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Increase in BNP in Response to Endothelin-Receptor Antagonist Atrasentan Is Associated With Incident Heart Failure

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ABSTRACT

BACKGROUND The endothelin receptor antagonist atrasentan reduced the risk of kidney failure in patients with type 2 diabetes mellitus and chronic kidney disease (CKD) in the SONAR (Study of Diabetic Nephropathy with Atrasentan) trial, although with a numerically higher incidence of heart failure (HF) hospitalization.

OBJECTIVES The purpose of this study was to assess if early changes in B-type natriuretic peptide (BNP) and body weight during atrasentan treatment predict HF risk.

METHODS Participants with type 2 diabetes and CKD entered an open-label enrichment phase to assess response to atrasentan 0.75 mg/day. Participants without substantial fluid retention (>3 kg body weight increase or BNP increase to >300 pg/mL), were randomized to atrasentan 0.75 mg/day or placebo. Cox proportional hazards regression was used to assess the effects of atrasentan vs placebo on the prespecified safety outcome of HF hospitalizations.

RESULTS Among 3,668 patients, 73 (4.0%) participants in the atrasentan and 51 (2.8%) in the placebo group developed HF (HR: 1.39; 95% CI: 0.97-1.99; $P = 0.072$). In a multivariable analysis, HF risk was associated with higher baseline BNP (HR: 2.32; 95% CI: 1.81-2.97) and percent increase in BNP during response enrichment (HR: 1.46; 95% CI: 1.08-1.98). Body weight change was not associated with HF. Exclusion of patients with at least 25% BNP increase during enrichment attenuated the risk of HF with atrasentan (HR: 1.02; 95% CI: 0.66-1.56) while retaining nephroprotective effects (HR: 0.58; 95% CI: 0.44-0.78).

CONCLUSIONS In patients with type 2 diabetes and CKD, baseline BNP and early changes in BNP in response to atrasentan were associated with HF hospitalization, highlighting the importance of natriuretic peptide monitoring upon initiation of atrasentan treatment. (Study Of Diabetic Nephropathy With Atrasentan [SONAR]; NCT01858532)
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Endothelin-1 is a potent vasoconstrictor and has been implicated in the progression of chronic kidney disease (CKD) by exerting multiple pathophysiological effects. Inhibition of the endothelin A receptor leads to improvements in kidney morphology, podocyte function, and activation of anti-inflammatory and antifibrotic pathways in experimental studies.[1] In clinical studies in patients with CKD, endothelin receptor antagonism has been shown to reduce albuminuria and blood pressure.[2-4] These findings led to the design of the SONAR trial, a multicenter, double-blind, placebo-controlled clinical trial to assess the long-term efficacy and safety of the endothelin A receptor antagonist atrasentan.[5] The trial showed that atrasentan significantly reduced the risks of kidney outcomes in patients with type 2 diabetes and CKD.[6]

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Endothelin receptor antagonists (ERAs) may increase sodium and fluid retention, which may lead to heart failure.[7-9] To mitigate the risk of sodium retention and heart failure (HF) hospitalization, the SONAR trial design included an active 6-week open-label treatment phase, a response enrichment period during which all patients were treated with atrasentan 0.75 mg/day.[5] The aim of the enrichment period was to identify patients who responded to and tolerated atrasentan. Patients who did not tolerate atrasentan as defined by clinical signs of fluid retention or development of HF were excluded. Despite these precautionary measures, there was a higher proportion of fluid retention-related adverse events (36.6% vs 32.3%) and a numerically higher incidence of hospitalized HF (3.5% vs 2.6%) with atrasentan compared with placebo, respectively.[6]

The aim of this post hoc analysis of the SONAR trial was to determine if changes in B-type natriuretic peptide (BNP) and body weight, as clinical indicators of fluid retention, as well as development of edema during 6-week treatment with atrasentan predict the risk of HF after randomization. This analysis serves as an impetus to further optimize the design of future clinical trials with ERAs and mitigate the risk of HF hospitalizations in susceptible patients.

METHODS

STUDY DESIGN AND POPULATION. The SONAR protocol and primary results have been published previously.[5] In brief, the SONAR trial enrolled patients with type 2 diabetes and an estimated glomerular filtration rate (eGFR) of 25-75 mL/min/1.73 m^2 of body surface area, a urine albumin-to-creatinine ratio (UACR) of 300-5,000 mg/g, and BNP ≤200 pg/mL.[5,6] All patients were on a recommended and stable dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks before the start of the enrichment period. Exclusion criteria of relevance to this analysis were diagnosis of or previous HF hospitalization, current symptoms or signs suggestive of HF, or history of severe peripheral edema requiring diuretic agents. We defined responder participants as those who had a ≥30% reduction in UACR from start to end of response enrichment without substantial fluid retention (defined as an increase in body weight ≥3 kg or increase in BNP to 300 pg/mL or more) and who did not have an increase in creatinine more than 0.5 mg/dL or 20% from baseline. The SONAR protocol was approved by a central or local ethics committee at all study sites before any study-specific procedure commenced, and the trial was conducted in accordance with the Declaration of Helsinki.

All responder patients who tolerated atrasentan and a selection of nonresponder patients subsequently proceeded to the randomization visit and were assigned in a 1:1 ratio to continue atrasentan 0.75 mg/day or to transition to placebo. Patients were followed for a median of 2.2 years, at which time the trial was stopped by a decision from the sponsor because of a lower than anticipated event rate of the primary composite outcome. For this analysis, responders and nonresponders were combined because the effects on HF hospitalizations were similar in responders (HR: 1.33; 95% CI: 0.85-2.07) and nonresponders (HR: 1.54; 95% CI: 0.83-2.86).

OUTCOMES. Body weight was monitored throughout the enrichment period, and blood samples were collected before and at the end of the 6-week

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

BNP = B-type natriuretic peptide

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

ERA = endothelin receptor antagonist

HF = heart failure

UACR = urinary albumin-to-creatinine ratio

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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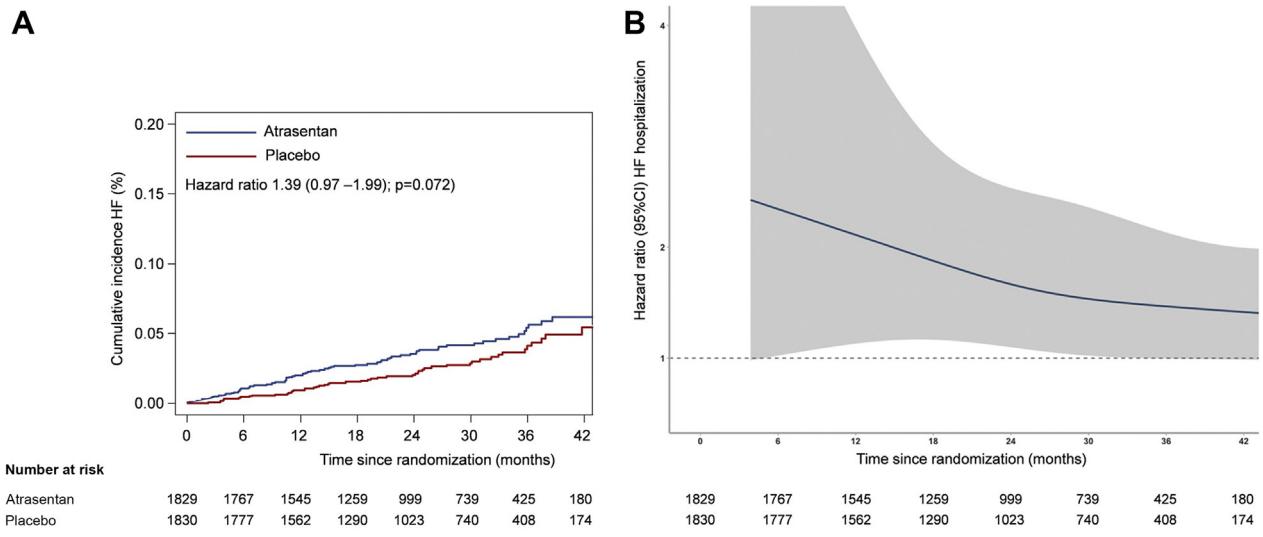
FIGURE 1 Cumulative Incidence and HR for HF Hospitalization



(A) Kaplan-Meier curve for heart failure (HF) events (responders and nonresponders combined). Participants on atrasentan had a numerically higher incidence of HF with 73 events vs 51 events in the placebo group. **(B)** HR for HF with atrasentan compared with placebo over time.

enrichment period for analysis of change in BNP. Adverse events of special interest, including hypervolemia, edema, and HF, were assessed with prespecified standardized queries. Edema was monitored at each study-related visit and classified as none, modest, moderate, or severe. A specific case report form was used for prospective capture of HF-related adverse events. A masked independent event adjudication committee (EAC) formally adjudicated all events including HF hospitalization outcomes using well-developed processes and prespecified outcome definitions, as previously described. HF hospitalization was defined as a hospitalization ≥24 hours in duration with acute HF supported by documented symptoms, physical examination findings, objective test results, and treatment specifically for acute HF.[5]

STATISTICAL ANALYSIS. We performed all analyses in accordance with the intention-to-treat principle. We determined the risk of HF hospitalization (atrasentan vs placebo) by calculating the time to first event, applying proportional Cox hazards regression. The treatment effect in the model was adjusted for log transformed UACR values, serum albumin, age, eGFR at randomization, and cardiovascular disease history, as described earlier.[6] For patients who experienced more than 1 event during follow-up, survival time to the first relevant endpoint was used in each analysis. We assessed the timing of effects on HF hospitalization with atrasentan by calculating the HR and 95% CIs with the data set truncated and reanalyzed in incremental cuts at each day postrandomization. Data were plotted overtime using locally weighted scatterplot smoothing. We confirmed the assumptions of the proportional hazards model by inspection of the log-cumulative hazard function of each treatment group and by including an interaction term between treatment assignment and time as a time-varying covariate.

We performed Cox proportional hazards regression to determine which patient characteristics were associated with HF hospitalization. We considered patient characteristics recorded at the start of the enrichment period (baseline) and changes during enrichment, calculated as the absolute or percentage difference from baseline to 6 weeks. We first determined univariable associations for candidate risk markers and then those with significant univariable associations were entered in a single multivariable Cox regression model that also included randomized treatment. We log-transformed UACR and BNP because of their skewed distribution before entering them in the Cox proportional hazards model. We also performed univariable and multivariable logistic regression analysis to determine which baseline patient characteristics were associated with an increase in BNP of at least 25% during response enrichment.

Absolute effects of atrasentan on HF hospitalization were modeled to estimate effects for 1,000

TABLE 1 Patient Characteristics Before Enrichment

	Participants With HF			Participants Without HF			*P* Value
	Total (N = 124)	Atrasentan (n = 73)	Placebo (n = 51)	Total (N = 3,544)	Atrasentan (n = 1,761)	Placebo (n = 1,783)	Total With HF vs Total Without HF
Age, y	66.6 ± 7.8	66.5 ± 8.0	66.8 ± 7.5	64.4 ± 8.8	64.5 ± 8.8	64.4 ± 8.8	0.0025
Female	41 (33.1)	27 (37.0)	14 (27.5)	905 (25.5)	431 (24.5)	474 (26.6)	0.0752
Race							
White	86 (69.4)	52 (71.2)	34 (66.7)	2,024 (57.1)	1,014 (57.6)	1,010 (56.6)	
Black	9 (7.3)	4 (5.5)	5 (9.8)	215 (6.1)	105 (6.0)	110 (6.2)	0.0155
Asian	24 (19.4)	13 (17.8)	11 (21.6)	1,174 (33.1)	576 (32.7)	598 (33.5)	
Other	5 (4.0)	4 (5.5)	1 (2.0)	131 (3.7)	66 (3.8)	65 (3.7)	
Ethnicity							
Hispanic	15 (12.1)	13 (17.8)	2 (3.9)	825 (23.3)	418 (23.7)	407 (22.8	0.0050
Non-Hispanic	109 (87.9)	60 (82.2)	49 (96.1)	2,719 (76.7)	1,343 (76.3)	1,376 (77.2)	
Blood pressure, mm Hg							
Systolic	140.7 ± 14.8	140.7 ± 14.0	140.7 ± 16.1	136.1 ± 15.2	136.3 ± 15.1	135.8 ± 15.3	0.0009
Diastolic	73.4 ± 11.0	72.3 ± 10.6	74.8 ± 10.6	75.0 ± 9.9	75.1 ± 9.9	74.8 ± 9.9	0.1009
Body weight, kg	92.4 ± 23.0	93.3 ± 25.4	91.0 ± 19.1	85.0 ± 19.3	85.1 ± 19.7	84.9 ± 18.9	0.0006
HbA_{1c}	7.7 ± 1.5	7.8 ± 1.4	7.7 ± 1.7	7.6 ± 1.5	7.6 ± 1.4	7.6 ± 1.5	0.2078
Serum creatinine, μmol/L	159.6 ± 45.6	157.8 ± 48.1	162.2 ± 42.2	149.3 ± 43.1	149.1 ± 43.8	149.5 ± 42.4	0.0148
eGFR, mL/min/1.73 m^2	38.8 ± 12.8	39.0 ± 13.0	38.5 ± 12.6	43.4 ± 13.8	43.7 ± 13.9	43.2 ± 13.7	0.0001
Hemoglobin, g/L	127.5 ± 17.8	128.1 ± 18.7	126.7 ± 16.8	129.3 ± 17.1	130.0 ± 17.2	128.7 ± 16.9	0.2660
Hematocrit, %	38.1 ± 5.0	38.3 ± 5.2	37.7 ± 4.8	38.8 ± 5.0	39.0 ± 5.0	38.6 ± 5.0	0.0955
Albumin, g/L	37.3 ± 3.8	37.2 ± 3.8	37.5 ± 3.9	39.2 ± 3.6	39.3 ± 3.6	39.1 ± 3.5	<0.0001
UACR, mg/g	1,234 [759-2,082]	1,114 [728-2,196]	1,536 [843-2,077]	816 [453-1,531]	820 [462-1,544]	814 [445-1,521]	<0.0001
BNP, pg/mL	85 [58-131]	81 [57-130]	91 [63-132]	47 [25-85]	47 [26-84]	46 [25-86]	<0.0001
CV disease history	20 (16.1)	14 (19.2)	6 (11.8)	535 (15.1)	251 (14.3)	284 (15.9)	0.8508
Medication							
Diuretic	116 (93.5)	67 (91.8)	49 (96.1)	2,949 (83.2)	1,468 (83.4)	1,481 (83.1)	0.0034
Beta-blockers	82 (66.1)	47 (64.4)	35 (68.6)	1,449 (40.9)	727 (41.3)	722 (40.5)	<0.0001
Statins	101 (81.5)	57 (78.1)	44 (86.3)	2,812 (79.3)	1,380 (78.4)	1,432 (80.3)	0.6475
Insulin	90 (72.6)	54 (74.0)	36 (70.6)	2,225 (62.8)	1,110 (63.0)	1,115 (62.5)	0.0333
SGLT2	0 (0)	0 (0)	0 (0)	53 (1.5)	21 (1.2)	32 (1.79)	N/A

Values are mean ± SD, n (%), or median [25th-75th percentile]. All baseline characteristics are measured at start of enrichment except HbA_{1c}, which was only measured at randomization.

BNP = B-type natriuretic peptide; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HF = heart failure; N/A = not applicable; SGLT2 = sodium glucose cotransporter 2; UACR = urinary albumin-to-creatinine ratio.

participants treated for 5 years. This was done in the overall cohort and in subgroups defined by excluding participants with risk markers for HF. We calculated the absolute effects on these outcomes using the HR from the SONAR trial for the HF hospitalization or kidney outcome from each subset of participants and applied these HRs to the absolute event rate specific to each subset of participants.

Baseline characteristics were compared with unpaired 2-sided Student's *t*-tests or chi-square statistics where appropriate. We performed the analyses using SAS version 9.3 (SAS Institute). A *P* value <0.05 was considered to indicate statistical significance.

RESULTS

PATIENT FLOW AND CHARACTERISTICS. Among 5,117 participants who entered the 6-week response enrichment period, 5,107 started open-label treatment with atrasentan. During response enrichment, 478 (9.3%) participants were excluded based on a body weight increase of at least 3 kg and 96 (1.9%) were excluded because of a BNP of at least 300 pg/mL (Supplemental Tables 1 and 2). Caucasian men with a higher blood pressure, UACR, and body weight were more often excluded based on the body weight criterion, whereas those with higher baseline BNP were more likely to be excluded based on the BNP exclusion criterion (Supplemental Tables 1 and 2). A higher body weight and BNP at the end of response enrichment were associated with a 1-step worsening in edema during response enrichment (Supplemental Table 3).

Overall, 3,668 patients were randomly assigned to continue treatment with atrasentan (n = 1,834) or transition to placebo (n = 1,834), of whom 2,648 were

TABLE 2 Predictors of Heart Failure

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Baseline		
Atrasentan treatment	1.44 (1.00-2.05)	1.39 (0.97-1.99)
Age (per 5 y)	1.16 (1.04-1.28)	
Female	1.50 (1.03-2.18)	1.60 (1.08-2.37)
Race		
White	Ref.	
Black	1.04 (0.53-2.08)	
Asian	0.46 (0.29-0.73)	
Other	0.98 (0.40-2.42)	
Ethnicity		
None	Ref.	Ref.
Hispanic	1.96 (1.14-3.37)	2.24 (1.30-3.86)
Blood pressure (per 5 mm Hg)		
Systolic	1.12 (1.05-1.18)	
Diastolic	0.94 (0.86-1.02)	
Body weight (per 5 kg)	1.09 (1.05-1.13)	1.07 (1.02-1.11)
HbA_{1c} (%)	1.10 (0.98-1.23)	
eGFR (per 5 mL/min/1.73 m^2)	0.86 (0.80-0.93)	0.90 (0.83-0.97)
BNP (per log pg/mL)	2.37 (1.92-2.92)	2.32 (1.81 - 2.97)
Hemoglobin (per 5 g/dL)	0.96 (0.91-1.01)	
Hematocrit (per 0.01%)	0.97 (0.93-1.00)	
Albumin (g/dL)	0.88 (0.84-0.92)	
UACR (per log mg/g)	1.92 (1.54-2.40)	1.71 (1.36-2.13)
CV disease history	1.48 (0.91-2.41)	
Medication		
Diuretic use	2.75 (1.34-5.63)	2.20 (1.07-4.53)
Beta-blocker use	2.81 (1.94-4.07)	1.70 (1.15-2.51)
Statin use	1.09 (0.69-1.71)	
Insulin use	1.66 (1.12-2.46)	
Changes during enrichment		
Body weight, (per kg)	1.06 (0.94-1.19)	
BNP (per log unit change)	1.00 (0.76-1.33)	1.46 (1.08-1.98)
eGFR (per mL/min/1.73 m^2)	0.98 (0.96-1.01)	
Hemoglobin (per g/dL)	0.98 (0.96-1.01)	
Hematocrit (per 0.01%)	0.97 (0.93-1.00)	
Edema		
No edema	Ref.	Ref.
Modest edema	1.43 (0.99-2.07)	1.18 (0.81-1.73)
Moderate/severe edema	3.30 (1.74-6.27)	2.18 (1.12-4.22)

Abbreviations as in Table 1.

classified as UACR responders (UACR reduction >30%) and 1,020 as UACR nonresponders (UACR reduction ≤30%). The mean age of all randomized participants was 64.5 ± 8.8 years, 25.8% were women, mean eGFR was 43.3 ± 13.8 mL/min/1.73 m^2, mean body weight 85.3 ± 19.5 kg, median UACR 829 mg/g (25th-75th percentile: 458-1,556 mg/g) and BNP 48 pg/mL (25th-75th percentile: 26-87 pg/mL). A history of a cardiovascular disease event was present in 555 (15.1%) patients.

EFFECT OF ATRASENTAN ON THE RISK OF HF HOSPITALIZATION. During a median follow-up of 2.2 years, 124 adjudicated HF hospitalization events were recorded of which 73 (4.0%) occurred in the atrasentan group (event rate 1.9 per 100 patient-years) and 51 (2.8%) in the placebo group (event rate 1.3 per 100 patient-years) resulting in a HR of 1.39 (95% CI: 0.96-1.99; $P = 0.072$) (Figure 1A). The impact of atrasentan on the relative risk of HF hospitalization over time is shown in Figure 1B. Tests for the assumption of proportional did not reach statistical significance ($P = 0.071$).

ASSOCIATIONS BETWEEN PATIENT CHARACTERISTICS AT BASELINE AND HF HOSPITALIZATION. Participants with incident HF hospitalization were older, more likely to be White, and less likely to be Asian. They had a higher systolic blood pressure, body weight, UACR, and BNP; had a lower eGFR; and were more likely to be treated with diuretic agents, beta-blockers, and insulin at the start of enrichment (Table 1). Univariable modelling showed 11 variables to be associated with HF hospitalizations. In a multivariable model, female sex, Hispanic ethnicity, each unit increment in body weight, log BNP, log UACR, each unit decrement in eGFR, use of diuretic agents and beta-blockers, increase in log BNP, and development of moderate/severe edema during the enrichment period remained statistically significantly associated with the development of HF events (Table 2). Results were similar in responder and nonresponder subgroups (Supplemental Table 4). In the multivariable model adjusting for all identified risk markers, the HR for HF hospitalization with atrasentan compared with placebo only slightly attenuated compared with the univariable model (Table 2).

RISK OF HF HOSPITALIZATIONS AND PROTECTION AGAINST MAJOR KIDNEY EVENTS. Among the overall SONAR population, there were 24 (95% CI: −3 to 61) more HF events with atrasentan compared with placebo for every 1,000 patients treated for 5 years. There were 72 (95% CI: 27-104) fewer primary kidney outcomes for every 1,000 patients treated for 5 years. Exclusion of patients with a BNP increase exceeding biological variation (≥25%) during the enrichment period (n = 1,418) decreased the number of excess HF hospitalization events for every 1,000 patients treated for 5 years to 11 and 2, respectively (Table 3). Further exploration of the association between changes in BNP during enrichment and excess risk of HF demonstrated that using higher BNP thresholds led to fewer patients being excluded, but excess risk for HF remained present until a BNP threshold of approximately 25% increase (Central Illustration). The benefit of atrasentan for protection against major kidney outcomes remained present regardless of

TABLE 3 Risk of HF Hospitalization and Protection Against Major Kidney Events in Participant Groups Without Risk Factors for HF Hospitalization

		Participants With Heart Failure					
	Participants Excluded	Atrasentan (n = 1,834)	Placebo (n = 1,834)	Heart Failure	Primary Kidney Outcome	Excess Heart Failure Among 1,000 Participants Treated for 5 y, n (95% CI)	Kidney Outcomes Prevented Among 1,000 Participants Treated for 5 y, n (95% CI)
All	0	73 (4.0)	51 (2.8)	1.39 (0.97-1.99)	0.71 (0.58-0.89)	24 (−3 to 61)	72 (27 to 104)
Female	946 (25.8)	46 (3.3)	37 (2.8)	1.17 (0.76-1.80)	0.80 (0.63-1.02)	11 (−15 to 49)	49 (−5 to 91)
Systolic BP >140 mm Hg	1,368 (37.3)	35 (3.1)	26 (2.2)	1.35 (0.81-2.24)	0.69 (0.51-0.93)	26 (−4 to 75)	74 (15 to 116)
Body weight >100 kg	749 (20.4)	52 (3.6)	35 (2.4)	1.44 (0.94-2.21)	0.65 (0.51-0.83)	23 (−3 to 61)	54 (−7 to 99)
eGFR <35 mL/min/1.73 m^2	1,238 (33.8)	39 (3.2)	26 (2.1)	1.51 (0.92-2.48)	0.66 (0.47-0.93)	21 (−3 to 58)	53 (26 to 75)
UACR >2,500 mg/g	413 (11.3)	58 (3.6)	41 (2.5)	1.42 (0.95-2.12)	0.78 (0.60-1.03)	20 (−11 to 70)	51 (11 to 81)
Moderate/severe edema	134 (3.7)	68 (3.8)	45 (2.6)	1.45 (0.99-2.11)	0.70 (0.56-0.87)	26 (−1 to 64)	74 (32 to 110)
BNP >125 pg/mL	470 (12.8)	54 (3.4)	36 (2.3)	1.46 (0.96-2.23)	0.74 (0.59-0.94)	24 (−2 to 63)	60 (14 to 99)
BNP change >25%	1418 (38.7)	43 (3.9)	41 (3.7)	1.02 (0.66-1.56)	0.58 (0.44-0.78)	2 (−29 to 47)	105 (54 to 141)
Female and BNP change >25%	1981 (54.0)	30 (3.6)	30 (3.6)	0.92 (0.55-1.53)	0.69 (0.51-0.95)	−7 (−37 to 43)	101 (53 to 136)

Values are n (%) or HR (95% CI), unless otherwise indicated.
Abbreviations as in Table 1.

the BNP change during enrichment. We repeated this analysis in patients with a baseline BNP <50 or >50 pg/mL, and in both subgroups, the HR for HF hospitalization attenuated to approximately 1.0 after exclusion of patients with >25% increase in BNP (Supplemental Table 5). Furthermore, the association between change in BNP during the enrichment period and risk of heart failure was consistent across subgroups defined by baseline age, sex, body weight, baseline BNP, eGFR and UACR (Supplemental Figure 1).

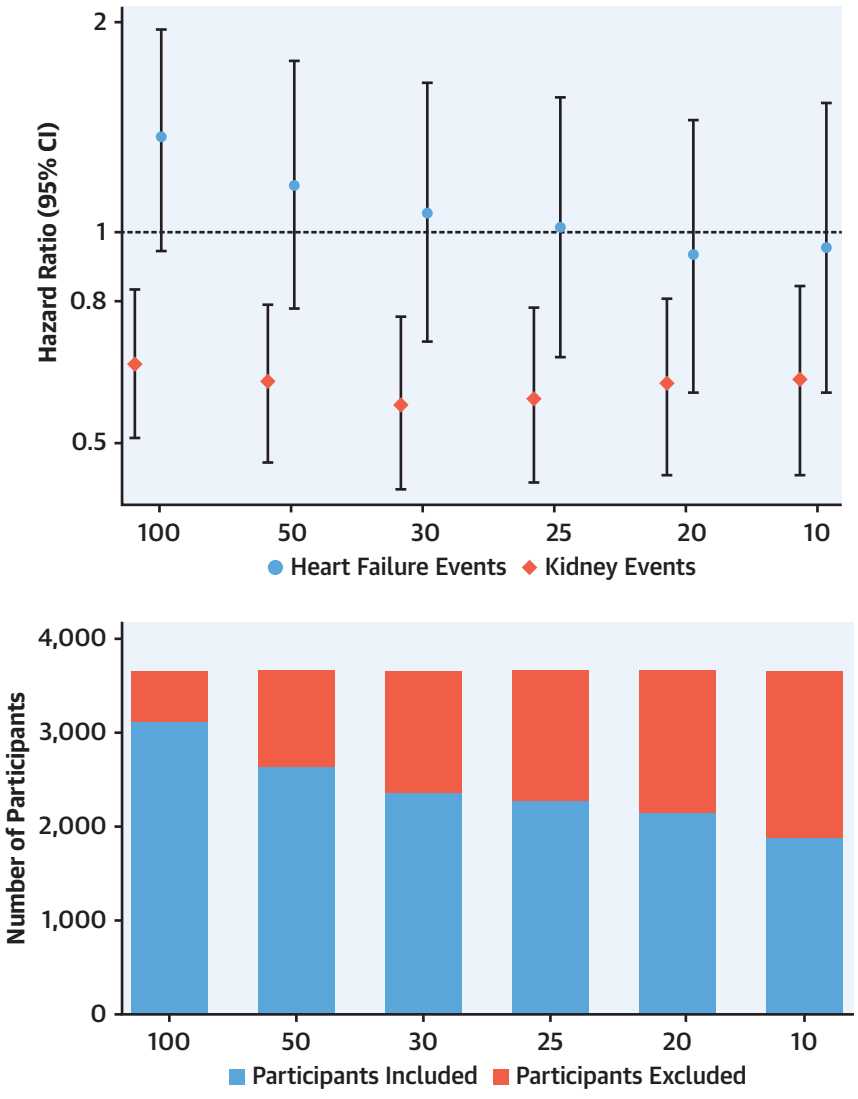
PATIENT CHARACTERISTICS ASSOCIATED WITH BNP CHANGES DURING THE ENRICHMENT PERIOD. Logistic regression analysis was performed to assess which baseline patient characteristics were associated with a 25% increase in BNP during enrichment. This analysis revealed that older patients, beta-blocker use, a higher UACR and a lower eGFR, BNP, diastolic blood pressure, or hemoglobin were associated with a higher likelihood of a BNP increase of at least 25% (Table 4).

DISCUSSION

The SONAR trial demonstrated that a low dose of the ERA atrasentan reduced major kidney outcomes in carefully selected patients with type 2 diabetes and CKD but also increased the risk of fluid retention-related adverse events and numerically increased HF hospitalization. In this analysis of the SONAR trial, we explored strategies for early identification of patients at risk of edema and HF following ERA initiation for future clinical trials. The results show that female sex, a higher BNP, body weight, and UACR, as well as early increases in BNP during atrasentan treatment, are associated with HF hospitalization. Moreover, we demonstrated that exclusion of patients with an increase in BNP exceeding the biological variation of the peptide (25%) during 6-week open-label atrasentan treatment attenuated the risk of HF with atrasentan while the kidney protective benefits were retained. These data suggest that monitoring of BNP might identify vulnerable patients at risk of HF events during treatment with atrasentan.

In prior trials, treatment with ERAs was reported to cause fluid retention and increased the risk of HF. The phase 3 ASCEND (A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of the Endothelin Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy) trial, which recruited patients with type 2 diabetes and CKD, was terminated prematurely after a median follow-up of 4 months because of excess HF in the avosentan treatment group.[10] The SONAR trial enrolled patients with type 2 diabetes and chronic kidney disease who are at high risk of HF. To minimize the risk of fluid retention and excess HF events, the SONAR trial excluded patients who were deemed at risk for HF, including those with a medical history of HF, severe peripheral edema, or screening BNP ≥200 pg/mL. This strategy succeeded in enrollment of a cohort of patients in whom the risk of HF hospitalization was relatively low. Although direct comparisons between trials should be interpreted with caution, the annual HF event rate in the placebo

CENTRAL ILLUSTRATION **Heart Failure Hospitalization and Kidney Endpoint HRs After Using Different B-Type Natriuretic Peptide Cutoffs for Patient**



Smeijer JD, et al. J Am Coll Cardiol HF. 2022;10(7):498–507.

Heart failure and kidney endpoint HRs after exclusion of patients with different B-type natriuretic peptide (BNP) cutoffs during enrichment. Using higher BNP thresholds led to fewer patients being excluded **(bottom),** but excess risk for HF remained present until a BNP threshold of approximately 25% increase. The scatter plot (95% CI) **(top)** indicates the HR with atrasentan compared with placebo for heart failure hospitalization **(red)** and primary kidney outcome **(blue)** at different thresholds of percent BNP increase to exclude patients during atrasentan treatment. The **bar graph at the bottom** shows the number of patients excluded at each threshold.

group of the SONAR trial (1.3%) was lower compared with the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (2.5%), a clinical trial in a similar cohort of patients with type 2 diabetes and CKD.[11] Moreover, the annual HF hospitalization rate with avosentan in the ASCEND trial was 18.0% compared with 1.9% in the atrasentan group in the SONAR trial.[6,10] These comparisons support that the strict inclusion criteria and the SONAR enrichment period resulted in enrollment of participants with relatively low incident HF.

Apart from exclusion of patients before exposure to atrasentan, the SONAR trial also employed an

TABLE 4 Predictors of BNP >25% Change During Enrichment

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age (per 5 y)	0.99 (0.96-1.03)	1.07 (1.03-1.12)
Female	1.17 (1.04-1.32)	
Race		
White	Ref.	
Black	0.98 (0.78-1.24)	
Asian	1.04 (0.93-1.16)	
Other	1.08 (0.92-1.62)	
Blood pressure		
Systolic (per 5 mm Hg)	0.96 (0.95-0.98)	
Diastolic (per 5 mm Hg)	0.93 (0.90-0.96)	0.94 (0.91-0.98)
Body weight (per 5 kg)	0.98 (0.96-0.99)	0.97 (0.95-0.99)
HbA_{1c}	0.96 (0.92-1.01)	
eGFR (per 5 mL/min/1.73 m^2)	0.95 (0.93-0.97)	0.96 (0.93-0.99)
BNP (per log pg/mL)[a]	0.54 (0.50-0.58)	0.44 (0.40-0.48)
Hemoglobin (per 5 g/L)	0.97 (0.96-0.99)	0.96 (0.94-0.98)
Albumin (per 1 g/L)	1.02 (1.00-1.04)	
UACR	0.97 (0.90-1.03)	
CV disease history	0.90 (0.75-1.08)	
Medication		
Diuretic use	1.00 (0.86-1.16)	
Beta-blockers use	1.21 (1.05-1.38)	1.81 (1.55-2.11)
Statin use	1.12 (0.95-1.32)	
SGLT2 use	0.93 (0.56-1.56)	
Insulin use	0.94 (0.83-1.06)	

[a]The inverse correlation between baseline BNP and BNP >25% change during enrichment may reflect a regression to the mean.

Abbreviations as in Table 1.

enrichment design to select patients who tolerated atrasentan during 6-week atrasentan treatment. During the enrichment period, 574 patients were discontinued because of body weight increase ≥3 kg or a BNP increase ≥300 pg/mL. Nevertheless, despite these precautionary measures and careful patient selection, there was a higher proportion of fluid retention and HF with atrasentan compared with placebo. We explored whether exclusion of patients based on other criteria than body weight change or absolute BNP levels might have further decreased the excess risk of HF with atrasentan and found that exclusion of patients with a BNP increase of at least 25% reduced HF risk while retaining the kidney protective effects of atrasentan. Exclusion of patients with moderate/severe edema during enrichment did not reduce the HR for incident HF. Although the development of edema and increase in BNP can both be a consequence of fluid retention, they could reflect partially distinct pathophysiological mechanisms. Release of BNP is induced by increased stretch and atrial and ventricular pressures indicative of intravascular congestion. In contrast, peripheral edema is related to presence of extravascular tissue congestion and may not directly reflect increases in cardiac filling pressure and HF risk.[12]

In this analysis female sex was associated with a higher HR for HF, and exclusion of women resulted in a decrease in the incidence of HF with atrasentan. An analysis of the interindividual variability in atrasentan exposure showed significantly lower clearance and higher exposure to atrasentan among female patients in the SONAR trial.[13] Although the effect size was modest, the higher atrasentan exposure may at least in part explain the higher HF risk. The change from baseline in BNP during enrichment appeared to be similar between women and men, suggesting that specific sex-related factors are likely involved. It could be possible that women enrolled in SONAR were more likely to have HF with preserved ejection fraction. Future research is required to determine if pharmacodynamic or other sex-specific differences in response to atrasentan explain the higher risk in women in the SONAR trial.

The well-established relationship between worsening of kidney function and incident HF was also observed in the present study. Patients with a lower eGFR and higher albuminuria at baseline were at higher risk of HF events, independent of whether they were assigned to treatment with atrasentan or placebo. A previous study from the SONAR trial demonstrated that the efficacy of atrasentan on major kidney outcomes and HF hospitalization is consistent according to baseline eGFR or UACR categories.[14] Taken together, these data indicate that both albuminuria and eGFR are markers of HF risk but do not modify the kidney protective effect of atrasentan. Other baseline variables associated with the risk of HF were use of diuretic agents or beta-blockers. Because beta-blockers have been shown to protect against worsening of heart failure and are consequently part of the guideline recommended therapy for patients with HF, it is likely that the association between beta-blockers and HF reflects confounding by indication and not a direct causal association.

A few clinical trials with ERA are ongoing to assess the effects of ERA on kidney function. These trials enroll patients at low risk of edema or HF or use strategies to mitigate HF risk. The PROTECT (A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; NCT03762850) and ALIGN (Atrasentan in Patients With IgA Nephropathy; NCT04573478) trials assess the effects of sparsentan and atrasentan respectively in high-risk patients with IgA Nephropathy and significant proteinuria while the DUPLEX trial (Study of

Sparsentan in Patients With Primary Focal Segmental Glomerulosclerosis [FSGS]; NCT03493685) examines the long-term kidney protective effects of sparsentan in patients with focal segmental glomerulosclerosis. In contrast to ERAs, sodium glucose cotransporter 2 inhibitors and the mineralocorticoid receptor antagonist finerenone reduce the risk of kidney failure and heart failure in patients with diabetic kidney disease.[11,15,16] In this respect, it is interesting that a post hoc analysis of the SONAR trial suggested that adding a SGTL2 inhibitor to atrasentan may offset fluid and salt retention in response to ERA.[17] Other trials, such as ZENITH (Zibotentan and Dapagliflozin for the Treatment of CKD; NCT04724837), are ongoing to assess the effects of ERA in combination with sodium glucose cotransporter 2 inhibitors in patients with CKD.

STUDY STRENGTHS AND LIMITATIONS. This study has several strengths, including a multicenter international trial in a large cohort of patients with diabetes and CKD that increase risk for kidney and HF outcomes, novel screening and enrichment strategies, and prospective capture and formal adjudication of HF events. A limitation of this study is the post hoc nature of the analyses, which are prone to residual confounding. The SONAR trial was not designed to detect effects on HF hospitalization, and the early discontinuation of the trial diminished statistical power to assess the effects of atrasentan on HF hospitalization. Moreover, exclusion of participants with a >25% increase in BNP further diminishes statistical power to robustly characterize effects of atrasentan on HF hospitalization. Validation of these findings in separate clinical trials is therefore required. Second, the carefully selected cohort of patients enrolled in the trial limits generalizability of the results to the broader population of patients with type 2 diabetes and CKD. In this respect, we note that although exclusion of patients with increases in BNP of at least 25% improved the balance between excess HF hospitalization events and prevented kidney events, a significant portion (38.7%) of all randomized patients would have been excluded from treatment, of whom not all necessarily develop HF hospitalization and may still benefit in terms of kidney outcomes. Better predictors of fluid retention in response to endothelin receptor antagonists are therefore desired. Third, exclusion of patients with increases in body weight and BNP during the enrichment period likely weakened the strength of the association between changes in body weight or BNP and HF hospitalization. Thus, our results of the association between changes in BNP during atrasentan and heart failure are likely an underestimation.

CONCLUSIONS

In patients with type 2 diabetes, low eGFR, and elevated levels of albuminuria who are at high risk of volume overload, changes in BNP but not body weight during initial administration of the endothelin receptor antagonist atrasentan was associated with subsequent HF hospitalization. The results of this study highlight the value of monitoring natriuretic peptides on initiation of atrasentan in carefully selected patients with type 2 diabetes and CKD and suggests caution if BNP increases more than 25% from baseline values.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The endothelin receptor antagonist atrasentan has been demonstrated to reduce the risk of kidney failure in patients with type 2 diabetes and CKD, but its adverse effects on fluid retention and HF may ultimately limit its use in patients at increased risk for cardiac decompensation. Early changes in BNP in response to atrasentan are independently associated with the development of HF, suggesting that monitoring of BNP may aid in identifying those at risk of developing HF.

TRANSLATIONAL OUTLOOK: Changes in BNP appear to be a useful biomarker to identify patients at increased risk of HF in response to endothelin receptor antagonists. Patient selection for future clinical trials based on early changes in BNP in response to endothelin receptor antagonists can help to prospectively validate the utility of this approach.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.