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Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF

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Aims We studied the characteristics and clinical outcome related to diuretic response and the effects of serelaxin in patients hospitalized for acute heart failure (AHF).

Methods and results RELAX-AHF was a double-blind, placebo-controlled trial, enrolling 1161 patients admitted to hospital for AHF who were randomized to 48 h i.v infusions of placebo or serelaxin (30 μg/kg per day) within 16 h from presentation. Diuretic response was defined as Δ weight kg/[(total i.v. dose)/40 mg] + [(total oral dose)/80 mg)] furosemide (or equivalent loop diuretic dose) up to day 5. Median diuretic response was −0.42 (−1.00, −0.14) kg/40 mg. A poor diuretic response was independently associated with Western-like region (Western Europe, North America, Israel, and Poland), lower diastolic blood pressure, the absence of oedema, higher blood urea nitrogen, and lower levels of aspartate aminotransferase and potassium (all $P < 0.01$). Randomization to serelaxin was associated with lower doses of i.v. loop diuretics and slightly less weight loss, resulting in a neutral effect on diuretic response. Worse diuretic response was independently associated both with less relief of dyspnoea, measured with a visual analogue scale (VAS) at day 5 (primary endpoint; $P = 0.0002$), and with a higher risk of cardiovascular death or rehospitalization for heart failure or renal failure through day 60 (secondary endpoint, $P < 0.0001$), but not with increased 180-day cardiovascular mortality ($P = 0.507$).

Conclusions In patients hospitalized for AHF, a poor diuretic response was associated with a poor in-hospital and early post-discharge clinical outcome. Serelaxin had a neutral effect on diuretic response.
Trial registration: NCT00520806

Keywords Heart failure • Renal function • Diuretic response

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Introduction

Acute heart failure (AHF) is a life-threatening condition needing immediate medical attention and often requiring urgent hospital admission.[1,2] Hospitalization for AHF is associated with a high risk of both in-hospital and post-discharge mortality and hospital readmission for heart failure.[3−7] Several studies tried to identify patients at risk, but they could only moderately predict mortality and poorly predict readmission.[8−11] In addition, most of the factors predicting outcome in these models are non-modifiable, such as age.

Treatment options in AHF are often limited to treatment with i.v. loop diuretics. However, not every patient responds well to their diuretic treatment, although our understanding of diuretic resistance is limited. Therefore, there is a need to better characterize and understand factors related to a poor diuretic response. Recently, we and others showed that a poor diuretic response, defined as weight loss per unit loop diuretic during the first 5 days after hospital admission, was strongly associated with in-hospital worsening heart failure, and predicted mortality and heart failure rehospitalization.[12,13] In addition, rolofylline, an adenosine A1 antagonist, was shown to improve diuretic response, although the neutral findings of PROTECT halted the development of rolofylline. Serelaxin is a novel drug that holds promise for the treatment of patients with AHF.[14,15] However, the effects of serelaxin on diuretic response have so far not been studied. In the present study, we aimed to describe patient characteristics, incidence of worsening renal function, and outcomes related to diuretic response in AHF patients. In addition, we studied the effects of serelaxin on diuretic response, both at the end of infusion of serelaxin at 48 h and at 5 days after hospital admission.

Methods

Study design

RELAX-AHF was a phase III randomized, double-blind, placebo-controlled, parallel-group, international trial comparing the i.v. administration of serelaxin for up to 48 h, started within 16 h of presentation, with placebo in patients hospitalized for AHF with dyspnoea, congestion on chest radiography, increased natriuretic peptide levels, mild to moderate renal insufficiency, and systolic blood pressure >125 mmHg. Patients were enrolled in the USA, Israel, Western Europe (France, Germany, Italy, The Netherlands, and Spain), Poland, Hungary, Romania, and Argentina. The background, design, and main results have been published elsewhere.[14,15] This trial is registered at ClinicalTrials.gov (NCT00520806), complies with the Declaration of Helsinki, and a locally appointed ethics committee or institutional review board has approved the research protocol with written informed consent obtained from each patient.

Procedures

In the RELAX-AHF phase III study, blood samples, weight, and diuretic dose were collected in all patients at baseline and at 24 h (day 1); 48 h (day 2); on days 3 and 4, if in hospital; and on days 5, 14, and 60 for standard haematology and chemistry at a central laboratory using commercially available, validated assays. Samples for biomarkers including troponin T and NT-proBNP were collected at baseline and days 2, 5, and 14, and were analysed centrally. The endpoints of interest were (i) change in patient-reported dyspnoea as quantified by the area under the curve (AUC) of the change from baseline in visual analogue scale (VAS) scores (0−100 mm scale) from baseline to day 5 (a primary endpoint of RELAX-AHF); (ii) cardiovascular death or readmission to hospital for heart failure or renal failure through day 60 (a secondary endpoint of RELAX-AHF); and (iii) cardiovascular death through day 180. As specified in the analysis plan for the main study, the dyspnoea VAS score was imputed as the worst observed score following a death or worsening heart failure event when calculating the AUC of the change from baseline. All deaths and rehospitalizations were adjudicated by the clinical events committee.

Definitions

Diuretic response was defined as change in weight (kg) from baseline to day 5/[(total i.v. dose)/40 mg] + [(total oral dose)/80 mg] furosemide up to day 5. The last available weight was substituted for a missing day 5 weight. Additional comparative analyses were performed on diuretic response from baseline to 48 h. Loop diuretic doses considered equivalent to 40 mg of furosemide were 2 mg of bumetanide, 20 mg of torasemide, and 50 mg of ethacrynic acid. Worsening renal function was defined as an increase in serum creatinine of ≥0.3 mg/dL to day 5 (or day 4, if day 5 was missing)).

Statistical analyses

Mean and standard deviation, or geometric mean and 95% confidence interval, are presented for continuous variables, and absolute and relative frequencies for categorical variables. Because its distribution was highly skewed, and associations with outcomes non-linear, diuretic response was grouped by tertiles for analysis. Baseline characteristics were compared among diuretic response tertiles using the Jonckheere−Terpstra (J-T) trend test. Patients with missing values of diuretic response were deleted from the analyses in which diuretic response appears as an outcome variable. For analyses of clinical endpoints in which diuretic response appears as an explanatory factor, missing values of diuretic response were imputed so as to include those patients, thus preserving comparability with other such analyses. Sample sizes in the tables reflect these distinctions.

A multivariable cumulative logit model predicting diuretic response was developed using backwards elimination in the full study population, with $P < 0.10$ as the criterion for retention in the model. The treatment group-specific median or mode was imputed for missing continuous and categorical variables, respectively. A list of potential covariates was reduced by choosing one representative in certain groups of related covariates to represent the effect, e.g. alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or haemoglobin or haematocrit, based on the lowest Akaike information criterion (AIC) in univariable analyses. The linearity of the association between the log cumulative odds and selected continuous candidate predictors was then assessed using restricted cubic splines, and, if significant non-linearity was found (at $P < 0.10$), we used the dichotomy or quadratic or cubic polynomial which had the lowest AIC. The interaction of each effect with serelaxin was then tested and, where significant at $P < 0.10$, the interaction was added to the effects to consider in the backwards elimination.

The associations of diuretic response with clinical outcomes (dyspnoea VAS AUC to day 5, cardiovascular death, or heart failure/renal failure rehospitalization through day 60, and cardiovascular

mortality through day 180) were adjusted for covariates found to be associated with these outcomes in the placebo group only using multivariable linear regression and Cox regression models. Wald test χ^2 statistics and *P*-values are reported. SAS release 9.3 (SAS Institute, Cary, NC, USA) was used for all analyses.

Role of the funding source

The study was designed by the members of the executive committee, which included two Corthera clinical scientists, and was part of a phase II/III trial design. Data collection and analysis were performed by contract research organizations. The study database was held both by the Sponsor and by Columbia University (New York, USA). The authors had access to tables and listings supplied by the sponsor and Columbia but did not have independent access to the study databases. The executive committee had full access to the final tables and figures. The authors not employed by the sponsor had ultimate editorial authority, with no interference by the sponsor in their final interpretation.

Results

The main results of RELAX-AHF have been published elsewhere.[14,15] During the first 5 days of hospital admission, the median weight change was −2.2 kg, median total i.v. dose of furosemide was 80 mg, and median total oral dose of furosemide was 160 mg. The majority of patients received furosemide (92.2%); torsemide was administered to 9.0%, bumetanide to 1.3%, and ethacrynic acid to 0.95%. (A given patient may have received more than one type of loop diuretic.) Of the 1161 patients randomized, 7 died by day 5 and were excluded from the analyses. Fifty-seven patients were missing data such that the diuretic response could not be derived, and 70 patients were missing data on worsening renal failure. Daily weights and loop diuretic doses are provided in the Supplementary material online *Figures S1* and *S2*.

Predictors of diuretic response

The median diuretic response was −0.42 kg/40 mg [interquartile range (IQR) −1.00, −0.14 kg/40 mg]. There were marked differences across the tertiles of diuretic response, as presented in *Table 1*. Poor responders (with higher diuretic response values) were more frequently found in Western-like countries (Western Europe, North America, Poland, and Israel). Also, poor diuretic responders were more likely to have ischaemic heart failure, a higher NYHA class 1 month prior to enrolment, lower systolic and diastolic blood pressures, fewer signs of congestion, and a poorer baseline renal function, and were more often on oral loop diuretics 1 month prior to enrolment. Other characteristics related to diuretic response are given in *Table 1*.

Independent predictors of diuretic response are presented in *Table 2*. The most significant predictors of a poor diuretic response were Western-like region (Western Europe, North America, Israel, and Poland), lower diastolic blood pressure, the absence of oedema, higher blood urea nitrogen (BUN), and lower levels of AST and potassium (all $P < 0.01$). Independent predictors of diuretic response at 48 h are presented in Supplementary material online *Table S1*, and were largely similar to the predictors of diuretic response at day 5.

Effects of serelaxin on diuretic response

The median (25th, 75th percentile) total i.v. loop diuretic dose before day 5 was 100 (20, 240) mg in the placebo group and 80 (0, 200) mg in the serelaxin group; median (25th, 75th percentile) total dose of oral loop diuretic dose through day 5 was 137.5 (40, 270) and 160 (80, 240), respectively. As defined for this analysis, median change in body weight at day 5 was −2.4 kg (IQR −4.8, −1.0) in the placebo group vs. −2.0 (IQR −4.0, −0.8) kg in the serelaxin group ($P = 0.133$). On univariable analysis, randomization to serelaxin was not associated with diuretic response: median of −0.42 (IQR −0.94, −0.15) kg/40 mg in the placebo group vs. −0.42 (IQR −1.09, −0.13) kg/40 mg in the serelaxin group ($P = 0.644$). Although a statistically significant serelaxin by EF interaction effect was included in the multivariable model, the slight worsening of diuretic response in the serelaxin group, and slight improvement in diuretic response in the placebo group, with increasing LVEF were small and possibly due to chance. In addition, we performed similar analyses on the effects of serelaxin on diuretic response at 48 h. As can be seen from *Table S2* of the Supplementary material online, there was no significant difference in diuretic response at day 2 between treatment groups.

Worsening renal function and diuretic response

Worsening renal function, defined as an increase in serum creatinine of ≥0.3 mg/dL to day 5 (or day 4, if day 5 was missing), occurred in 280 of the 1084 patients (26%) with available data. *Table 3* shows that patients with both worsening renal function and poor diuretic response (less than the median response) had the worst 60- and 180-day outcomes, but the risks were not more or less than the combined individual effects would predict (interaction *P*-values 0.72 and 0.53 for 60- and 180-day outcomes, respectively).

Diuretic response and clinical outcomes

In univariable analyses, diuretic response was significantly associated with the dyspnoea VAS AUC to day 5 ($P = 0.0015$; *Figure 1*) and cardiovascular death or heart failure/renal failure rehospitalization through day 60 ($P < 0.0001$; *Figure 2*) but not with cardiovascular mortality through day 180 ($P = 0.13$; *Table 4*). After multivariable adjustment for baseline characteristics, worse diuretic response remained independently associated with a poorer dyspnoea relief to day 5 ($P = 0.0002$; *Table 4*) and with 60-day cardiovascular death or heart failure/renal failure rehospitalization ($P < 0.0001$). These associations were independent of worsening renal function (*Figure 3*). Further adjustment for changes to day 2 in BUN, creatinine, sodium, total protein, and log NT-proBNP did not change these associations significantly. However, diuretic response was not independently associated with mortality through day 180 ($P = 0.507$).

Table 1 Baseline characteristics according to tertiles of diuretic response (defined as change in weight/[(total i.v. dose)/40 mg] + [(total oral dose)/80 mg)] furosemide up to day 5)

	≤ −0.75 kg/40 mg (*n* = 365)	≥ −0.75 to ≤ −0.22 kg/40 mg (*n* = 366)	> −0.22 kg/40 mg (*n* = 366)	*P*-value[a]
Demographics and heart failure characteristics				
Age (years)	71.5 (11.5)	72.7 (10.4)	72.2 (11.6)	0.4997
Male	220 (60.3)	228 (62.3)	237 (64.8)	0.2112
White/Caucasian	353 (96.7)	348 (95.1)	343 (93.7)	0.0590
Geographic region				<0.0001
Eastern EU	227 (62.2)	162 (44.3)	142 (38.8)	
Western EU	58 (15.9)	57 (15.6)	80 (21.9)	
South America	27 (7.4)	28 (7.7)	14 (3.8)	
North America	25 (6.8)	35 (9.6)	41 (11.2)	
Israel	28 (7.7)	84 (23.0)	89 (24.3)	
LVEF	39.2 (13.9)	38.6 (14.8)	37.9 (14.9)	0.0906
Ischaemic heart disease	155 (42.5)	215 (58.7)	207 (56.6)	0.0001
Time from presentation to randomization (h)	7.9 (4.5)	7.7 (4.6)	8.0 (4.8)	0.9190
CHF 1 month prior	242 (66.3)	293 (80.1)	292 (79.8)	<0.0001
NYHA class (I/II/III/IV) 30 days before admission				<0.0001
I	126 (34.6)	82 (22.6)	83 (23.1)	
II	108 (29.7)	112 (30.9)	73 (20.3)	
III	105 (28.8)	117 (32.2)	150 (41.7)	
IV	25 (6.9)	52 (14.3)	54 (15.0)	
Clinical signs				
Body mass index, kg/m^2	29.8 (6.0)	29.4 (5.6)	28.9 (5.4)	0.1033
Systolic blood pressure, mmHg	145.0 (16.5)	140.4 (15.3)	140.7 (16.9)	<0.0001
Diastolic blood pressure, mmHg	81.9 (14.4)	78.2 (13.7)	76.4 (13.6)	<0.0001
Heart rate, b.p.m.	81.7 (15.4)	78.5 (14.6)	78.1 (14.6)	0.0008
Respiratory rate, breaths/min	21.8 (4.4)	21.8 (4.6)	22.1 (5.0)	0.8207
HF hospitalization past year	96 (26.3)	131 (35.8)	154 (42.1)	<0.0001
Congestion at baseline				
Oedema	305 (83.6)	306 (83.8)	265 (72.4)	<0.0001
Orthopnoea	350 (96.2)	352 (96.2)	350 (95.6)	0.3781
JVP	283 (80.4)	275 (76.8)	252 (70.2)	0.0031
Dyspnoea on exertion	361 (99.7)	359 (99.7)	359 (99.4)	0.0907
Dyspnoea by VAS	44.6 (20.1)	43.9 (20.8)	43.5 (19.6)	0.1714
Rales	138 (37.8)	141 (38.5)	156 (42.6)	0.4716
Co-morbidities				
Hypertension	312 (85.5)	323 (88.3)	312 (85.2)	0.9256
Hyperlipidaemia	158 (43.3)	216 (59.0)	209 (57.1)	0.0002
Diabetes mellitus	151 (41.4)	189 (51.6)	183 (50.0)	0.0197
Cigarette smoking	45 (12.3)	45 (12.3)	46 (12.6)	0.9217
Stroke or other cerebrovascular event	44 (12.1)	49 (13.4)	58 (15.8)	0.1369
Peripheral vascular disease	46 (12.6)	53 (14.5)	43 (11.7)	0.7300
Asthma, bronchitis, or COPD	46 (12.6)	54 (14.8)	72 (19.7)	0.0086
AF at screening	176 (48.2)	147 (40.2)	133 (36.5)	0.0014
History of AF or atrial flutter	207 (56.7)	187 (51.1)	183 (50.0)	0.0694
History of CRT or ICD procedures	63 (17.3)	106 (29.0)	113 (30.9)	<0.0001
Myocardial infarction	100 (27.4)	136 (37.2)	147 (40.2)	0.0003
Depression	16 (4.4)	16 (4.4)	24 (6.6)	0.1817
Devices				
Pacemaker	33 (9.0)	41 (11.2)	44 (12.0)	0.1937
ICD	28 (7.7)	56 (15.3)	63 (17.2)	0.0002
Biventricular pacing	17 (4.7)	43 (11.7)	46 (12.6)	0.0003
Medication (day 0, except nitrates and loop diuretics)				
ACE inhibitor	202 (55.3)	214 (58.5)	187 (51.1)	0.2476
ACE inhitor or ARB	245 (67.1)	275 (75.1)	234 (63.9)	0.3507
ARB	56 (15.3)	66 (18.0)	58 (15.8)	0.8549
Beta-blocker	227 (62.2)	267 (73.0)	263 (71.9)	0.0048

Table 1 Continued

	≤ −0.75 kg/ 40 mg (*n* = 365	≥ −0.75 to ≤ −0.22 kg/ 40 mg (*n* = 366)	> −0.22 kg/ 40 mg (*n* = 366)	*P*-value[a]
Aldosterone antagonist	130 (35.6)	116 (31.7)	104 (28.4)	0.0368
I.v. loop diuretics	365 (100.0)	366 (100.0)	366 (100.0)	NA
Digoxin	85 (23.3)	53 (14.5)	74 (20.2)	0.2952
Nitrates at randomization	35 (9.6)	16 (4.4)	26 (7.1)	0.1897
Oral loop diuretics 30 days prior to randomization	25 (31.5)	47 (52.1)	67 (93.0)	<0.0001
Baseline labs				
Sodium, mmol/L	141.1 (3.6)	141.0 (3.3)	140.4 (3.8)	0.0137
Phosphate, mmol/L	1.18 (0.45)	1.19 (0.24)	1.19 (0.24)	0.4206
Calcium, mmol/L	2.27 (0.153)	2.26 (0.159)	2.27 (0.150)	0.6419
Haemoglobin, g/dL	13.01 (1.79)	12.62 (1.92)	12.71 (1.90)	0.0244
White blood cell count, $\times 10^9$/L	8.168 (2.697)	7.907 (2.654)	8.222 (2.927)	0.8668
Lymphocytes, %	18.39 (7.98)	18.71 (8.19)	17.41 (7.08)	0.2053
Potassium, mmol/L	4.32 (0.66)	4.26 (0.62)	4.25 (0.63)	0.2173
Creatinine, µmol/L	111.6 (32.2)	116.6 (32.0)	122.4 (33.9)	<0.0001
Uric acid, µmol/L	461.8 (135.9)	475.5 (125.6)	495.4 (144.8)	0.0018
Troponin T, µg/L	0.035 (0.032, 0.038)	0.034 (0.032, 0.038)	0.036 (0.033, 0.039)	0.2982
BUN, mmol/L	8.96 (3.36)	9.78 (3.73)	10.69 (4.54)	<0.0001
Cystatin C, mg/L	1.38(1.34, 1.42)	1.47 (1.42, 1.51)	1.54 (1.49, 1.58)	<0.0001
Alanine aminotransferase, U/L	25.3 (23.7, 27.1)	21.6 (20.3, 22.9)	23.1 (21.7, 24.6)	0.0349
NT-proBNP, ng/L	5218 (4760, 5720)	4861 (4417, 5349)	5107 (4659, 5599)	0.2983
NT-proBNP, ng/L in patients with AF present at screening	5566 (4979, 6223)	5203 (4546, 5955)	5086 (4455, 5806)	0.1929
NT-proBNP ng/L in patients with AF not present at screening	4909 (4247, 5675)	4645 (4070, 5302)	5133 (4531, 5814)	0.9200
eGFR, mL/min/1.73 m^2	55.36 (12.45)	52.91 (13.32)	51.52 (12.66)	<0.0001
Total cholesterol, mmol/L	4.20 (1.17)	3.98 (1.17)	4.06 (1.13)	0.0624
Glucose, mmol/L	7.34 (3.51)	7.91 (3.57)	8.04 (3.71)	0.0003
Albumin, g/L	39.99 (4.31)	40.04 (4.72)	40.58 (3.87)	0.1819

BUN, blood urea nitrogen; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; NA, not applicable; VAS, visual analogue scale.

[a]*P*-values are for the Jonckheere–Terpstra trend test, except for geographic region for which the Kruskal–Wallis test *P*-value is presented.

Discussion

The main finding of the present study is that a poor diuretic response is a strong and independent predictor of poorer dyspnoea relief and an increased risk of cardiovascular death or heart failure/renal failure hospital readmission through day 60 in patients admitted for AHF. Serelaxin treatment was associated with less diuretic use, but a neutral effect on diuretic response.

Recently, Valente *et al.* and Testani *et al.* presented a simple metric for diuretic responsiveness in patients admitted for AHF.[12,13] The metric of weight loss/unit loop diuretic had additive prognostic value on top of weight loss or dose of loop diuretic alone. In both studies, diuretic response was related to clinical outcome. The present study confirms these findings, but adds information on the predictors of diuretic response and the absence of an effect of serelaxin on diuretic response. We additionally showed that predictors of diuretic response and the effects of serelaxin were similar between 48 h and day 5.

Association between poor diuretic response and poor clinical outcome

The relationship between diuretic response and early outcomes has many potential causes. First, higher doses of loop diuretic might have adversely influenced clinical outcome. However, the DOSE-AHF (Diuretic Optimization Strategies Evaluation in Acute Heart Failure) trial, which compared a higher vs. a lower dose of diuretics in AHF patients, found that the higher dose was associated with greater diuresis and transient worsening of renal function, but did not significantly affect patients' global assessment of symptoms.[16] Secondly, patients with a poorer diuretic response might simply reflect sicker patients, and are therefore likely to have a poorer outcome. However, levels of NT-proBNP at admission were remarkably similar, and the predictive value of diuretic response remained remarkably consistent after adjusting for potential confounders. Thirdly, diuretic response might be a deleterious condition by itself, causing a poor clinical outcome. It is conceivable that a poor diuretic response results in less relief of dyspnoea, as was shown in the present study. Metra *et al.* previously demonstrated that less dyspnoea relief during hospitalization is independently related to a poorer clinical outcome.[17] Also, the association between diuretic response and clinical outcome seems to be mainly driven by early discharge rehospitalization, and less by mortality. These findings support that a poor diuretic response might cause less relief of dyspnoea and congestion, potentially leading to a greater risk of rehospitalization.

This is of importance for two reasons. First, we are better able to predict those patients at higher risk for rehospitalization,

Table 2 Multivariable predictors of poor diuretic response[a]

Covariate	OR	Lower 95% CI	Upper 95% CI	Wald χ^2	*P*-value
Region, Western-like	2.514	1.889	3.347	39.90	<0.0001
Weight (kg)	0.993	0.986	1.000	3.46	0.0630
Diastolic blood pressure (mmHg)	0.988	0.979	0.997	7.30	0.0069
Body temperature (°C)	0.654	0.471	0.910	6.35	0.0117
Respiratory rate (breaths/min)[b]				6.88	0.0321
Median (21) vs. 25th percentile (19)	0.941	0.878	1.008		
75th percentile (24) vs. median (21)	0.976	0.902	1.057		
HF hospitalization past year	1.364	1.056	1.763	5.63	0.0176
NYHA class 30 days prior				6.80	0.0779
NYHA II vs. I	0.768	0.551	1.069		
NYHA III vs. I	1.135	0.807	1.594		
NYHA IV vs. I	1.107	0.711	1.722		
Oedema				23.99	<0.0001
Oedema, 1 vs. 0	0.689	0.489	0.970		
Oedema, 2 vs. 0	0.531	0.374	0.753		
Oedema, 3 vs. 0	0.385	0.258	0.575		
Dyspnoea VAS (mm)[c]				6.72	0.0814
Median (45) vs. 25th percentile (30)	0.867	0.751	1.001		
75th percentile (57) vs. median (45)	0.852	0.747	0.971		
Percutaneous intervention	1.405	1.069	1.848	5.93	0.0149
Peripheral vascular disease	0.693	0.489	0.983	4.23	0.0397
Hyperthyroid	2.191	1.077	4.458	4.69	0.0304
Atrial fibrillation/flutter at screening	0.733	0.578	0.929	6.59	0.0103
BUN (mmol/L)	1.089	1.052	1.127	23.37	<.0001
Uric acid (μmol/L)	1.001	1.000	1.002	3.75	0.0529
Aspartate aminotransferase, log(U/L)	0.686	0.527	0.893	7.86	0.0050
Sodium (mmol/L)	0.960	0.927	0.993	5.53	0.0187
Potassium (mmol/L)	0.706	0.577	0.864	11.36	0.0007
Total protein (g/L)	1.022	1.003	1.042	4.92	0.0265
NT-proBNP, > median vs. ≤ median	0.735	0.571	0.945	5.76	0.0164
LVEF by serelaxin interaction				4.26	0.0390
LVEF (%), placebo	0.991	0.979	1.003		0.1472
LVEF (%), serelaxin	1.008	0.997	1.020		0.1634

Odds ratios (are for a one unit increase in the covariate unless otherwise specified.
BUN, blood urea nitrogen; CI, confidence interval; HF, heart failure; OR, odds ratio; VAS visual analogue scale.
[a]Cumulative logit model of diuretic response tertile.
[b]Non-linear association modelled as a quadratic polynomial.
[c]Non-linear association modelled as a cubic polynomial.

which is a major problem in patients who are admitted for AHF. Secondly, and more importantly, strategies that improve diuretic response might lead to improved clinical outcome and fewer rehospitalizations in patients with AHF. However, potential strategies to improve diuretic response remain to be established. First, addition of thiazides/chlorothalidon and/or azetazolamide might improve diuretic response, although this should be proven by prospective randomized controlled trials. Ultrafiltration might be another option to improve diuretic response in diuretic-resistant patients. In UNLOAD, in AHF patients with signs of volume overload, ultrafiltration resulted in greater weight and fluid loss than i.v. diuretics, but had no effect on mortality.[18] These beneficial effects could not be confirmed in a recent randomized trial, where loop diuretics were superior to ultrafiltration for the preservation of renal function, with a similar amount of weight loss.[19] However, a good diuresis was observed in both arms, indicating that these patients were not diuretic resistant, although the results might be different in a population of patients selected based on a poor diuretic response.

Mechanisms behind a poor diuretic response

What are the potential mechanisms behind the diuretic response? Obviously, patients with a poor diuretic response have a poorer renal function. However, similar to the studies by Valente *et al.* and Testani *et al.*, renal dysfunction explains only a part of poor diuretic response.[12,13] There are a number of explanations for this. First, Valente *et al.* demonstrated that diuretic-resistant patients more often had heart failure of ischaemic origin and signs of

Table 3 Clinical outcome according to worsening renal function and diuretic response

Clinical endpoints	No WRF, good diuretic response ($n = 389$)	No WRF, poor diuretic response ($n = 385$)	WRF, good diuretic response ($n = 136$)	WRF, poor diuretic response ($n = 138$)	Interaction *P*-value, unadjusted	Interaction *P*-value, adjusted[a]
Dyspnoea improvement by VAS AUC to day 5, mean (SD)	2788.1 (2600.4)	2356.2 (2735.0)	2889.2 (3187.7)	2348.5 (3309.3)	0.9988	0.2024
Cardiovascular death or rehospitalization for HF or renal failure through day 60, *n* (Kaplan–Meier %)	29 (7.49)	66 (17.33)	13 (9.56)	26 (19.05)	0.7362	0.7206
Cardiovascular mortality through day 180, *n* (Kaplan–Meier %)	23 (5.97)	26 (6.86)	10 (7.36)	16 (11.79)	0.7238	0.5262

A good diuretic response is defined as a response greater than the median.
AUC, area under the curve; HF, heart failure; SD, standard deviation; VAS, visual analogue scale; WRF, worsening renal function.
[a]Each outcome is adjusted for the covariates given in the footnotes to *Table 4*.

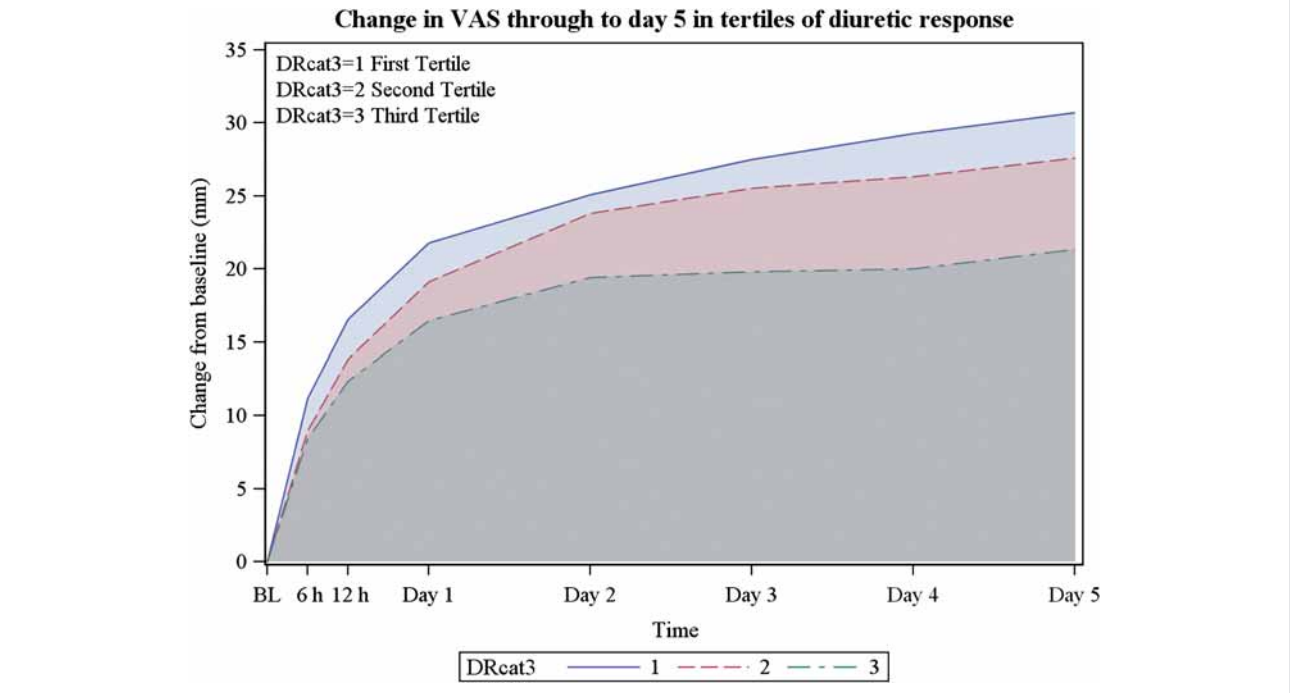

Figure 1 Changes in visual analogue scale through to day 5 in tertiles of diuretic response (DR).

atherosclerosis.[12] A similar picture emerges in the present study. Patients with a poor diuretic response more often had ischaemic heart failure, a previous myocardial infarction, dyslipidaemia, and diabetes. A poorer diuretic response in atherosclerotic patients might be caused by atherosclerotic kidneys that are less likely to respond to diuretics. Alternatively, the presence of renal artery stenosis may be prevalent in patients with ischaemic heart failure[20] and might also explain a poorer diuretic response, although we do not have any direct evidence for this. Secondly, patients with a poor diuretic response in the present study also had fewer signs of congestion. These patients might have AHF due to fluid redistribution, rather than fluid accumulation, and therefore they will not respond to diuretics. Loop diuretics might not be the best treatment option in these patients as they are not volume overloaded, and they might even be deleterious, causing relative dehydration and worsening renal function. So, it is reasonable to suggest that diuretic response is better in more congested patients with more peripheral oedema, but it should be noted

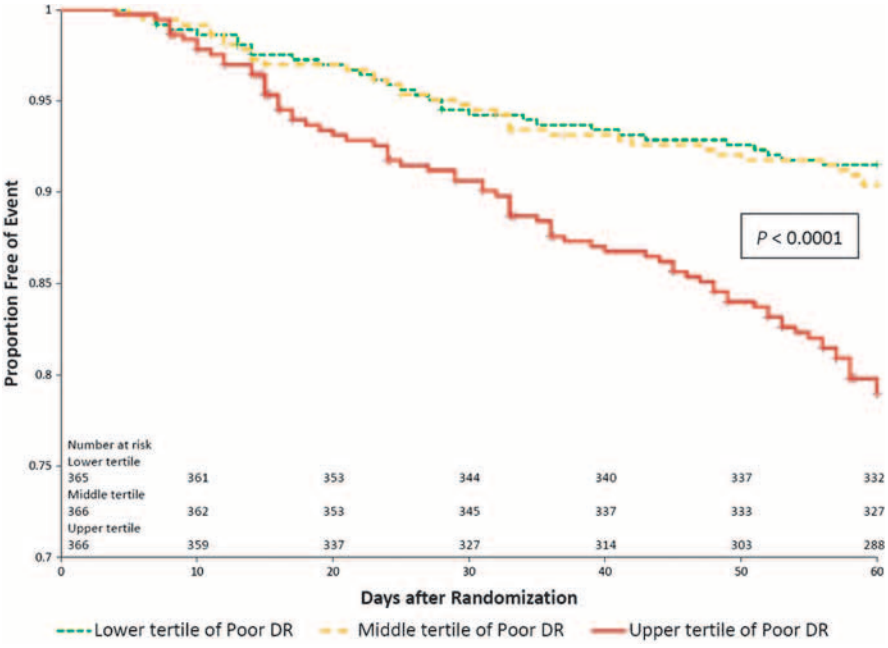

Figure 2 Kaplan–Meier survival curves presenting death or HF/RF readmission through day 60 according to tertiles of diuretic response. P < 0.0001 for log-rank test comparing diuretic response tertiles.

Table 4 Associations of diuretic response with selected outcomes

		Unadjusted		Adjusted	
Outcome	**Contrast**	**Measure of association (95% CI)**	***P*-value**	**Measure of association (95% CI)**	***P*-value**
Dyspnoea VAS AUC to day 5[a]			0.0002		0.0001
	T2 vs. T1	−355.944 (−751.753, 39.866)		−319.370 (−645.481, 6.740)	
	T3 vs. T1	−855.674 (−1265.072, −446.276)		−749.944 (−1096.009, −403.879)	
CV death or HF/RF rehospitalization through day 60[b]			<0.0001		0.0005
	T2 vs. T1	1.122 (0.702, 1.794)		0.919 (0.566, 1.494)	.
	T3 vs. T1	2.735 (1.806, 4.142)		1.855 (1.195, 2.879)	.
CV death through day 180[c]			0.1323		0.5069
	T2 vs. T1	0.865 (0.502, 1.490)		0.948 (0.533, 1.689)	.
	T3 vs. T1	1.417 (0.856, 2.347)		1.273 (0.722, 2.244)	.

T1 = first tertile (≤ −0.75 kg/40 mg), T2 = second tertile (> − 0.75 to ≤ −0.22 kg/40 mg), T3 = third tertile (> −0.22 kg/40 mg).
AUC, area under the curve; CI, confidence interval; CV, cardiovascular; HF, heart failure; RF, renal failure; VAS, visual analogue scale.
[a]Measure of association is mean change from linear regression model. Adjusted for age, weight, hypertension, mitral regurgitation, history of atrial fibrillation or flutter, USA-like region, dyspnoea on exertion, body temperature, troponin T, baseline dyspnoea VAS score, uric acid, alkaline phosphatase, and sodium.
[b]Measure of association is hazard ratio from Cox regression model. Adjusted for white race; NYHA class 30 days prior; systolic blood pressure; respiratory rate; number of HF hospitalizations in past year; orthopnoea; asthma, bronchitis, or COPD; hyperthyroid; lymphocyte %; blood urea nitrogen; phosphate; sodium; and total protein.
[c]Measure of association is hazard ratio from Cox regression model. Adjusted for USA-like region, systolic blood pressure, orthopnoea, angina, hyperthyroid, mitral regurgitation, atrial fibrillation or flutter at screening, white blood cell count, lymphocyte %, blood urea nitrogen, sodium, potassium, calcium, total protein, troponin T, and NT-proBNP.

that the poorer prognosis in diuretic-unresponsive patients was independent of the baseline level of congestion. Finally, we showed that worsening renal function (using the most commonly used definition of an increase in serum creatinine of ≥0.3 mg/dL to day 5) was not a predictor of clinical outcome. In addition, baseline BUN was an important predictor of diuretic response. This supports the concept that diuretic response is not primarily driven by glomerular filtration, but more by tubular function.[21] Therefore, markers of tubular function and/or damage might better predict diuretic response than markers of glomerular function. Unfortunately,

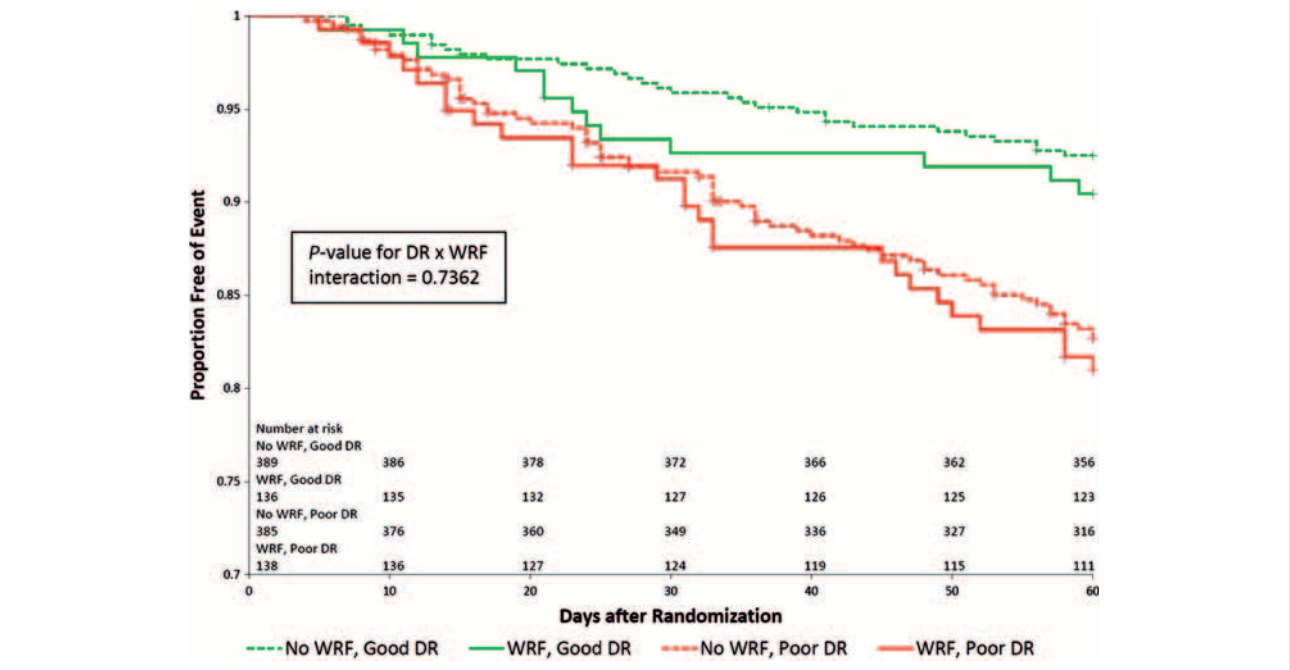

Figure 3 Kaplan–Meier survival curves presenting death or HF/RF readmission through day 60 in 1) patients with WRF and a poor diuretic response (<median); 2) patients with WRF and a good diuretic response (>median); 3) patients without WRF and a poor diuretic response (<median); 4) patients without WRF and a good diuretic response (>median). P = 0.7362 for Wald chi-square test of diuretic response- by-WRF interaction.

we did not collect urine in RELAX-AHF, and do not have data on plasma markers of tubular damage.

Effects of serelaxin on diuretic response

Despite a significant reduction in dyspnoea and lower 180-day mortality, serelaxin did not influence diuretic response in these patients. However, patients treated with serelaxin required lower doses of diuretics and had slightly less weight loss, which may have balanced the effects on diuretic response. Also, serelaxin was related to less deterioration of renal function. Therefore, the beneficial effects of serelaxin cannot be explained by improved diuretic response, and a potential explanation might be related to prevention of organ damage, as has been postulated previously.[22]

Limitations

The present study has obvious limitations that are related to the retrospective nature of the findings. Therefore, the suggestion that a poor diuretic response might cause a poor clinical outcome cannot be proven. Also, this study was not designed to examine the consequences of diuretic response, and therefore there are important data lacking, such as urinary collections and markers of tubular function/damage. Furthermore, it is well known that weight recordings are notoriously unreliable. In addition, diuretic doses might not always be properly recorded. Nevertheless, despite these limitation, the simple metric of weight loss divided by diuretic dose is clearly related to in-hospital and post-discharge outcome in patients admitted for AHF.

Conclusion and clinical implications

In a large cohort of patients admitted for AHF, a poor diuretic response was related to less improvement in dyspnoea through the first 5 days, and an increased risk of cardiovascular death or heart failure/renal failure rehospitalization through 60 days. Future studies should aim at predicting diuretic response in patients admitted with acute decompensated heart failure and should lead to prospective intervention studies, aiming to improve diuretic response, potentially leading to further improvement in dyspnoea, less early mortality, and fewer heart failure rehospitalizations.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Weight by treatment group and day.

Figure S2. Loop diuretic dose by treatment group and day.

Table S1. Multivariable predictors of poor diuretic response at 48 h.

Table S2. The effects of serelaxin on diuretic response at 48 h.

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