng.h/mL [95% confidence interval {CI}: 6.21% to 3.52%], $P < .01$) and greater BNP increase (3.08% per doubling in ng.h/mL [95% CI: 1.12% to 4.11%], $P < .01$) independent of estimated glomerular filtration rate, haemoglobin or BNP. Caucasian patients compared with black patients had greater UACR reduction (7.06% [95% CI: 1.38% to 13.07%]) and also greater BNP increase (8.75% [95% CI: 1.65% to 15.35%]). UACR response was not associated with BNP response (r = 0.06).

Conclusion: Atrasentan plasma exposure varied among individual patients and partially explained between-patient variability in efficacy and safety response.

KEYWORDS

atrasentan, diabetic kidney disease, endothelin receptor antagonist, pharmacodynamics, randomized controlled trial

1 | INTRODUCTION

Endothelin-1 (ET-1) is involved in the regulation of vascular tone and excretion of sodium and water.[1] ET-1 has been implicated in the progression of diabetic kidney disease by causing hypertension, proteinuria, extracellular matrix expansion, podocyte damage and tubulointerstitial injury.[2] Atrasentan is a selective endothelin receptor A antagonist (ERA) that reduces albuminuria in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).[1,3] ERAs including atrasentan can also cause fluid retention, reflected by increases in body weight or B-type natriuretic peptide (BNP), which may increase the risk of oedema and heart failure in high-risk patients.[4,5]

Prior studies showed that an atrasentan dose of 0.75 mg/day provides the most favourable balance between efficacy (albuminuria lowering) and safety (fluid retention) on a population level in patients with T2D and CKD. This dose was therefore selected for further development.[3,6,7] However, albuminuria-lowering and fluid-retention effects of atrasentan have been shown to vary considerably among patients even when patients receive the same dose of atrasentan.[8] Post hoc analyses of a phase 2 clinical trial in patients with T2D and CKD showed that part of this variability in kidney protection and fluid-retention effects of atrasentan can be explained by the plasma concentration of atrasentan and patient characteristics.[9,10] However, the sample size of this study was small, which limited the robustness and precision of the results.

The SONAR trial (clinicaltrials.gov trial registration number: NCT01858532) was performed to assess the long-term efficacy and safety of atrasentan in patients with T2D and CKD.[5] The trial design included an active run-in period, the so-called enrichment period, during which all patients were treated with 0.75 mg atrasentan once daily in order to select a population that showed a favourable response to atrasentan. Pharmacokinetic samples were collected in all patients included in the enrichment period. This allowed us to further investigate whether individual plasma exposure of atrasentan predicted the variable responses to atrasentan in both efficacy (albuminuria lowering) and safety (BNP increase).

2 | METHODS

2.1 | Study design and patient population

The study design and patient population of the SONAR trial have been described previously.[5,11] The study protocol was approved by appropriate national and institutional regulatory and ethical boards.[5,11]

In short, patients with T2D, an estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73 m^2, a urinary albumin-to-creatinine ratio (UACR) of 300-5000 mg/g, and BNP 200 pg/mL or lower, were eligible for enrolment. Exclusion criteria included previous hospital admission for heart failure and a history of severe peripheral or facial oedema. Stable treatment, for at least 4 weeks, with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was required before patients could enter the enrichment period of the trial. During the enrichment period, all patients were treated with 0.75 mg atrasentan once daily for 6 weeks, after which patients were stratified based on their albuminuria response. Patients who tolerated atrasentan and had a decrease in UACR of 30% or more were classified as responders, whereas patients with a UACR decrease of less than 30% were classified as non-responders. Patients could not proceed to the double-blind period of the trial if they experienced a weight gain of greater than 3 kg or if absolute BNP values exceeded 300 pg/mL or more at the last enrichment visit. Both the responder and non-responder participants who tolerated atrasentan were randomized in a double-blind period with a 1:1 ratio to receive atrasentan 0.75 mg once daily or matching placebo.

2.2 | Estimating individual atrasentan plasma exposure

A population pharmacokinetic model was developed to estimate individual pharmacokinetic variables during the enrichment phase.

Because the exact time of pharmacokinetic blood sampling and atrasentan dosing were recorded, time differences in the collection of blood samples among patients were corrected for and covariates associated with variability between patients in the pharmacokinetics of atrasentan could be identified.

Non-linear mixed effects models were used to develop the population pharmacokinetic model. The details of the model development are provided in the Supplementary Materials (see the supporting information). In short, the population pharmacokinetic model uses pharmacokinetic parameters such as clearance (CL) and volume of distribution (V_d) to describe the plasma-concentration time profile of atrasentan for each individual patient and allows incorporation of covariates that explain differences in CL and V_d between patients. The area under the plasma-concentration time curve (AUC), as a measure of plasma exposure, was calculated by dividing the dose by the individual CL at the last visit of the enrichment period. As the distributions of individual AUC and V_d values were skewed to the right, both variables were log-transformed to approximate a normal distribution for the remainder of the analysis.

2.3 | Analysis of variability in albuminuria and fluid retention response

In this analysis, UACR was used as an efficacy surrogate for kidney failure whereas BNP was used as a surrogate for fluid retention. For both markers, change from baseline was calculated as the log-transformed change from baseline. We first explored the relationship between plasma atrasentan exposure and BNP and UACR response by non-linear models assuming an Emax structure. Multivariable linear regression models were then used to assess whether the pharmacokinetic variables AUC and V_d were associated with the efficacy and safety response variables, independent of other patient characteristics. The patient characteristics considered were age, sex, race, ethnicity, baseline UACR, BNP, body weight, systolic blood pressure, eGFR, haemoglobin, and use of insulin and/or diuretics. Continuous variables are reported as mean with standard deviation or median with 25th to 75th percentiles where appropriate. Categorical variables are reported as numbers and percentages. For the multivariable model, a backward-selection approach was applied to select variables. Backward selection was based on significant improvement of the Akaike information criteria.

2.4 | Software

All datasets were prepared in R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria). Ggplot2 version 3.0.0 was used for all graphs. The stats package was used for the non-linear and linear regression analyses. NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA) was used for the population pharmacokinetic analysis and model simulations.

3 | RESULTS

The demographics and clinical characteristics of patients (n = 4775) with evaluable plasma concentrations during the enrichment period are presented in Table 1.

The median trough atrasentan concentration was 1.68 ng/mL (interquartile range [IQR]: 1.11 to 2.66 ng/mL) during the enrichment period. The pharmacokinetic model was adequate in describing the observed pharmacokinetic data. The model parameter estimates and a visual predictive check are displayed in Table 2 and Figure S1. The model-estimated median AUC was 43.8 ng.h/mL (IQR: 28.8 to 69.6 ng.h/mL) and the median V_d was 2051.1 L (IQR: 1152.0 to 3497.3) during the enrichment period of the SONAR trial. The 2.5th to 97.5th percentiles of AUC ranged from 12.6 to 197.5 ng.h/mL and

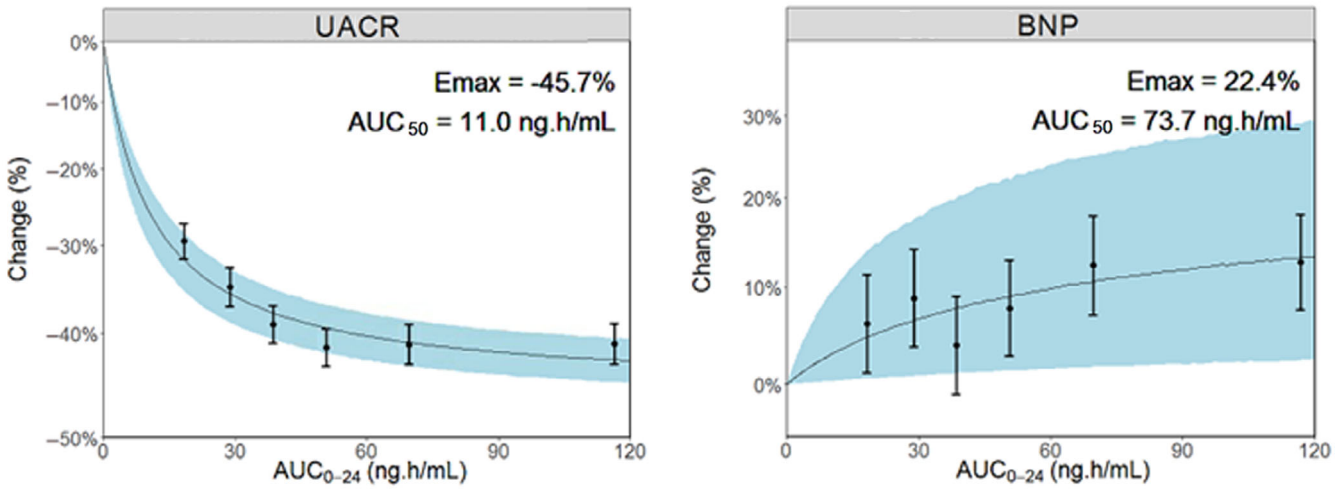

FIGURE 1 Exposure-response relationship between atrasentan and UACR and BNP. The observations are displayed as mean (•) with 95% CI (error bars) and model predictions are displayed as mean (•) with 95% CI (error bars) and mean (-) with 95% CI (area). AUC, area under the concentration-time-curve; BNP, B-type natriuretic peptide; UACR, urinary albumin-to-creatinine ratio

for V_d ranged from 285.2 to 9642.4 L, indicating large between-patient variability in the pharmacokinetics of atrasentan.

3.1 | Albuminuria and BNP response variability

At the end of the enrichment phase, median UACR change was −36.0%. The UACR change from baseline to week 6 was highly variable among patients with a 2.5th to 97.5th percentile of −76.2% to 44.5%. Median increase in BNP was 8.7%, again with high variability among patients (2.5th to 97.5th percentile −71.5% to 300.0%). The UACR change was not associated with BNP change (r = 0.06).

The exposure to atrasentan was associated with UACR and BNP changes at the end of enrichment (Figure 1). A maximum effect model, for which the model parameters are described in Table S1, estimated the maximum effects of atrasentan to be −45.7% (95% CI: −42.7 to −48.7) for UACR and 22.4% (95% CI: 5.2% to 39.6%) for BNP. For UACR, the average atrasentan AUC was higher than the AUC_{50} variables, indicating that the maximum effect was approached. For BNP, the average AUC was lower than the AUC_{50} variable, indicating that less than 50% of the maximum BNP effect was achieved.

To characterize the relationship between atrasentan pharmacokinetics in the context of other patient characteristics, univariable and multivariable linear regression were used. Univariable models identified the pharmacokinetic variables AUC and V_d, and the patient characteristics of age, race, body weight, eGFR, baseline UACR and baseline BNP, as associated with UACR response at the end of the enrichment phase (Table 3). In multivariable analyses, higher atrasentan AUC, age, body weight, eGFR and BNP and lower haemoglobin were associated with more UACR reduction. Black patients showed less UACR reduction compared with Caucasian patients.

In univariable analyses, the pharmacokinetic variables AUC and V_d, and the patient characteristics of race, ethnicity, systolic blood pressure, body weight, eGFR, haemoglobin and baseline BNP, were associated with BNP response (Table 4). In multivariable analyses, higher atrasentan AUC, age and UACR, and lower eGFR, haemoglobin and baseline BNP, were associated with a greater increase in BNP, whereas black and Hispanic patients had a lower increase in BNP.

TABLE 1 Baseline demographics of enrichment patients included in the analysis

	Enrichment
Number of patients	4775
Age (y)	64.3 (±8.8)
Sex (females)	1285 (26.9%)
Race	
Asian	1506 (31.5%)
Black	321 (6.7%)
Caucasian	2775 (58.1%)
Other	173 (3.6%)
Ethnicity (Hispanic or Latino)	1122 (23.5%)
Systolic blood pressure (mmHg)	138.2 (±15.8)
Body weight (kg)	85.8 (±19.7)
eGFR (mL/min per 1.73 m^2)	41.75 (±12.6)
Haemoglobin (g/L)	128.4 (±17.1)
Baseline UACR (mg/g)	829.0 [459.1-1556.1]
Baseline BNP (pg/mL)	48.0 [26.0-86.5]
Insulin use	3001 (62.8%)
Diuretic use	3870 (81.0%)

Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.
Note: Continuous variables are displayed as mean (SD) or median [IQR].

3.2 | Patient characteristics associated with the pharmacokinetics of atrasentan

The population pharmacokinetic model identified female sex, body weight and serum creatinine as factors significantly associated with CL and thus AUC (Table 4). The model estimated that females had a

TABLE 2 Population pharmacokinetic variable estimates

Variable description	Estimate	RSE (%)	IIV (CV%)	RSE (%)	IOV (CV%)	RSE (%)
First-order absorption rate constant (h^{-1})	0.4	N/E	N/E	N/E	N/E	N/E
Apparent clearance from central compartment (L. h^{-1})	16.3	1.1	50.8	1.6	42.9	1.7
Apparent volume of distribution for central compartment (L)	1670.0	8.1	100.4	2.1	N/E	N/E
Correlation between CL/F and V/F			r = 0.23			
Covariate effects	**Estimate**	**RSE (%)**				
Serum creatinine on CL/F	0.11	23.4				
Female sex on CL/F	−0.07	25.3				
Asian race on V/F	0.37	33.3				
Caucasian race on V/F	0.23	43.9				
Residual error	**Value**	**RSE (%)**				
Proportional (%)	8.1	17.0				

Abbreviations: CV, coefficient of variation; IIV, inter-individual variability; IOV, inter-occasion variability; N/E, not estimated; RSE, relative standard error.

TABLE 3 Evaluation of factors associated with variability between patients in albuminuria response (UACR change in percentage)

	Univariable		Multivariable	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Age (per year)	**−0.42 (−0.58, −0.26)**	**<.01**	**−0.26 (−0.42, −0.10)**	**<.01**
Sex (female)	−0.83 (−3.90, 2.33)	.60		
Race				
Asian	−2.32 (−5.27, 0.73)	.14	−1.57 (−4.78, 1.76)	.35
Black	**8.19 (2.26, 14.47)**	**<.01**	**7.06 (1.38, 13.07)**	**.01**
Caucasian	*Ref*		*Ref*	
Other	3.03 (−1.39, 2.33)	.07	−6.65 (−14.23, 1.62)	.11
Ethnicity (Hispanic or Latino)	−0.25 (−3.47, 3.07)	.88		
Systolic blood pressure (per 10 mmHg)	−0.17 (−0.96, 0.61)	.70		
Body weight (per 10 kg)	**0.73 (0.01, 1.44)**	**.05**	**−0.87 (−1.68, −0.06)**	**.04**
eGFR (per 10 mL/min/1.73 m^2)	**−6.31 (−6.96, −5.66)**	**<.01**	**−6.30 (−6.98, −5.63)**	**<.01**
Haemoglobin (per 10 g/L)	−0.17 (−0.96, 0.61)	.67	**1.29 (0.46, 2.12)**	**<.01**
UACR (per doubling in mg/g)[a]	**0.89 (0.14, 1.65)**	**.02**		
BNP (per doubling in pg/mL)[a]	**−0.96 (−1.72, −0.20)**	**.01**	**−1.37 (−2.49, −0.23)**	**.02**
Use of insulin (yes)	0.84 (−1.92, 3.68)	.56		
Use of diuretics (yes)	0.00 (−3.36, 3.48)	1.00		
Pharmacokinetic variables				
$AUC_{0\text{-inf}}$ (per doubling in ng.h/mL)[a]	**−6.07 (−7.37, −5.43)**	**<0.01**	**−4.88 (−6.21, −3.52)**	**<.01**
V_d (per doubling in L)[a]	**2.64 (1.87, 3.41)**	**<0.01**		

Note: Bold values represent significant covariates ($p < 0.05$).
Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.
[a]Baseline UACR and BNP, atrasentan plasma exposure ($AUC_{0\text{-inf}}$) and volume of distribution (V_d) were log-transformed.

6.7% (95% CI: 3.5% to 10.4%) higher AUC compared with males. Furthermore, an increase in body weight or serum creatinine translated to a lower atrasentan AUC (Table 2).

4 | DISCUSSION

Variability in the albuminuria and BNP treatment response to atrasentan was high in the SONAR trial, which may be attributable to a combination of pharmacokinetic and pharmacodynamic differences. Despite all patients receiving the same daily 0.75 mg atrasentan dose, plasma exposure to atrasentan varied substantially among patients. This between-patient variability in exposure accounted for part of the between-patient variability in surrogates for efficacy (albuminuria) and safety (BNP), independent of other patient characteristics.

Albuminuria was selected as a surrogate outcome for long-term kidney protection during the enrichment period of the SONAR trial.[11] We showed that the albuminuria-lowering effect of atrasentan was highly variable among patients during the enrichment phase of the SONAR trial, which could potentially indicate that the long-term kidney protective effect of atrasentan also varies among patients. This high variability in response to atrasentan has been observed before in phase 2 studies.[3,6] In an earlier, comparatively small phase 2 trial, a greater albuminuria reduction was observed in Asian patients compared with North American patients, which was linked to higher atrasentan plasma concentrations in Asian patients.[9,10] In the current study, the albuminuria response was similar between Asian and Caucasian patients. We do not have a clear explanation for the difference, but it is probable that the smaller phase 2 study led to chance findings. The large SONAR trial allowed us to assess the response in black patients, which could not be assessed in previous studies because of the small sample size. In SONAR, black patients experienced less albuminuria lowering compared with Caucasian patients. This effect remained present after accounting for differences in atrasentan exposure, suggesting that differences in pharmacodynamic response are involved.

The concentration of BNP is increased during fluid retention and has been associated with heart failure.[12,13] This safety marker was therefore selected in the enrichment phase of the SONAR trial to exclude patients who were prone to fluid retention.[11] The high between-patient variability in atrasentan treatment response was also reflected by the large between-patient variability in BNP responses. Atrasentan plasma exposure, as well as lower eGFR, partially explained the between-patient variability in BNP response. These findings are in line with a previous study reporting that higher atrasentan dose and lower eGFR were associated with more fluid retention.[14] In the current study, we also observed that black patients showed less BNP response, suggesting that both the efficacy and

TABLE 4 Evaluation of factors associated with variability between patients in BNP response (BNP change in percentage)

	Univariable		Multivariable	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Age (per year)	0.05 (−0.17, 0.27)	.65	**0.71 (0.49, 0.94)**	**<.01**
Sex (female)	−0.22 (−4.53, 4.28)	.92		
Race				
Asian	**6.86 (2.35, 11.57)**	**<.01**	−1.91 (−6.18, 2.56)	.40
Black	−3.40 (−10.80, 4.61)	.40	**−8.75 (−15.35, −1.65)**	**.02**
Caucasian	*Ref*		*Ref*	
Other	−0.63 (−6.49, 5.61)	.84	−6.90 (−17.15, 4.63)	.23
Ethnicity (Hispanic or Latino)	**−5.07 (−0.60, −9.34)**	**.03**	**−4.76 (−9.18, −0.12)**	**.05**
Systolic blood pressure (per 10 mmHg)	**−2.96 (−1.74, −4.19)**	**<.01**		
Body weight (per 10 kg)	**−1.32 (−2.32, −0.32)**	**<.01**		
eGFR (per 10 mL/min/1.73 m^2)	**−1.73 (−2.69, −0.76)**	**<.01**	**−2.30 (−3.23, −1.37)**	**<.01**
Haemoglobin (per 10 g/L)	**−1.34 (−2.44, −0.25)**	**.02**	**−2.32 (−3.43, −1.21)**	**<.01**
UACR (per doubling in mg/g)[a]	−0.08 (−1.12, 0.97)	.88	**2.53 (0.97, 4.11)**	**<.01**
BNP (per doubling in pg/mL)[a]	**−11.66 (−12.54, −10.77)**	**<.01**	**−17.82 (−19.12, −16.50)**	**<.01**
Use of insulin (yes)	−1.16 (−4.93, 2.76)	.56		
Use of diuretics (yes)	−0.15 (−4.82, 4.74)	.95		
Pharmacokinetic variables				
$AUC_{0\text{-}inf}$ (per doubling in ng.h/mL)[a]	**1.89 (0.50, 3.30)**	**<.01**	**3.08 (1.12, 4.11)**	**<.01**
V_d (per doubling in L)[a]	**−1.13 (−2.17, −0.09)**	**.03**		

Note: Bold values represent significant covariates ($p < 0.05$).
Abbreviations: BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.
[a]Baseline UACR and BNP, atrasentan plasma exposure ($AUC_{0\text{-}inf}$) and volume of distribution (V_d) were log-transformed.

safety response in these patients is blunted. Interestingly, the diminished albuminuria and BNP response persisted after accounting for differences in plasma atrasentan exposure, suggesting that ethnic/race differences in sensitivity to ET-1, which have been described for blood pressure response to ET-1,[15] may account for the blunted effect in black patients. Finally, previous studies found that haemoglobin was associated with atrasentan-induced fluid retention.[14] This factor also emerged from our univariable and multivariable models, confirming the predictive value of this factor.

Between-patient variability in atrasentan plasma exposure was also high and contributed to the individual treatment response. In the population pharmacokinetic model, body weight was identified as the primary factor that explained variability in both plasma exposure and the V_d, which confirms previous findings of phase 2 trials.[9,16] Additionally, sex and serum creatinine partially explained between-patient variability in plasma exposure, which suggests that kidney function might influence the pharmacokinetics of atrasentan. However, renal excretion does not contribute to the clearance of atrasentan and, to our knowledge, no influence of kidney function on the clearance of atrasentan has been previously reported. In this analysis, eGFR could not be identified as a significant covariate in the population pharmacokinetic model. The effect size of serum creatinine and sex on atrasentan exposure was minimal and therefore the contribution of these patient characteristics is regarded as not clinically relevant.

The enrichment period of the SONAR trial aimed to select patients likely to respond to atrasentan and to exclude patients prone to fluid retention, which is important in diabetic kidney disease patients who are at a significant risk of fluid retention and heart failure because of their underlying disease. Importantly, we found that the UACR response was not associated with the BNP response. Therefore, the current analysis raises the question of whether it is possible to enhance the response to atrasentan in therapy-resistant patients by increasing the dose of atrasentan without increasing atrasentan-induced fluid retention. The relationship between plasma exposure and albuminuria indicates that additional albuminuria lowering can be achieved by increasing the plasma exposure using a higher dose of atrasentan. However, the maximum dose is limited by the fluid-retention effects of atrasentan, and increasing the atrasentan plasma exposure will also result in more fluid retention.[10] This highlights the need for establishing a therapeutic window, during which fluid retention is kept at a minimum, while albuminuria lowering is optimized. For patient populations that are less vulnerable to developing fluid retention, such as black patients or patients with preserved kidney function, an increase in atrasentan dose could potentially be effective and tolerated. Individualizing the dose based on individual patient characteristics may be considered to improve the benefit/risk profile in diabetic kidney disease where fluid retention needs to be very carefully monitored and managed.

The limitation of this study is that the population pharmacokinetic analysis was mainly based on trough concentrations obtained after a single dose level of atrasentan, which could have influenced our results. First, we excluded all plasma samples below the lower limit of quantification (LLOQ). However, the number of LLOQ was low (6.9%) and it has been shown previously that excluding LLOQ samples has minimal impact on the estimation of exposure when the number of excluded LLOQ samples is less than 20%.[17] Second, the estimation of the atrasentan plasma exposure could be influenced as plasma samples were mainly collected in the overall population of the SONAR trial. To enhance the estimation of plasma exposure, more informative sampling strategies should be considered for future phase 3 trials. For example, by including a pharmacokinetic substudy, in which more samples are collected per occasion in part of the treated population, as was carried out in a large cardiovascular outcome trial for aleglitazar.[18] Third, in this analysis, we assumed that atrasentan plasma exposure is stable throughout the enrichment period. Finally, this analysis is based on short-term changes during the enrichment period of the SONAR trial. The effect of these predictors on long-term outcomes should therefore still be confirmed.

In conclusion, between-patient variability in efficacy (albuminuria) and safety (BNP) of 0.75 mg atrasentan could be attributed in part to atrasentan plasma exposure and patient characteristics. Patients with a higher exposure to atrasentan had a larger reduction in albuminuria, but also a larger increase in BNP. Tailoring atrasentan dose in diabetic kidney disease on the basis of individual patient characteristics could potentially improve the benefit/risk profile for each patient.

ACKNOWLEDGEMENTS

We would like to thank all the patients and investigators who participated in the SONAR trial. JS is supported by a grant from the Novo Nordisk Foundation (grant number NNF OC0013659). HJLH is supported by a VIDI grant from the Netherlands Organization for Scientific Research (917.15.306). The SONAR trial was funded by AbbVie.

CONFLICT OF INTEREST

JVK, JJVM and JS have no competing interests. HJLH is a consultant to AbbVie, AstraZeneca, Boehringer Ingelheim, Bayer, Chinook, CSL Behring, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, Novo Nordisk and Retrophin. He received research support from AstraZeneca, AbbVie, Boehringer Ingelheim and Janssen. DEK is a consultant to AbbVie, Chinook, Janssen and Retrophin. RCR is consultant for AstraZeneca, Novonordisk, Janssen, Boehringer Ingelheim and has been a speaker for AstraZeneca, Boehringer Ingelheim, AbbVie, Takeda, Amgen, and Janssen. He received research support from AstraZeneca, AbbVie and GSK. GB is a consultant for Bayer, Relypsa, Janssen, Merck and Vascular Dynamics. RCR serves on advisory boards for Boehringer and AstraZeneca and has been a speaker for AstraZeneca, Boehringer Ingelheim, AbbVie, Takeda, Amgen and Janssen. FFH is a consultant for and has received honoraria from AbbVie and AstraZeneca. DWK received grant funding from Bayer, Novartis and the National Institutes of Health, and has been a consultant for AbbVie, Bayer, Merck, Boehringer Ingelheim, Corvia, CinRx, GlaxoSmithKline (GSK), Duke Clinical Research Institute, St Luke's Medical Center and AstraZeneca. HM is a consultant for AbbVie, Boehringer-ingelheim and Teijin Pharma. VP has served on Steering Committees for trials funded by AbbVie, Boehringer Ingelheim, GSK, Janssen, Novo Nordisk, Retrophin and Tricida; and has participated in scientific presentations or advisory boards with AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Brisol-Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier and Tricida. ST participates on a steering committee for Bayer Fidelio/Figaro studies, and speaker's bureaux with Servier and Pfizer. DdZ serves on advisory boards or is a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma and Mitsubishi Tanabe; participates in steering committees or is a speaker for AbbVie and Janssen; and is on the data safety and monitoring committees for Bayer. H-HP serves as a consultant for AbbVie.

AUTHOR CONTRIBUTIONS

JVK analysed the data. JVK, HJLH and JS interpreted the data. JVK and HJLH wrote the first draft of the manuscript. The other authors revised the draft manuscript for important intellectual content. All the authors contributed to data collection and all the authors approved the manuscript for submission.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14252.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Abbvie but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Abbvie.

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REFERENCES

1. Kohan DE. Endothelin, hypertension and chronic kidney disease: new insights. *Curr Opin Nephrol Hypertens*. 2010;19(2):134-139.
2. Richter CM. Role of endothelin in chronic renal failure—developments in renal involvement. *Rheumatology*. 2006;45(Suppl 3):336-338.
3. de Zeeuw D, Coll B, Andress D, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol*. 2014;25(5):1083-1093.
4. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol*. 2010;21(3):527-535.

5. Heerspink HJL, Parving HH, Andress DL, 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;393(10184):1937-1947.
6. Kohan DE, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol*. 2011;22(4):763-772.
7. Webb DJ, Coll B, Heerspink HJL, et al. Longitudinal assessment of the effect of atrasentan on thoracic bioimpedance in diabetic nephropathy: a randomized, double-blind, placebo-controlled trial. *Drugs R D*. 2017;17(3):441-448.
8. Heerspink HJL, Andress DL, Bakris G, et al. Baseline characteristics and enrichment results from the SONAR trial. *Diabetes Obes Metab*. 2018;20(8):1829-1835.
9. Heerspink HJ, Makino H, Andress D, et al. Comparison of exposure response relationship of atrasentan between North American and Asian populations. *Diabetes Obes Metab*. 2017;19(4):545-552.
10. Koomen JV, Stevens J, Mostafa NM, Parving HH, de Zeeuw D, Heerspink HJL. Determining the optimal dose of atrasentan by evaluating the exposure-response relationships of albuminuria and bodyweight. *Diabetes Obes Metab*. 2018;20(8):2019-2022.
11. Heerspink HJL, Andress DL, Bakris G, 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):1369-1376.
12. Cowie MR, Mendez GF. BNP and congestive heart failure. *Prog Cardiovasc Dis*. 2002;44(4):293-321.
13. Mukoyama M, Nakao K, Saito Y, et al. Increased human brain natriuretic peptide in congestive heart failure. *N Engl J Med*. 1990;323(11):757-758.
14. Kohan DE, Lambers Heerspink HJ, Coll B, et al. Predictors of atrasentan-associated fluid retention and change in albuminuria in patients with diabetic nephropathy. *Clin J Am Soc Nephrol*. 2015;10(9):1568-1574.
15. Gregoski MJ, Buxbaum SG, Kapuku G, et al. Interactive influences of ethnicity, endothelin-1 gene, and everyday discrimination upon nocturnal ambulatory blood pressure. *Ann Behav Med*. 2013;45(3):377-386.
16. Lin CW, Mostafa NM, Andress DL, Brennan JJ, Klein CE, Awni WM. Relationship between atrasentan concentrations and urinary albumin to creatinine ratio in Western and Japanese patients with diabetic nephropathy. *Clin Ther*. 2018;40(2):242-251.
17. Ahn JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn*. 2008;35(4):401-421.
18. Koomen JV, Heerspink HJL, Schrieks IC, et al. Exposure and response analysis of aleglitazar on cardiovascular risk markers and safety outcomes: an analysis of the AleCardio trial. *Diabetes Obes Metab*. 2020;22(1):30-38. https://doi.org/10.1111/dom.13862.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Koomen JV, Stevens J, Bakris G, et al. Inter-individual variability in atrasentan exposure partly explains variability in kidney protection and fluid retention responses: A post hoc analysis of the SONAR trial. *Diabetes Obes Metab*. 2021;23:561–568. https://doi.org/10.1111/dom.14252