New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction

Heerspink, Hiddo J L; Kohan, Donald E; de Zeeuw, Dick

Published in:
Kidney International

DOI:
10.1016/j.kint.2020.09.026

New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction

see commentary on page 301

OPEN

Hiddo J.L. Heerspink[1], Donald E. Kohan[2] and Dick de Zeeuw[1]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and [2]Division of Nephrology, University of Utah, Salt Lake City, Utah, USA

The diuretic effects achieved with sodium glucose co-transporter 2 inhibitors (SGLT2i) may offset fluid retaining effects of the endothelin receptor antagonist (ERA) atrasentan while effects on albuminuria and kidney protection of both drug classes may be complimentary due to distinct mechanisms of action. Here, post-hoc analysis of the SONAR trial, in patients with type 2 diabetes and chronic kidney disease, show that six-weeks treatment with combined SGLT2i/atrasentan versus atrasentan alone decreased body weight, a surrogate for fluid retention, and further decreased albuminuria. Thus, these promising findings support future clinical studies to characterize the long-term efficacy and safety of combined SGLT2i/ERA treatment.

Kidney International (2021) **99,** 346–349; https://doi.org/10.1016/j.kint.2020.09.026

KEYWORDS: endothelin receptor antagonist; sodium glucose co-transporter 2 inhibitors; type 2 diabetes; chronic kidney disease; heart failure

Correspondence: *Hiddo J.L. Heerspink, Department Clinical Pharmacy and pharmacology, University Medical Center Groningen, Hanzeplein 1, 9700 RB, Groningen, The Netherlands. E-mail: h.j.lambers.heerspink@umcg.nl*

Received 29 June 2020; revised 20 August 2020; accepted 16 September 2020; published online 2 November 2020

The SONAR and CREDENCE randomized controlled clinical trials have demonstrated the kidney-protective effects of the endothelin receptor antagonist (ERA) atrasentan and the sodium glucose cotransporter 2 (SGLT2i) inhibitor canagliflozin in patients with type 2 diabetes and chronic kidney disease (CKD), respectively.[1,2] The mechanisms by which these agents afford kidney protection are distinct yet possibly complementary. SGLT2i blocks the SGLT2 transporter in the proximal tubule, which leads to glycosuria and diuresis associated with reductions in hemoglobin A1c (HbA1c), blood pressure, body weight, and albuminuria, as well as reduced glomerular hyperfiltration and anti-inflammatory effects.[3] ERAs inhibit the endothelin A receptor, leading to reductions in albuminuria and blood pressure in addition to direct anti-inflammatory and antifibrotic effects.[4]

Unlike SGLT2i, ERAs may increase sodium and fluid retention, which may lead to heart failure. Although precautionary measures were incorporated into the SONAR trial to manage fluid retention, there was a higher proportion of fluid retention-related adverse events (36.6% vs. 32.3%) and a numerically higher incidence of hospitalized heart failure (3.5% vs. 2.6%) with atrasentan compared with placebo.[2] The diuretic effects achieved with SGLT2 inhibitors may offset the sodium and fluid retention effects of ERAs. Therefore, the combination of these therapies—ERA and SGLT2 inhibition—holds promise for augmenting kidney protection via distinct mechanisms, while potentially mitigating fluid retention.

We previously reported that the albuminuria decrease with atrasentan was consistent irrespective of SGLT2i use before enrollment in the SONAR trial, suggesting that the effects of atrasentan are additive to SGLT2i.[5] However, this does not answer the question of whether initiation with combined SGLT2i/atrasentan treatment further decreases albuminuria and mitigates fluid retention compared with atrasentan treatment alone. Therefore, we performed a post hoc analysis of the SONAR trial to test this hypothesis.

RESULTS

During the 6-week active open-label (enrichment) period of the SONAR trial, 14 patients with type 2 diabetes and CKD

Table 1 | Baseline characteristics of the atrasentan/SGLT2i group and matched atrasentan group

Characteristic	Atrasentan and SGLT2i ($N = 14$)	Atrasentan ($N = 42$)	Standardized Difference	Atrasentan ($N = 5093$)
Age, y, mean (SD)	66.1 (6)	65.0 10)	0.131	64.4 (8.8)
Female sex, *n* (%)	4 (28.6)	13 (31.0)	0.051	1390 (27.2)
Race, *n* (%)			0.121	
White	9 (64.3)	25 (69.0)		3001 (58.9)
Black	1 (7.1)	5 (11.9)		351 (6.9)
Asian	4 (28.6)	9 (21.4)		1552 (30.5)
Other	0 (0)	3 (7.1)		189 (3.7)
Body weight, kg, mean (SD)	101.6 (27)	101.7 (27)	0.003	86.0 (20)
Systolic blood pressure, mmHg, mean (SD)	142.4 (23)	142.7 (14)	0.015	137.5 (15)
HbA1c, %, mean (SD)	8.1 (1.4)	7.9 (1.4)	0.122	7.6 (1.5)
eGFR, ml/min per 1.73 m^2, mean (SD)	42.3 (8)	40.6 (13)	0.155	41.5 (13)
UACR, mg/g, median [IQR]	465 [353–873]	632 [414–1111]	0.070	871 [464–1675]
BNP, pg/ml, median [IQR]	52 [26–93]	51 [28–86]	0.089	50 [27–91]
Diuretics, *n* (%)	13 (92.9)	38 (90.5)	0.084	4112 (80.7)

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; SD, standard deviation; UACR, urinary albumin:creatinine ratio.
Baseline characteristics of all patient receiving atrasentan alone during the enrichment period in SONAR are also presented.

initiated treatment with SGLT2i in combination with atrasentan. Canagliflozin was the most frequently initiated SGLT2i ($n = 6$), followed by empagliflozin ($n = 4$), dapagliflozin ($n = 3$), and luseogliflozin ($n = 1$). SGLT2is were used 79% of the time during the 6-week enrichment period, with all patients using an SGLT2i for the last 2 weeks of the enrichment period. These 14 patients were matched at a 1:3 ratio with patients who used atrasentan alone (details provided in Supplementary Data). After matching, baseline characteristics were balanced between the combined SGLT2i/atrasentan and atrasentan groups (Table 1).

As shown in Figure 1, after 6 weeks of treatment, body weight, a surrogate for fluid retention, increased by 0.6 kg (95% confidence interval [CI], 0.0–1.1 kg) in the atrasentan only group and decreased by 0.7 kg (95% CI, -0.3 to 1.6 kg) in the combined SGLT2i/atrasentan group, for a between-group difference of 1.2 kg (95% CI, 0.1–2.3 kg; $P = 0.028$). This effect was accompanied by a numerical decrease in B-type natriuretic peptide (BNP) (Supplementary Table S1). SGLT2i/atrasentan combination treatment was also associated with a 27.6% (95% CI, 3.6%–45.6%; $P = 0.028$) larger reduction in urinary albumin:creatinine ratio (UACR) compared with atrasentan alone (Figure 1). Results were similar between the SGLT2i/atrasentan combination group and all patients who received atrasentan treatment alone during the enrichment period (Supplementary Table S2).

DISCUSSION

Despite advancements in pharmacotherapy for patients with type 2 diabetes and CKD, including the proven clinical benefits of SGLT2i, mortality and morbidity remain high, producing a significant financial and societal burden. The remaining "residual" risk during SGLT2i is closely connected with high residual albuminuria.[6] The ERA atrasentan decreases albuminuria and the risk of major kidney outcomes, but its use is associated with fluid retention. The results of this post hoc analysis of the SONAR trial suggests that combination treatment with SGLT2i and atrasentan minimizes the fluid-retaining properties of atrasentan, while the combination further ameliorates albuminuria, potentially enhancing long-term kidney protection.

The design of the SONAR trial included a 6-week active run in phase (enrichment period), during which all patients received 0.75 mg of atrasentan daily, to identify patients who tolerated and responded to atrasentan.[7] Although SGLT2i use was not permitted during the enrichment period, 14 patients initiated SGLT2i therapy during enrichment. This provided an opportunity to assess for the first time the combined effects on fluid status and albuminuria of SGLT2i and atrasentan versus atrasentan alone. Open- label use of ERAs did not occur in the CREDENCE trial; therefore, it is impossible to confirm the synergistic effects of these drug classes in the CREDENCE trial.

Previous studies have shown that patients with impaired glycemic control, impaired kidney function, and insulin resistance are prone to developing fluid retention during ERA treatment. These patients are also at greater risk of progressive kidney function loss, making SGLT2i-ERA combination treatment particularly attractive for patients with diabetes and CKD. In these patients, insulin resistance and mitochondrial dysfunction are recognized metabolic risk markers of progressive kidney function loss. Interestingly, both insulin resistance and mitochondrial function improve in response to ERAs and SGLT2i.[8–11] Whether combination treatment further mitigates these metabolic disorders, and whether such potential synergistic effects translate into long-term clinical benefits, require further study.

In the SONAR trial, patients with a body weight increase of >3 kg or a BNP level of at least 300 pg/ml at the end of the enrichment period were excluded from further trial participation, because these patients were considered at risk of developing edema and heart failure during atrasentan treatment. The rationale for using body weight and BNP as surrogates for fluid retention was that in a previous clinical trial

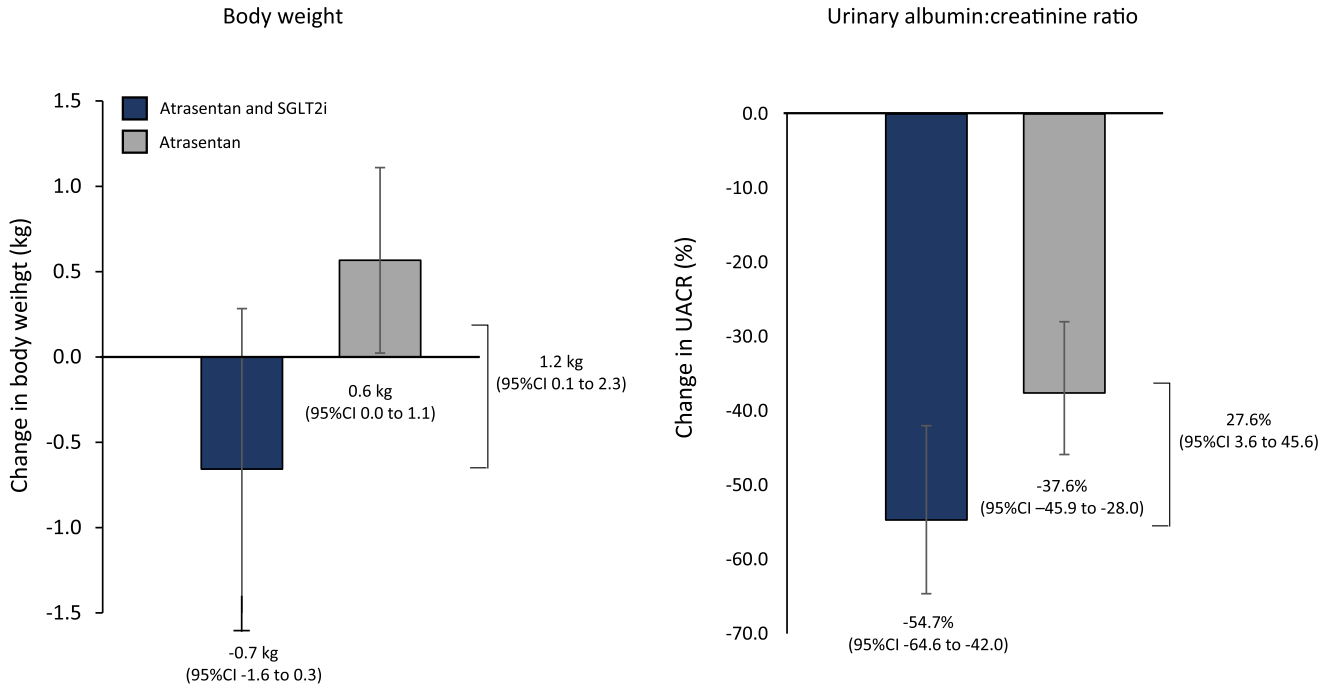

Figure 1 | Effects of 6 weeks combined SGLT2i and atrasentan treatment compared with atrasentan along treatment on surrogates of fluid retention (body weight) and kidney protection (urinary albumin:creatinine ratio).

with the less-selective ERA avosentan, an increase in body weight during the first weeks of treatment with avosentan was significantly associated with an elevated risk of edema and heart failure.[12] Other studies have shown that an early increase in BNP is predictive of heart failure.[13] Thus, these markers were also used as surrogates for fluid retention in the current study.

The results of this study should be interpreted with care, given the small number of patients and the nonrandomized post hoc comparisons. In addition, we assessed only the short-term treatment effects of SGLT2i/atrasentan combination therapy. Future studies are needed to characterize the long-term efficacy and safety.

In conclusion, combining SGLT2i with the ERA atrasentan may exert beneficial synergistic effects that augment albuminuria reduction while offsetting fluid retention. These promising findings support future randomized controlled trials designed to assess the long-term efficacy and safety of combined endothelin receptor antagonist SGLT2i combination treatment in high-risk patients with type 2 diabetes and CKD.

SHORT METHODS

We performed a post hoc analysis of the SONAR trial (ClinicalTrials.gov identifier NCT01858532). The design and primary results of the SONAR trial, a randomized double-blind, placebo-controlled event-driven clinical trial, have been published previously.[2,7] The trial enrolled 5017 adults with type 2 diabetes and an estimated glomerular filtration rate between 25 and 75 ml/min per 1.73 m^2 of body surface area, a UACR between 300 and 5000 mg/g, and a 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 eligible patients received open-label treatment with 0.75 mg/d atrasentan to identify atrasentan "responders". At each study visit, concomitant medication was recorded. Records for each SGLT2i concomitant medication initiation and cessation were available at study visits.

We examined the effect of combined treatment with atrasentan and SGLT2i versus atrasentan alone on body weight and UACR as surrogates for fluid retention and kidney protection, respectively, during the enrichment period of the SONAR trial. Change in body weight was used as surrogate for fluid retention on the basis of a previous study demonstrating that an increase in body weight during treatment with ERAs predicts the development of congestive heart failure.[12] Change in BNP, which was statistically significantly correlated with change in body weight in the SONAR trial (each 1-kg increase in body weight during the enrichment period was associated with 7.3% increase in BNP; $P < 0.001$), served as another proxy of fluid retention. The change in body weight was defined as the change from baseline to the last available enrichment visit. Participating investigators and patients were instructed to measure body weight using the same device and circumstances. Change in UACR was based on 6 first morning void urine samples collected at the start and end of the enrichment period. All laboratory parameters including UACR were measured in a central laboratory.

Participants starting the combination of atrasentan and SGLT2i were matched with participants starting atrasentan alone using propensity score matching. Details of the propensity score matching are provided in Supplementary Data. Matching was performed to balance demographics, laboratory measurements, and medication use at a 1:3 matching ratio. A 1:3 matching ratio was used to increase the precision of the effect estimates when sufficient control subjects are available.[14] Balance in baseline characteristics between groups was considered adequate when standardized differences in baseline characteristics were <0.20.[15] The effect of atrasentan and SGLT2i

versus atrasentan alone on UACR and body weight was assessed by analysis of covariance with treatment as factor and baseline UACR (log-transformed) or body weight as covariate. Analyses were performed in Stata/SE 13 (StataCorp, College Station, TX).

DISCLOSURE

HJLH is supported by a VIDI (917.15.306) grant from the Netherlands Organisation for Scientific Research; has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bayer, Chinook, CSL Pharma, Gilead, Janssen, NovoNordisk, Mundipharma, Mitsubishi Tanabe, and Retrophin; and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen. DdZ has served as a consultant for AbbVie, Fresenius, Boehringer Ingelheim, Bayer, Mitsubishi Tanabe, Mundipharma, Janssen, and Retrophin. The other author declared no competing interests.

ACKNOWLEDGMENTS

HJLH is supported by a VIDI grant from the Netherlands Organisation for Scientific Research (917.15.306).

AUTHOR CONTRIBUTIONS

HJLH, DK, and DdZ were involved in data collection. HJLH and DdZ designed the study. HJLH wrote the first draft of the short report. DK and DdZ contributed with critical revisions for intellectual content.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Mean (95% confidence interval) changes from baseline in cardiorenal risk markers during combined SGLT2i/atrasentan treatment versus atrasentan alone in the matched cohort.

Table S2. Mean (95% confidence interval) changes from baseline in cardiorenal risk markers during combined SGLT2i/atrasentan treatment versus atrasentan alone in all patients who entered the enrichment period.

REFERENCES

1. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
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. Heerspink HJL, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134:752–772.
4. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86:896–904.
5. Heerspink HJL, Andress DL, Bakris G, et al. Baseline characteristics and enrichment results from the SONAR trial. *Diabetes Obes Metabol*. 2018;20:1829–1835.
6. Waijer SW, Xie D, Inzucchi SE, et al. Short-term changes in albuminuria and risk of cardiovascular and renal outcomes in type 2 diabetes mellitus: a post hoc analysis of the EMPA-REG OUTCOME trial. *J Am Heart Assoc*. 2020;9:e016976.
7. 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.
8. Ahlborg G, Shemyakin A, Böhm F, et al. Dual endothelin receptor blockade acutely improves insulin sensitivity in obese patients with insulin resistance and coronary artery disease. *Diabetes Care*. 2007;30:591–596.
9. Kern M, Klöting N, Mark M, et al. The SGLT2 inhibitor empagliflozin improves insulin sensitivity in db/db mice both as monotherapy and in combination with linagliptin. *Metabolism*. 2016;65:114–123.
10. Pena MJ, de Zeeuw D, Andress D, et al. The effects of atrasentan on urinary metabolites in patients with type 2 diabetes and nephropathy. *Diabetes Obes Metab*. 2017;19:749–753.
11. Mulder S, Heerspink HJL, Darshi M, et al. Effects of dapagliflozin on urinary metabolites in people with type 2 diabetes. *Diabetes Obes Metab*. 2019;21:2422–2428.
12. Hoekman J, Heerspink HJL, Viberti G, et al. Predictors of congestive heart failure after treatment with an endothelin receptor antagonist. *Clin J Am Soc Nephrol*. 2014;9:490–498.
13. Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem*. 2006;52:1528–1538.
14. Rassen JA, Shelat AA, Myers J, et al. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf*. 2012;21(Suppl 2):69–80.
15. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. *Health Serv Outcomes Res Methodol*. 2001;2:169–188.