Systolic blood pressure reduction during the first 24 hours of an acute heart failure admission: Friend or foe?

Gad Cotter, MD‡, Marco Metra, MD§, Beth A. Davison, PhD‡, Guillaume Jondeau, MD#, John G. F. Cleland MD∗, Robert C. Bourge, MD\, Olga Milo, MD ‡, Christopher M. O'Connor, MD††, John D. Parker, MD¶, Guillermo Torre-Amione, MD PhD‡‡, Dirk J. van Veldhuisen, MD§§, Isaac Kobrin, MD# #; Maurizio Rainisio, PhD **; Stefanie Senger, PhD‡, Christopher Edwards ‡, John J. V. McMurray, MD\\, John R. Teerlink, MD†, for the VERITAS Investigators

‡Momentum Research, Inc., Durham, NC, USA, gadcotter@momentum-research.com; bethdavison@momentum-research.com; olgamilo@momentum-research.com; stefaniesenger@momentum-research.com; ChrisEdwards@momentum-research.com; §University of Brescia, Piazza Spedali Civili, Brescia, Italy, metramarco@libero.it; ∗University of Hull, Kingston upon Hull, UK, National Heart & Lung Institute, Royal Brompton and Harefield Hospitals NHS Trust, Imperial College, London, UK., J.G.Cleland@hull.ac.uk; #Service de cardiologie, Hôpital Bichat, 75877 Paris Cedex 18, France, guillaume.jondeau@bch.aphp.fr; \University of Alabama at Birmingham, Birmingham, Alabama, USA, bbourge@uab.edu ; ††Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA, christophe.oconnor@duke.edu ; ¶Division of Cardiology, Mount Sinai Hospital, Toronto, Ontario, Canada, John.Parker@uhn.on.ca; ‡‡Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas, USA, GTorre@tmhs.org; §§University Medical Centre, Groningen, The Netherlands, d.j.van.veldhuisen@umcg.nl; ## Kobrin Associates, GmbH, Basel, Switzerland, itzikkob@gmail.com; ** Abanovus srl, Italy, Maurizio.Rainisio@AbaNovus.com; \\University of Glasgow, Glasgow, United Kingdom, John.McMurray@glasgow.ac.uk; †University of California San Francisco and the San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA john.teerlink@ucsf.edu

Address for correspondence: Dr. Gad Cotter, Momentum Research, Inc., 3100 Tower Blvd, Suite 802, Durham, NC, 27707, USA. Phone: 1-9192871824 Fax: 1-9192871825 Email: gadcotter@momentum-research.com

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Abstract

Changes in systolic blood pressure (SBP) during an admission tor acute heart failure (AHF), especially those leading to hypotension, have been suggested to increase the risk of adverse outcomes.

Methods: We analysed the association of SBP decrease during the first 24 hours from randomisation with serum creatinine changes at the last time point available (72 hours), using linear regression, and with 30- and 180-day outcomes, using Cox regression in 1257 patients in the VERITAS study.

Results: After multivariable adjustment including baseline SBP, greater SBP decrease at 24 hours from randomisation was associated with greater creatinine increase at 72 hours and greater risk of 30-day all-cause death, worsening HF or HF readmission. The HR for each 1 mmHg decrease in SBP at 24 hours for 30-day death, worsening HF or HF rehospitalisation was 1.01 (95% CI 1.00-1.02, p=0.021). Equally, the HR for each 1 mmHg decrease in SBP at 24 hours for 180-day all-cause mortality was 1.01 (95% CI 1.00-1.03, p=0.038). The associations of SBP decrease with outcomes did not differ by tezosentan treatment group, although tezosentan treatment was associated with a greater SBP decrease at 24 hours.

Conclusions: In the current post-hoc analysis, SBP decrease during the first 24 hours was associated with increased renal impairment and adverse outcomes at 30 and 180 days. Caution, with special attention to blood pressure monitoring, should be exercised when giving vasodilating agents to AHF patients.

Introduction

Vasodilating agents are among the recommended first-line therapies in patients admitted for acute heart failure (AHF)(1,2) despite a lack of evidence supporting their efficacy beyond the first hours of admission (3). A drop in systolic blood pressure (SBP) during the first days of admission has been observed in several studies (4-6); however, the predictors of SBP decreases and the associations of such blood pressure decreases with outcomes were not reported in detail. An analysis of one small study did suggest that SBP reduction may be associated with untoward pathophysiological effects such as worsening of kidney function (7). Such a potential deleterious effect of a SBP decrease may explain, at least in part, the results of some clinical studies where pharmacologically induced SBP decreased, leading to renal function deterioration and subsequent adverse outcomes (8-10). This conclusion was strengthened by a recent analysis of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial which suggested that hypotension is relatively common during AHF hospitalisation, and carries a significant negative prognostic impact on 30-day outcomes (11). In the current manuscript, we assess predictors of SBP changes at 24 hours from study drug initiation (24-48 hours from admission) and their associations with worsening kidney function and clinical outcomes in the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies (VERITAS) (4,5).

Methods

The VERITAS study comprised two, identical, concurrent randomised trials that evaluated the efficacy of tezosentan administration within 24 hours of hospital presentation for AHF (4,5). Patients were included who reported dyspnea at rest after receipt of intravenous diuretics and who had at least two of four objective heart failure signs: elevated natriuretic peptides; pulmonary edema on physical examination; pulmonary congestion or edema on chest x-ray; or left ventricular systolic dysfunction evidenced by

reduced ejection fraction or wall motion index. Patients with a SBP ≤ 100 mHg, or ≤ 120 mmHg if receiving a vasodilator, were excluded. Patients enrolled in error more than 24 hours after presentation and patients without a measured SBP at 24 hours were excluded from the analyses.

Routine laboratory measures at baseline, 24 and 72 hours were obtained locally, while troponin I and B-type natriuretic peptide (BNP) were assayed centrally. Patients were followed for worsening heart failure through 30 days, and vital status was assessed at six months.

Statistical analysis

Summary statistics reported for continuous variables are the mean and standard deviation, or the median (IQR) for skewed variables; proportions in each category are presented for categorical variables. Patients were grouped by tertiles of the change in SBP from baseline to 24 hours and baseline characteristics compared using ANOVA or Cochran-Mantel-Haenszel chi-square tests, as appropriate. Linear regression was used to model the associations of baseline characteristics with the change in SBP from baseline to 24 hours. Non-linearity of the association between each continuous variable and SBP change was assessed by testing the contribution of the non-linear terms of a restricted cubic spline transformation with four knots. A linear spline, quadratric or cubic polynomial, or log transformation was chosen, based on the Akaike's Information Criterion, to model non-linear associations. Ten multiple imputation datasets assuming multivariate normality were used for missing baseline covariates (11), and parameter estimates were averaged over these imputation datasets using Rubin's algorithm (14). A multivariable model was selected in each imputation dataset from among the baseline characteristics using backwards elimination with a retention criterion of $P<0.05$; the final model included those covariates included in at least 6 of the 10 imputation datasets. The unadjusted association of SBP change at 24 hours with creatinine change at 72 hours was assessed using linear regression. Logistic regression was used to provide the odds ratios for the association between SBP change at 24 hours and

an increase in creatinine of ≥0.3 mg/dL at 72 hours, with covariates for multivariable adjustment selected using the same methodology as above.

Associations between the SBP changes and 30-day all-cause death or HF readmission and 180-day all-cause death were examined using Cox proportional hazards models. Potential confounding was addressed through multivariable adjustment for baseline SBP and covariates previously found to be prognostic of these outcomes (14).

SAS® 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

Of the 1449 patients randomised, 102 who were enrolled more than 24 hours from presentation were excluded and 90 patients were missing the change in SBP at 24 hours, leaving 1257 patients for analysis. Patients' baseline characteristics by tertiles of SBP change at 24 hours are presented in table 1. Unadjusted and multivariable-adjusted associations of baseline characteristics and SBP decrease at 24 hours are presented in table 2. Predictors of a larger SBP drop at 24 hours were lack of atrial fibrillation or diabetes mellitus, higher baseline SBP, longer QRS interval, higher BUN, and lower WBC count. Respiratory rate, heart rate, and creatinine had non-linear relationships with SBP change. Tezosentan treatment was associated with a larger mean SBP decrease at 24 hours (mean difference 6.17, 95% CI 4.39-7.96, p<0.001).

SBP change at 24 hours was inversely associated with change in creatinine at 72 hours (figure 1). The relationship had an inflection point around -15 mmHg; i.e., SBP decreases > 15 mmHg were associated with a numerical acceleration in creatinine increase, although the departure from non-linearity was not statistically significant (p=0.5910). Overall, 222 (20.8%) patients had a creatinine change of ≥ 0.3 mg/dL at 72 hours. Patients with larger decreases in SBP at 24 hours were more likely to have a creatinine change ≥ 0.3 mg/dL at 72 hours (OR per 1-mmHg greater decrease in SBP 1.01, 95% CI 1.00-1.02,

p=0.0272). The association of SBP change with creatinine increase did not differ significantly by tezosentan treatment (interaction p=0.7239). After multivariable adjustment for factors found to be associated with creatinine change ≥ 0.3 mg/dL at 72 hours in the VERITAS database (Supplemental Table) - age, renal impairment, time from admission to randomization, respiratory rate, and eGFR – the association of SBP change with a creatinine change ≥ 0.3 mg/dL was of borderline statistical significance (OR per 1 mmHg decrease in SBP 1.01, 95% CI 1.00-1.01, p=0.0941). Tezosentan treatment was not significantly associated with the risk of a creatinine increase ≥ 0.3 mg/dL, and further adjustment for tezosentan treatment did not affect the association of SBP change with the outcome.

Similarly, SBP decrease at 24 hours was associated with a greater risk of adverse outcomes at both 30 and 180 days. All-cause death, worsening HF or HF readmission through 30 days occurred in 395/1257 (31.4%) patients and 165/1257 (13.1%) died through day 180. After multivariable adjustment, the HR for each 1-mmHg decrease in SBP at 24 hours for 30-day death, worsening HF or HF rehospitalisation was 1.01 (95% CI 1.00-1.02, p=0.021), and this association did not differ by randomised treatment (interaction p=0.3409). A larger decrease at 24 hours in SBP was also associated with increased risk of all-cause mortality at 180 days. For 30-day death, WHF or HF readmission, covariates for multivariable adjustment were age, heart rate, respiratory rate, history of CHF, history of diabetes, history of COPD, systolic blood pressure, renal impairment, baseline dyspnea VAS, albumin, BUN, hemoglobin, and sodium (13). For 180-day all-cause death these were age, heart rate, history of IHD/PVD/Stroke, systolic blood pressure, baseline dyspnea VAS, history of COPD, albumin, BUN, WBC and sodium (13). After multivariable adjustment, the HR for each 1 mmHg decrease in SBP at 24 hours for 180-day all-cause mortality was 1.01 (95% CI 1.00-1.03 p=0.038). There was no interaction between SBP decrease and outcomes in tezosentan-treated versus placebo-treated patients (interaction p=0.1414). Figure 2 depicts the association of 180-day mortality with SBP decrease at different time points through 24 hours, suggesting a lack of significance in the first 12 hours and an increased effect of SBP decrease with time.

Discussion

The present analysis of VERITAS suggests an inverse correlation between SBP changes and renal function as measured by creatinine changes at 72 hours, as well as 30- and 180-day outcomes in patients with AHF. Patients with larger decreases in blood pressure were especially prone to creatinine increases as well as increased risks of 30-day death, worsening HF or HF readmission, and 180-day mortality.

The results of these analyses are largely in line with those of previous studies, although confirming and supplementing them. In a small analysis of the Pre-RELAX-AHF phase 2 study, Voors et al (7) have shown that BP decrease is associated with renal function deterioration. An analysis of the larger ASCEND-HF study (11), has demonstrated that hypotension, strictly defined as SBP decrease to < 90 mmHg regardless of initial BP, was associated with increased risk of adverse outcome at 30 days, but not with renal impairment at day 10 or discharge. As the restrictions imposed by the selection of the subgroup analysed in ASCEND-HF (i.e., pts with hypotension defined by a specific cut-off and assessment of renal function distant from the event) limit the analysis to a specific subgroup of patients, it is possible that a relative decrease in SBP rather than reaching an arbitrary threshold is more important prognosticaly. Indeed, in the present analysis baseline-adjusted SBP decreases were associated with both more adverse outcomes and more renal impairment, regardless of baseline SBP of magnitude of decrease in SBP.

The relationship between SBP changes and outcomes after vasodilating agents has not been thoroughly studied in the past. In the current analysis, no interaction was found between the association of SBP decrease, drug therapy and outcomes (p=0.1414 for 180 days mortality), although as reported previously, active therapy with tezosentan was associated with a greater SBP decrease. Thus, the increased risk associated with larger drop in SBP may have neutralised the beneficial effects of the new treatment.

Other previous studies have suggested that such SBP lowering induced by active interventions may lead to more adverse outcomes. In earlier studies where doses of nesiritide higher than those given in ASCEND-HF were administered, nesiritide therapy led to more hypotension, renal impairment and increased mortality (9). This finding was however not replicated in the ASCEND-HF study where lower doses of nesiritide were administered. In the REVIVE study, similar findings were reported with more hypotension in the active arm which was associated with a trend towards earlier mortality (8), especially in patients enrolled with lower BP at screening. Finally, in the recently reported TRUE-AHF study, administration of ularitide was associated with a greater SBP decrease in the active arm (approximately 10 mmHg at 24 hours), an increase in creatinine and a numerical increase in early mortality at 180-240 days (10). These results can be explained by some negative effects of BP decrease on end organ perfusion such as kidneys (7), although data on the mechanism of why such BP decrease may be detrimental are not available. These findings may be an underestimation of the true negative effects of BP reduction in AHF as creatinine is not a perfect measure of kidney dysfunction (15). On the other hand, no studies examining the effects of agents with vasodilating effects have ever demonstrated beneficial effects in patients with AHF beyond the first few hours of admission. Most importantly, the effects of IV nitrates administration beyond the first 1-2 hours of admission have never been examined in detail, and despite that these agents are recommended in the guidelines for the treatment of AHF (1). Interestingly, our data also show that early changes in SBP have no relationship with outcomes whereas the changes occurring beyond 12 hours from admission are associated with worse outcomes. Hence, the totality of the evidence – both the current and previous analyses as well as prospective studies – begs the question whether vasodilatation, long held as a pillar of therapy for AHF, does indeed benefit patients beyond the first hours of administration, especially once normal values of SBP are reached. These data would suggest that our knowledge of the effects of vasodilatation in AHF is incomplete and studies to examine such effects may be urgently needed. In the meantime, physicians should exercise

caution when administering vasodilating agents to patients with AHF, especially when they cause significant reduction of SBP > 15-25 mmHg or a low SBP is reached.

Limitations

The current analysis is a post-hoc analysis from the VERITAS and as such should be seen as hypothesis-generating and not definitive.

Conclusions

Systolic blood pressure decreases in patients with AHF are associated with more early renal impairment and an increase in adverse outcomes at 30 and 180 days. Studies examining the effect of vasodilating agents such as IV nitrates in AHF are urgently needed, and until such studies are performed caution should be exerted in the administration of these agents to patients with AHF especially when significant falls in SBP are observed.

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Table 1: Baseline Characteristics by Tertiles of Systolic BP Change to 24 Hours

	Statistic	SysBP Chg (<= -19) (N=423)	SysBP Chg (>-19 to <=-3) (N=424)	SysBP Chg (> -3) (N=410)	P-value [1]	Overall (N=1257)
Age (years)	Mean (SD)	71.0 (12.01)	69.9 (11.93)	69.9 (12.49)	0.3321	70.3 (12.14)
Gender: Males	n (%)	238 (56.3%)	263 (62.0%)	241 (58.8%)	0.4522	742 (59.0%)
Race: White	n (%)	353 (83.5%)	371 (87.5%)	362 (88.3%)	0.0409	1086 (86.4%)
Time to randomization (hours)	Mean (SD)	10.2 (6.64)	10.9 (7.02)	11.4 (6.87)	0.0423	10.8 (6.86)
BMI (kg/m2)	Mean (SD)	29.2 (6.47)	28.8 (6.01)	28.9 (6.28)	0.7039	28.9 (6.25)
Treated with Tezosentan	n (%)	242 (57.2%)	242 (57.1%)	157 (38.3%)	<.0001	641 (51.0%)
Atrial fibrillation on admission	n (%)	96 (22.7%)	112 (26.7%)	118 (29.1%)	0.0364	326 (26.2%)
History of CHF	n (%)	299 (70.9%)	325 (77.4%)	291 (71.9%)	0.7249	915 (73.4%)
History of COPD	n (%)	74 (17.5%)	84 (19.9%)	74 (18.0%)	0.8303	232 (18.5%)
History of diabetes	n (%)	211 (49.9%)	216 (51.1%)	184 (44.9%)	0.1519	611 (48.6%)
History of hyperlipidemia	n (%)	142 (33.6%)	158 (37.4%)	145 (35.4%)	0.5818	445 (35.4%)
History of hypertension	n (%)	361 (85.3%)	329 (77.8%)	317 (77.3%)	0.0035	1007 (80.2%)
History of smoking	n (%)	28 (6.6%)	31 (7.3%)	37 (9.0%)	0.1926	96 (7.6%)
History of IHD, PVD, stroke	n (%)	284 (67.1%)	302 (71.4%)	294 (71.7%)	0.1484	880 (70.1%)
History of mitral/aortic valve disease	n (%)	75 (17.7%)	63 (14.9%)	65 (15.9%)	0.4573	203 (16.2%)
History of renal impairment	n (%)	161 (38.2%)	166 (39.6%)	138 (34.1%)	0.2312	465 (37.3%)
History of liver disease	n (%)	30 (7.1%)	36 (8.6%)	31 (7.7%)	0.7631	97 (7.8%)
Previous PCI or CABG	n (%)	136 (32.2%)	159 (37.6%)	150 (36.6%)	0.1779	445 (35.4%)
On IV Nitrates at Randomization	n (%)	73 (17.3%)	65 (15.3%)	69 (16.8%)	0.8622	207 (16.5%)
IV Furosemide Dose through 24 hours (mg)	Median (IQR)	40.0 (0.0, 120.0)	40.0 (0.0, 120.0)	40.0 (0.0, 120.0)	0.6385	40.0 (0.0, 120.0)
Ace Inhibitors	n (%)	224 (53.0%)	236 (55.7%)	204 (49.8%)	0.3622	664 (52.8%)
Beta Blockers	n (%)	201 (47.5%)	216 (50.9%)	176 (42.9%)	0.1905	593 (47.2%)
Angiotensin Inhibitors	n (%)	55 (13.0%)	41 (9.7%)	35 (8.5%)	0.0345	131 (10.4%)
Calcium Channel Blockers	n (%)	78 (18.4%)	42 (9.9%)	63 (15.4%)	0.1980	183 (14.6%)
Oral Loop Diuretics	n (%)	136 (32.2%)	121 (28.5%)	115 (28.0%)	0.1931	372 (29.6%)
Systolic blood pressure (mmHg)	Mean (SD)	147.3 (23.11)	126.8 (17.82)	121.9 (16.84)	<.0001	132.1 (22.37)
Respiratory rate (breaths/min)	Mean (SD)	26.5 (4.43)	26.0 (3.87)	26.2 (4.22)	0.1661	26.2 (4.18)
Heart rate (bpm)	Mean (SD)	84.4 (16.97)	83.6 (18.16)	83.2 (17.78)	0.5998	83.7 (17.63)
ECG QRS interval (ms)	Mean (SD)	113.4 (35.40)	114.2 (36.22)	112.0 (34.82)	0.6713	113.2 (35.48)
Baseline dyspnea VAS (mm)	Mean (SD)	62.8 (23.57)	63.2 (23.12)	61.9 (23.06)	0.7096	62.6 (23.24)
Albumin (g/L)	Mean (SD)	38.0 (5.01)	37.4 (5.27)	37.8 (5.18)	0.3683	37.7 (5.16)
ALT (U/L)	Median (IQR)	18.2 (12.0, 29.0)	18.6 (12.7, 30.0)	18.7 (12.7, 28.1)	0.4938	18.6 (12.6, 29.1)
BUN (mmol/L)	Median (IQR)	8.2 (6.0, 11.2)	8.3 (6.4, 11.2)	7.9 (6.2, 11.0)	0.0204	8.2 (6.2, 11.1)
Creatinine (umol/L)	Mean (SD)	115.7 (40.08)	118.7 (36.82)	116.1 (39.16)	0.4711	116.8 (38.70)
Hemoglobin (g/dL)	Mean (SD)	13.4 (1.88)	13.3 (1.84)	13.4 (1.94)	0.9834	13.3 (1.88)

	Statistic	SysBP Chg (<= -19) (N=423)	SysBP Chg (>-19 to <=-3) (N=424)	SysBP Chg (> -3) (N=410)	P-value [1]	Overall (N=1257)
Sodium (mmol/L)	Mean (SD)	139.1 (3.92)	138.6 (4.06)	138.6 (4.03)	0.1231	138.7 (4.01)
WBC (10**9/L)	Mean (SD)	9.7 (3.58)	9.5 (3.70)	10.2 (4.18)	0.0162	9.8 (3.84)
BNP (pg/mL)	Median (IQR)	437.0 (153.0, 949.0)	419.0 (153.0, 968.0)	404.0 (152.0, 903.0)	0.6709	416.0 (153.0, 936.0)
Troponin I (ng/mL)	Median (IQR)	0.0400 (0.0005, 0.1260)	0.0350 (0.0005, 0.1290)	0.0340 (0.0005, 0.1285)	0.5221	0.0360 (0.0005, 0.1275)

[1] P-value according to CMH chi-square for Categorical variables and F-test for Continuous variables

Table 2: Univariable and Multivariable Associations of Baseline Characteristics with Systolic BP Decrease at 24 Hours

		Univariable Models		Multivariable Models	
Predictor	**Estimate for Change of:**	**Estimate (95% CI)**	**P-value**	**Estimate (95% CI)**	**P-value**
Age	10	0.23 (-0.67, 1.12)	0.623		
Gender: Males	Yes vs. No	-2.13 (-4.34, 0.09)	0.060		
Race: White	Yes vs. No	-3.13 (-6.31, 0.04)	0.053		
Time to randomization (hours)	1	-0.24 (-0.40, -0.08)	0.003		
BMI (kg/m2)	1	0.06 (-0.12, 0.24)	0.497		
Atrial fibrillation on admission	Yes vs. No	-4.40 (-6.87, -1.92)	<0.001	-3.34 (-5.43, -1.26)	0.002
History of CHF	Yes vs. No	-0.74 (-3.21, 1.74)	0.561		
History of COPD	Yes vs. No	-0.67 (-3.48, 2.14)	0.642		
History of diabetes	Yes vs. No	0.80 (-1.38, 2.99)	0.470	-2.22 (-4.04, -0.40)	0.017
History of hyperlipidemia	Yes vs. No	-0.49 (-2.77, 1.79)	0.675		
History of hypertension	Yes vs. No	4.00 (1.28, 6.72)	0.004		
History of smoking	Yes vs. No	-1.60 (-5.70, 2.51)	0.446		
History of IHD, PVD, stroke	Yes vs. No	-0.73 (-3.11, 1.65)	0.550		
History of mitral/aortic valve disease	Yes vs. No	0.75 (-2.21, 3.71)	0.618		
History of renal impairment	Yes vs. No	0.39 (-1.87, 2.66)	0.732		
History of liver disease	Yes vs. No	0.23 (-3.85, 4.31)	0.912		
Previous PCI or CABG	Yes vs. No	-1.98 (-4.26, 0.30)	0.089		
On IV Nitrates at Randomization	Yes vs. No	-0.12 (-3.06, 2.82)	0.936		
IV Furosemide Dose through 24 hours (mg)	5	-0.01 (-0.05, 0.04)	0.810		
Systolic blood pressure (mmHg)	1	0.47 (0.43, 0.51)	<0.001	0.49 (0.45, 0.53)	<0.001
Respiratory rate <=24 breaths/min	5	-0.40 (-4.35, 3.56)	0.036		
Respiratory rate >24 breaths/min	5	2.03 (0.46, 3.59)			
Heart rate (bpm)*	94.50 vs. 82.00	0.35 (-0.42, 1.13)	0.357	1.33 (0.67, 1.99)	<0.001
	82.00 vs. 71.00	0.90 (-0.05, 1.85)		1.77 (0.98, 2.57)	
ECG QRS interval (ms)	1	0.00 (-0.03, 0.04)	0.777	0.05 (0.03, 0.08)	<0.001
Dyspnea VAS	1	0.02 (-0.03, 0.06)	0.478		
Albumin (g/L)	1	0.09 (-0.15, 0.32)	0.469		
ALT (U/l)	Doubling	-0.80 (-1.93, 0.34)	0.169		
BUN (mmol/L)	Doubling	0.38 (-1.21, 1.96)	0.642	1.53 (0.18, 2.87)	0.026
Creatinine <= 120 (umol/L)	5	-0.32 (-0.65, 0.01)	0.099		
Creatinine > 120 (umol/L)	5	0.22 (-0.02, 0.46)			
Hemoglobin (g/dL)	1	-0.00 (-0.58, 0.58)	0.992		

Sodium (mmol/L)	3	0.67 (-0.15, 1.49)	0.112		
WBC (10**9/L)	1	-0.27 (-0.56, 0.01)	0.060	-0.33 (-0.56, -0.09)	0.006
BNP (pg/mL)	Doubling	0.29 (-0.28, 0.86)	0.314		
Troponin-I (ng/mL)	Doubling	-0.03 (-0.30, 0.24)	0.848		
Treated with Tezosetan	Yes vs. No	6.85 (4.71, 9.00)	<.001	6.17 (4.39, 7.96)	<0.001

**** Non-linear association modeled as quadratic transformation. Estimates for the 75th percentile vs. the median, and for the median vs. the 25th percentile are presented.***

Figure 1: Association of SBP change at 24 hours with creatinine change at 72 hours. The predicted value of the change in creatinine relative to the average change is plotted as a restricted cubic spline function of SBP change with knots at -45, -18, -4, 20 mmHg. Vertical tick marks represent individual patient values of the SBP change. Vertical reference lines for the 5th, 25th, 50th, 75th, and 95th percentiles of the SBP change distribution are shown.

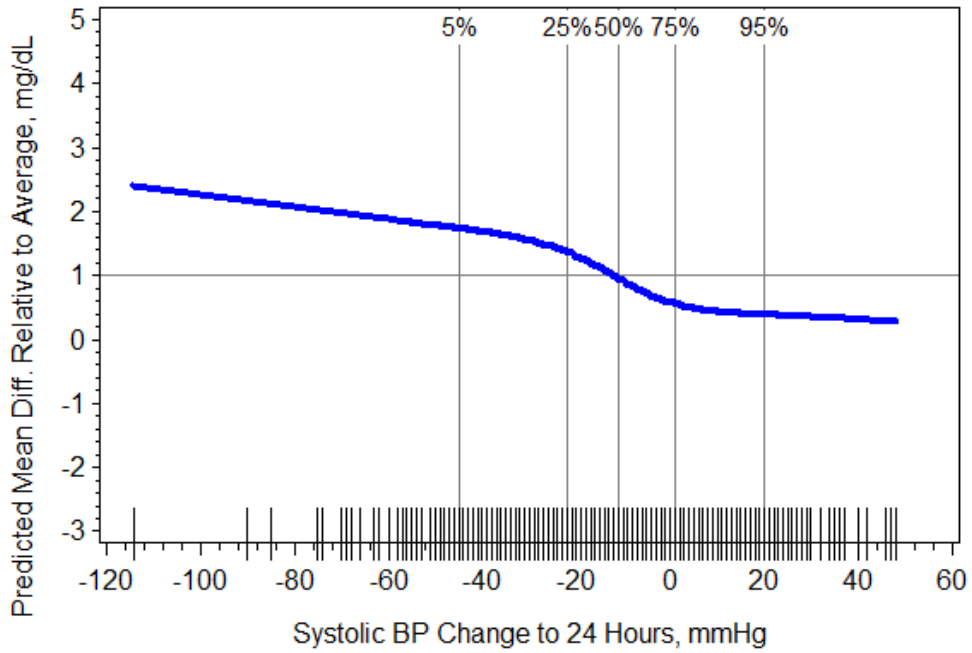

Figure 2: Association of SBP decrease by time from randomization with 180-day all-cause death. The hazard ratio per 1-mmHg greater decrease in SBP with associated 95% confidence intervals is given.