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RESEARCH ARTICLE

Worsening renal function in acute heart failure in the context of diuretic response

Johanna E. Emmens[1†], Jozine M. ter Maaten[1†], Yuya Matsue[2,3], Sylwia M. Figarska[1], Iziah E. Sama[1], Gad Cotter[4], John G.F. Cleland[5,6], Beth A. Davison[4], G. Michael Felker[7,8], Michael M. Givertz[9], Barry Greenberg[10], Peter S. Pang[11], Thomas Severin[12], Claudio Gimpelewicz[12], Marco Metra[13], Adriaan A. Voors[1]*, and John R. Teerlink[14]

[1]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; [3]Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; [4]Momentum Research and Inserm U942 MASCOT, Paris, France; [5]Robertson Centre for Biostatistics and Clinical Trials, Institute of Health and Well-Being, University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK; [6]National Heart & Lung Institute, Imperial College, London, UK; [7]Division of Cardiology, Department of Medicine, Duke University, Durham, NC, USA; [8]Duke Clinical Research Institute, Durham, NC, USA; [9]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; [10]University of California San Diego Health, Sulpizio Cardiovascular Institute, La Jolla, CA, USA; [11]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [12]Novartis Pharma, Basel, Switzerland; [13]Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; and [14]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California, San Francisco, CA, USA

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Background For patients with acute heart failure (AHF), substantial diuresis after administration of loop diuretics is generally associated with better clinical outcomes but may cause creatinine to rise, suggesting renal function decline. We investigated the interaction between diuretic response and worsening renal function (WRF) on clinical outcomes in patients with AHF.

Methods and results In two AHF cohorts (PROTECT, $n = 1698$ and RELAX-AHF-2, $n = 5586$ in current analysis), the prognostic impact of WRF (creatinine ≥0.3 mg/dl increase baseline—day 4; sensitivity analyses incorporated baseline renal function) by diuretic response (kg weight loss/40 mg furosemide equivalent baseline—day 4) was investigated with regard to (cardiovascular) death or cardiovascular/renal hospitalization using subpopulation treatment effect pattern plots (STEPP) and survival analyses. WRF occurred in 286 (16.8%) and 1031 (18.5%) patients in PROTECT and RELAX-AHF-2, respectively. Patients with WRF had higher left ventricular ejection fraction and lower estimated glomerular filtration rate at baseline ($p < 0.05$), and received higher doses of loop diuretics and had a worse diuretic response ($p < 0.001$). In patients with a poor diuretic response (≤0.35 kg weight loss/40 mg furosemide equivalent as identified by STEPP), WRF was associated with higher risk of (cardiovascular) death or cardiovascular/renal hospitalization ($p < 0.001$ both cohorts), but this was not the case for patients with a good diuretic response ($p = 0.900$ both cohorts).

Conclusion In two large cohorts of patients with AHF, WRF in the first 4 days was not associated with worse outcomes when patients had a good diuretic response. The occurrence of WRF in patients with AHF should therefore be considered in the context of diuretic response.

Keywords Acute heart failure • Worsening renal function • Diuretic response • Decongestion • Outcomes

*Corresponding author. Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ, Groningen, The Netherlands. Tel: +31 50 3616161, Fax: +31 50 3618062, Email: a.a.voors@umcg.nl

[†]Shared first author.

Introduction

Worsening renal function (WRF), a term used to describe dynamic changes (decline) of renal function, occurs in 20% to 30% of patients with acute heart failure (AHF) and is associated with greater morbidity and mortality.[1,2] Haemodynamic derangements in AHF often lead to reduced renal perfusion and increased central venous pressure, so patients with WRF might often have more severe heart failure. However, WRF may also be explained by other factors. For example, WRF can be caused by the initiation or up-titration of renin–angiotensin–aldosterone system inhibitors, which is generally associated with improved clinical outcomes.[3–6] Also, WRF may reflect tubuloglomerular feedback due to greater diuresis and natriuresis, a physiological response to salt loss leading to renal afferent vasoconstriction, thereby reducing glomerular perfusion pressure and filtration. Such a physiological renal response to increased diuresis that is associated with WRF might not necessarily be related to worse clinical outcomes. In fact, several studies have shown that haemoconcentration, consistent with greater diuresis, was associated with better clinical outcomes despite being strongly associated with WRF.[7–9] In addition, a recent study showed that several markers of decongestion modified the association between estimated glomerular filtration rate (eGFR) decline and adverse outcome.[10] Finally, we and others have shown that a good diuretic response is associated with better clinical outcomes.[11–16] However, it is currently unclear if patients with a good diuretic response still have favourable outcomes if it is associated with WRF. Furthermore, it is unclear how to recognize when WRF is not associated with a poor prognosis. We investigated the hypothesis that the association between WRF and clinical outcomes depends on diuretic response in two large cohorts of patients with AHF.

Methods

Patient populations

The current analysis included patient-level data from the Relaxin in Acute Heart Failure 2 (RELAX-AHF-2) and the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trials.

In brief, RELAX-AHF-2 was a multicentre, randomized, double-blind, placebo-controlled trial investigating the effects of early administration of serelaxin added to standard care on cardiovascular (CV) mortality and worsening heart failure in patients admitted for AHF.[17,18] Inclusion criteria included, among others, an eGFR of 25–75 ml/min/1.73 m^2, brain natriuretic peptide (BNP) ≥500 pg/ml or N-terminal pro brain natriuretic peptide (NT-proBNP) ≥2000 pg/ml (for patients ≥75 years of age or with atrial fibrillation at the time of randomization BNP ≥750 pg/ml or NT-proBNP ≥3000 pg/ml), and the expectation that the patient would receive intravenous therapy for at least 48 h. The overall results of the trial were neutral. For the current analysis, 5586 out of 6545 patients with available creatinine measurements at baseline and day 4 were included.

PROTECT was a multicentre trial investigating the effects of rolofylline in patients with AHF (n = 2033) with mild to moderate renal function impairment (estimated creatinine clearance of 20–80 ml/min).[19,20] Inclusion criteria included, among others, BNP ≥500 pg/ml or NT-proBNP ≥2000 pg/ml and ongoing intravenous loop diuretic therapy. The overall results were neutral. For the current analysis, 1698 patients with available creatinine measurements at baseline and day 4 were included. Characteristics of patients excluded from the current analysis are shown in online supplementary *Table S1*.

Definition of worsening renal function

Worsening renal function was defined as a creatinine increase ≥0.3 mg/dl between baseline and day 4.[21,22] This was chosen to allow time for better differentiation in responsiveness to diuretics and for tailoring diuretic doses by the clinicians to clinical response. Urinary output was not available. Sensitivity analyses were conducted with WRF defined as (i) a combined increase of ≥0.3 mg/dl and ≥25% increase in creatinine and (ii) ≥30% eGFR decrease between baseline and day 4 to also incorporate correction for baseline creatinine/eGFR.[21,22] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Diuretic response and other decongestion variables

Total diuretic dose was defined as total intravenous dose of loop diuretics plus 0.5 x total oral dose (to adjust for biological availability[16,23]) administered between baseline and day 4. Diuretic response was then defined as change in body weight between baseline and day 4 indexed per dose of 40 mg furosemide that was administered during that time period (equivalent doses: 1 mg bumetanide, 20 mg torsemide, and 50 mg ethacrynic acid).[11,12,16,23] Sensitivity analyses were also performed for crude weight change between baseline and day 4 not indexed per diuretic dose and diuretic response between baseline and day 3, calculated in the same manner as described above but until day 3, for all definitions of WRF. Finally, sensitivity analyses were conducted with percentage change in haemoglobin concentration and change in estimated plasma volume (ΔePV) between baseline and day 4, and percentage change in NT-proBNP concentration between baseline and day 7 for RELAX-AHF-2 and percentage change in BNP concentration between baseline and day 5 for PROTECT. ΔePV was calculated using the Strauss formula[24]:

$$\Delta ePV = 100\times \frac{\text{haemoglobin (baseline)}}{\text{haemoglobin (day 4)}} \times \frac{1-\text{haematocrit (day 4)}}{1-\text{haematocrit (baseline)}} - 100$$

In this formula, haematocrit was expressed as fractions.

Endpoints

The endpoints of focus were the combined endpoints of both cohorts; 180-day CV death or heart/renal failure hospitalization in RELAX-AHF-2 and 60-day death from any cause or CV or renal hospitalization in PROTECT.

Statistical analysis

Descriptive statistics were used to examine differences in clinical variables, laboratory values, and decongestion variables between patients

who experienced WRF and those who did not. Data are presented as medians (with 1st and 3rd quartiles) and as frequencies (percentage) for categorical variables. Continuous normally distributed variables were tested with the Student's independent *t*-test, skewed variables with the Mann–Whitney U test, and categorical variables with chi-squared tests.

Values for measures of decongestion at which presence of WRF conferred equal or better survival relative to absence of WRF were identified using subpopulation treatment effect pattern plot (STEPP) analysis. STEPP is a graphical method that allows visual exploration of differential treatment effect across the continuum of a variable, in the case of this study for example diuretic response.[25,26] STEPP creates overlapping subpopulations which makes it an accurate, robust, and reliable statistical tool to explore differences amongst subgroups of a continuous variable. This greatly increases the precision of the estimated effect, improves statistical power to detect heterogeneity, and decreases the false-negative discovery rate. In PROTECT, the size of each subgroup (r2) was set to 350 with 280 patients in common among consecutive subpopulations (r1). In RELAX-AHF-2, r2 was set to 900 and r1 to 720. This resulted in the removal of 20% of patients and addition of 20% new patients between consecutive subpopulations for both cohorts. This process ends when all patients are included in at least one subpopulation. The depicted STEPP plots show the risk of presence of WRF against increasing medians of each subpopulation. Statistical significance was evaluated by performing permutations tests, which was set at 2500. To conclude that there is a significant interaction, plots should show a divergent and consistent pattern along the continuum of the biomarker.

In addition, interaction plots were constructed using the simPH package with 1000 simulations. Statistical significance of interaction was estimated by Cox proportional hazard analysis using an interaction term, with inclusion of treatment arm in the model. Cox proportional hazard analysis was also conducted to investigate the relationships of groups stratified by WRF/no WRF and good/poor diuretic response with the combined endpoints with adjustment for previously established prediction models for both cohorts.[27,28] Those included age, sex, baseline creatinine, study treatment, pulmonary disease, atrial fibrillation/flutter, blood urea nitrogen, cerebrovascular accident, composite of NT-proBNP or BNP z-score, depression, oedema, grouped geographical region, haemoglobin, history of diabetes mellitus, peripheral arterial occlusive disease, prior heart failure hospitalization, respiratory rate, sodium, and systolic blood pressure for RELAX-AHF-2, and age, sex, baseline creatinine, treatment allocation, previous heart failure hospitalization, peripheral oedema, systolic blood pressure, sodium, urea, creatinine, and albumin for PROTECT. Kaplan–Meier plots were constructed using the survminer package. Additional packages that were used in analysis included the packages foreign, ggplot2, nephro, psych, and survival. A two-tailed *p*-value <0.05 was considered statistically significant. Statistical analyses were performed with RStudio (version 1.3.1073, R Foundation for Statistical Computing, Vienna, Austria), www.r-project.org.

Results

Baseline characteristics

About half of patients in the current study subset from RELAX-AHF-2 had heart failure with reduced ejection fraction (HFrEF) [median left ventricular ejection fraction (LVEF) 38% (29%–50%) whereas the median LVEF in PROTECT was 30% (23%–40%)] (*Table 1*). In RELAX-AHF-2, median eGFR was 50 (38–62) ml/min/1.73 m^2 whereas in PROTECT this was 46 (34–62) ml/min/1.73 m^2, and 2307 (41.3%) patients were in New York Heart Association (NYHA) class III/IV in RELAX-AHF-2, which was the case for 1338 (78.8%) in PROTECT. WRF occurred in 1031 (18.5%) of patients in RELAX-AHF-2 and 286 (16.8%) of patients in PROTECT. Patients who developed WRF had, among others, higher LVEF, higher systolic blood pressure, and lower eGFR at baseline (all $p < 0.05$). Patients who developed WRF also required higher doses of loop diuretics and had a worse diuretic response between baseline and day 4 (all $p < 0.001$).

Subpopulation treatment effect pattern plots

We found a divergent and consistent STEPP pattern across the continuum of diuretic response with regard to the combined endpoints of both cohorts (180-day CV death or heart/renal failure hospitalization in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalization in PROTECT), displayed in *Figure 1*. In RELAX-AHF-2, this interaction was statistically significant (supremum $p = 0.030$). STEPP demonstrated a crossover in relative risk of WRF for the combined endpoint that was considered as clinically relevant. According to STEPP of RELAX-AHF-2, a threshold of >0.35 kg weight loss/40 mg furosemide was estimated and dichotomized into 'good diuretic response' and 'poor diuretic response.' In PROTECT, 868 (53.4%) patients had a good diuretic response, in RELAX-AHF-2 this was the case for 3053 (56.9%). Sensitivity analyses were conducted for other definitions of WRF, which included correction for baseline renal function, and showed consistent results (online supplementary *Figures S1* and *S2*). Interaction plots, depicted in online supplementary *Figure S3*, also showed similar trends.

STEPP analyses for diuretic response between baseline and day 3 did not show statistically significant interactions (data not shown).

Online supplementary *Figures S4–S6* show sensitivity analyses for STEPP for crude weight change not indexed per diuretic dose. Although some statistically significant interactions between weight change and the prognostic value of WRF were found, these were smaller and less consistent compared with diuretic response.

Online supplementary *Figures S7–S9* show sensitivity analyses for STEPP for percentage change of haemoglobin concentration and ΔePV between baseline and day 4, and percentage BNP (PROTECT)/NT-proBNP (RELAX-AHF-2) change between baseline and day 7 and day 5, respectively. These did not show a consistent divergent pattern across their continuum.

Worsening renal function is associated with worse outcome, but not in the context of a good diuretic response

In *Figures 2A* and *3A*, for RELAX-AHF-2 and PROTECT, respectively, Kaplan–Meier curves are shown for WRF development vs.

Table 1 Baseline characteristics of PROTECT and RELAX-AHF-2 according to development of worsening renal function

	RELAX-AHF-2 ($n = 5586$)			PROTECT ($n = 1698$)		
	No WRF ($n = 4555$)	WRF ($n = 1031$)	*p*-value	No WRF ($n = 1412$)	WRF ($n = 286$)	*p*-value
Age (years)	74 (66 to 81)	76 (68 to 83)	**<0.001**	72 (62 to 78)	73 (64 to 78)	0.122
Female sex, *n* (%)	1821 (40.0)	459 (44.5)	**0.008**	481 (34.1)	82 (28.7)	0.090
Race (white), *n* (%)	4498 (94.4)	967 (93.8)	0.767	1354 (95.9)	274 (95.8)	1
BMI (kg/m^2)	29 (25 to 33)	29 (26 to 34)	**0.043**	28 (24 to 32)	27 (24 to 32)	0.884
NYHA class III/IV, *n* (%)[a]	1911 (57.5)	396 (50.6)	0.399	1119 (83.4)	219 (79.9)	0.290
Systolic blood pressure (mmHg)	138 (130 to 149)	141 (132 to 155)	**<0.001**	123 (110 to 140)	130 (115 to 140)	**<0.001**
Diastolic blood pressure (mmHg)	80 (71 to 89)	79 (70 to 88)	**0.002**	74 (66 to 80)	75 (69 to 85)	**0.022**
Heart rate (bpm)	80 (70 to 92)	79 (69 to 90)	**0.005**	80 (70 to 90)	76 (69 to 89)	0.055
LVEF (%)	40 (30 to 50)	40 (30 to 52)	**0.001**	30 (22 to 40)	31 (25 to 45)	**0.032**
<40%	2293 (53.2)	433 (44.4)	**<0.001**	489 (73.3)	95 (66.9)	0.148
≥50%	1052 (24.4)	310 (31.8)	**<0.001**	76 (11.4)	28 (19.7)	**0.011**
Heart failure aetiology, *n* (%)			0.231			
Ischaemic	1805 (53.3)	416 (55.8)				
Non-ischaemic	1579 (46.7)	329 (44.2)				
History of ischaemic heart disease, *n* (%)				983 (69.8)	204 (68.9)	0.649
Previous hospitalization for heart failure, *n* (%)[b]	2324 (54.5)	497 (52.4)	0.242	706 (50.0)	148 (51.7)	0.635
No. of hospitalizations for heart failure within previous year, *n* (%)			0.882			0.578
≥3 hospitalizations	210 (9.2)	45 (9.2)		134 (19.0)	32 (21.8)	
1–2 hospitalizations	1417 (61.7)	297 (60.6)		569 (80.6)	115 (78.2)	
No hospitalizations	668 (29.1)	148 (30.2)				
Length of hospital stay (days)	7 (6 to 10)	8 (6 to 11)	**<0.001**	8 (6 to 14)	8 (7 to 14)	0.616
ACEi/ARB, *n* (%)	2960 (68.9)	704 (70.5)	0.345	1073 (76.0)	211 (73.8)	0.471
Beta-blocker, *n* (%)	3230 (75.2)	722 (72.3)	0.064	1074 (76.1)	215 (75.2)	**0.045**
MRA, *n* (%)	1387 (32.3)	243 (24.3)	**<0.001**	683 (64.2)	165 (57.7)	**0.045**
Haematocrit (%)	39 (35 to 43)	37 (33 to 41)	**<0.001**	40 (36 to 45)	39 (36 to 42)	**<0.001**
Haemoglobin (mmol/L)	7.9 (7.1 to 8.8)	7.6 (6.8 to 8.4)	**<0.001**	7.9 (7.1 to 8.8)	7.6 (6.9 to 8.4)	**0.003**
Sodium (mmol/L)	140 (137 to 142)	140 (138 to 142)	0.854	140 (137 to 142)	140 (138 to 143)	0.137
Potassium (mmol/L)	4.3 (3.9 to 4.7)	4.4 (4.0 to 4.8)	**<0.001**	4.2 (3.9 to 4.6)	4.3 (3.9 to 4.7)	0.245
Creatinine (mg/dl)	1.3 (1.1 to 1.5)	1.3 (1.1 to 1.7)	**<0.001**	1.3 (1.1 to 1.7)	1.5 (1.2 to 1.9)	**<0.001**
eGFR (ml/min/1.73 m^2)	51 (39 to 62)	46 (36 to 58)	**<0.001**	48 (35 to 63)	42 (33 to 55)	**<0.001**
BUN (mg/dl)	24 (19 to 32)	26 (20 to 34)	**<0.001**	29 (22 to 40)	31 (24 to 45)	**0.009**
ALAT (U/L)	23 (16 to 37)	21 (14 to 32)	**<0.001**	21 (15 to 32)	20 (15 to 28)	0.093
ASAT (U/L)	27 (20 to 36)	24 (19 to 34)	**<0.001**	25 (19 to 33)	23 (19 to 33)	0.085
NT-proBNP (ng/L)	5048 (2926 to 9280)	5459 (2810 to 9871)	0.513			
BNP (ng/L)				467 (258 to 830)	397 (261 to 709)	0.151
Weight change baseline—day 4 (kg)	−2.8 (−5.0 to −1.20)	−2.5 (−4.4 to −1.0)	**0.002**	−2.5 (−4.3 to −1.0)	−2.1 (−4.0 to −1.0)	0.063
Total diuretic dose baseline—day 4 in mg furosemide equivalent	230 (160 to 330)	260 (190 to 380)	**<0.001**	230 (140 to 365)	260 (160 to 508)	**<0.001**
Diuretic response baseline—day 4 (kg/40 mg furosemide equivalent)	−0.44 (−0.86 to −0.18)	−0.36 (−0.68 to −0.13)	**<0.001**	−0.40 (−0.83 to −0.15)	−0.30 (−0.67 to −0.11)	**<0.001**
% change in haemoglobin baseline—day 4	−0.8 (−5.8 to 4.8)	0.0 (−5.7 to 5.9)	0.194	1.9 (−2.9 to 7.0)	2.7 (−2.0 to 8.9)	**0.043**
ΔePV baseline—day 4	1.2 (−7.4 to 10.5)	0.6 (−8.4 to 10.0)	0.302	−3.2 (−11.8 to 5.1)	−4.9 (13.3 to 3.6)	0.121
% change (NT-pro)BNP baseline—day 5 or day 7[c]	−49.9 (−72.4 to −20.1)	−56.0 (−77.3 to −31.5)	0.088	−39.3 (−59.4 to −12.0)	−36.7 (−62.1 to −5.1)	0.410

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ΔePV, delta estimated plasma volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; WRF, worsening renal function.

[a]Available in 3438 patients in RELAX-AHF-2 and 1615 in PROTECT.

[b]Ever in RELAX-AHF-2, in the past year for PROTECT.

[c]NT-proBNP change between baseline and day 5 in RELAX-AHF-2, BNP change between baseline and day 7 in PROTECT.

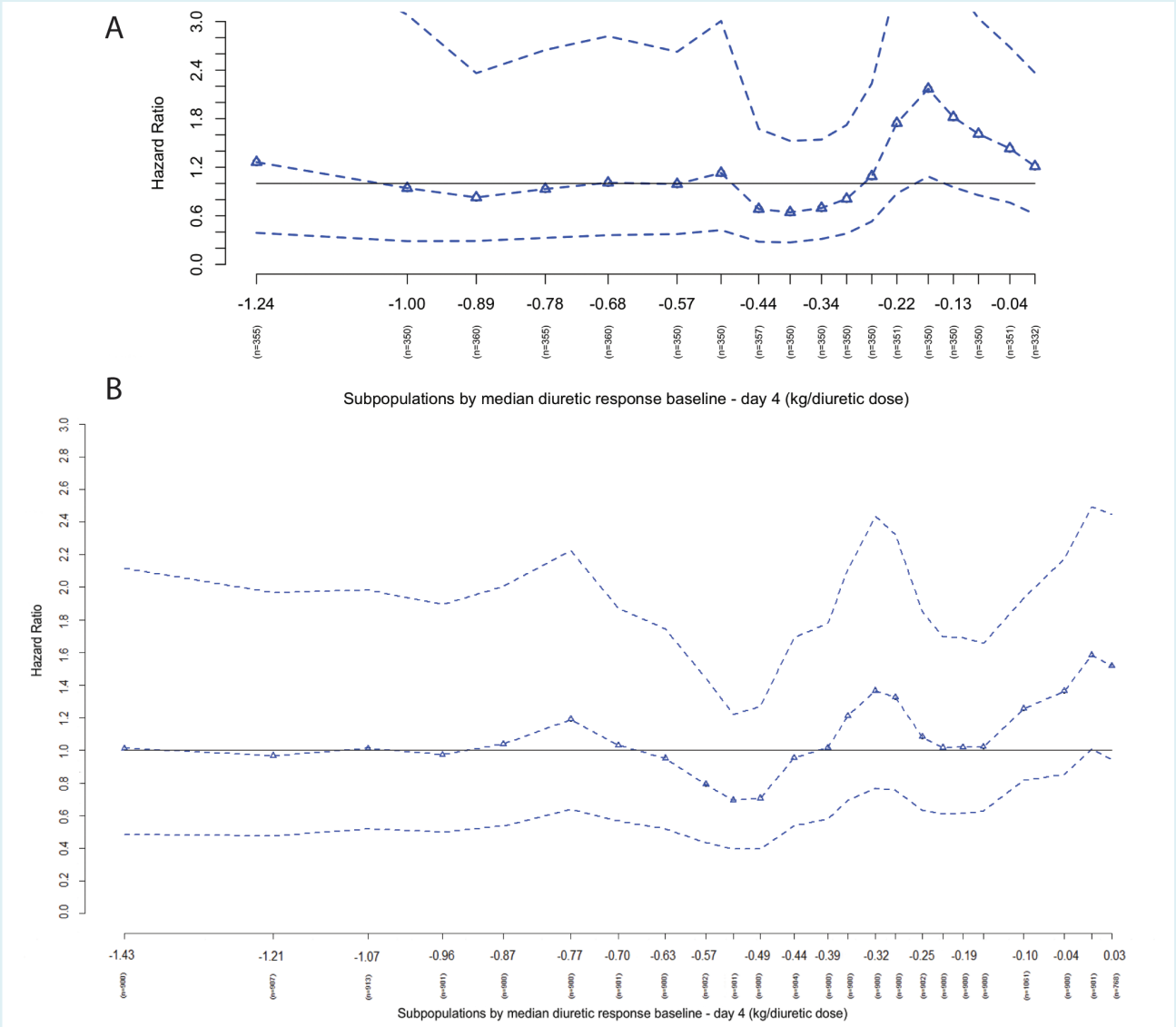

Figure 1 Subpopulation treatment effect pattern plots (STEPP) of worsening renal function (WRF) by diuretic response with regard to combined endpoints*. STEPP plots show the hazard ratio of presence of WRF relative to no WRF across a continuum of overlapping subpopulations of diuretic response. Each triangle indicates the hazard ratio corresponding with the median diuretic response of that subpopulation, with the dashed lines representing the 95% confidence interval of the hazard ratio. (*A*) PROTECT, $p = 0.119$; (*B*) RELAX-AHF-2, $p = 0.030$. *180-day cardiovascular death or heart/renal failure hospitalization in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalization in PROTECT.

no WRF development. Development of WRF was associated with increased 180-day CV death or heart/renal failure hospitalization risk in RELAX-AHF-2 ($p = 0.002$), and increased 60-day death from any cause or CV or renal hospitalization risk in PROTECT ($p = 0.015$). After additional stratification for diuretic response (*Figures 2B* and *3B* for RELAX-AHF-2 and PROTECT, respectively), in patients with a good diuretic response, WRF was not associated with worse outcomes ($p = 0.900$ for both PROTECT and RELAX-AHF-2), whereas WRF with a poor diuretic response was (both cohorts $p < 0.001$). Consistent results were observed for subgroups of HFrEF and heart failure with preserved ejection fraction (HFpEF) in RELAX-AHF-2 (as per study design, there were too few HFpEF patients in PROTECT for reliable replication). Cox regression analysis, depicted in online supplementary *Table S2*, confirmed these findings, where, even after multivariable adjustment, patients with a poor diuretic response had a higher risk of the combined endpoints compared with patients with a good diuretic response, irrespective of WRF.

In *Table 2*, differences in event rates of 180-day death and the combined endpoints in patients with WRF stratified by good diuretic response and poor diuretic response are shown. Patients with a good diuretic response had, in both cohorts, lower event

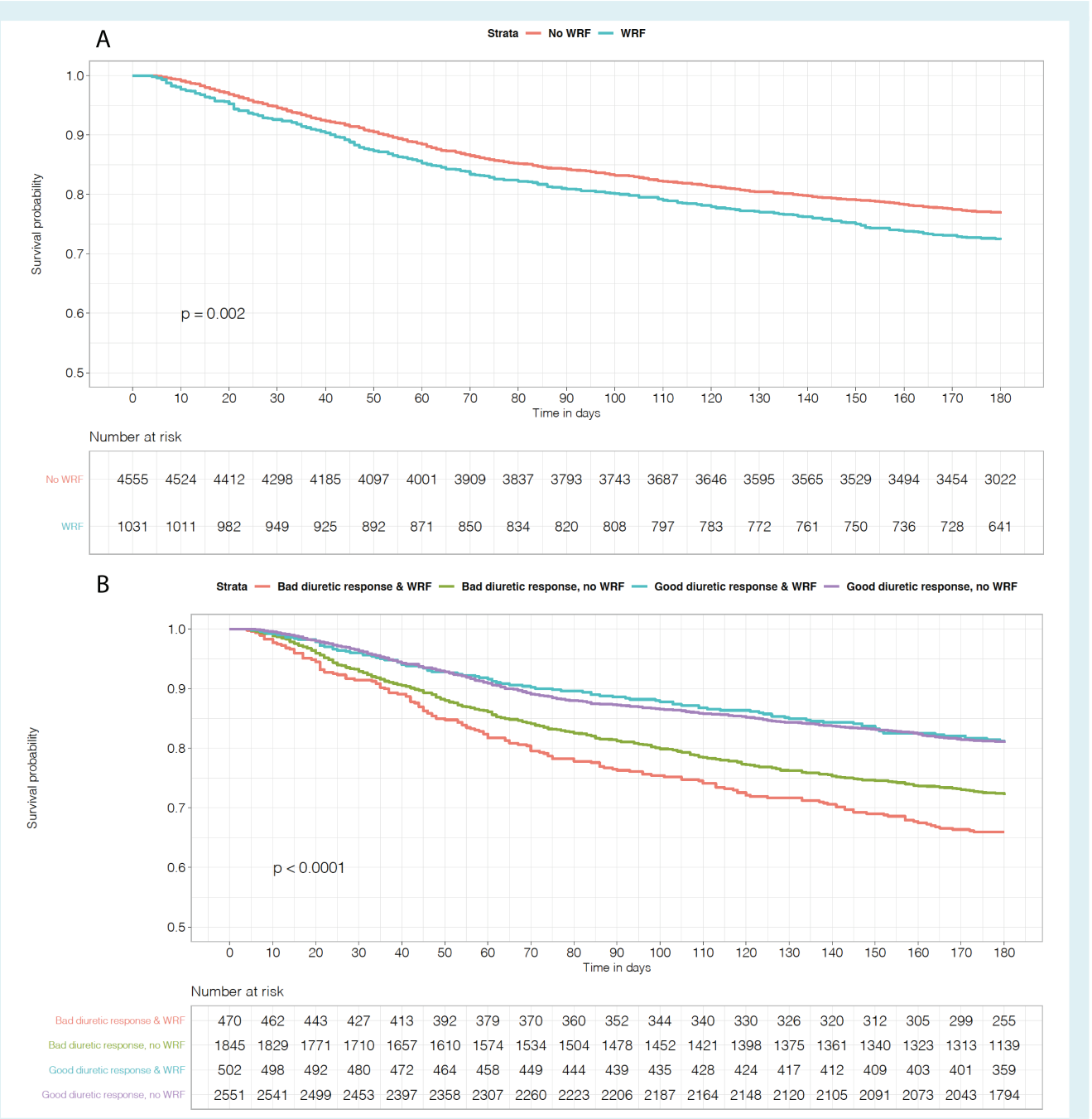

Figure 2 Kaplan–Meier curves for presence vs. absence of worsening renal function (WRF) and in the context of good* vs. poor diuretic response in RELAX-AHF-2. *Defined as >Δ −0.35 kg/40 mg furosemide equivalent between baseline and day 4. (*A*) Kaplan–Meier curves for WRF vs. no WRF; (*B*) Kaplan–Meier curves for WRF vs. no WRF and good diuretic response vs. poor diuretic response.

rates of 180-day mortality as well as the combined endpoint (all $p < 0.01$).

The median percentage increase of serum creatinine between baseline and day 4 was even larger in the group with WRF and a good diuretic response (33%) vs. WRF and a poor diuretic response (28%; $p = 0.025$) in PROTECT. In RELAX-AHF-2, there was no difference (39% vs. 38%; $p = 0.817$). A complete overview of the percentage change in serum creatinine and blood urea nitrogen according to presence/absence of WRF and good/poor diuretic response depicted in histograms is provided in online supplementary *Figures S10* and *S11* for RELAX-AHF-2 and PROTECT, respectively. No subgroups could be identified with a percentage increase of serum creatinine that, despite a good diuretic response, was associated with increased risk of the combined endpoints (online supplementary *Figure S12*).

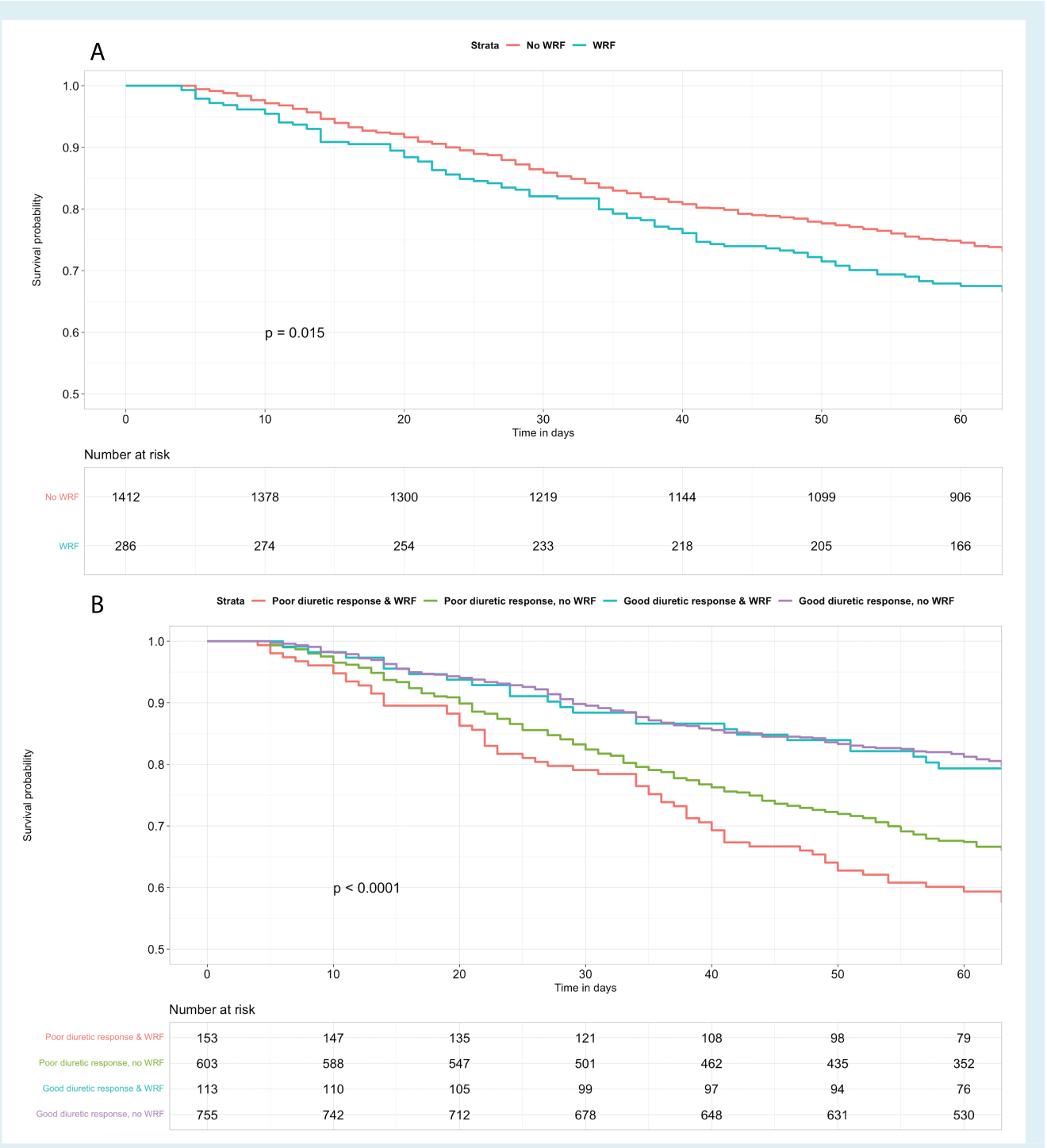

Figure 3 Kaplan–Meier curves for presence vs. absence of worsening renal function (WRF) and in the context of good* vs. poor diuretic response in PROTECT. *Defined as >Δ −0.35 kg/40 mg furosemide equivalent between baseline and day 4. (*A*) Kaplan–Meier curves for WRF vs. no WRF; (*B*) Kaplan–Meier curves for WRF vs. no WRF and good diuretic response vs. poor diuretic response.

Discussion

This analysis shows that patients with AHF and WRF do not have a worse clinical outcome if this is associated with a good diuretic response.

Worsening renal function in context

Several studies have shown that a greater diuretic response was associated with improved outcomes.[11–16] WRF caused by tubuloglomerular feedback due to diuresis and natriuresis might not be

Table 2 Differences in event rates between patients with good[a] or poor diuretic response in patients with worsening renal function

Outcome, *n* (%)	PROTECT		
	Poor diuretic response (*n* = 153)	Good diuretic response (*n* = 113)	*p*-value
180-day death	41 (27)	6 (5)	**<0.001**
60-day death or cardiovascular or renal hospitalization	65 (42)	23 (20)	**<0.001**
Death	22 (14)	1 (<0.1)	**<0.001**
Cardiovascular or renal hospitalization	44 (29)	22 (19)	0.112
Outcome, *n* (%)	**RELAX-AHF-2**		
	Poor diuretic response (*n* = 470)	Good diuretic response (*n* = 502)	*p*-value
180-day death	76 (16)	50 (10)	**0.005**
180-day cardiovascular death or heart/renal failure hospitalization	157 (33)	94 (19)	**<0.001**
Cardiovascular death	55 (12)	37 (7)	**0.028**
Heart/renal failure hospitalization	112 (24)	57 (11)	**<0.001**

[a]Defined as >Δ −0.35 kg/40 mg furosemide equivalent between baseline and day 4.

associated with worse clinical outcomes. In addition to clinical outcomes, in the context of aggressive diuresis, WRF is not associated with increased markers of tubular injury.[14] Conversely, patients with a poor ability to excrete sodium in response to loop diuretics, had higher levels of tubular injury markers and higher risk of mortality.[29] Contemporary research therefore increasingly focuses on the interpretation of WRF in the context of decongestion in AHF. Thus, we hypothesized that the association between WRF and clinical outcomes depends on a patient's concomitant diuretic response to loop diuretics.

The need for interpretation of WRF in the context of decongestion is supported by several previous studies. A previous analysis in PROTECT showed that WRF according to a creatinine increase ≥0.3 mg/dl was only associated with poor outcome if residual congestion was present, defined with a clinical congestion score based on orthopnoea, oedema, and jugular venous pressure.[30] Similarly, a previous study in the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome Study (CARRESS) and Diuretic Optimization Strategies Evaluation (DOSE) cohorts, showed that WRF was not associated with poor outcomes as long as NT-proBNP levels were decreasing as well.[31] Another study in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) cohort showed that the association between WRF and poor outcome was significantly modified by increases in haematocrit, albumin, and total protein between baseline and 7 days.[10] Similar trends were observed for NT-proBNP and BNP decrease and weight loss, but these did not reach statistical significance.[10] Such evidence contributed to a recent position statement from the Heart Failure Association (HFA) of the European Society of Cardiology, which strongly recommended interpretation of WRF in the context of decongestion.[22]

The current analysis adds to these previous studies in the following ways: (i) a much larger group of patients, including both HFrEF and HFpEF, (ii) WRF analysed in context of diuretic response early in the course of hospitalization, (iii) use of combined endpoints that include heart/renal failure hospitalization [arguably more clinically relevant in the face of (residual) congestion], (iv) robust sensitivity analysis for different definitions of WRF and other decongestion variables, and finally (v) implementing STEPP methodology to identify clinically relevant cut-off values.

The position statement issued by the HFA of the European Society of Cardiology lists criteria to define a good diuretic response based on either urinary sodium, urinary output, net fluid loss, or weight loss (all indexed per 40 mg furosemide equivalent), based on data showing that certain quantiles (or above/below median) of diuretic response were associated with improved outcomes.[22] Our study is the first to show that this relationship between a good diuretic response and better outcomes remains strongly present even if WRF occurs. Our threshold for diuretic response of >0.35 kg weight loss per 40 mg furosemide is consistent with the identified approximate values of a poor diuretic response in other studies,[22] although lower than the values they used to define a good diuretic response (ranging from >0.6 to 1.0 kg weight loss/40 mg furosemide equivalent).[22] Our analysis suggests that diuretic response can be considered to be 'good enough' at lower levels. We ensured the validity of our results by including sensitivity analyses for other definitions of WRF, including a fall in eGFR ≥30% to allow comparison with the results of EVEREST.[10] Our results differ from the definition of diuretic response proposed in the above mentioned statement also with respect to the time of assessment of the diuretic response, 4 days after randomization in the present analysis vs. 2 to 6 h after the first diuretic administration in the HFA statement. An earlier assessment would have the advantage for clinical practice of allowing an early change in diuretic doses and this may be particularly important if diuretic therapy is started at relatively low doses as outlines in that document. However, such early assessment is less likely to occur in the context of a large multicentre clinical trial.

Caution is however recommended with extreme changes in serum creatinine, often defined as a doubling of creatinine or an absolute serum creatinine >3.5 mg/dl.[22] Although we did not identify any rises in serum creatinine that were associated with adverse outcomes in patients who had a concomitant good diuretic response, extreme rises in creatinine were rare in the current analysis, and it was therefore difficult to show reliable data according to diuretic response in these extremer changes in serum creatinine.

However, we did not find a divergent and consistent STEPP pattern across the continuum of percentage change in haemoglobin,

ΔePV, and (NT-pro)BNP. For the latter, it must be kept in mind that values of (NT-pro)BNP were only available in (much) smaller subsets of patients and, subsequently, carry less power. For ΔePV and change in haemoglobin, this was unexpected since they have both been associated with clinical outcomes in both acute and chronic heart failure,[7,9,32] but might be explained by the fact that changes in haematocrit are often small, and changes in haematocrit and haemoglobin can also reflect different processes, such as bleeding, splenic pooling, postural changes, and underlying diseases (such as inflammation). Haemoconcentration has also previously been shown to not be strongly related to clinically assessed congestion.[33] This finding was however contrary to findings in EVEREST, where a significant interaction was found between WRF and variables of haemoconcentration (change in haematocrit, albumin, and total protein) with regard to death.[10] As for (NT-pro)BNP, it might be possible that NT-proBNP and BNP levels are partly confounded by the fact that they are filtered by the kidney, and might certainly be a good risk marker, but it might not be a variable accurate enough to reflect decongestion and put WRF in context. Similar to the EVEREST study,[10] a study in the DOSE trial also did not show an interaction between eGFR decline and NT-proBNP concentrations with regard to mortality.[34]

Limitations

Limitations include the fact that NT-proBNP in RELAX-AHF-2 and BNP in PROTECT were only measured in (much) smaller subgroups and therefore provided less reliable results. Also, our results are most applicable to patients with an eGFR of approximately 20 to 80 ml/min/1.73 m^2 due to the inclusion criteria for PROTECT and RELAX-AHF-2. The retrospective nature of this analysis within clinical trial populations is also a limitation, including the fact that the combined endpoints of the clinical trials were predefined to be established at different time points. Also, findings from clinical trial cohorts might not necessarily translate to real-world practice where accuracy of weight and urine output measurements might differ. Calculation of diuretic response as indexed per 40 mg of furosemide equivalent might be cumbersome, but dose and route of administration in electronic patient systems could easily circumvent this problem. Moreover, although more convenient, crude weight loss appeared to be a less reliable measurement to determine whether WRF is harmful or not. Application of the STEPP method to a clinical congestion score proved not to be feasible due to the limited range of values of a congestion score. Finally, as WRF and diuretic response were assessed between baseline and day 4 to allow for early risk/benefit indication by clinicians, no claims can be made about later shifts from good to poor diuretic response and vice versa.

Future perspectives and clinical application

Knowledge on how and when WRF is a sign of poor clinical outcomes and when it can be considered as harmless is of paramount importance to prevent down-titration of diuretic doses leading to residual congestion. The current study might aid physicians by showing that diuretic response is a suitable variable to put WRF into context and provides an estimate of how much diuretic response confers good outcomes. The occurrence of WRF should thus not incontrovertibly lead to the decision to down-titrate or even cease treatments aimed at achieving decongestion. Further validation is however warranted to determine whether a minimum diuretic response of >0.35 kg weight loss per dose of 40 mg furosemide equivalent could be a reasonable estimation of a good diuretic response to base treatment decisions on in clinical practice. Research is warranted to investigate whether diuresis/natriuresis-guided therapy in AHF indeed results in better outcomes for these patients. Currently, the Pragmatic Urinary Sodium-based Treatment algoritHm in Acute Heart Failure (PUSH-AHF) study is underway, which compares natriuresis-guided treatment with standard of care in AHF patients (ClinicalTrials.gov identifier: NCT04606927).

Conclusion

In two large cohorts of patients with AHF, WRF in the first 4 days was not associated with worse outcomes when patients had a good diuretic response. This finding should be considered when making decisions about diuretic management in patients with AHF.

Supplementary Information

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

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