Diuretic response in acute heart failure: clinical characteristics and prognostic significance

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Received 9 September 2013; revised 13 January 2014; accepted 27 January 2014; online publish-ahead-of-print 28 February 2014

See page 1235 for the editorial comment on this article (doi:10.1093/eurheartj/ehu121)

Aim

Diminished diuretic response is common in patients with acute heart failure, although a clinically useful definition is lacking. Our aim was to investigate a practical, workable metric for diuretic response, examine associated patient characteristics and relationships with outcome.

Methods and results

We examined diuretic response (defined as Δ weight kg/40 mg furosemide) in 1745 hospitalized acute heart failure patients from the PROTECT trial. Day 4 response was used to allow maximum differentiation in responsiveness and tailoring of diuretic doses to clinical response, following sensitivity analyses. We investigated predictors of diuretic response and relationships with outcome. The median diuretic response was −0.38 (−0.80 to −0.13) kg/40 mg furosemide. Poor diuretic response was independently associated with low systolic blood pressure, high blood urea nitrogen, diabetes, and atherosclerotic disease (all \( P < 0.05 \)). Worse diuretic response independently predicted 180-day mortality (HR: 1.42; 95% CI: 1.11–1.81, \( P = 0.005 \)), 60-day death or renal or cardiovascular rehospitalization (HR: 1.34; 95% CI: 1.14–1.59, \( P < 0.001 \)) and 60-day HF rehospitalization (HR: 1.57; 95% CI: 1.24–2.01, \( P < 0.001 \)) in multivariable models. The proposed metric—weight loss indexed to diuretic dose—better captures a dose–response relationship. Model diagnostics showed diuretic response provided essentially the same or slightly better prognostic information compared with its individual components (weight loss and diuretic dose) in this population, while providing a less biased, more easily interpreted signal.

Conclusions

Worse diuretic response was associated with more advanced heart failure, renal impairment, diabetes, atherosclerotic disease and in-hospital worsening heart failure, and predicts mortality and heart failure rehospitalization in this post hoc, hypothesis-generating study.

Keywords

Diuretics • Heart failure • Diuretic resistance • Cardiorenal syndrome • Worsening renal function • Renal dysfunction • Prognosis • Mortality • Rehospitalization

Introduction

Heart failure (HF) is a growing public health problem and the leading cause of hospitalization in Europe and the USA.1,2 Loop diuretics are a cornerstone of acute heart failure (AHF) therapy—administered to up to 90% of hospitalized patients3,4—and while some observational data suggest higher doses are associated with worse outcomes,5–7 others found no difference after case matching.8 The question of whether diuretics cause poor outcome or merely reflect disease severity remains unanswered,9,10 data on optimal posology and

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administration are conflicting at best, although the prospective Diuretic Optimization Strategies Evaluation (DOSE) trial suggests that safety concerns associated with high-dose diuretics may be unfounded.

A frequently mentioned complication of diuretic therapy in AHF is diuretic resistance, which is associated with worsening renal function (WRF) and cardiorenal syndromes. Existing definitions of resistance—which include congestion refractory to ‘standard’ diuretic therapy, reduced diuresis and natriuresis upon repeated dosing, and persistent congestion despite increasing (>80 mg oral furosemide) daily diuretic doses—are of limited use. Despite the clinical importance of the issue, few studies have explicitly examined the importance of effective decongestion using diuretics within the setting of AHF.

Heart failure guidelines recommend using weight loss to monitor volume status, and correlations between weight loss and outcomes have been reported. However, post-discharge changes in body weight only predicted rehospitalization and were unrelated to mortality in one study, highlighting the limitations of examining body weight alone, while others found diuretic dose did not predict weight loss. This is perhaps unsurprising, considering both the non-linear dose–response relationship and the diuretic resistance commonly seen in HF. A simple, continuous, quantitative measure for diuretic response—combining decongestive effect and diuretic dose—may help better unravel diuretic ‘resistance’ and open new avenues toward individualized, tailored treatment. The aim of this study was to define a clinically applicable measure for diuretic response, characterize the unresponsive patient, and determine the prognostic significance of diuretic response.

Methods

Study design and procedures

A total of 2033 adult patients with a history of HF were enrolled in the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial, a multicentre, randomized, double-blind, placebo-controlled trial with neutral results. Study design and main results have been published previously.

The trial was conducted in accordance with the Declaration of Helsinki and approved by all local Ethics Committees. All the patients provided written informed consent.

Heart failure signs and symptoms, serum creatinine, and blood urea nitrogen (BUN) were assessed daily until discharge or Day 6, and on Days 7 and 14. Other laboratory values were measured at least at baseline and Days 2, 7, and 14. Body weight was recorded from baseline through Day 4. Estimated glomerular filtration rate (eGFR) was calculated using the simplified modification of diet in renal disease equation. Total diuretic dose was defined as the i.v. plus 0.5 oral dose from randomization through Day 3, to correct for biological availability.

Study population

Of the 2033 included patients, subjects with missing data for diuretic response (n = 278), >20 kg weight loss (n = 3), or who underwent dialysis through Day 4 (n = 7) were excluded from analysis, resulting in a primary study population of 1745 patients.

Measuring diuretic response

We propose a quantitative measure for diuretic response: weight change on Day 4 per 40 mg of furosemide administered on Days 1–3 (equivalent doses: bumetanide: 1 mg, torsemide: 20 mg). As diuretic resistance develops over time, weight change on Day 4 and loop diuretics administered on Days 1–3 were selected to allow time for greater differentiation in responsiveness and for tailoring of diuretic doses to clinical response. Our proposed measure for diuretic response—in effect an indexed weight change variable—was chosen in part based on available data. Sensitivity analyses were performed, examining alternative combinations of weight loss (a surrogate for decongestion in the absence of data on diuresis) and diuretic dose and administration routes—comparing response on Days 2, 3, and 4, changes in responsiveness over time, and definitions using only i.v. diuretics, within the full population and the placebo group. As reduced diuretic responsiveness in AHF is primarily a concern in patients with manifest volume overload, we performed sensitivity analyses in a subset of patients with objective signs of congestion—any oedema and any rates at baseline (n = 1368)—and in the congested subset excluding patients receiving inotropes or vasodilators on Days 1–4 (n = 1192).

Endpoints

The primary endpoint was a trichotomous outcome of treatment success (marked or moderate dyspnoea improvement at 24 and 48 h), no change, or treatment failure. Secondary endpoints were 180-day mortality, 60-day HF rehospitalization, and 60-day death or renal or cardiovascular rehospitalization.

Statistical analysis

Considering the design of PROTECT, analyses were performed in the intention-to-treat population, correcting for study treatment. Continuous variables are summarized as means ± SD or median (inter-quartile range) as appropriate. Student’s t-test or ANOVA (normal distribution) and Wilcoxon or Kruskal–Wallis (skewed distribution) tests were used for group comparisons. Linear trends across categories were tested using general linear models for continuous covariates with polynomial contrasts, and non-parametric tests for trend for categorical variables. No imputations were performed.

Multivariable regression models were constructed via backward elimination and validated using bootstrap re-sampling (Supplementary material online, Methods). Kaplan–Meier survival estimates and Cox proportional hazards models were used to examine associations with endpoints. Harrell’s C-index (higher is better), Akaike’s Information Criterion (AIC, lower is better), and continuous net reclassification improvement (NRI) were used to evaluate differences between models including diuretic response vs. individual components (Supplementary material online, Methods). Tests were two-tailed, and an unadjusted P-value of <0.05 was considered statistically significant. All analyses were performed using R: A Language and Environment for Statistical Computing, version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and identifiers of diuretic response

Baseline characteristics of the entire study population are presented in Supplementary material online, Table S1. Patients excluded from analysis had lower blood pressures and worse NYHA class, renal
# Table 1: Baseline characteristics per quintile of diuretic response

<table>
<thead>
<tr>
<th>Diuretic response (kg/40 mg furosemide)</th>
<th>Demographics</th>
<th>Medical history</th>
<th>Clinical profile</th>
<th>Prior medication use</th>
<th>Laboratory values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex (% male)</td>
<td>Beta-blockers [% (n)]</td>
<td>NYHA class [% (n)]</td>
<td>ACEI or ARB [% (n)]</td>
<td>Creatinine (mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>Potassium (mmol/L)</td>
<td>I–II</td>
<td>Beta-blockers [% (n)]</td>
<td>eGFR (mL/min/1.73 m²)</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²)</td>
<td>≥+ Orthopnoea [% (n)]</td>
<td>III</td>
<td>MRAs [% (n)]</td>
<td>Blood urea nitrogen (mg/dL)</td>
</tr>
<tr>
<td></td>
<td>LVEF (%)</td>
<td>≥+ NYHA class</td>
<td>≥+</td>
<td>ACEI or ARB [% (n)]</td>
<td>Sodium (mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Systolic BP (mmHg)</td>
<td>≥+ Clinical profile</td>
<td>ICD therapy [% (n)]</td>
<td>Beta-blockers [% (n)]</td>
<td>Potassium (mmol/L)</td>
</tr>
<tr>
<td></td>
<td>Heart rate (b.p.m.)</td>
<td>≥+ Prior medication use</td>
<td>CRT therapy [% (n)]</td>
<td>MRAs [% (n)]</td>
<td>Haemoglobin (g/dL)</td>
</tr>
<tr>
<td></td>
<td>Rolofylline [% (n)]</td>
<td>≥+ Laboratory values</td>
<td>Stroke [% (n)]</td>
<td>MRAs [% (n)]</td>
<td>Cholesterol (mmol/L)</td>
</tr>
<tr>
<td></td>
<td>PVD [% (n)]</td>
<td>≥+ Chronic obstructive pulmonary disease [% (n)]</td>
<td>Chronic obstructive pulmonary disease [% (n)]</td>
<td>MRAs [% (n)]</td>
<td>BNP (mg/dL)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diuretic response</th>
<th>−1.33 (−1.95 to 0.07) (n = 349)</th>
<th>−0.70 (−0.80 to −0.60) (n = 349)</th>
<th>−0.38 (−0.44 to −0.33) (n = 351)</th>
<th>−0.18 (−0.24 to −0.13) (n = 347)</th>
<th>0.00 (−0.04 to 0.18) (n = 349)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>66.2 (231)</td>
<td>70.1 ± 11.6</td>
<td>33.7 ± 11.7</td>
<td>128.6 ± 16.3</td>
<td>77.4 ± 11.8</td>
<td>0.631</td>
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<tr>
<td></td>
<td>67.9 (237)</td>
<td>69.5 ± 11.8</td>
<td>33.1 ± 11.3</td>
<td>121.6 ± 17.2</td>
<td>75 ± 11.7</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>63.5 (223)</td>
<td>28.6 ± 6.3</td>
<td>12.5 ± 12.5</td>
<td>125.6 ± 17.2</td>
<td>74.8 ± 10.9</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>71.8 (249)</td>
<td>28.9 ± 5.7</td>
<td>32.5 ± 12.5</td>
<td>121.6 ± 17.9</td>
<td>72.1 ± 11.3</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>66.2 (231)</td>
<td>28.7 ± 5.8</td>
<td>29.6 ± 13</td>
<td>120.9 ± 18</td>
<td>79.5 ± 15.3</td>
<td>0.001</td>
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<tr>
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<td>79.3 ± 15.2</td>
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</tr>
<tr>
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<td>51 (178)</td>
<td>66.2 (231)</td>
<td>51 (178)</td>
<td>66.2 (231)</td>
<td>0.002</td>
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<tr>
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<td>43.6 (152)</td>
<td>67.9 (237)</td>
<td>43.6 (152)</td>
<td>67.9 (237)</td>
<td>0.001</td>
</tr>
<tr>
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<td>44.4 (156)</td>
<td>63.5 (223)</td>
<td>44.4 (156)</td>
<td>63.5 (223)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>71.8 (249)</td>
<td>52.4 (182)</td>
<td>71.8 (249)</td>
<td>52.4 (182)</td>
<td>71.8 (249)</td>
<td>0.001</td>
</tr>
<tr>
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<td>69.8 ± 11.8</td>
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<td>0.037</td>
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<td>12.5 ± 12.5</td>
<td>12.5 ± 12.5</td>
<td>0.037</td>
</tr>
</tbody>
</table>

BMI, body mass index; LVEF, left ventricular ejection fraction; BP, blood pressure; JVP, jugular venous pressure; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PVD, peripheral vascular disease; NYHA, New York Heart Association; ICD, internal cardiac defibrillator; ACEI, angiotensin-converting enzyme inhibitor; ARB, aldosterone receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.
function, and outcomes (Supplementary material online, Tables S1– 2). Baseline characteristics per quintile of diuretic response are presented in Table 1.

The mean weight change on Day 4 was $-2.8 \pm 3.0$ kg. The median diuretic dose through Day 3 was 240 mg (140–400) and 1702 (97%) patients received furosemide. The median diuretic response was $-0.38$ ($-0.80$ to $-0.13$) kg/40 mg furosemide. Poor responders showed strong differences in baseline characteristics, including more frequent renal impairment, diabetes, and ischaemic heart disease, but less hypertension and atrial fibrillation (all $P < 0.05$). Trends were similar in the placebo group and the congested subgroups (Supplementary material online, Tables S3–5).

Predictors of diuretic response are presented in Table 2. Low systolic blood pressure, low serum potassium, high BUN, diabetes, and atherosclerotic disease were associated with poor diuretic response. Rolofylline treatment independently predicted good diuretic response (all $P < 0.05$). Patients on rolofylline showed a better diuretic response than those on placebo $[-0.39$ ($-0.82$ to $-0.14$) vs. $-0.38$ ($-0.75$ to $-0.13$) kg/40 mg furosemide, $P = 0.018$], despite excellent baseline matching (Supplementary material online, Table S6). This effect was driven by greater weight loss for rolofylline vs. placebo ($3.0 \pm 2.8$ vs. $2.6 \pm 2.9$ kg, $P = 0.019$) as diuretic doses through Day 3 were similar [240 (140–380) vs. 240 (140–412) mg, $P = \text{n.s.}$] There were no interactions between any of the predictors, patient characteristics, study treatment or renal function parameters (BUN, eGFR, or serum creatinine).

Clinical, mortality, and rehospitalization outcomes

Across quintiles, patients with a poor diuretic response had worse outcomes on all endpoints (Figure 1 and Table 3). Patterns for the placebo group alone and in patients with manifest signs of congestion (with and without inotrope use) were similar (Supplementary material online, Tables S7–9).

In Cox proportional hazards models, worse diuretic response was associated with poor outcome (all $P < 0.001$), and remained independently associated with a poor outcome even after multivariable adjustment (Tables 4 and 5, all $P < 0.05$). There were no interactions between diuretic response and renal function (BUN, eGFR, and serum creatinine), study treatment, left ventricular ejection fraction, or other patient characteristics. Similar patterns were seen in the placebo and congested subgroups (Supplementary material online, Table S10).

Figure 2 shows the adjusted Cox hazard function for diuretic response for the 180-day mortality endpoint, fitted using a penalized spline function. Unadjusted Kaplan–Meier survival estimates across quintiles showed consistent survival benefit for a better diuretic response (log-rank $P < 0.001$) (Figure 3).

Sensitivity analyses

Associations between responsiveness on Days 2 and 3 and measures using i.v. doses only were examined; all showed consistent, similar patterns in baseline characteristics and outcomes, with the chosen

### Table 2 Multivariable linear regression model, predictors of diuretic response

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>T-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Day 1 (per SD)</td>
<td>$-0.119$</td>
<td>$(-0.16$ to $-0.08$</td>
<td>$-6.059$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Systolic BP (per SD)</td>
<td>$-0.081$</td>
<td>$(-0.12$ to $-0.04$</td>
<td>$-4.178$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>$0.193$</td>
<td>$(0.12$ to $0.27$</td>
<td>$4.858$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>$0.087$</td>
<td>$(0.01$ to $0.16$</td>
<td>$2.192$</td>
<td>$0.029$</td>
</tr>
<tr>
<td>Past PCI</td>
<td>$0.102$</td>
<td>$(0.01$ to $0.19$</td>
<td>$2.267$</td>
<td>$0.024$</td>
</tr>
<tr>
<td>Past beta-blocker use</td>
<td>$0.118$</td>
<td>$(0.03$ to $0.21$</td>
<td>$2.603$</td>
<td>$0.009$</td>
</tr>
<tr>
<td>Log BUN (per SD)</td>
<td>$0.106$</td>
<td>$(0.07$ to $0.15$</td>
<td>$5.259$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Serum potassium (per SD)</td>
<td>$-0.104$</td>
<td>$(-0.14$ to $-0.07$</td>
<td>$-5.421$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Rolofylline treatment</td>
<td>$-0.122$</td>
<td>$(-0.2$ to $-0.04$</td>
<td>$-3.091$</td>
<td>$0.002$</td>
</tr>
<tr>
<td>Spironolactone use</td>
<td>$-0.125$</td>
<td>$(-0.2$ to $-0.05$</td>
<td>$-3.183$</td>
<td>$0.001$</td>
</tr>
<tr>
<td>Metozalone use</td>
<td>$0.212$</td>
<td>$(0.04$ to $0.38$</td>
<td>$2.464$</td>
<td>$0.014$</td>
</tr>
</tbody>
</table>

SD, standard deviation; BP, blood pressure; PCI, percutaneous coronary intervention; BUN, blood urea nitrogen.
<table>
<thead>
<tr>
<th>Diuretic response (kg/40 mg furosemide)</th>
<th>−1.33 (−1.95 to 0.07) (n = 349)</th>
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<th>−0.38 (−0.44 to −0.33) (n = 351)</th>
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<th>0.00 (−0.04 to 0.18) (n = 349)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change Day 1–4 (kg)</td>
<td>−5.7 ± 3</td>
<td>−3.9 ± 2</td>
<td>−2.8 ± 1.8</td>
<td>−2.1 ± 1.6</td>
<td>0.5 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total diuretic dose, Day 1 – 3 (mg)</td>
<td>130 (100–180)</td>
<td>200 (140–280)</td>
<td>240 (160–400)</td>
<td>380 (240–607.5)</td>
<td>330 (200–640)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thiazide diuretics during admission</td>
<td>15.2 (53)</td>
<td>18.3 (64)</td>
<td>16.8 (59)</td>
<td>23.6 (82)</td>
<td>21.2 (74)</td>
<td>0.009</td>
</tr>
<tr>
<td>Inotropes during admission [% (n)]</td>
<td>2 (7)</td>
<td>1.4 (5)</td>
<td>4 (14)</td>
<td>8.6 (30)</td>
<td>14.6 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inotropes or vasodilators during admission [% (n)]</td>
<td>13.8 (48)</td>
<td>12 (42)</td>
<td>14.8 (52)</td>
<td>19 (66)</td>
<td>21.8 (76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WRF, Day 7 [% (n)]</td>
<td>21.9 (75)</td>
<td>16 (54)</td>
<td>18.2 (62)</td>
<td>26.8 (90)</td>
<td>25.1 (84)</td>
<td>0.016</td>
</tr>
<tr>
<td>WRF, Day 14 [% (n)]</td>
<td>21.9 (75)</td>
<td>18.6 (63)</td>
<td>22 (75)</td>
<td>25 (84)</td>
<td>29.6 (99)</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment failure due to death [% (n)]</td>
<td>0.3 (1)</td>
<td>0.9 (3)</td>
<td>0.3 (1)</td>
<td>0.9 (3)</td>
<td>1.1 (4)</td>
<td>0.218</td>
</tr>
<tr>
<td>Treatment failure due to worsening Heart failure [% (n)]</td>
<td>3.4 (12)</td>
<td>4.9 (17)</td>
<td>5.7 (20)</td>
<td>14.1 (49)</td>
<td>18.3 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment failure due to WRF [% (n)]</td>
<td>11.4 (39)</td>
<td>8.9 (30)</td>
<td>10 (34)</td>
<td>14.1 (47)</td>
<td>16 (53)</td>
<td>0.011</td>
</tr>
<tr>
<td>Treatment failure due to HF rehospitalization [% (n)]</td>
<td>0.3 (1)</td>
<td>0 (0)</td>
<td>0.3 (1)</td>
<td>0.3 (1)</td>
<td>0.3 (1)</td>
<td>0.722</td>
</tr>
<tr>
<td>Haemoconcentration on Day 4 [% (n)]</td>
<td>65.8 (156)</td>
<td>66.4 (176)</td>
<td>61.6 (165)</td>
<td>55.7 (151)</td>
<td>47.1 (123)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>180-day mortality [% (n)]</td>
<td>8 (28)</td>
<td>12.6 (44)</td>
<td>14 (49)</td>
<td>21.9 (76)</td>
<td>24.9 (87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-day Heart failure rehospitalization [% (n)]</td>
<td>7.4 (26)</td>
<td>8.9 (31)</td>
<td>15.7 (55)</td>
<td>19 (66)</td>
<td>23.2 (81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-day death or renal or cardiovascular rehospitalization [% (n)]</td>
<td>15.8 (55)</td>
<td>19.2 (67)</td>
<td>27.9 (98)</td>
<td>35.2 (122)</td>
<td>38.4 (134)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unadjusted incidence rates are reported. WRF, worsening renal function; HF, heart failure. WRF ≥ 0.3 mg/dL creatinine increase from baseline.
definition presenting the largest effect size and smallest P-value in models (data not shown). Trends across quintiles of diuretic response were examined separately in patients receiving low vs. high dose furosemide (above and below the median dose of 240 mg on Days 1–3, i.e. an average of 80 mg furosemide per day), which showed improved diuretic response was consistently associated with similar differences in baseline characteristics (including low systolic blood pressure, worse renal function, diabetes, and atherosclerotic...
The incidence of 180-day mortality, 60-day heart failure rehospitalization and 60-day death or cardiovascular or renal rehospitalization was also consistently higher across quintiles in both groups (all $P$ for trend < 0.05). Patients on high vs. low diuretic doses did have worse 180-day and 60-day outcomes (unadjusted log-rank $P < 0.001$), though these differences did not persist after multivariable correction (covariates form Tables 4–5) in survival models (all $P = \text{n.s.}$).

Next, we examined the effect of changes in diuretic response over time. Patients were divided into three groups, based on whether they remained in the same quintile of diuretic response or were reclassified between Day 2 and Day 4. In univariable Cox models, corrected for baseline (Day 2) diuretic response, patients with stable vs. improving diuretic response did not show any statistically significant differences in 180-day mortality or the 60-day endpoints. Patients with worsening diuretic response, however, were more likely to meet all endpoints (all $P < 0.05$). After multivariable correction, this only held for the 60-day outcomes [corrected for covariates in Tables 4 and 5; 60-day HF rehospitalization: hazard ratio (HR) 1.48, 95% confidence interval (CI) 1.13–1.93, $P = 0.004$; 60-day death or renal or cardiovascular rehospitalization: HR: 1.49, 95% CI: 1.22–1.81, $P < 0.001$].

**Diuretic response vs. weight change and diuretic dose**

Analyses were performed to evaluate the added value of introducing diuretic response compared with its individual components (weight change and diuretic dose) as covariates in Cox proportional hazards models. In univariable models, diuretic response showed a greater effect size per SD than weight change and diuretic dose alone (Tables 4–5).

In multivariable 180-day mortality models, inclusion of diuretic response vs. its components showed similar performance, with a trend favouring diuretic response; in the full-study population, Harrell’s

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**Figure 2** Adjusted hazard ratio for 180-day mortality for diuretic response. Adjusted for model 3 covariates (Table 4). Legend: dark blue: hazard function, fitted using a penalized spline, light blue: 95% CI; grey: density plot.

**Figure 3** Survival per quintile of diuretic response. Unadjusted Kaplan–Meier survival curves.
C-index (higher is better) and AIC (lower is better)—measures for model performance and fit—were similar for both models (0.720 and 3409, respectively, for both), while the continuous NRI—a measure for reclassification improvement—slightly favoured diuretic response (0.01, 95% CI: −0.26–0.18). In patients with manifest congestion, diuretic response showed a slightly stronger trend towards an improved performance for Harrell’s C-index (0.717 vs. 0.712), AIC (2464 vs. 2468), and continuous NRI (0.08, 95% CI: −0.16–0.31). Similar patterns for diuretic response vs. the components were observed for 60-day death or renal or cardiovascular rehospitalization in the full population (Harrell’s C-index 0.650 vs. 0.647, AIC 6425 vs. 6432, continuous NRI 0.16, 95% CI: −0.06–0.28) and the congested subgroup (Harrell’s C-index 0.651 vs. 0.646, AIC 4643 vs. 4650 continuous NRI 0.23, 95% CI: −0.11–0.37).

Diuretic response showed a better performance than its components in 60-day heart failure rehospitalization models. In the full population, the diuretic response model outperformed diuretic dose and weight change individually (C-index 0.692 vs. 0.686; AIC 3537 vs. 3550; continuous NRI 0.29, 95% CI: 0.04–0.47). These effects were also present in patients with manifest congestion (C-index 0.681 vs. 0.672; AIC 2538 vs. 2554; continuous NRI 0.35, 95% CI: 0.01–0.47).

**Discussion**

We showed that poor diuretic response is associated with more advanced HF, renal impairment, diabetes, atherosclerotic disease, and in-hospital worsening HF, and independently predicts HF rehospitalization and mortality.

Current definitions of diuretic resistance are all similar—failure to diurese (or decongest) in response to escalating doses of diuretics. Diuretic absorption and efficacy is reduced in HF patients, and response is blunted further in AHF. Yet despite a solid pathophysiological understanding of the underlying mechanisms, data examining both diuretic dose and effects in HF populations are scarce. Most studies have focused on diuretic dosage and outcomes, while the prognostic significance of effects on body weight or urinary output—as proxies for volume status—has not been examined prospectively in HF. Post hoc analyses from the DOSE trial indicate weight loss is associated with a better outcome, though Hasselblad et al. found no association between diuretic dose and weight loss in a post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial. Van der Meer et al. have shown that haemoconcentration—a marker for intravascular decongestion—correlates with weight loss, lower diuretic doses, and lower mortality. In a recent study, Testani et al. retrospectively investigated what they termed diuretic efficiency in two AHF populations—net fluid output indexed to diuretic dose, and dichotomized into high and low efficiency. Similarly to our analyses, they found an independent prognostic effect on survival.

The proposed diuretic response metric—weight loss indexed to diuretic dose—reflects a ‘dose–response’ effect that can be understood intuitively. On a conceptual level, it can limit the bias intrinsic to each individual component; weight loss, for example, is not merely a marker for diuretic responsiveness, which may in part explain the inconsistent associations between weight loss and outcomes in past studies—better in DOSE and PROTECT, no differences in ESCAPE. A sicker patient may have accumulated more weight, and thus have the potential to lose more weight, but correction for diuretic dose should allow for ‘correct’ classification. Similarly, diuretic dose reflects a variety of patient and physician-related factors, so examining dose without its effect can lead to bias. While diuretic response does not capture an individual patient’s (non-linear) dose–response curve, it does allow identification of patients with blunted response. This is supported by the observations that haemoconcentration was more common in good responders, that thiazides—often used to address loop diuretic resistance—were prescribed more often to less responsive patients, and that metozalone use independently predicted a poor diuretic response.

The value on Day 4 was chosen to reflect the fact resistance to diuretics is a dynamic process, not a static one, as outlined below. Sensitivity analyses showed consistent patterns in baseline characteristics and outcomes irrespective of high vs. low diuretic dose. We did note that patients who developed worsening diuretic response over time had a greater risk of rehospitalization outcomes in particular; while the initial diuretic response after 1 day of treatment is already predictive of outcome, responsiveness at a later time provides more accurate prognostic information. From a clinical perspective, examination of diuretic response is best suited for patients with manifest volume overload rather than those with redistribution HF alone. The findings in the congested group bear this out, with higher HRs and lower P-values on all endpoints in multivariable models and a slightly better model fit. Based on various measures for model performance (Harrell’s C-index, AIC, and continuous NRI), diuretic response essentially provided the same prognostic information as the component variables in our population, even outperforming them for the prediction of HF rehospitalization. We believe this equivalence may be accepted, considering diuretic response provides a ‘cleaner’ signal for the matter under investigation. Further research will be necessary to confirm this.

**Determinants of diuretic response**

In our study, patients with a poor diuretic response showed signs of more advanced HF and worse renal function. Comorbid conditions underlying both HF and renal impairment—including diabetes, atherosclerosis, and low haemoglobin levels—were also more common. The complex underlying physiology is reflected in the strong overlap with these and other clinical characteristics. Most were not independently predictive, suggesting strong collinearity with many of these variables; diuretic response may therefore merely reflect the confluence of these factors. The recent study by Testani et al. examining a fluid output-based diuretic efficiency metric showed some similarities to our results; diabetes, elevated BUN levels and a reduced eGFR were more common in poor responders. However, these analyses were limited in part by incomplete data on diuretic doses, examination of a dichotomized rather than continuous metric, and a lack of analyses examining independent predictors of efficiency, making meaningful comparisons difficult.
Diuretics exert their effects via the kidney, relying on secretion and to a minor degree on glomerular filtration to achieve therapeutic concentrations in the tubule. Diabetes and atherosclerosis can both cause glomerular damage and glomerulosclerosis, affecting GFR, while the Renin-Angiotensin system activation and inflammation common to both conditions likely also contributes to a reduced response.\(^35\) - \(^37\) Haemodynamic impairment in HF causes congestion and reduced renal perfusion, while feedback mechanisms designed to preserve renal blood flow, GFR, and sodium levels lead to WRF and further congestion.\(^35\) In untreated HF, short-term decongestion with diuretics can acutely lower certain neurohormone levels.\(^38\) However, chronic diuretic use may cause structural changes in the tubular epithelium, resulting in sodium retention, worsening congestion, and neurohormonal activation, necessitating higher diuretic doses, with the potential for more renal damage.\(^17\) As a result of these effects, patients with AHF display a steeper dose—response curve than healthy controls or HF patients in a compensated state.\(^21\)

An intriguing finding in our study was the relatively small difference in renal function between good and poor responders—a difference of only 9 mL/min/1.73 m\(^2\) in estimated GFR, 0.2 mg/dL in creatinine, and 7 mg/dL in BUN between bottom and top quintiles of diuretic response. Except BUN, none of these renal function parameters independently predicted diuretic response outright, and there were no interactions with diuretic response in survival models. This is in contrast with the traditional view of diuretic resistance, in which renal function is the primary determinant. The explanation may lie in the limitations of creatinine (and creatinine-based GFR estimates) as a marker for renal function, as it provides no direct information about tubular function or injury. Novel tubular or combined (urinary) markers, such as cystatin C, NGAL, NAG, or KIM-1, may provide better insights into diuretic resistance phenomena.\(^39\) Another interesting finding was the relatively high incidence of WRF in the best quintile of diuretic response, despite better long-term outcomes. This is consistent with findings by Metra et al.\(^40\) indicating that effective decongestion is more important than (transient) WRF.

Interestingly, rololofylline independently predicted diuretic response. As this effect was driven by weight loss, not diuretic dose, it suggests either a direct diuretic effect, or potentiation of diuretics via improved haemodynamics, consistent with findings from earlier trials.\(^23\) - \(^25\) Metra et al.\(^25\) previously noted an association between improvement in dyspnoea and rololofylline, though it should be noted that overall, rololofylline’s effects on clinical outcomes were neutral, which, combined with safety concerns,\(^42\) resulted in discontinuation of the development programme. In PROTECT, patients received diuretics based on clinical assessment, and those with a poor diuretic response received higher doses and had worse outcomes. Although rololofylline did not prevent WRF,\(^43\) there is still a strong need for adjuvant therapies that improve diuresis without compromising renal function.

**Clinical perspectives**

Loop diuretic therapy remains the cornerstone of decongestive treatment in AHF, despite a lack of convincing evidence or consensus on optimal dosage,\(^45\) and mixed evidence on survival impact.\(^5\) - \(^8\), \(^46\), \(^47\) Alternative decongestive treatments, such as ultrafiltration, may be effective, but remain unproven.\(^26\), \(^48\), \(^49\)

We feel the simple measure of weight change per unit of diuretic provides better insight into patient response to therapy than examining weight loss or diuretic dose independently; diuretic dose provides insufficient information, as higher doses with adequate weight loss will be misclassified, while weight loss alone does not reflect the degree of resistance. Once validated and investigated further, diuretic response could be used in clinical research settings to help identify patients who might benefit from alternative or adjuvant decongestive therapies.

**Limitations**

This study is a post hoc analysis of a randomized clinical trial, with all attendant limitations. The excluded subpopulation differed significantly from the analysed group, with higher incidences of multiple co-morbidities and worse outcomes. Multivariable modelling alone may not be sufficient to account for the differences, and our findings should be considered hypothesis-generating. Furthermore, available data did not allow extensive investigation of differences in diuretic responsiveness in HF with reduced vs. preserved ejection fraction. The true degree of volume overload in the congested subgroup also cannot be ascertained with certainty, as both oedema and rales may have other causes or be due to redistribution. Additionally, diuretic response as defined in this study is a linear relationship, while the dose—response relationship in vivo is S-shaped, and dependent on individual patient characteristics.\(^21\) making it difficult to model accurately post hoc.

Given the focus on diuretic response, data on urinary output and fractional sodium excretion would be preferred, although body weight is easily measured and recommended for monitoring volume status.\(^31\) The results from Testani et al.\(^34\) indicate indexed net fluid output contains similar prognostic information, and validation and comparison of both metrics in the same populations would be valuable. The study protocol did not specify how to assess weight, which could affect data quality. Serial measurements of these variables should be considered for all future AHF trials.

**Conclusion**

In this retrospective study, we present a novel measure for diuretic response in acute HF—weight loss indexed to diuretic use. This metric yielded at least equivalent prognostic information compared with its component parts, while providing a more easily interpreted signal for patient response to diuretics. Further research will be needed to confirm our findings. In this study, patients with a poor diuretic response had more advanced HF, worse renal function and were more likely to have a history of atherosclerosis and diabetes. Poor diuretic response was strongly and independently associated with less dyspnoea relief and an increased incidence of in-hospital worsening HF, as well as post-discharge mortality and rehospitalization for HF. Early identification of subjects with impaired diuretic response may open doors towards patient-tailored treatment strategies.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Conflict of interest:** M.A.E.V, K.D., M.F., and H.L.H. have nothing to disclose. A.A.V. has received speaker and consultancy fees from Merck and NovaCardia. D.J.V.V. has received Board Membership
fees from Amgen, BG Medicine, Biocontrol, Johnson and Johnson, Novartis, Sorbent, and Vifor. B.M.M. has received consulting fees from NovaCardia, sponsors of the study, and from Merck, that purchased the rights to rolofylline after the completion of the PROTECT pilot study. C.M.O.C. is a consultant to Merck. M.M. has received honoraria and reimbursements from NovaCardia, sponsors of the study, and from Merck, that purchased the rights to rolofylline after completion of the PROTECT pilot study. P.P. has received honoraria after completion of the PROTECT pilot study.

References


