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Association of Early Blood Pressure Decrease and Renal Function With Prognosis in Acute Heart Failure

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the association between systolic blood pressure (SBP) drop, worsening renal function (WRF), and prognosis in patients with acute heart failure (AHF).

BACKGROUND A large drop in SBP early after hospital admission for AHF might be associated with increased risk for WRF and prognosis. However, there is a paucity of data regarding the interaction between WRF and a drop in SBP on clinical outcomes.

METHODS A post hoc analysis among 6,544 patients with AHF enrolled in the RELAX-AHF-2 (Relaxin in Acute Heart Failure-2) trial was performed. Blood pressure was uniformly and repetitively measured. Peak SBP drop was defined as the difference between baseline SBP and lowest SBP documented during the first 48 hours. WRF was defined by an increase in serum creatinine of ≥0.3 mg/dL from baseline to day 5.

RESULTS Peak SBP drop was independently associated with a higher risk for WRF (HR: 1.11 per 10 mm Hg SBP drop; $P < 0.001$), 5-day worsening heart failure (HR: 1.12 per 10 mm Hg SBP drop; $P = 0.006$), and 180-day cardiovascular death (HR: 1.09 per 10 mm Hg SBP drop; $P = 0.026$) after adjustment for potential confounders including baseline SBP. There was no interaction between the prognostic value of early SBP drop according to the presence or absence of WRF.

CONCLUSIONS In patients hospitalized for AHF, a greater early drop in SBP was associated with a higher incidence of WRF, worsening heart failure, and an increased risk for 180-day cardiovascular death. However, the association between SBP drop and prognosis was not influenced by WRF. (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF [RELAX-AHF-2]; NCT01870778) (J Am Coll Cardiol HF 2021;9:890–903) © 2021 by the American College of Cardiology Foundation.

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A drop in systolic blood pressure (SBP) early after hospital admission for acute heart failure (AHF) occurs frequently, and some studies have demonstrated an association among blood pressure drop, worsening renal function (WRF), and poor prognosis (1-3). However, these studies are hampered by variations in blood pressure measurements and a limited number of events, and thus a clear association among these 3 factors has yet to be elucidated. Although we previously reported that higher left ventricular ejection fraction is associated with less reduction in blood pressure, other factors associated with a greater SBP drop in the acute phase remained to be clarified (4). Moreover, the analysis used data based on blood pressure measured at only 2 time points (baseline and day 5), although repetitive measurements were performed during the first 48 hours of the study period and did not capture the transient SBP drop that sometimes occurs in patients with AHF. We also previously reported a significant association between peak SBP drop within 48 hours of hospital admission for AHF and WRF, but we could not demonstrate an association with clinical outcome, because of a small number of events (3). In addition, accumulating evidence suggests that WRF is not always associated with deleterious outcomes, and its prognostic implication depends strongly on the clinical context in which it occurs (5,6). To our knowledge, no study has investigated the prognostic implication of an early drop in SBP and the influence of WRF, even though these 2 events frequently occur together.

Therefore, the aim of this study was to investigate the association among an early drop in SBP, changes in renal function, and clinical outcome in a large and contemporary cohort of patients hospitalized for AHF, on the basis of intensive and uniform assessment of blood pressure measurements (7).

METHODS

PATIENT POPULATION. This was a post hoc analysis of the RELAX-AHF-2 (Relaxin in Acute Heart Failure-2) trial (NCT01870778). The background, design, and main results have been described previously (7,8). Briefly, 6,545 patients with AHF received either serelaxin 30 μg/kg per day or placebo infusion for 48 hours within 16 hours of presentation of AHF. Eligibility criteria were as follows: AHF diagnosis, SBP ≥125 mm Hg at screening, dyspnea at rest or mild exertion, intravenous diuretic agent use, glomerular filtration rate 25 to 75 mL/min/1.73 m^2, and elevated brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) level. Subjects were excluded from the study if vasodilators (including nesiritide), positive inotropic agents and vasopressors, or mechanical support for AHF were provided within 2 hours prior to screening or planned to be performed during the study drug infusion period. Only if the patient had SBP >150 mm Hg at screening, intravenous nitrates at a dose of ≤0.1 mg/kg/h were allowed to be administered. The ethics committee at each trial center approved the trial, and all patients provided written informed consent.

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

BNP = brain natriuretic peptide

CV = cardiovascular

NT-proBNP = N-terminal pro-brain natriuretic peptide

SBP = systolic blood pressure

WHF = worsening heart failure

WRF = worsening renal function

STUDY PROCEDURES AND BLOOD PRESSURE MEASUREMENT. All patients enrolled in the study were assigned to receive either serelaxin 30 μg/kg/d or matching placebo as a continuous intravenous infusion for 48 hours. Blood pressure measurements were recorded at 30 minutes and 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 hours of study drug administration. Predefined protocol-based study drug dose adjustment was performed for all participants; when SBP dropped by >40 mm Hg from baseline at any time point, but SBP was still >100 mm Hg, the study drug infusion rate was halved for the remainder of the infusion period. If SBP declined to <100 mm Hg, the study drug was discontinued.

DEFINITIONS OF PEAK SBP DROP, WRF, AND PROGNOSTIC ENDPOINTS. Peak SBP drop was defined as the difference between the baseline value and the lowest value recorded during the first 48 hours of the study period. For instance, if baseline SBP was 150 mm Hg and the lowest SBP during 48 hours was 125 mm Hg, the peak SBP drop was 25 mm Hg (not −25 mm Hg). WRF was defined by a serum creatinine increase of ≥0.3 mg/dL through day 5 (or on day 4 if day 5 creatinine measurement was not available) (4). As the original coprimary endpoint was 5-day worsening heart failure (WHF) and 180-day cardiovascular (CV) death, these 2 endpoints were used as prognostic endpoints. In accordance with the original definition, WHF was defined as worsening signs or symptoms of heart failure that led to an intensification of treatment for heart failure or death from any cause or rehospitalization for heart failure among patients who had been discharged before day 5. Additional protocol details are described elsewhere (7,8).

STATISTICAL ANALYSIS. Baseline characteristics are summarized by tertiles of peak SBP drop within the first 48 hours of the study period. Data are presented as mean ± SD when normally distributed, as median (interquartile range) for skewed variables, and as

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TABLE 1 Baseline Patient Characteristics by Tertiles of Peak Systolic Blood Pressure Drop Within the First 48 Hours

	Tertile 1 (0-19 mm Hg) (n = 2,225)	Tertile 2 (19-31 mm Hg) (n = 2,378)	Tertile 3 (31-119 mm Hg) (n = 1,941)	*P* Value
Age (y)	74 (66-81)	74 (66-81)	76 (67-82)	<0.001
Male	1,333 (59.9)	1,463 (61.5)	1,111 (57.2)	0.016
Race				
White	2,055 (92.4)	2,207 (92.8)	1,753 (90.3)	
Other	35 (1.6)	34 (1.4)	23 (1.2)	
Geographic region				<0.001
Europe	1,773 (79.7)	1,903 (80.0)	1,455 (75.0)	
America/other	452 (20.3)	475 (20.0)	486 (25.0)	
Medical history				
Hypertension	2,036 (91.5)	2,110 (88.9)	1,728 (89.1)	0.006
Diabetes mellitus	1,091 (49.1)	1,086 (45.7)	836 (43.1)	<0.001
Myocardial infarction	708 (32.1)	810 (34.4)	625 (32.5)	0.225
AF/atrial flutter	1,208 (54.4)	1,256 (53.0)	1,000 (51.7)	0.215
Peripheral arterial occlusive disease	315 (14.4)	298 (12.6)	264 (13.8)	0.220
Cerebrovascular accident	369 (16.6)	359 (15.1)	280 (14.5)	0.139
Asthma/bronchitis/COPD	535 (24.1)	560 (23.6)	487 (25.1)	0.490
Depression	223 (10.1)	212 (8.9)	188 (9.7)	0.424
Heart failure characteristics				
History of heart failure	1,692 (44.6)	1,818 (76.5)	1,343 (69.2)	<0.001
History of hospitalization for heart failure	1,158 (55.8)	1,284 (57.1)	895 (50.1)	<0.001
Ischemic etiology	936 (55.4)	977 (53.9)	694 (51.8)	0.142
NYHA functional class 1 mo before admission for index heart failure event				
I	63 (3.8)	78 (4.4)	69 (5.3)	0.081
II	621 (37.5)	689 (38.6)	538 (41.2)	
III	794 (47.9)	832 (46.6)	557 (42.6)	
IV	179 (10.8)	185 (10.4)	143 (10.9)	
Left ventricular ejection fraction (%)	40 (30-50)	36 (28-50)	40 (30-50)	<0.001
Cardiac resynchronization therapy	86 (3.9)	99 (4.2)	69 (3.6)	0.596
Implantable cardioverter-defibrillator	184 (8.3)	228 (9.6)	164 (8.5)	0.237
Baseline heart failure medication				
ACE inhibitor or ARB	1,472 (69.8)	1,602 (71.1)	1,226 (66.8)	0.011
Beta-blocker	1,576 (74.7)	1,715 (76.2)	1,358 (74.0)	0.273
Aldosterone antagonist	648 (30.7)	749 (33.3)	463 (25.2)	<0.001
Oral loop diuretic	1,417 (67.2)	1,497 (66.5)	1,119 (61.0)	<0.001
Oral loop diuretic at screening in furosemide equivalent dose	40 (20-80)	40 (20-80)	40 (20-80)	0.474
Physical examination				
Weight (kg)	83 (70-96)	82 (70-95)	81 (68-95)	0.011
BMI (kg/m^2)	29.2 (25.5-33.3)	28.9 (25.5-33.0)	28.8 (25.0-33.2)	0.197
Systolic blood pressure (mm Hg)	134 (128-142)	137 (130-147)	148 (138-163)	<0.001
Diastolic blood pressure (mm Hg)	77 (69-85)	80 (70-88)	81 (70-93)	<0.001
Pulse rate (beats/min)	78 (69-90)	80 (70-88)	81 (72-93)	<0.001
Respiratory rate (breaths/min)	21 (18-24)	21 (18-24)	21 (18-24)	0.651
Edema				<0.001
1+	583 (28.4)	668 (29.7)	587 (32.0)	
2+	775 (37.7)	773 (34.4)	583 (31.8)	
3+	442 (21.5)	457 (20.3)	351 (19.1)	
Clinical congestion composite score	5 (3-6)	5 (3-6)	5 (3-6)	0.353

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frequency (percentage) for categorical variables. Baseline characteristics were analyzed using analysis of variance for normally distributed variables and the Kruskal-Wallis test for skewed variables. For categorical variables, the chi-square test was used. If necessary, variables were transformed for further analyses.

To assess determinants of peak SBP drop, a multivariable linear regression model was developed to evaluate the decline in SBP levels from baseline to 48

TABLE 1 Continued

	Tertile 1 (0-19 mm Hg) (n = 2,225)	Tertile 2 (19-31 mm Hg) (n = 2,378)	Tertile 3 (31-119 mm Hg) (n = 1,941)	*P* Value
Laboratory				
Hemoglobin (g/L)	126 (112-139)	127 (113-142)	126 (113-140)	0.064
Creatinine (μmol/L)	115 (97-142)	114 (97-138)	111 (94-140)	0.001
eGFR (mL/min/1.73 m^2)	50 (39-62)	52 (40-63)	51 (40-63)	0.007
BUN (mmol/L)	8.8 (68.0-12.2)	8.6 (6.5-11.1)	8.2 (6.4-10.9)	0.088
Sodium (mmol/L)	140 (137-142)	140 (137-142)	140 (138-142)	0.024
NT-proBNP (pg/mL)	5,116 (3,065-9,923)	4,990 (2,813-9,227)	6,058 (3,019-10,217)	0.478
BNP (pg/mL)	347 (219-587)	354 (229-552)	300 (214-464)	0.012
Treatment with serelaxin	932 (41.9)	1,196 (50.3)	1,123 (57.9)	<0.001
Intravenous nitrates at randomization	111 (5.0)	106 (4.5)	143 (7.4)	<0.001
Amount of IV loop diuretic agents, furosemide dose equivalent (mg) 24 h/day 1 to day 5 or discharge if earlier	160 (60-280)	160 (80-280)	140 (60-280)	0.038
Oral loop diuretic agents, total dose (mg) taken during days 1-5	260 (174-425)	280 (180-439)	280 (180-430)	0.300

Values are median (interquartile range) or n (%).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; IV = intravenous; NT-proBNP = N-terminal pro–brain natriuretic peptide; NYHA = New York Heart Association.

hours using baseline patient clinical characteristics and routine laboratory parameters. As patients in the RELAX-AHF-2 trial had either NT-proBNP or BNP measured during hospitalization, we used log transformation and conversion into *z*-score to combine both biomarkers to obtain a composite of the NT-proBNP or BNP *z*-score.

The association between peak SBP drop and WRF was assessed in a binary logistic regression model. Cox proportional hazards models were constructed for 180-day CV death and 5-day WHF to evaluate the prognostic effect of peak SBP drop. In the multivariable model, adjustment was performed for predictors identified previously (9), namely, creatinine; hemoglobin; sodium; blood urea nitrogen; asthma, bronchitis, or chronic obstructive pulmonary disease; peripheral arterial occlusive disease; respiration rate; SBP; body mass index; edema; intravenous loop diuretic agents (total dose in furosemide U) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; treatment with serelaxin; composite of NT-proBNP or BNP *z*-score; sex; and age for 180-day CV death. Creatinine; hemoglobin; sodium; blood urea nitrogen; cerebrovascular accident; depression; asthma, bronchitis, or chronic obstructive pulmonary disease; atrial fibrillation or flutter; peripheral arterial occlusive disease; pulse rate; respiration rate; SBP; edema; intravenous loop diuretic agents (total dose in furosemide U) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; actual study treatment; geographic region; composite of NT-proBNP or BNP *z*-score; sex; and age were evaluated for 5-day WHF and WRF (9). Baseline SBP was included in all multivariable models for adjustment. The presence of a significant interaction between study treatment and the peak SBP drop on WRF and prognostic outcome were evaluated in an interaction analysis that included study treatment × peak SBP drop. For univariable and multivariable linear regression models for the peak drop in SBP within 48 hours of baseline and the Cox regression model, the results for all patients and for the placebo (no-serelaxin) groups are shown separately for comparison given that the study drug itself may have influenced the peak SBP drop. Two-sided *P* values <0.05 were considered to indicate statistical significance, and all statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing).

RESULTS

PATIENT CHARACTERISTICS AND PREDICTORS OF PEAK SBP DROP. Of the 6,545 patients randomized to the treatment groups, 3,274 patients were allocated to treatment with serelaxin. As 1 patient had no SBP recorded, we included a total of 6,544 patients for subsequent analyses. Overall, the median peak SBP drop was 24 mm Hg (interquartile range: 15-33 mm Hg). Baseline characteristics of patients stratified by tertiles of peak SBP are shown in Table 1. The factors associated with the peak SBP drop in univariable and multivariable linear regression analyses are shown in Table 2. In the multivariable linear

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TABLE 2 Univariable and Multivariable Linear Regression Models of Peak Drop in Systolic Blood Pressure Within 48 Hours From Baseline

	Univariable Model (All Patients)		Univariable Model (Placebo/Nothing Patients Only)		Multivariable Model (Placebo/Nothing Patients Only) Model $R^2 = 0.22$ Adjusted $R^2 = 0.21$ Overall $P < 0.001$		Multivariable Model (All Patients) Model $R^2 = 0.25$ Adjusted $R^2 = 0.24$ Overall $P < 0.001$	
	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Treatment with serelaxin	3.56 (2.88 to 4.25)	<0.001					3.45 (2.79 to 4.11)	<0.001
Age (per 1 y)	0.06 (0.03 to 0.09)	<0.001	0.04 (−0.01 to 0.08)	0.096	0.05 (0.01 to 0.1)	0.027	0.08 (0.05 to 0.11)	<0.001
Male	−1.16 (−1.87 to −0.46)	<0.001	−1.57 (−2.54 to −0.6)	0.002	0.47 (−0.63 to 1.58)	0.399	0.06 (−0.17 to 1.38)	0.127
Systolic blood pressure (per 1 mm Hg)	0.44 (0.42 to 0.46)	<0.001	0.42 (0.39 to 0.45)	<0.001	0.42 (0.39 to 0.46)	<0.001	0.45 (0.42 to 0.47)	<0.001
Pulse rate (per 1 beat/min)	0.05 (0.03 to 0.07)	<0.001	0.06 (0.03 to 0.09)	<0.001	0.07 (0.04 to 0.10)	<0.001	0.07 (0.05 to 0.09)	<0.001
Respiratory rate (per 1 breath/min)	0.02 (−0.06 to 0.10)	0.606	0.02 (−0.09 to 0.13)	0.725	−0.07 (−0.18 to 0.04)	0.191	−0.06 (−0.14 to 0.01)	0.106
Geographic region: Europe	−1.69 (−2.53 to −0.86)	<0.001	−1.67 (−2.83 to −0.5)	0.005	−1.07 (−2.25 to 0.12)	0.078	−1.51 (−2.21 to −0.83)	<0.001
Medical history								
Diabetes mellitus	−1.63 (−2.33 to −0.94)	<0.001	−1.73 (−2.69 to −0.77)	<0.001	−1.54 (−2.51 to −0.57)	0.002	−1.52 (−2.21 to −0.83)	<0.001
AF/atrial flutter	−0.46 (−1.15 to 0.24)	0.197	−0.02 (−0.98 to 0.94)	0.972	0.87 (−0.14 to 1.87)	0.092	0.76 (0.05 to 1.47)	0.036
Peripheral arterial occlusive disease	−0.26 (−1.27 to 0.75)	0.614	−0.87 (−2.26 to 0.52)	0.22	−0.88 (−2.28 to 0.51)	0.214	−0.48 (−1.47 to 0.5)	0.336
Cerebrovascular accident	−0.48 (−1.44 to 0.48)	0.325	−0.53 (−1.83 to 0.77)	0.422	0.38 (−0.89 to 1.66)	0.554	0.39 (−0.53 to 1.3)	0.409
Asthma/bronchitis/COPD	0.45 (−0.36 to 1.26)	0.276	−0.1 (−1.21 to 1.01)	0.858	0.4 (−0.69 to 1.48)	0.471	0.72 (−0.06 to 1.49)	0.072
Depression	0.47 (−0.70 to 1.65)	0.431	0.58 (−1.04 to 2.19)	0.484	−0.74 (−2.31 to 0.83)	0.357	−0.28 (−1.41 to 0.85)	0.632
History of hospitalization for heart failure	−1.08 (−1.79 to −0.37)	0.003	−1.39 (−2.38 to −0.4)	0.006	0.44 (−0.54 to 1.42)	0.38	0.78 (0.09 to 1.47)	0.028
Intravenous loop diuretic agents at randomization	−0.01 (−0.01 to 0.00)	0.027	−0.01 (−0.02 to 0.00)	0.113	0.0 (−0.01 to 0.01)	0.488	0.0 (−0.01 to 0.00)	0.232
Edema								
1+	−1.14 (−2.26 to −0.03)	0.045	−1.56 (−3.12 to 0.00)	0.05	−1.96 (−3.48 to −0.45)	0.011	−1.53 (−2.6 to −0.47)	0.005
2+	−2.91 (−4.00 to −1.82)	<0.001	−3.25 (−4.77 to −1.73)	<0.001	−3.31 (−4.80 to 1.83)	<0.001	−3.22 (−4.26 to −2.18)	<0.001
3+	−2.51 (−3.71 to −1.31)	<0.001	−3.27 (−4.93 to −1.6)	<0.001	−3.88 (−5.53 to −2.23)	<0.001	−2.51 (−3.67 to −1.35)	<0.001
Sodium	0.02 (−0.06 to 0.10)	0.578	−0.02 (−0.13 to 0.09)	0.675	−0.15 (−0.26 to −0.04)	0.007	−0.12 (−0.20 to 0.04)	0.004
Creatinine (per 1 μmol/L)	−0.02 (−0.03 to −0.01)	<0.001	−0.02 (0.04 to −0.01)	0.001	−0.15 (−0.26 to −0.04)	0.007	−0.03 (−0.04 to −0.01)	<0.001
Blood urea nitrogen (per 1 mg/dL)	−0.06 (−0.08 to −0.03)	<0.001	−0.03 (−0.07 to 0.01)	0.091	0.06 (0.01 to 0.11)	0.019	0.05 (0.02 to 0.09)	0.005
Hemoglobin	0.0 (−0.01 to 0.02)	0.618	0.01 (−0.02 to 0.03)	0.541	0.03 (0.00 to 0.06)	0.02	0.02 (0.00 to 0.04)	0.015
Composite z-score of NT-proBNP and BNP	−0.50 (−0.84 to −0.15)	0.005	−0.21 (−0.69 to 0.27)	0.381	0.03 (−0.46 to 0.52)	0.901	−0.17 (−0.52 to 0.17)	0.321

Abbreviations as in Table 1.

regression analysis performed in the placebo group, the strongest predictor of a greater peak SBP drop within 48 hours was a higher baseline SBP. Other independent predictors of a greater early SBP drop were older age; higher pulse rate; absence of history of diabetes; less peripheral edema; higher hemoglobin, creatinine, and blood urea nitrogen levels; and lower serum sodium levels. The adjusted R^2 value of the final model was 0.21. However, the R^2 value of the model with only baseline SBP was 0.21. When the serelaxin and placebo groups were analyzed together, treatment with serelaxin was significantly associated with greater peak SBP drop in both univariable and multivariable linear regression models. Otherwise, predictors of a greater SBP drop were largely similar.

RELATIONSHIP AMONG PEAK SBP DROP, WRF, AND PROGNOSTIC OUTCOMES. Table 3 and the Central Illustration show the association between the peak SBP drop and the incidence of WRF. In univariable Cox regression analyses, a >10 mm Hg drop in blood pressure was associated with a 15% greater risk for WRF ($P < 0.001$). This association remained statistically significant after adjustments for potential confounders, including baseline SBP (HR: 1.11; 95% CI: 1.07-1.16; $P < 0.001$). Likewise, a greater SBP drop was associated with a higher risk for both 5-day WHF (HR: 1.12; 95% CI: 1.03-1.22; $P = 0.006$) and 180-day CV death (HR: 1.09; 95% CI: 1.01-1.18; $P = 0.026$) even after adjustment for potential confounders, including baseline SBP (Table 2, Central Illustration). We also performed exploratory analyses regarding the

TABLE 3 Association Among Peak SBP Drop (Per 10 Mm Hg Drop) Within 48 Hours From Baseline, WRF, WHF, and 180-Day Cardiovascular Mortality

	WRF (n = 5,250, Number of Events = 1,470)[a]		5-Day WHF (n = 5,250, Number of Events = 388)[a]		180-Day Cardiovascular Death (n = 5,195, Number of Events = 476)[b]	
Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Unadjusted	1.15 (1.11-1.2)	<0.001	1.04 (0.97-1.12)	0.276	1.00 (0.94-1.07)	0.983
Adjusted for baseline SBP	1.10 (1.05-1.14)	<0.001	1.09 (1.01-1.18)	0.033	1.07 (0.99-1.15)	0.078
Adjusted for baseline model	1.11 (1.07-1.16)	<0.001	1.12 (1.03-1.22)	0.006	1.09 (1.01-1.18)	0.026

[a]Variables used for adjustment: creatinine (μmol/L); hemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dL); cerebrovascular accident; depression; asthma, bronchitis, or COPD; atrial fibrillation or flutter; peripheral arterial occlusive disease; pulse rate (beats/min); respiration rate (breaths/min); systolic blood pressure (mm Hg); edema; IV loop diuretic agents (total dose in furosemide units) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; actual study treatment; geographic region; composite of NT-proBNP or BNP *z*-score; sex; and age (y). [b]Variables used for adjustment: creatinine (μmol/L); hemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dL); asthma, bronchitis, or COPD; peripheral arterial occlusive disease; respiration rate (breaths/min); systolic blood pressure (mm Hg); body mass index (kg/m^2); edema; IV loop diuretic agents (total dose in furosemide U) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; treatment with serelaxin; composite of NT-proBNP or BNP *z*-score; sex; and age (y).

SBP = systolic blood pressure; WHF = worsening heart failure; WRF = worsening renal function; other abbreviations as in Tables 1 and 2.

association between peak SBP drop and more proximate causes of CV mortality using 30-day and 60-day CV death and found that this association was attenuated and turned to be not significant after adjustment for the covariates (for 30-day CV death: HR: 1.08; 95% CI: 0.94-1.24; $P = 0.267$; for 60-day CV death: HR: 1.07; 95% CI: 0.96-1.20; $P = 0.207$). We found no significant interaction between treatment with serelaxin or placebo and the prognostic impact of SBP drop in univariable and multivariable models ($P > 0.37$ for all) (Supplemental Table 1). WRF was not significantly associated with an increased risk for 180-day CV death after adjustment for other covariates (HR: 1.12; 95% CI: 0.91-1.39; $P = 0.273$).

To evaluate whether the prognostic impact of a greater SBP drop was influenced by the occurrence of WRF, we stratified patients into 3 groups; peak SBP drop below the median (n = 2,730) and peak SBP drop equal to or above the median with WRF (n = 801) and without WRF (n = 1,708).

With regard to 5-day WHF, significant group differences were observed on Kaplan-Meier curve analysis, and those with peak SBP drop above the median with WRF were associated with the worst outcome (**Figure 1**). In unadjusted and adjusted Cox regression, we also found that above-median SBP drop with WRF, but not without WRF, was associated with significantly higher risk for 5-day WHF even after adjustment for other covariates (**Table 3**). However, in the interaction plots, a marginal but not significant interaction between peak SBP drop and WRF on the risk for 5-day WHF was found in all unadjusted and adjusted models (**Figure 2**).

Regarding the outcome of 180-day CV death, no group differences were identified for 180-day CV mortality in Kaplan-Meier curves (**Figure 1**). The same result was observed when we stratified patients into 4 groups; peak SBP drop below the median with (n = 680) and without (n = 2,050) WRF and peak SBP drop equal to or above the median with (n = 801) and without (n = 1,708) WRF (Supplemental Figure 1). Likewise, unadjusted and SBP-adjusted Cox regression models showed that both groups with peak SBP drop above the median had poorer outcomes (**Table 4**), and we found no statistically significant difference between the groups with above-median SPB drop with and without WRF ($P = 0.779$). In addition, no significant interactions were found between peak SBP drop on a continuous scale and WRF on 180-day CV mortality (P for interaction >0.20 for all unadjusted and adjusted models) (**Figure 2**).

We further developed linear mixed-model plots to illustrate the temporal differences of percentage serum creatinine changes until discharge, stratified by tertile values of peak SBP drop (Supplemental Figure 2). Large changes in creatinine values were generally associated with a larger SBP drop, and we observed that an increase in creatinine from baseline occurred at a relatively early time point and that trajectories were almost parallel afterward.

DISCUSSION

In this post hoc analysis of RELAX-AHF-2 trial data, we found a greater peak SBP drop early after hospital admission for AHF was significantly and independently associated with a higher incidence of WRF. Furthermore, a greater peak SBP drop was significantly associated with a higher risk for 5-day WHF and 180-day CV death, but WRF was not. Finally, the association between a greater early SBP drop and higher risk for 5-day WHF and 180-day CV death was not significantly influenced by the occurrence of WRF.

The present study used data from the RELAX-AHF-2 trial. In this trial involving patients hospitalized for AHF, serelaxin treatment did not result in a lower

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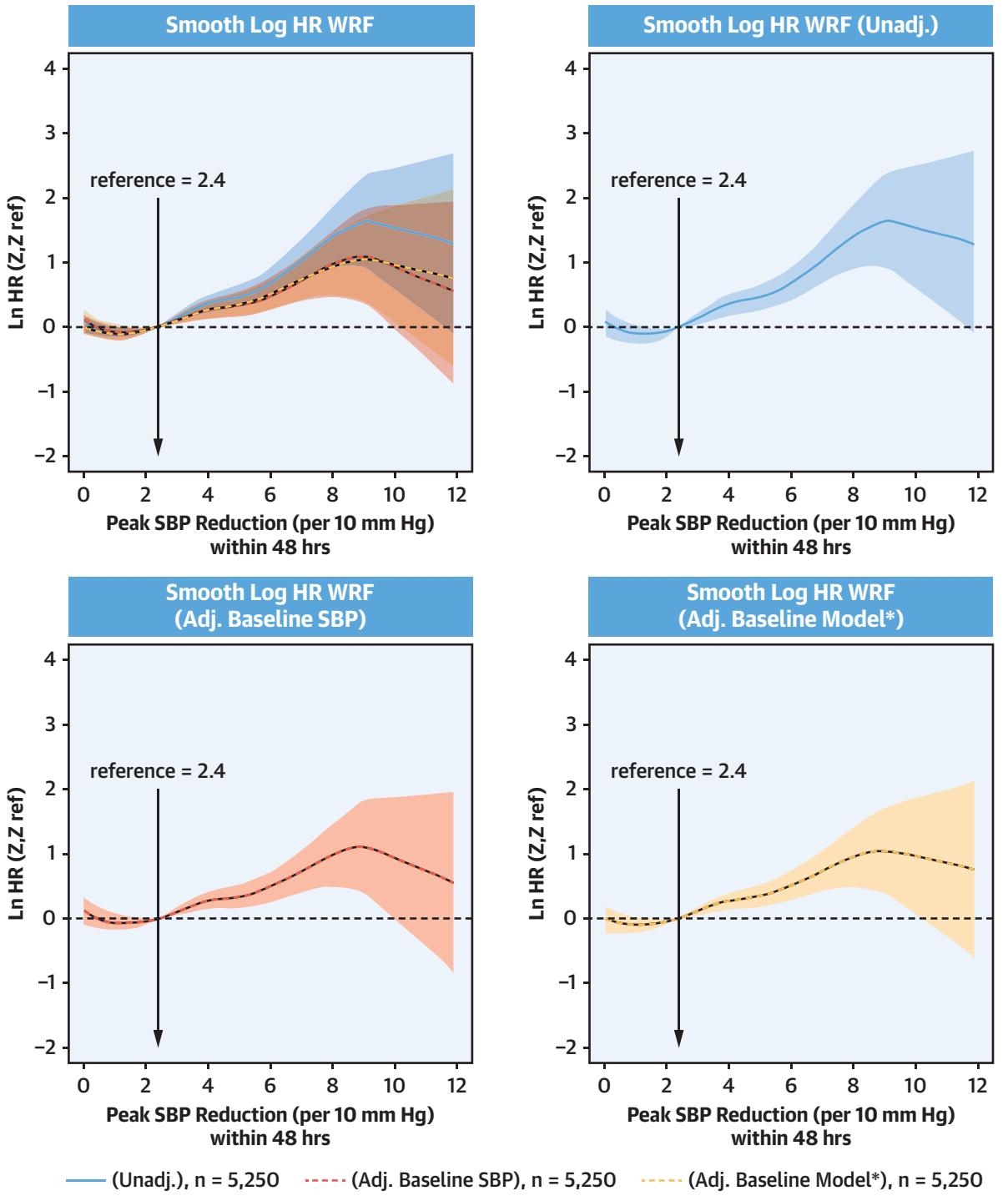
CENTRAL ILLUSTRATION **Smooth Log-Hazard Plot for Worsening Renal Function, 180-Day Cardiovascular Death, and 5-Day Worsening Heart Failure With Peak Systolic Blood Pressure Drop Within 48 Hours**



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The risk for worsening renal function **(A)**, 180-day cardiovascular death **(B)**, and 5-day worsening heart failure **(C)** over the spectrum of systolic blood pressure (SBP) drop was evaluated using a smooth log-hazard plot for unadjusted (Unadj.) and adjusted (Adj.) models. Peak SBP drop was positively associated with the risk for all 3 outcomes in an unadjusted model. This association was retained even after adjustment for baseline model.

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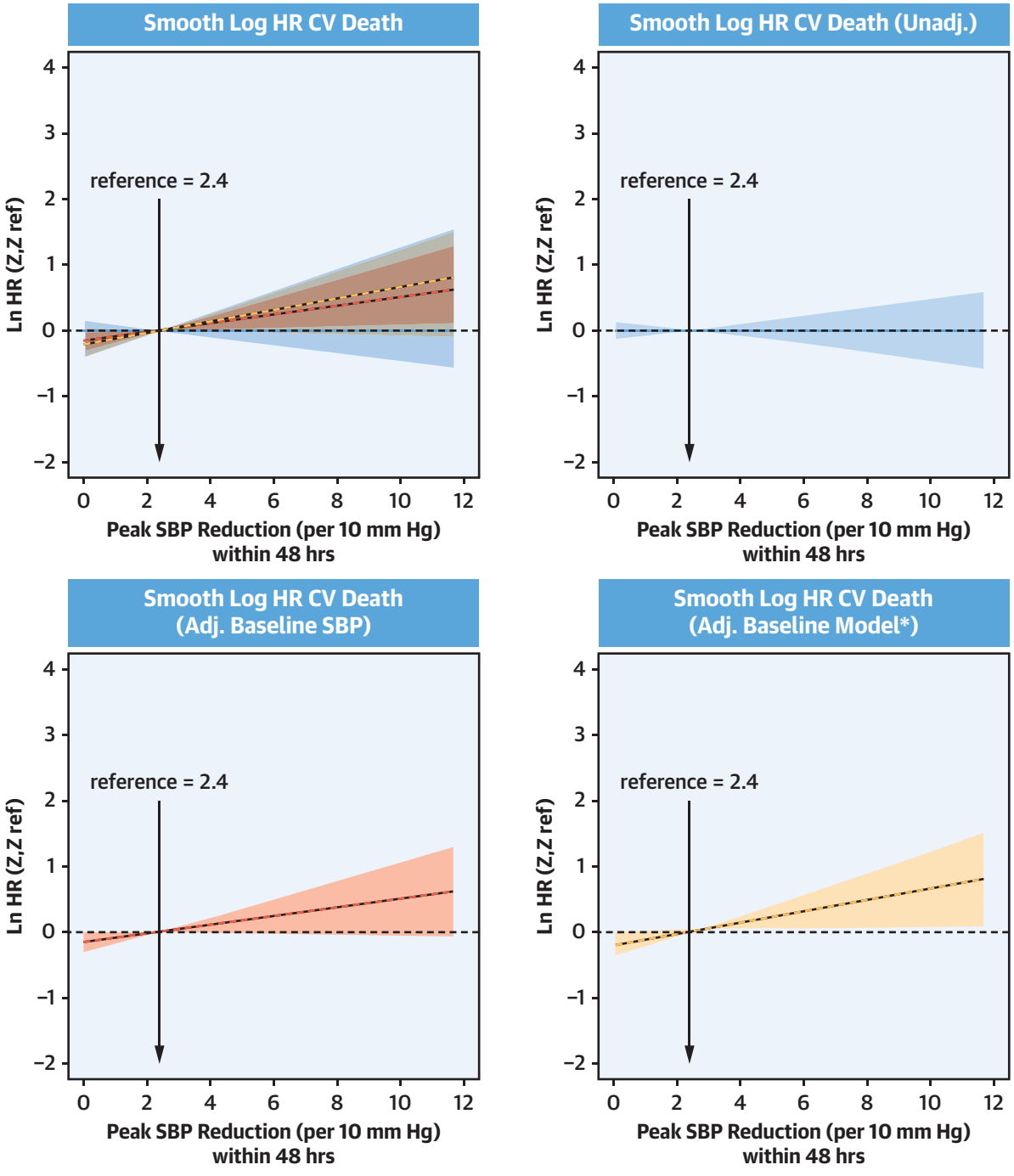
CENTRAL ILLUSTRATION Continued



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CENTRAL ILLUSTRATION Continued

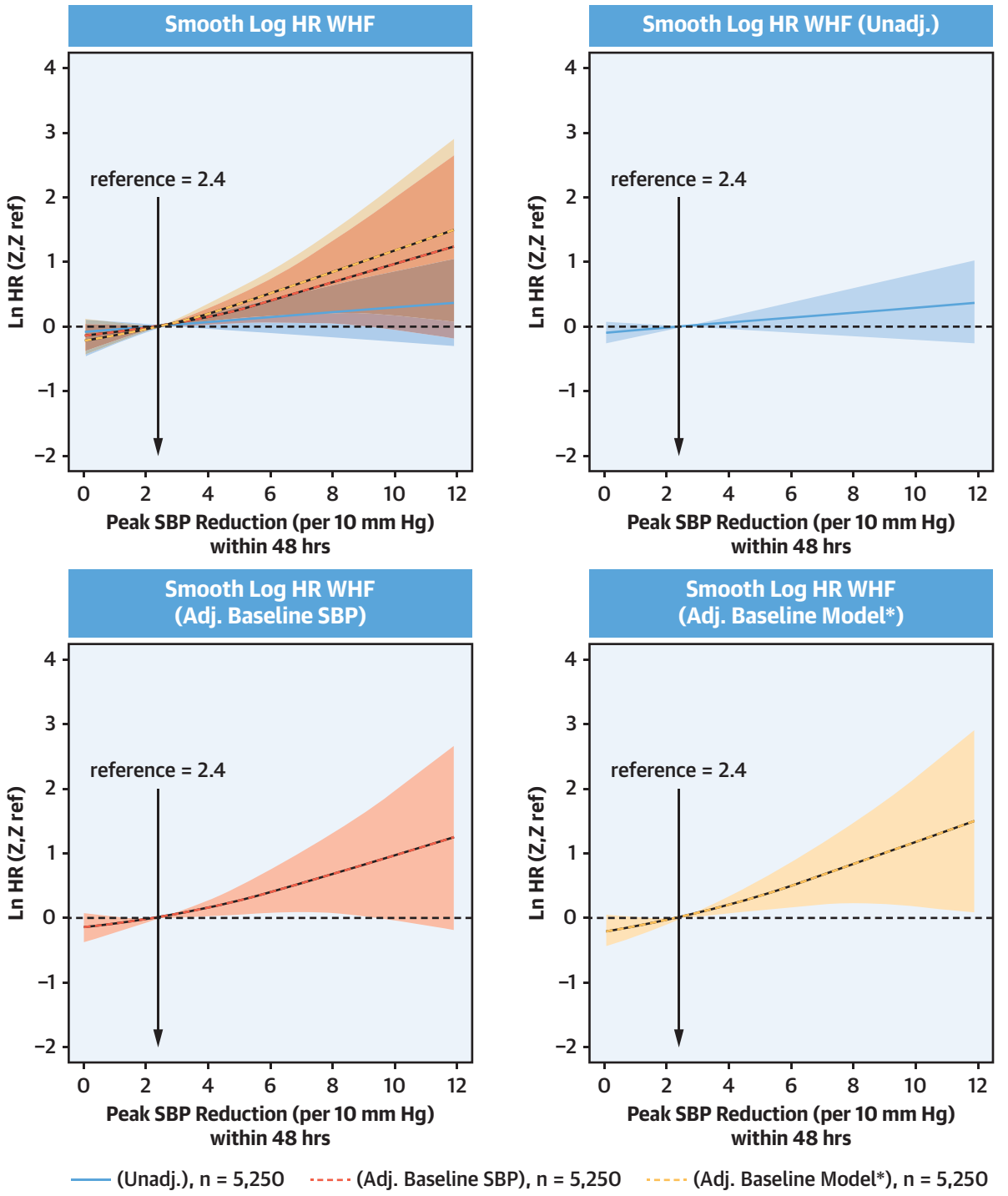

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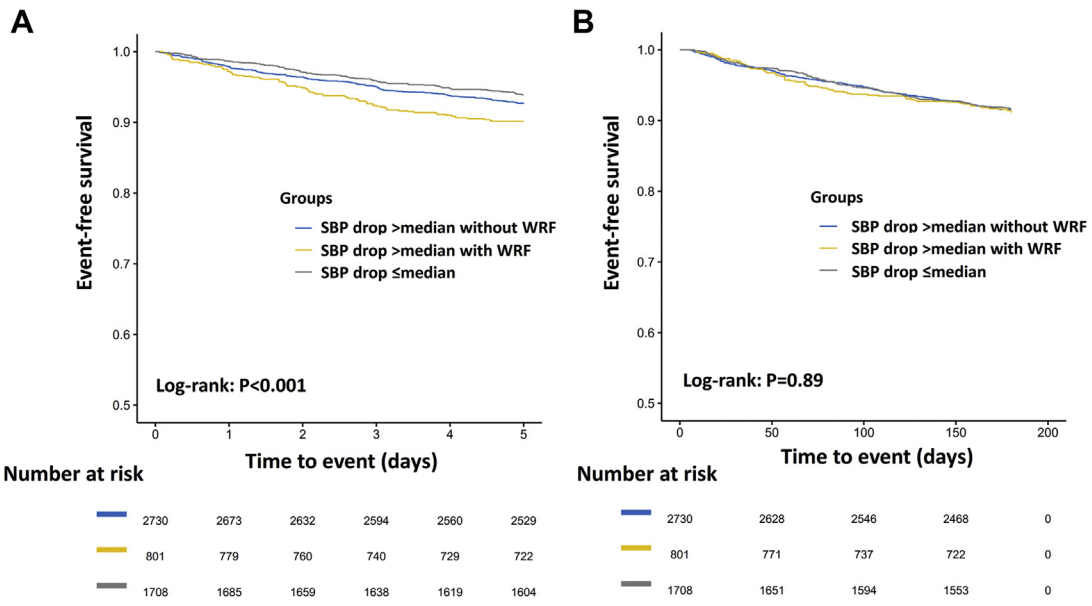
FIGURE 1 **Kaplan-Meier Curves for 5-Day Worsening Heart Failure and 180-Day Cardiovascular Death Stratified by SBP Drop Above or Equal to or Below the Median Value (24 mm Hg) Within 48 Hours With and Without WRF**



There were significant group differences in 5-day worsening heart failure **(A)** in Kaplan-Meier curve analysis, and these differences were retained in multivariable Cox regression model (see Table 2). As for 180-day cardiovascular mortality **(B)**, no group differences were found in both Kaplan-Meier curve analysis and univariate and multivariable Cox regression analysis (Table 2). SBP = systolic blood pressure; WRF = worsening renal function.

incidence of 5-day WHF or death from CV causes at 180 days compared with placebo (7). However, serelaxin was significantly associated with a greater drop in SBP. In addition, we identified several other predictors of an early drop in SBP, such as older age; higher pulse rate; absence of history of diabetes; less peripheral edema; higher hemoglobin, creatinine, and blood urea nitrogen levels; and lower serum sodium levels. However, the strongest predictor of SBP drop was a higher baseline SBP value. It should be noted that the poor predictive value of the final model was driven almost completely by higher baseline SBP. This finding was not substantially altered by including and excluding the serelaxin treatment group, and the same factors were identified to be associated with peak SBP drop except for serelaxin treatment. Although a higher baseline SBP value was also strongly associated with a greater SBP drop in another study (2), this finding could be explained by "regression toward the mean" rather than a specific pathophysiological mechanism. Instead, our results imply that SBP drop is not readily predictable from patient characteristics or baseline information other than baseline SBP. It should also be acknowledged that the present study was focused on the changes in SBP that occurred only during the first 48 hours of hospital admission.

The association between a greater SBP drop in the early phase of hospitalization and WRF observed in the present study could be explained by impaired compensatory mechanisms occurring in patients with heart failure. In healthy subjects, the kidney usually can maintain renal perfusion pressure with its autoregulatory responses even when systemic blood pressure changes considerably. However, this compensatory system is blunted in patients with heart failure, and the decrease in systemic blood pressure can be directly associated with a reduction in renal blood flow and subsequent decline in the glomerular filtration rate (10). Another possible explanation for this association is treatment with drugs used to modulate the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which may lead to both SBP drop and WRF. However, we did not find any association between the use of these agents and creatinine rise in a previous analysis (4).

One of the objectives of our study was to demonstrate that WRF did not modify the prognostic impact

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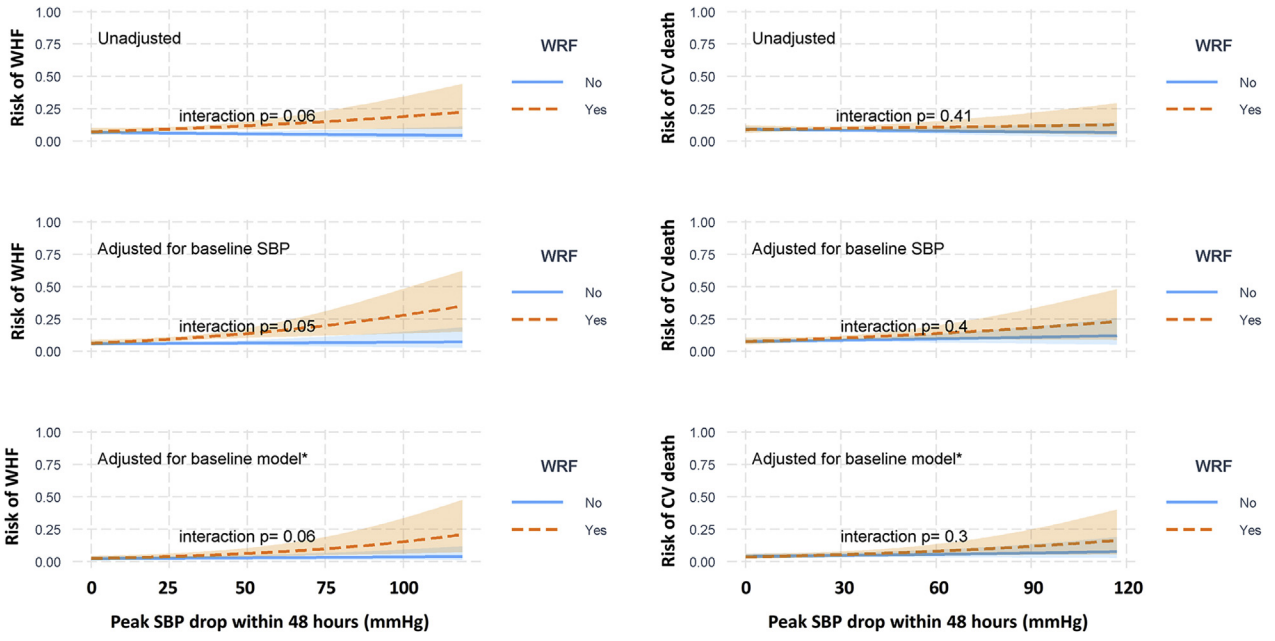
FIGURE 2 Interactions Between WRF and Peak SBP Drop on 5-Day Worsening Heart Failure and 180-Day Cardiovascular Mortality



There was a marginal but not significant interaction between peak SBP drop and WRF on the risk for 5-day worsening heart failure in both unadjusted and adjusted models. Likewise, no interaction was found between peak SBP drop and WRF on the risk for 180-day cardiovascular death. **Shaded areas** represent 95% CIs. *Adjusted for creatinine (μmol/L); hemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dL); asthma, bronchitis, or chronic obstructive pulmonary disease; peripheral arterial occlusive disease; respiration rate (breaths/min); systolic blood pressure (mm Hg); body mass index (kg/m^2); edema; intravenous loop diuretic agents (total dose in furosemide units) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; actual study treatment; composite of N-terminal pro–brain natriuretic peptide or brain natriuretic peptide *z*-score; sex; and age (years). Abbreviations as in Figure 1.

of SBP drop in AHF. Interestingly, a recent position statement from the Heart Failure Association of the European Society of Cardiology on changes in renal markers during the treatment of AHF suggests that the combination of WRF and SBP drop may be associated with poor prognosis and recommends avoiding hypotension during decongestion (11). However, the statement does not suggest that worse outcomes related to a greater SBP drop are driven by WRF. Although worse baseline renal function is strongly and consistently associated with worse clinical outcomes, the association between WRF and clinical outcome is not consistent (12). Accumulating evidence suggests that in some patients, WRF can even be associated with better outcomes. For instance, WRF occurring during favorable ongoing diuresis and improvement in heart failure status was associated with a better prognosis in patients with AHF (13). Therefore, the association between WRF and clinical outcome seems to depend on the clinical context in which WRF occurs. This is supported by our findings that WRF was not strongly related to 180-day CV death.

A substudy of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) study demonstrated that 21.8% of all participants experienced hypotension predominantly during the first 48 hours, but hypotension had no significant effect on changes in creatinine levels overtime (14). Nevertheless, hypotension was associated with worse prognosis (30-day mortality, 30-day heart failure hospitalization, and 30-day mortality or all-cause hospitalization) independent of other prognostic factors including baseline SBP. The discordance between the results of the ASCEND-HF study and those of the present study in terms of the association between SBP drop and WRF may be attributable to differences in the definition of a blood pressure drop. In the ASCEND-HF study, hypotension was reported by the investigators on the basis of their clinical judgment according to the patients' ambulatory blood pressure, and an SBP cutoff of 90 mm Hg was used if they were uncertain about patients' ambulatory SBP. This implies that no standardized definition of hypotension was used; thus, the clinical applicability of this finding is not

TABLE 4 Associations Between Above-Median Peak SBP Drop With and Without WRF and 5-Day WHF and 180-Day Cardiovascular Death

	Unadjusted		Adjusted for Baseline SBP		Adjusted for Baseline Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
5-d WHF						
SBP drop equal to or below median	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
SBP drop above median with WRF	1.40 (1.05-1.87)	0.023	1.62 (1.19-2.19)	0.002	1.65 (1.22-2.24)	0.001
SBP drop above median without WRF	0.85 (0.65-1.10)	0.211	0.94 (0.71-1.23)	0.631	0.99 (0.75-1.30)	0.941
180-d cardiovascular death (n = 4,200, number of events = 368)						
SBP drop equal to or below median	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
SBP drop above median with WRF	1.09 (0.81-1.46)	0.575	1.3 (0.96-1.76)	0.096	1.35 (0.99-1.83)	0.059
SBP drop above median without WRF	1.08 (0.86-1.36)	0.490	1.23 (0.97-1.55)	0.087	1.29 (1.01-1.63)	0.039

Covariates for 5-d WHF: creatinine (μmol/L); hemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dL); cerebrovascular accident; depression; asthma, bronchitis, or COPD; atrial fibrillation or flutter; peripheral arterial occlusive disease; pulse rate (beats/min); respiration rate (breaths/min); systolic blood pressure (mm Hg); edema; IV loop diuretic agents (total dose in furosemide U) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; actual study treatment; grouped geographic region; composite of NT-proBNP or BNP *z*-score; sex; and age (y). Covariates for 180-d cardiovascular death: creatinine (μmol/L); hemoglobin (g/L); sodium (mmol/L); blood urea nitrogen (mg/dL); asthma, bronchitis, or COPD; peripheral arterial occlusive disease; respiration rate (breaths/min); systolic blood pressure (mm Hg); body mass index (kg/m^2); edema; IV loop diuretic agents (total dose in furosemide U) at baseline; known history of diabetes mellitus; prior heart failure hospitalization; actual study treatment; composite of NT-proBNP or BNP *z*-score; sex; and age (years).

Abbreviations as in Tables 1 to 3.

clear. Moreover, hypotension was not quantitatively evaluated, which possibly lessened the power to detect the association between SBP drop and WRF in patients with AHF.

One of the strengths of our study is the uniform, precise, and repetitive (multiple time points) measurement of blood pressure during the acute phase of AHF, which enabled a better evaluation of the association between blood pressure changes and WRF. Indeed, 2 other studies that quantitatively measured the drop in SBP consistently showed a significant positive association between SBP drop and incidence of WRF (2,15). A subanalysis of the VERITAS (Tezosentan in Acute Heart Failure) study showed that a quantitatively evaluated SBP drop during the first 24 hours (2 time points) was associated with WRF and poor prognosis (2). Our results corroborate and reinforce these associations using more time points and precise blood pressure data from a larger number of patients. However, it should also be noted that our study showed this association independently of baseline SBP values, whereas the association between SBP drop and WRF was not adjusted for baseline SBP in the VERITAS study. As high baseline SBP is strongly associated with both WRF and greater SBP drop (12,15), it is not surprising that patients with greater SBP drop are likely to have a higher incidence of WRF if this confounder is not adjusted for in multivariable analysis.

STUDY LIMITATIONS. An important limitation of this analysis that should be emphasized is that the primary objective was to examine the prognostic impact of SBP changes that were observed during a limited time window (ie, the first 48 hours of hospitalization). Therefore, our study results can be confounded by treatments that have occurred after this early time period and the related management after discharge and changes in blood pressure and renal function that occurred after this time window. The lack of association between peak SBP drop and 30-day and 60-day CV death may support this possibility. As we could not capture these potential confounders for all patients and perform adjustment, our study results should be regarded as hypothesis generating. This limitation should be taken into account when interpreting the study results, which showed the lack of interaction between SBP drop and WRF on prognostic outcomes.

A second limitation is that our results might not be applicable to patients with AHF who do not meet the inclusion criteria of the RELAX-AHF-2 study, especially those with SBP <125 mm Hg. Given that patients with low SBP are already at high risk for poor prognosis, the association between SBP drop and poor prognosis should be further studied in cohorts including patients with lower baseline SBP values. Notably, the use of intravenous vasodilators was allowed only in small dosages (≤0.1 mg/kg/h) and only if the patient's SBP was >150 mm Hg at screening in the RELAX-AHF-2 trial. Given that vasodilators are the third most frequently used drugs in patients with AHF, and they also affect SBP, this point should be considered when applying our study results to patients with AHF. Also, we could not incorporate important biomarkers, including cardiac troponin, into our analysis because data were available in a very limited number of patients.

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CONCLUSIONS

We found that an early drop in SBP observed during the first 48 hours of a hospitalization for AHF was associated with WRF, 5-day WHF, and 180-day CV mortality. However, WRF was not strongly related to worse outcomes, and the prognostic value of a drop in SBP on 5-day WHF and 180-day CV death was not modified by the occurrence of WRF. Further studies are required to clarify the causality between changes in blood pressure and renal function and their impact on prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Greater SBP drop in the acute phase was associated with higher incidence of WRF, 5-day WHF, and higher 180-day CV mortality. The negative impact of large SBP drop on prognosis is independent of its association between peak SBP drop and WRF.

TRANSLATIONAL OUTLOOK: It is unclear whether these study results are applicable to patients with AHF whose blood pressure is relatively low. Further exploration of the pathophysiological background of SBP drop, WRF, and prognosis is warranted.

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KEY WORDS acute heart failure, blood pressure, renal dysfunction

APPENDIX For supplemental figures and a table, please see the online version of this paper.