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RESEARCH LETTER

Diuretic medication and change in fluid retention biomarkers during treatment with the endothelin receptor antagonist atrasentan

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1 | BACKGROUND

Endothelin-1 is an endogenous peptide that has been implicated in the progression of chronic kidney disease (CKD).[1] ET_A receptor inhibition with atrasentan reduced the risk of major clinical kidney outcomes in patients with type 2 diabetes and CKD in the SONAR trial.[2] However, ET_A receptor antagonists (ERAs), including atrasentan, can cause sodium and fluid retention, leading to oedema and possibly heart failure.[3,4] The nephron site(s) responsible for ERA-induced fluid retention are uncertain. Collecting duct-specific knockout of ET_A receptors in mice prevented atrasentan-induced fluid retention, suggesting involvement of the epithelial Na^+ channel (ENaC).[3] In addition, endothelin-1 can inhibit proximal tubule Na^+/H^+ exchanger-3 and loop of Henle $Na^+/K^+/2Cl^-$ co-transporter activity; while these effects have been primarily ascribed to activation of the ET_B receptor, there is evidence that ET_A and ET_B receptors can interact.[2,3] Thus, ERA-induced fluid retention could potentially involve actions throughout multiple segments of the nephron.[3]

To reduce the risk of fluid retention, the SONAR trial excluded patients with a history of heart failure, recommended diuretic treatment, and implemented a 6-week open label response enrichment period prior to randomization to identify and exclude patients with severe fluid retention in response to atrasentan.[5] Despite these precautionary measures, there was a higher proportion of fluid retention-related adverse events and a numerically higher incidence of hospitalization for heart failure with atrasentan compared with placebo.[2] Different diuretic agents were used in the SONAR trial to manage fluid retention. However, it is unclear whether a particular class of diuretics, targeting a specific nephron segment, more effectively mitigated atrasentan-induced fluid retention. We, therefore, performed a post hoc analysis of the SONAR trial to firstly determine if diuretics reduce body weight and increase haematocrit in response to ERA-induced fluid retention. Secondly, we assessed and compared the degree of fluid retention for patients using different classes of diuretics.

2 | METHODS

We performed a post hoc analysis of the SONAR trial (ClinicalTrials.gov identifier NCT01858532). The design, enrichment results and primary results of the SONAR trial, a randomized double-blind, placebo-controlled clinical trial, have been published previously.[2,5,6] The trial enrolled 5107 adults with type 2 diabetes and an estimated

glomerular filtration rate (eGFR) between 25 and 75 mL/min per 1.73 m^2 of body surface area, a urinary albumin creatinine ratio (UACR) between 300 and 5000 mg/g, and a B-type natriuretic peptide (BNP) not exceeding 200 pg/mL. All patients used a maximally tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker. The design of the SONAR trial included a 6-week enrichment period, during which all patients received open-label treatment with 0.75 mg/d atrasentan to identify atrasentan 'responders', defined as those who had a 30% or greater reduction in UACR from start to end of response enrichment without substantial fluid retention.

At each study visit, concomitant medication was recorded. Records for initiation and cessation of diuretic concomitant medication were available at study visits. Diuretic agents of interest were loop and thiazide diuretics, as these classes of diuretics were most commonly prescribed for the management of oedema and heart failure.[2] We examined the effect of diuretic treatment on body weight, BNP and haematocrit, as proxies for fluid retention, during the 6-week open-label response enrichment phase. Participating investigators and participants were instructed to measure body weight using the same device and circumstances. All laboratory variables, including BNP and haematocrit, were measured in a central laboratory.

To address the first aim of this post hoc analysis, we investigated patients who initiated diuretic treatment during the enrichment phase and analysed the change in body weight and haematocrit before and after initiation of diuretic medication using analysis of variance. Body weight after initiation of diuretic medication was used as the dependent variable, and the initiated class of diuretic medication (loop or thiazide), age, sex, eGFR, UACR and race at baseline, as well as the change in body weight before initiation of diuretic medication, as covariates. To address the second study aim, we compared the changes in BNP, body weight and haematocrit among patients who were using stable doses of a loop or thiazide diuretic or a combination of both from baseline to the end of the enrichment phase, using analysis of variance with age, sex, body weight, eGFR, UACR and race at baseline as covariates. Finally, we calculated the changes in BNP, body weight and haematocrit from randomization to 1 month of treatment in the double-blind phase for the atrasentan and placebo treatment groups. All analyses were performed with the software package 'R', version 4.1.0. (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Among 5107 participants who started 6-week open-label treatment with atrasentan, 4045 (79.2%) used diuretic medication at baseline of the enrichment phase. Of those, 1514 patients used a loop diuretic, 1303 used a thiazide diuretic, and 93 used a combination of both a loop and a thiazide diuretic in a stable dose throughout the enrichment phase. Patients on a loop diuretic were more often White, had a higher body weight and UACR, and had a lower eGFR compared with patients on a thiazide diuretic (Table S1). In multivariable adjusted analyses, there was no statistically significant difference in change in fluid retention biomarkers between patients using a stable dose of a loop or a thiazide diuretic, or a combination of both, during the response enrichment period (Table 1).

TABLE 1 Change in surrogate biomarkers of fluid retention during the enrichment phase for patients with a stable diuretic dose

Biomarker	Loop ($n = 1514$)	Thiazide ($n = 1303$)	Loop + thiazide ($n = 93$)	Total ($n = 2910$)
BNP (% change)	6.9 (3.5, 10.5)	9.2 (5.4, 13.2)	2.0 (−10.3, 15.9)	7.8 (5.2, 10.4)
Haematocrit (% difference)	−2.35 (2.55)	−2.33 (2.59)	−2.27 (2.09)	−2.34 (2.56)
Body weight (kg difference)	0.5 (1.5)	0.5 (1.5)	0.3 (1.7)	0.5 (1.5)

Abbreviations: BNP, B-type natriuretic peptide; Loop, only loop diuretics; Thiazide, only thiazide diuretics; Total, all patients on a stable dose of loop, thiazide or combination of both.

TABLE 2 Change in body weight and haematocrit before and after escalation of diuretic medication during the enrichment phase (EP).

Phase	Diuretic subgroup	Δbody weight (SD)	ΔHCT (SD)	*n*
Before	Total	1.8 (1.6)	−2.55 (2.29)	441
	Loop	1.8 (1.7)	−2.58 (2.32)	339
	Thiazide	1.5 (1.5)	−2.47 (2.24)	102
After	Total	−0.7 (1.5)	−0.18 (1.98)	441
	Loop	−0.8 (1.5)	−0.15 (2.01)	339
	Thiazide	−0.4 (1.4)	−0.27 (1.88)	102

Note: change in haematocrit not available for participants who started a diuretic around the second visit of the EP, as there was no haematocrit measurement during the second visit. BNP was only measured twice during the EP, which prevented measuring the change in BNP before and after starting diuretics.
Abbreviations: BNP, B-type natriuretic peptide; HCT, haematocrit; Loop, only loop diuretics; SD, standard deviation; Thiazide, only thiazide diuretics.

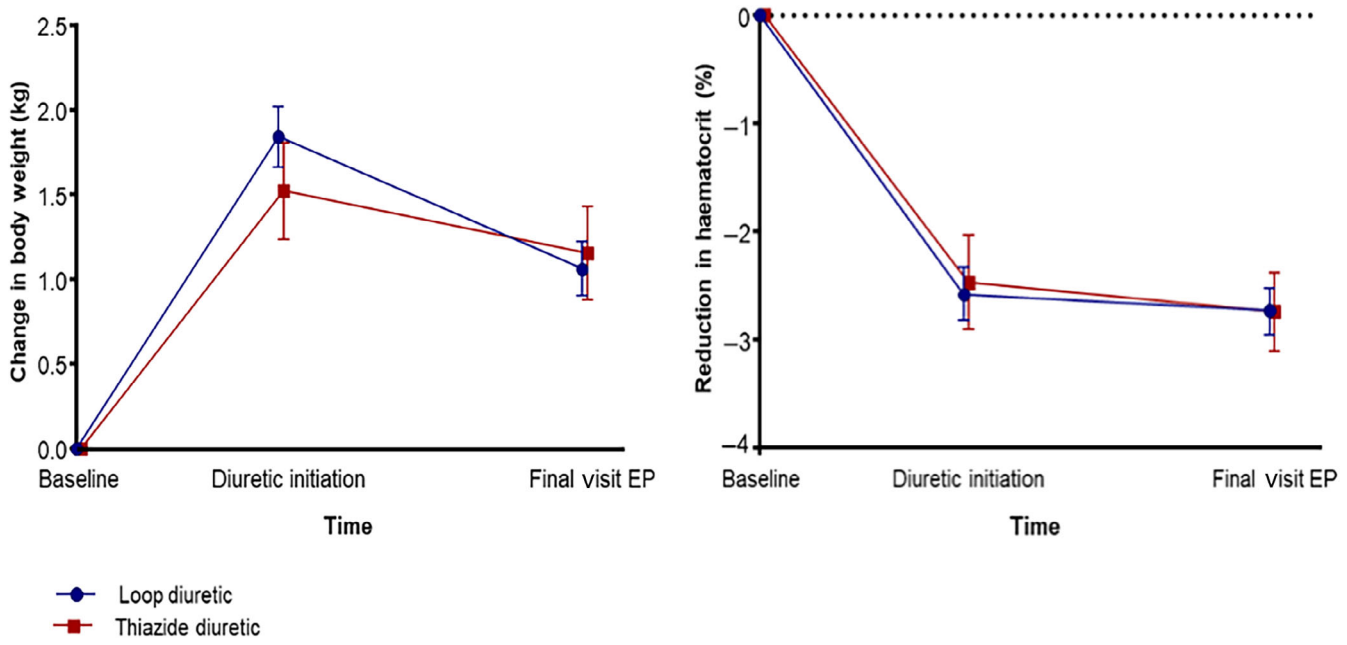

FIGURE 1 Change in body weight (left) and haematocrit (right) before and after initiation of diuretic medication during the enrichment phase. EP, enrichment phase

There were 441 patients who initiated diuretic medication during the response enrichment period with available biomarker measurements before and after initiation. Their baseline demographic and clinical characteristics are presented in Table S1B. Among these patients, the mean body weight increase was 1.8 (standard deviation [SD] 1.6) kg prior to the start of diuretic treatment. After the start of a diuretic, body weight decreased by 0.7 (SD 1.5) kg (Table 2, Figure 1). There was no significant difference in the change in fluid retention biomarkers between patients who initiated a loop versus a thiazide diuretic (−0.8 vs. −0.4 kg, $P = .086$).

Among 2120 participants on a stable dose of a loop or a thiazide diuretic or a combination of both throughout the enrichment phase who advanced to the double-blind phase of the clinical trial, the mean body weight, haematocrit and BNP changes during the response enrichment period were 0.5 (SD 1.5) kg, −2.5% (SD 2.5%) and 6.9% (95% CI 4.0%, 9.9%), respectively. These proxies of fluid retention were reversed among patients who transitioned to placebo at randomization, but persisted in those who continued atrasentan. Specifically, 1 month after randomization, body weight decreased by 0.8 (SD 1.6) kg in the placebo group, with no differences between patients using loop or thiazide diuretics (Table S2). By contrast, body weight decreased by 0.1 (SD 1.4) kg in the atrasentan group (Table S2). Similarly, patients who transitioned to placebo had a 1.9% (SD 2.9%) increase in haematocrit and a 4.3% (95% CI −8.5%, 0.1%) decrease in BNP, without clear differences between the two diuretic subgroups, while patients who continued atrasentan had a 0.1% (SD 2.4%) decrease in haematocrit and 3.6% (95% CI −0.6%, 7.8%) increase in BNP 1 month after randomization.

4 | CONCLUSIONS

This post hoc analysis compared changes in biomarkers for fluid retention in participants using different classes of diuretic agents during treatment with the ET_A receptor antagonist atrasentan during the SONAR trial.

Loop and thiazide diuretics are frequently used in patients with CKD, with loop diuretics recommended in patients with more advanced kidney disease. As expected, patients with more advanced CKD, reflected by a lower eGFR, higher UACR and lower haemoglobin, were more frequently using loop compared with thiazide diuretics. However, after accounting for differences in patient characteristics between patients using loop and thiazide diuretics, we did not observe a significant difference in fluid retention biomarkers between patients stably using these two classes of diuretic agents. Escalation of diuretic treatment during the enrichment phase was accompanied by a marked reversal in weight gain and haematocrit change. Fluid retention in response to atrasentan was reversed during the first month of the double-blind phase in patients who transitioned to placebo.

Interestingly, another post hoc analysis of the SONAR trial showed that combination of an ERA with a sodium-glucose co-transporter-2 inhibitor (SGLT2i), a kidney protective drug with diuretic properties, may mitigate atrasentan-induced fluid retention, while further lowering albuminuria.[7] Several studies on ERAs in combination with SGLT2is for patients with CKD are ongoing, for example, the ZENITH trial (NCT04724837). These and other prospective studies are required to assess which diuretic management regimen is the most effective in minimizing ERA-induced fluid retention.

A limitation of this post hoc analysis was the inability to assess the effect of ENaC inhibitors on atrasentan-induced fluid retention because very few patients in SONAR used amiloride or triamterene during the enrichment phase. Noteworthily, peroxisome proliferator-activated receptor γ (PPARγ) agonists (although excluded in the SONAR trial) cause fluid retention that is attributed to ENaC activation[8]; a study with the PPARγ agonist rosiglitazone showed that potassium-sparing diuretics targeting ENaC were effective in reducing fluid retention during treatment.[9] Second, we used proxies for fluid retention but did not assess fluid status by gold-standard measurements. Finally, patient enrolment in the SONAR trial commenced in 2013 and few patients were using SGLT2is, the current guideline-recommended treatment for patients with type 2 diabetes and CKD.[10]

In conclusion, the shift from weight gain to weight loss after the start of diuretic medication suggests a clear short-term beneficial effect of diuretics on fluid balance during atrasentan treatment, without evidence for either loop or thiazide diuretics having a superior effect on fluid retention.

AUTHOR CONTRIBUTIONS

DS and HJLH designed the study and analysed the data. JDS and HJLH wrote the first draft of the manuscript. All authors contributed to the interpretation of the data. All authors provided input into subsequent drafts and approved the final version for submission.

CONFLICT OF INTEREST STATEMENT

JDS declares no competing interest. DEK has served as a consultant for AbbVie, AstraZeneca, Chinook Therapeutics and Travere Therpeutics. DdZ served on advisory boards and/or speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi-Tanabe, Travere Pharmaceuticals; Steering Committees and/or speaker for AbbVie and Janssen; Data Safety and Monitoring Committees for Bayer. Honoraria paid to Institution and consultant/speaker. HJLH has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, CSL Behring, Gilead, Janssen, Novo Nordisk, Mundipharma, Mitsubishi Tanabe and Retrophin; and has received grants from AbbVie, AstraZeneca, Boehringer Ingelheim and Janssen.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15110.

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, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86:896-904.
2. 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;393:1937-1947.
3. Kohan DE, Rossi NF, Inscho EW, Pollock DM. Regulation of blood pressure and salt homeostasis by endothelin. *Physiol Rev*. 2011;91:1-77.
4. Stuart D, Chapman M, Rees S, Woodward S, Kohan DE. Myocardial, smooth muscle, nephron, and collecting duct gene targeting reveals the organ sites of endothelin a receptor antagonist fluid retention. *J Pharmacol Exp Ther*. 2013;346:182-189.
5. 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;20:1369-1376.
6. Heerspink HJL, Andress DL, Bakris G, et al. Baseline characteristics and enrichment results from the SONAR trial. *Diabetes Obes Metab*. 2018;20:1829-1835.
7. Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. *Kidney Int*. 2020;99:346-349. doi:10.1016/j.kint.2020.09.026
8. Fu Y, Gerasimova M, Batz F, et al. PPARγ agonist-induced fluid retention depends on αENaC expression in connecting tubules. *Nephron*. 2015;129:68-74.
9. Viswanathan V, Mohan V, Subramani P, et al. Effect of spironolactone and amiloride on thiazolidinedione-induced fluid retention in south Indian patients with type 2 diabetes. *Clin J Am Soc Nephrol*. 2013;8:225-232.
10. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med*. 2020;174:385-394. doi:10.7326/M20-5938

SUPPORTING INFORMATION

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

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