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Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF

Adriaan A. Voors[1]*, Beth A. Davison[2], G. Michael Felker[3], Piotr Ponikowski[4], Elaine Unemori[5], Gadi Cotter[2], John R. Teerlink[6], Barry H. Greenberg[7], Gerasimos Filippatos[8], Sam L. Teichman[5], and Marco Metra[9] on behalf of the Pre-RELAX-AHF study group

[1]Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; [2]Momentum Research Inc., Durham, NC, USA; [3]Duke Clinical Research Institute, Durham, NC, USA; [4]Heart Disease Center, 4th Military Clinical Hospital, Wroclaw, Poland; [5]Corthera, San Mateo, CA, USA; [6]University of California, San Francisco, CA, USA; [7]University of California, San Diego, CA, USA; [8]Athens University Hospital, Athens, Greece; and [9]University of Brescia, Brescia, Italy

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Aims We aimed to determine the relation between baseline systolic blood pressure (SBP), change in SBP, and worsening renal function (WRF) in acute heart failure (AHF) patients enrolled in the Pre-RELAX-AHF trial.

Methods and results The Pre-RELAX-AHF study enrolled 234 patients within 16 h of admission (median 7 h) for AHF and randomized them to relaxin given intravenous (i.v.) for 48 h or placebo. Blood pressure was measured at baseline, at 3, 6, 9, 12, 24, 36, and 48 h and at 3, 4, and 5 days after enrolment. Worsening renal function was defined as a serum creatinine increase of $\geq$0.3 mg/dL by Day 5. Worsening renal function was found in 68 of the 225 evaluable patients (30%). Patients with WRF were older (73.5 $\pm$ 9.4 vs. 69.1 $\pm$ 10.6 years; $P = 0.003$), had a higher baseline SBP (147.3 $\pm$ 19.9 vs. 140.8 $\pm$ 16.7 mmHg; $P = 0.01$), and had a greater early drop in SBP (37.9 $\pm$ 16.0 vs. 31.4 $\pm$ 12.2 mmHg; $P = 0.004$). In a multivariable model, higher age, higher baseline creatinine, and a greater early drop in SBP, but not baseline SBP, remained independent predictors of WRF. Furthermore, WRF was associated with a higher Day 60 ($P = 0.01$), and Day 180 ($P = 0.003$) mortality.

Conclusions Worsening renal function in hospitalized AHF patients is related to a poor clinical outcome and is predicted by a greater early drop in SBP.
Trial registration clinicaltrials.gov identifier NCT00520806.

Keywords Acute heart failure • Renal function • Creatinine • Blood pressure • Mortality

Introduction

Renal dysfunction is a frequent finding in patients hospitalized for acute heart failure (AHF) and it is related to a poorer prognosis.[1] In addition, further deterioration of renal function [worsening renal function (WRF)] occurs in approximately one-third of patients.[2–7] Worsening renal function during hospitalization was found to be strongly related to a poorer outcome as well, independent of baseline renal function.[2–9] Moreover, the occurrence of WRF during HF-related hospitalization is associated with higher hospitalization costs and longer hospital stay.[8] Early identification of patients at risk of WRF is therefore clinically important.

Several studies have identified factors associated with WRF. Two of the most common predictors of WRF are a poorer renal function at admission and the presence of diabetes.[3–10] In some studies, higher blood pressure at admission was also related to a greater risk of WRF.[3–5,11,12] This is consistent with the finding that patients with hypertension are more likely to

* Corresponding author. Tel: +31 50 3612355, Fax: +31 50 3614391, Email: a.a.voors@thorax.umcg.nl

have an increase in serum creatinine concentration when the blood pressure is lowered.[13] However, none of these studies reported on the change in blood pressure related to WRF, in particular in patients with hypertension.

The relaxin for the treatment of patients with acute heart failure trial (Pre-RELAX-AHF) was a multicentre pilot phase trial aimed at the assessment of the dose response and effects on symptoms, outcomes, and safety of relaxin, a natural human peptide with vasodilator properties, in patients with AHF and preserved or elevated systolic blood pressure. The study demonstrated a favourable effect of relaxin on dyspnoea improvement and clinical outcomes, which was also associated with a reduced use of diuretics.[14,15] In the Pre-RELAX-AHF trial, blood pressure and serum creatinine were measured serially during the first 5 days of hospitalization. In the current study, we evaluated the relation between baseline blood pressure, an early change in blood pressure, and the risk of WRF in patients hospitalized for AHF and included in the Pre-RELAX-AHF study.

Methods

Patients

The present study included patients enrolled in the Pre-RELAX-AHF study.[14] (Appendix) The design and results of Pre-RELAX-AHF have been described extensively elsewhere.[14] In brief, men and women aged >18 years, hospitalized for AHF, with a systolic blood pressure (SBP) > 125 mmHg, and with impaired renal function (estimated glomerular filtration rate of 30–75 mL/min/1.73 m^2, calculated with the simplified modification of diet in renal disease [sMDRD] equation),[16] were eligible for inclusion in the study. Acute heart failure was defined by the presence of all of the following at screening: dyspnoea at rest or with minimal exertion, pulmonary congestion on chest X-ray, and elevated natriuretic peptide levels [brain natriuretic peptide (BNP) $\geq$ 350 ng/L or NT-proBNP $\geq$ 1400 ng/L].

Procedures

The study was approved by the relevant ethics committees, institutional review boards, and regulatory authorities, and conducted under the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided informed written consent prior to participation. By protocol, the study drug infusion was to be terminated if the patient's SBP was reduced to <100 mmHg or by >40 mmHg compared with baseline, in two successive measurements taken 15 min apart. Investigators were not prohibited from utilizing any standard medication thought necessary to treat patients enrolled in the study, including additional vasodilators.

Blood pressure was measured at baseline, at 3, 6, 9, 12, 24, 36, and 48 h and at Days 3, 4, and 5. Blood samples for laboratory measurements, including serum creatinine, were taken at baseline and at 12 h, then daily through to discharge, at Days 5 and 14, and were analysed at a central laboratory. Vital status and rehospitalization information was collected over the telephone on Days 30, 60, and (vital status only at) 180. When the last enrolled patient reached Day 60, all patients who were between Day 60 and Day 180 of follow-up were contacted by telephone, to complete the study.

Definitions

Baseline SBP was the average of the screening and baseline measurement. All blood pressure measurements were performed supine, after 5 min of rest.

Peak drop in SBP was calculated as the difference between baseline and the lowest value measured during the first 48 h of the study.

Worsening renal function was defined as an increase in serum creatinine of 0.3 mg/dL or more from baseline at any time through Day 5. Subjects who died prior to Day 5 were omitted from the analysis.

Statistical analysis

For continuous variables, means $\pm$ standard deviations are shown, unless otherwise noted, and means are compared using *t*-tests. Proportions were compared using χ^2 tests. The ordered categorical variable New York Heart Association (NYHA) class was compared using a Cochran–Mantel–Haenszel test. Odds ratios (OR) and associated confidence intervals (CI), and *P*-values for Wald χ^2 tests, for predictors of WRF were computed from logistic regression models, and are presented for a 1SD increase (or decrease) for continuous variables. Multivariable-adjusted predictors of WRF were assessed in a logistic regression model. Candidate variables entered into this model included predictors of WRF during hospitalization for AHF previously identified by others and found to be associated with WRF with $P < 0.20$ in the present study, i.e. age, baseline SBP, NYHA-class, BNP, and baseline serum creatinine.[3–11,15–17] Additional models were made for adjustment for all previous factors with weight change, relaxin treatment, and dose of diuretics added. A backward selection procedure was used with the criterion for keeping at $\alpha = 0.1$. Kaplan–Meier estimates of the rates of all-cause mortality through Days 60 and 180, cardiovascular death through Day 180, and heart failure re-admission through Day 60 are presented. Event times of 5 days or less were excluded from these analyses. Patients with and without WRF were compared using log-rank tests. Length of initial hospital stay was set to the maximum observed value +1 for subjects who died in-hospital. Groups were compared with respect to days alive out of hospital and length of initial hospital stay using Wilcoxon rank sum tests.

Results

Patients

The patients' characteristics have been extensively described elsewhere.[14,15] In brief, 234 AHF patients were entered into the study. Creatinine values that allowed a classification of WRF were available for 225 (96%) of these patients; two patients who died within 5 days and two patients with no follow-up creatinine value (and thus a determination of WRF could not be made) were excluded from the analysis. Mean age of the present patient population was 70.4 $\pm$ 10.4 years, 55.6% were male, 96.9% were white, 85.8% had a history of hypertension, and 69.6% had ischaemic heart failure.

Prevalence and clinical correlates of worsening renal function

Worsening renal function was found in 68 of the 225 evaluable patients (30%). Characteristics of patients with and without

Table 1 Baseline characteristics of patients with and without worsening renal function

	Worsening renal function		*P*-value
	Yes ($n = 68$) Mean (SD) or (%)	No ($n = 157$) Mean (SD) or (%)	
Age (years)	73.5 (9.4)	69.1 (10.6)	0.003
Male	54.4%	56.1%	0.82
Medical history			
Atrial fibrillation	39.7%	51.9%	0.09
Asthma, bronchitis, or COPD	17.6%	15.9%	0.75
Diabetes	47.0%	42.3%	0.52
Hypertension	89.7%	84.1%	0.27
Ischaemic heart failure	73.5%	67.9%	0.40
Peripheral vascular disease	19.1%	10.2%	0.07
Stroke	17.6%	15.9%	0.75
NYHA class 1 month prior to presentation			
1	0	4 (2.8%)	0.33
2	18 (30.5%)	32 (22.7%)	
3	18 (30.5%)	70 (49.7%)	
4	23 (39.0%)	35 (24.8%)	
Baseline vital signs			
Systolic blood pressure (mmHg)	147.3 (19.9)	140.8 (16.7)	0.01
Diastolic blood pressure (mmHg)	81.9 (14.4)	80.3 (12.3)	0.38
Pulse (bpm)	81.1 (14.5)	81.1 (14.9)	0.98
Weight (kg)	79.4 (15.5)	81.8 (18.2)	0.36
Baseline laboratory values			
BNP>500 or NT-proBNP>2000 pg/mL	80.9%	71.3%	0.13
Haemoglobin (g/dL)	13.0 (1.7)	13.1 (1.8)	0.66
BUN (mg/dL)	28.8 (12.4)	26.4 (11.1)	0.14
Serum creatinine (g/dL)	1.4 (0.5)	1.3 (0.4)	0.19
eGFR (sMDRD)	55.9 (22.2)	59.4 (19.8)	0.24
Changes during treatment			
Lowest SBP within 48 h (mmHg)	112.6 (16.7)	111.6 (13.5)	0.66
Peak drop in SBP within 48 h (mmHg)	37.9 (16.0)	31.4 (12.2)	0.004
Total dose intravenous loop diuretics			
Day 0	39.4 (75.1)	22.8 (43.8)	0.0386
Day 1	90.3 (164.5)	31.0 (38.6)	<0.0001
Days 0 and 1	129.7 (210.1)	53.7 (65.6)	<0.0001
Medications administered from presentation to randomization			
ACE inhibitor	40 (58.8%)	97 (61.8%)	0.6761
Angiotensin Receptor blocker	6 (8.8%)	6 (3.8%)	0.1252
Beta-blocker	34 (50.0%)	92 (58.6%)	0.2328
Hydralazine	2 (2.9%)	3 (1.9%)	0.6302
Nitrates	20 (29.4%)	28 (17.8%)	0.0517
Digoxin	11 (16.2%)	34 (21.7%)	0.3454
Calcium channel blocker	9 (13.2%)	24 (15.3%)	0.6896

SBP, systolic blood pressure; NYHA, New York Heart Association; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; sMDRD, simplified modification of diet in renal disease.

WRF are shown in *Table 1*. Patients with WRF were older (73.5 ± 9.4 vs. 69.1 ± 10.6 years; $P = 0.003$), had a higher baseline SBP (147.3 ± 19.9 vs. 140.8 ± 16.7; $P = 0.01$), and had a greater early drop in SBP (37.9 ± 16.0 vs. 31.4 ± 12.2; $P = 0.004$) through the first 48 h. *Figure 1* shows that the drop in SBP during the first 5 days was larger in patients developing WRF. This difference was particularly evident during the first few hours.

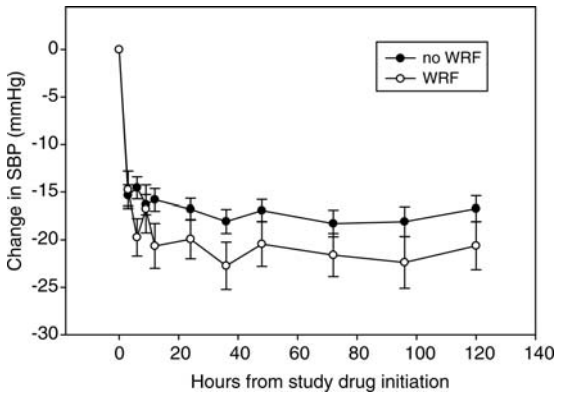

Figure 1 Change in systolic blood pressure between baseline and Day 5 in patients with and without worsening renal function. Data are presented as mean ± standard error.

Table 2 Clinical outcome in patients with and without worsening renal function

	WRF ($n = 68$)	No WRF ($n = 157$)	*P*-value
Days of initial hospitalization[b]	10.0 (±10.5)	8.0 (±10)	0.05
HF re-admission—Day 60	3; 4.8%	12; 7.9%	0.42
60-day all-cause mortality	8; 11.8%	5; 3.3%	0.01
180-day all-cause mortality	11; 17.2%	7; 5.2%	0.003
CV-death—Day 180[a]	5; 8.2%	5; 3.9%	0.16

[a]Number of events; Kaplan–Meier estimate of event rate. *P*-value for log-rank test.
[b]Median (±interquartile range). *P*-value for Wilcoxon rank sum test.
WRF, worsening renal function; HF, heart failure.

Worsening renal function related to morbidity and mortality

Patients with WRF had a poorer prognosis compared with patients without WRF (*Table 2*). In particular, 60- and 180-day mortality was significantly higher in patients with WRF. Length of stay was longer, but the rate of re-admissions was not increased in patients with WRF.

Predictors of worsening renal function

Univariable and multivariable predictors of WRF are shown in *Table 3*. In univariable analysis, a higher age, NYHA functional Class IV, a higher baseline SBP, and a greater drop in blood pressure during the first 48 h, were related to a higher risk of WRF. However, we did not find a significant correlation between peak SBP drop and either weight change or intravenous (i.v.) loop diuretic dose.

When adjusted for these potential confounders, a higher age, a higher baseline creatinine, and a greater early drop in SBP, but not baseline SBP, remained independent predictors of WRF. When

Table 3 Univariable and multivariable predictors of worsening renal function in patients with acute heart failure. Odds ratios are presented as per standard deviation increase, unless indicated otherwise

	Univariable models		Multivariable model		Multivariable model further adjusted for weight change		Multivariable model further adjusted for relaxin treatment		Multivariable model further adjusted for IV diuretic dose	
	OR and 95% CI	*P*-value	OR and 95% CI	*P*-value	OR and 95% CI	*P*-value	OR and 95% CI	*P*-value	OR and 95% CI	*P*-value
Peak drop in SBP within 48 h (per 13.8 mmHg increase)	1.59 (1.19–2.13)	0.002	1.45 (1.04–2.00)	0.0267	1.40 (1.00–1.96)	0.0492	1.45 (1.04–2.01)	0.0282	1.41 (1.01–1.98)	0.0454
Age (per 10.4 year increase)	1.62 (1.17–2.25)	0.004	1.58 (1.06–2.30)	0.0225	1.58 (1.07–2.34)	0.0215	1.63 (1.10–2.43)	0.0156	1.49 (1.00–2.22)	0.0498
Baseline creatinine (per 0.48 mg/dL increase)	1.22 (0.93–1.61)	0.16	1.41 (1.04–1.93)	0.0297	1.31 (0.95–1.81)	0.1036	1.40 (1.02–1.91)	0.036	1.30 (0.94–1.80)	0.1063
NYHA (i.v. vs. others)	1.93 (1.01–3.70)	0.046	1.80 (0.91–3.54)	0.0917	1.98 (0.99–3.98)	0.0549	1.84 (0.93–3.66)	0.08	1.77 (0.88–3.55)	0.1083
Admission BNP > 500 or NT-proBNP > 2000 pg/mL	1.70 (0.85–3.41)	0.14								
Baseline SBP (per 17.9 mmHg increase)	1.43 (1.07–1.90)	0.015								
Weight change (baseline to 48 h) (per 2.15 kg increase)	1.37 (1.00–1.86)	0.0487			1.43 (1.01–2.02)	0.0421				
Relaxin (pooled treatment vs. placebo)							0.66 (0.32–1.38)	0.2728		
Total dose i.v. loop diuretics Days 0–1 (per 132 mg increase)	1.92 (1.30–2.86)	0.0012							1.74 (1.15–2.62)	0.0084

NYHA, New York Heart Association; BNP, brain natriuretic peptide; NT-proBNP, N terminal pro brain natriuretic peptide.

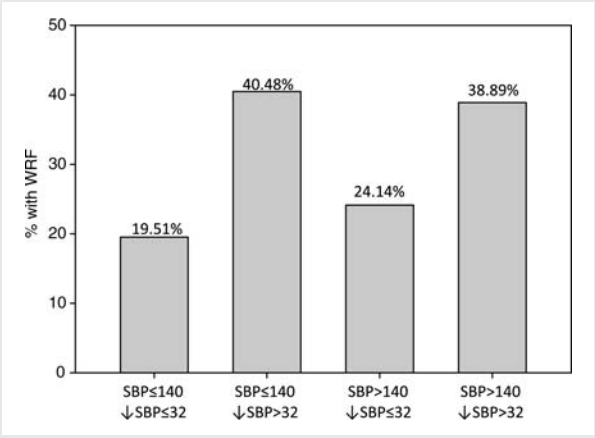

Figure 2 Percentage of patients with worsening renal function according to baseline systolic blood pressure (below or above 140 mmHg) and peak drop in systolic blood pressure (below or above 32 mmHg) during the first 48 h.

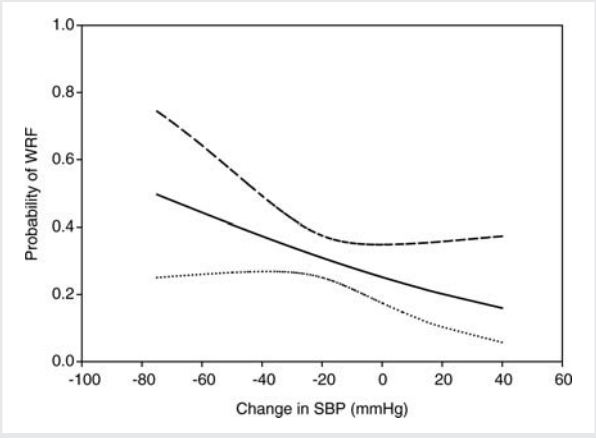

Figure 3 Risk of worsening renal function plotted against a peak drop in systolic blood pressure between baseline and 48 h. Data are presented as the mean (solid line) ± 95% confidence limits (dashed and dotted lines).

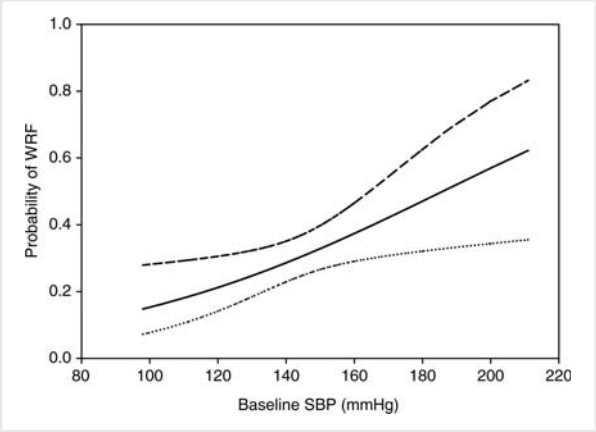

Figure 4 Risk of worsening renal function plotted against baseline systolic blood pressure during admission for acute heart failure. Data are presented as the mean (solid line) ± 95% confidence limits (dashed and dotted lines).

weight change during hospitalization was added to the model, then less weight loss was related to an increased risk of worsening renal function, although a drop in SBP remained independently related to WRF as well (*Table 3*). The addition of the use of relaxin did not change the model, and was not related to worsening renal function (*Table 3*). Finally, a higher dose of loop diuretics was also independently related to an increased risk of worsening renal function, although a drop in SBP remained independently related to WRF as well (*Table 3*). *Figure 2* shows that in both patients with a higher and a lower baseline SBP, a greater drop in SBP within 48 h was associated with a higher rate of WRF. *Figure 3* shows the continuous association between the maximum change in blood pressure during the first 48 h and the risk of developing WRF. *Figure 4* shows the continuous association between baseline SBP and the risk of developing WRF.

Relaxin treatment, worsening renal function, and changes in blood pressure

The main results of the study have been published previously[14,15] showing beneficial effects of relaxin on dyspnoea relief and clinical outcomes. In Pre-RELAX-AHF, the SBP decrease from baseline to 24 h in relaxin-treated patients was larger than in placebo-treated patients (mean decrease from baseline to 24 h was 14.0 ± 13.5 mmHg in placebo vs. 19.0 ± 15.4 mmHg in all relaxin-treated groups combined $P = 0.026$). Most of this effect was driven by a numerically larger drop in SBP in patients with higher baseline SBP. In patients with SBP > median (140 mmHg) the drop in SBP from baseline to 24 h was 15.0 ± 17.1 mmHg in placebo vs. 23.3 ± 17.4 mmHg in all relaxin-treated patients ($P = 0.037$) while in patients with SBP ≤ median at baseline the SBP drop to 24 h was 13.1 ± 10.0 mmHg in placebo vs. 15.5 ± 12.6 mmHg in relaxin. Furthermore, after adjustment for baseline SBP, estimated glomerular filteration rate (eGFR), and haemoglobin, the mean peak SBP decrease within 48 h was greater in all relaxin-treated patients compared with placebo-treated patients (−34.5 and −30.1 mmHg in the relaxin- and placebo-treated patients, respectively, pooled SD = 12.2, $P = 0.025$).

With regard to creatinine changes, neither lower (10 and 30 μg/kg/day combined) nor higher (100 and 250 μg/kg/day combined) relaxin doses were related to higher proportions of patients with WRF than placebo (35.0, 30.9, and 26.3%, respectively; $P = 0.26$ and 0.61 compared with placebo, respectively).

Discussion

The present study shows that a greater drop in SBP within the first 48 h after hospitalization for AHF was independently associated with a higher risk of WRF. Worsening renal function was associated with a higher 60- and 180-day mortality. This is the first

study that reports on the association between an early change in SBP and WRF in AHF patients.

Besides a larger early drop in SBP, higher age and poorer baseline renal function were also independently related to an increased risk of WRF. The association between poorer admission renal function and the risk of WRF has been shown in a number of previously published reports.[3–12,17–19] In a univariable analysis, we found that a higher baseline SBP also predicted WRF. This is similar to four other studies. Owan *et al.*[11] and Logeart *et al.*[12] reported a higher risk of WRF during hospital admission for AHF in patients with a history of hypertension. Krumholz *et al.*[4] found that both a history of hypertension and an admission blood pressure of >200 mmHg were associated with an increased risk of WRF during a hospitalization for AHF. Similarly, Forman *et al.*[5] found that an admission SBP >160 mmHg was independently associated with a higher risk of WRF. However, in the present study, we additionally assessed changes in SBP after treatment, and patients with a higher baseline SBP also had a larger early drop in SBP. In a multivariable analysis, only a drop in SBP remained independently related to a higher risk of WRF. This suggests that the associations between baseline SBP and WRF might be caused by the increased risk of a larger drop in SBP in patients with a higher baseline SBP.

The pathophysiology behind our findings can be explained by the auto-regulatory response of the kidney.[20] When renal perfusion pressure rises due to an increased blood pressure, the kidney will constrict its afferent arteriole, and possibly also its interlobal arteries. When blood pressure drops, afferent vasodilation occurs, and if blood pressure drops even further, efferent vasoconstriction will occur as well. By doing so, the kidney can maintain constant glomerular capillary perfusion, pressure, and filtration, over a wide range of blood pressures. However, in case of longstanding hypertension, there is a blunted ability of the pre-glomerular circulation to dilate in response to a drop in SBP, which will cause an exaggerated decrease in intraglomerular pressure.[13] This explanation is consistent with the findings of the present study that both a higher baseline blood pressure at baseline and a drop in blood pressure are related to a higher risk of WRF.

Interestingly, less weight loss was also independently related to an increased risk of worsening renal function. Patients with more weight loss were probably more congested, which is associated with higher central venous pressures. It is well known that a higher central venous pressure has been closely related to an impaired renal function in heart failure patients.[21] So, in congested patients, it is reasonable to assume that more decongestion is beneficial for the kidney. A higher dose of diuretics was also related to a higher risk of worsening renal function. This is not unexpected since diuretics have been shown to impair renal function in heart failure patients, probably by a so-called tubuloglomerular feedback mechanism. Salt loss is sensed in the distal tubule of the kidney, leading to release of adenosine. Adenosine then binds to the adenosine A1-receptor, causing afferent vasoconstriction, thereby reducing renal blood flow, which is a main determinant of renal function in patient with HF.[21] However, a recent randomized clinical trial failed to show a beneficial effect of adenosine A1-blockers in AHF.[22]

The prognostic importance of impaired renal function was demonstrated by longer length of stay and increased 60- and 180-day mortality. This finding supports previous studies consistently demonstrating that WRF is associated with increased mortality.[2–7] The rate of re-admission was not increased in patients with WRF, which may potentially be related to their increased mortality, reducing the number of patients with severe heart failure that could have been re-admitted.

Relaxin has multiple actions potentially beneficial for the treatment of patients with AHF, including increased production of nitric oxide, vascular endothelial growth factor, and matrix metalloproteinases and inhibition of endothelin and angiotensin II.[23] In the Pre-RELAX-AHF study, relaxin was associated with a more rapid and sustained relief of dyspnoea and other clinical outcomes, with a favourable safety profile.[14,15] Although patients treated with relaxin had a larger drop in SBP throughout therapy, the additional SBP reduction was, on average only ~5 mmHg. This may be related to several factors. First, patients treated with relaxin tended to receive less i.v. nitrates and less i.v. loop diuretics. This reduced concomitant therapy—which is probably the result of treatment modifications by physicians observing higher blood pressure (BP) drops in patients treated with relaxin—may explain some of the reduced BP decrease observed with relaxin. Second, the BP lowering effect of relaxin was dependent on baseline BP and was more pronounced (and significant) in patients with higher (>median) baseline SBP than in patients with lower (≤median) systolic BP. This effect is different to results observed in case of other therapies with vasodilating properties, suggesting that the effects of relaxin are more in line with countering vasoconstriction than simple vasodilatation, a property that may explain some of its efficacy in Pre-RELAX-AHF. Overall, there was a neutral effect of relaxin on renal function, compared with placebo. This is in contrast to the findings of favourable effects of relaxin on intra-renal haemodynamics, and renal function in experimental studies.[23] In both male and ovariectomized female rats, relaxin increased GFR, and effective renal plasma flow by 33 and 49% over baseline, respectively.[24] These effects were mediated by the endothelial endothelin B receptor subtype, presumably on endothelial cells and nitric oxide. Irrespective of the mechanism, data from the present study support the use of the lower dose of 30 μg/kg/day of relaxin in an ongoing phase III trial. The present data are clinically relevant, since patients with WRF are at risk of a longer length of stay and higher 60- and 180-day mortality. This study demonstrates that specific attention should be paid to renal function in patients with a high SBP at admission and a larger drop in SBP during the first 48 h. Although a causal relationship between a change in blood pressure and WRF has not been proven, it seems reasonable to suggest that a sudden drop in blood pressure might be harmful for the kidneys.[12] In fact, renal blood flow seems to be the major driving factor that explains the frequent occurrence of renal dysfunction in patients with heart failure.[20,21]

There are a few important limitations to this study. First, this is a *post-hoc* analysis of the Pre-RELAX-AHF study, which was not specifically designed to study the effects of relaxin on renal function. Second, the number of patients was small, and these results should therefore be considered as hypothesis generating. Third,

the most important limitation is the previously discussed relation between a higher baseline SBP and a larger drop in SBP. However, from a clinical perspective, these will be largely the same patients. Our data therefore suggest that careful monitoring and lowering of blood pressure in these patients might prevent WRF, and might even improve clinical outcome.

In conclusion, in patients hospitalized for AHF, WRF is independently predicted by a greater drop in SBP during the first 48 h of hospitalization. Worsening renal function was strongly related to a poorer clinical outcome up to 180 days after hospital admission.

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Conflict of interest : A.A.V., G.M.F., P.P., J.R.T., B.H.G., G.F., and M.M. received consulting fees from Corthera. B.A.D. and G.C. are employees of Momentum Research. Momentum Research has received grants and direct payment for conducting clinical research from Corthera. E.U. and S.L.T. are employees of Corthera.

Appendix

Pre-RELAX-AHF study group

Co-Principal Investigators: M. Metra (Italy), J.R. Teerlink (USA). *Executive Committee*: G.M. Felker (USA), A.A. Voors (Netherlands), P. Ponikowski (Poland), B. Greenberg (USA), B.A. Davison (USA), S.L. Teichman (USA), E. Unemori (USA), G. Cotter (USA). *Independent Data Safety Monitoring Board*: B.M. Massie (Chair; USA), S. Goldstein (USA), M. Bohm (Germany), G. Francis (USA), C.E. Davis (USA). *Site Investigators*: Russia—S. Boldueva, V. Moiseev, Z. Shogenov, M. Ruda, A. Vishnevsky, M. Boyarkin, V. Simanenkov, S. Tereschenko, Y. Shwartz, O. Orlikova, M. Arkhipov, I. Libov, R. Sardinov, A. Suvorov; Israel—A. Marmor, A. Katz, R. Zimlichman, M. Omary, R. Hershkoviz, S. Goland, A. Keren, D. Aronson; Poland—P. Ponikowski, J. Grzybowski, W. Musial; Hungary—D. Apró, G. Lupkovics; Italy—M. Metra; Romania—C. Stamate, A. Salajan, A. Matei; USA—P. Levy, P. Pang, S. Collins, D. Gupta; Belgium—W. Van Mieghem, L. Muyldermans, G. Vervoort.

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