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ORIGINAL RESEARCH

Systolic Blood Pressure and Outcome in Patients Admitted With Acute Heart Failure: An Analysis of Individual Patient Data From 4 Randomized Clinical Trials

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BACKGROUND: In acute heart failure (AHF), systolic blood pressure (SBP) is an important clinical variable. This study assessed the association between SBP and short-term and long-term outcomes in a large cohort of patients with AHF.

METHODS AND RESULTS: This is an analysis of 4 randomized controlled trials investigating serelaxin versus placebo in patients admitted with AHF and SBPs from 125 to 180 mm Hg. Outcomes were 180-day all-cause mortality and a composite end point of all-cause mortality, worsening heart failure, or hospital readmission for heart failure the first 14 days. Left ventricular ejection fraction (LVEF) was examined as LVEF<40% and LVEF≥40%. Multivariable Cox regression models were adjusted for known confounders of outcomes in AHF. A total of 10 533 patients with a mean age of 73 (±12) years and a mean SBP of 145 (±7) mm Hg were included. LVEF was assessed in 9863 patients (93%); 4737 patients (45%) had LVEF<40%. Increasing SBP was inversely associated with 180-day mortality (adjusted hazard ratio [$HR_{adjusted}$], 0.93; 95% CI, 0.89–0.98; P=0.008 per 10 mm Hg increase) and with the composite end point ($HR_{adjusted}$, 0.90; 95% CI, 0.85–0.94; P<0.001 per 10 mm Hg increase). A significant interaction with LVEF was observed, revealing that SBP was not associated with mortality in patients with LVEF≥40% ($HR_{adjusted}$, 0.98; 95% CI, 0.91–1.04; per 10 mm Hg increase), but was strongly associated with increased mortality in LVEF<40% ($HR_{adjusted}$, 0.84; 95% CI, 0.77–0.92; per 10 mm Hg increase).

CONCLUSIONS: Elevated SBP is associated with favorable short-term and long-term outcomes in patients with AHF. In our predefined subgroup analysis, we found that baseline SBP was not associated with mortality in LVEF≥40%, but was strongly associated with mortality in patients with LVEF<40%.

Key Words: acute heart failure ■ blood pressure ■ left ventricular ejection fraction ■ mortality ■ worsening heart failure

Acute heart failure (AHF) accounts for ≈1 000 000 hospital visits in the United States per year, making AHF the most common discharge diagnosis among patients aged >65 years.[1] An episode of AHF is detrimental for patients involving significant morbidity, and register studies have shown a 1-year mortality rate of ≥20%.[2,3] In the days following a hospital admission, approximately 10% to 30% develop in-hospital worsening heart failure (WHF) with the need for escalation of treatment.[3] Blood pressure plays an important role regarding etiology, prognosis, and clinical management.[4] Systolic blood pressure (SBP) reflects the product of vascular tone and systolic myocardial function. Acutely elevated SBP increases afterload, which, together with

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CLINICAL PERSPECTIVE

What Is New?

- In patients with acute heart failure with preserved ejection fraction, blood pressure is not associated with short-term and long-term outcomes.

What Are the Clinical Implications?

- In patients with systolic heart failure, blood pressure is strongly associated with mortality.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
SBP	systolic blood pressure
WHF	worsening heart failure

diastolic and systolic myocardial dysfunctions, contributes to the pathophysiology of AHF with backward failure leading to pulmonary or systemic congestion.[5,6] In AHF, preload and afterload reduction are important for the initial treatment.[6] Thus, the current standard-of-care therapy for AHF without hypotension includes afterload and preload reduction with loop diuretics and vasodilators. There is evidence for afterload reduction by using vasodilators only for patients with acute pulmonary edema; however, none of these treatments have conclusively been shown to improve outcomes in broad AHF populations.[6–8]

SBP varies considerably among patients with AHF from <100 mm Hg to >180 mm Hg.[4,9] Low SBP in the first hours of hospitalization is associated with a poor outcome,[4,9–11] but less is known of how the SBP interacts with left ventricular ejection fraction (LVEF) on clinical outcomes in patients with preserved SBP. In this study, we assessed the relationship between SBP and short-term and long-term outcomes in patients with reduced or preserved LVEF in patients hospitalized for AHF who were randomly assigned in 4 large clinical trials.[12–15]

METHODS

Anonymized data and materials have been made publicly available upon request to Norvatis as part of Norvatis' Data Sharing Program.

Design

This was a retrospective cohort study of 10 533 patients with AHF prospectively included in 4 randomized clinical trials as part of the Relax-AHF program. All trials tested the hypothesis that intravenous serelaxin, a recombinant form of human relaxin-2 with vasodilatory effects, is superior to standard-of-care therapy alone in patients admitted because of AHF.[16] All studies were multinational, prospective, randomized controlled trials comparing serelaxin as an add on to standard-of-care therapy versus standard-of-care therapy alone in patients hospitalized for AHF. A total of 2 studies, Relax-AHF-EU (efficacy and safety of serelaxin when added to standard of care in patients with acute heart failure: results from a PROBE study) and Relax-AHF-Asia (the efficacy, safety, and tolerability of additional serelaxin administration to standard therapy in Asian patients with acute heart failure),[12,15] were open-label with blinded end point evaluation, whereas 2 other studies, effects of serelaxin in patients with acute heart failure (Relax-AHF-1) and serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF-2): a randomised, placebo-controlled trial, were double blinded with placebo.[13,14] The first patient was included in October 11, 2009, and the last study terminated inclusion on April 25, 2017. The 4 studies had similar inclusion and exclusion criteria. All trial designs and main results have previously been published (Relax-AHF-Asia was terminated before planned sample size had been included because of the neutral results from Relax-AHF-2).[12,15,17,18] In brief, Relax-AHF-2 was neutral, whereas a meta-analysis of all trials have showed small, although statistically significant, benefits of seralaxin.[19] A post hoc statistical analysis plan was formulated before starting the current analyses.

The ethics committees approved all trials in each country, and informed consent was obtained according to local regulations. Good Clinical Practice was followed. All trials are registered at ClinicalTrials.gov (identifiers NCT02064868, NCT02007720, NCT01870778, and NCT00520806) and comply with the Declaration of Helsinki. The executive committees of each trial, in collaboration with the sponsor (Novartis Pharma), developed the protocols and oversaw the execution of each trial and the analysis and interpretation of the results.

Study Participants

Patients eligible for enrollment were adults (aged ≥18 years) and admitted to the hospital for AHF and randomly assigned within 16 hours. All patients had (1) dyspnoea, (2) pulmonary congestion on chest radiograph, (3) elevated BNP (brain-type natriuretic peptide) or NT-proBNP (N-terminal pro–brain natriuretic peptide), (4) SBP from 125 to 180 mm Hg measured at least 2 times with calibrated equipment while bedridden, (5) estimated glomerular filtration rate [eGFR] from 25 to 75 mL/min per 1.73 m^2),

and (6) symptomatic after receiving at least 40 mg of loop diuretics. Criteria for natriuretic peptide levels differed slightly between the 4 studies, but the minimum requirement was a BNP≥500 pg/mL or NT-proBNP≥2000 pg/mL. The main exclusion criteria were treatment with other intravenous heart failure (HF) drugs (except low-dose intravenous nitrates≤0.1 mg/kg/h in patients with SBP>150 mm Hg at screening), known significant pulmonary or valvular disease, AHF caused by arrhythmias, or persistent heart rate>130 beats per minute. A detailed list of eligibility criteria can be seen in the initial publications.[17,20,21] LVEF of patients was assessed before they were randomly assigned or during hospitalization, and patients were divided into "LVEF<40%" or "LVEF≥40%". In addition, we did sensitivity analyses of patients divided into 3 categories based on theEuropean Society of Cardiology 2016 guidelines (LVEF<40% [HF with reduced ejection fraction], LVEF 40%–49% [HF with mid-range ejection fraction], and LVEF≥50% [HF with preserved ejection fraction]).[6]

Intervention and Blood Pressure

Patients were randomly allocated in a 1:1 ratio (except Relax-AHF-EU, which allocated 1:2 in favor of serelaxin) to a 48-hour infusion of serelaxin (at a dose of 30 µg per kilogram per day). Blood pressure was monitored closely with several measurements while patients were bedridden and before they were randomly assigned to ensure a stable blood pressure at the time of randomization.

Outcomes

For this post hoc analysis, the outcomes were (1) all-cause mortality through day 180 and (2) a short-term composite outcome consisting of all-cause mortality, WHF, or hospital readmission for HF through day 15. WHF was defined as progress in signs or symptoms of HF that lead to an intensification of treatment for HF. Such treatment was defined as initiation or increased dose of intravenous therapy with loop diuretics or nitrates or need for mechanical ventilation, hemodialysis, intra-aortic balloon pump, or a ventricular-assist device. There were some differences in the definition of WHF between the studies,[12–14,21] and in the Relax-AHF-II and Relax-AHF-ASIA trials, WHF was not considered after day 5. For the Relax-AHF-I and Relax-AHF-II trials, readmission for renal failure was also considered as a readmission for HF. In the Relax-AHF-EU trial, patients were followed up until day 30 only, and patients from this study are censored after 30 days in mortality analyses.

Statistical Analysis

This study's primary exposure variable, SBP, was examined as both a continuous and categorical variable. The predefined subgroups were group A, patients with normal to mildly elevated SBP (125–145 mm Hg) and group B, patients with moderately elevated SBP (146–180 mm Hg). These groups were defined based on a preliminary analysis in the statistical analysis plan of the mean SBP in the Relax-AHF-EU trial, which was 145.8 mm Hg at randomization. The SBP value used in the analyses was the blood pressure measurements reported at randomization in the Case Report Forms of the trials.

Associations with the short-term composite end point and 180-day mortality were evaluated using univariable and multivariable Cox regression models after checking for assumptions of linearity and proportionality. Multivariable models are adjusted for age, sex, baseline body mass index, LVEF<40%, serum eGFR, allocated treatment (placebo/serelaxin), diabetes, ischemic heart disease, and atrial fibrillation/flutter. These variables were predefined in the statistical analysis plan and chosen based on experience from the main trials and because these factors are known to affect outcomes in AHF. An additional covariate: "Including study", was also included in the multivariate models by request from the statistical reviewer. Hazard ratios (HRs) and their 2-sided 95% CIs were presented. Mortality analysis of blood pressure groups was assessed by Kaplan–Meier plots and calculated with the log-rank test. An additive proportional hazard model with smoothing splines was fitted to illustrate the HR for each end point related to SBP as a continuous variable. Baseline data are presented as mean±SD and medians with quartile 1 and quartile 3 and compared using the chi-square test for categorical data and the Mann-Whitney U and Kruskal–Wallis tests for continuous data. The Student *t* test was used for parametric data. Multivariable models were assessed for a potential interaction of systolic cardiac function by adding the interaction term of LVEF (LVEF<40% versus LVEF≥40%) and blood pressure group (A versus B). A 2-sided *P* value of <0.05 was considered statistically significant, and no adjustments were made for multiple comparisons. Statistical analyses were performed using the SAS statistical software version 9.4 (SAS Institute, Cary, NC). Figures were made in R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The total population in the Relax-AHF trials consisted of 11 226 patients, with 1161 (10%) from Relax-AHF-1, 6545 (58%) from Relax-AHF-2, 2650 (24%) from Relax-AHF-EU, and 870 (8%) from Relax-AHF-ASIA. Patient populations from the 4 studies were slightly different regarding several baseline variables; however, the differences were small and without apparent clinical

significance (data are presented for each study in Table S1). We excluded 669 patients (6%) because of a baseline SBP value either missing or deviating from the inclusion criteria of 125 to 180 mm Hg. Therefore, the current study population consisted of 10 557 patients with AHF with the majority of 6915 patients (65%) in group A and 3642 patients (35%) in group B (Figure 1). Overall, the population was aged 73±12 years, had a median of 7 (quartile 1–quartile 3, 5–11) hours from admission to randomization, and had a mean SBP of 142±14 mm Hg, and 5671 (54%) were allocated to receive serelaxin. LVEF data were available in 9863 patients (93%) (in 8519 patients, the LVEF was assessed before randomization). A total of 4737 patients (45%) had LVEF<40%.

After 15 days, 992 patients (9%) were categorized as having the short-term composite outcome. WHF was present/detected in 8% of patients, rehospitalization for HF occurred in 1% of patients, and death from all causes within 15 days occurred in 2% of patients. The all-cause mortality rate at 180 days was 9%. Median length of hospital stay was 7 (quartile 1–quartile 3, 5–11) days.

Baseline Characteristics

The mean SBP was 134±6 mm Hg in group A and 158±9 mm Hg in group B (Table 1). Patients in group A were more often men (4270 [66%] versus 2029 [56%]; *P*<0.0001), had atrial fibrillation/flutter at admission more often (3138 [45%] versus 1459 [40%]; *P*<0.0001), had LVEF<40% more often (3471 [50%] versus 1266 [35%]), and had received less intravenous nitrates at randomization (3% versus 11%). History of HF and ischemic heart disease were more prevalent in group A, whereas hypertension and diabetes were less prevalent in group A. Concomitant

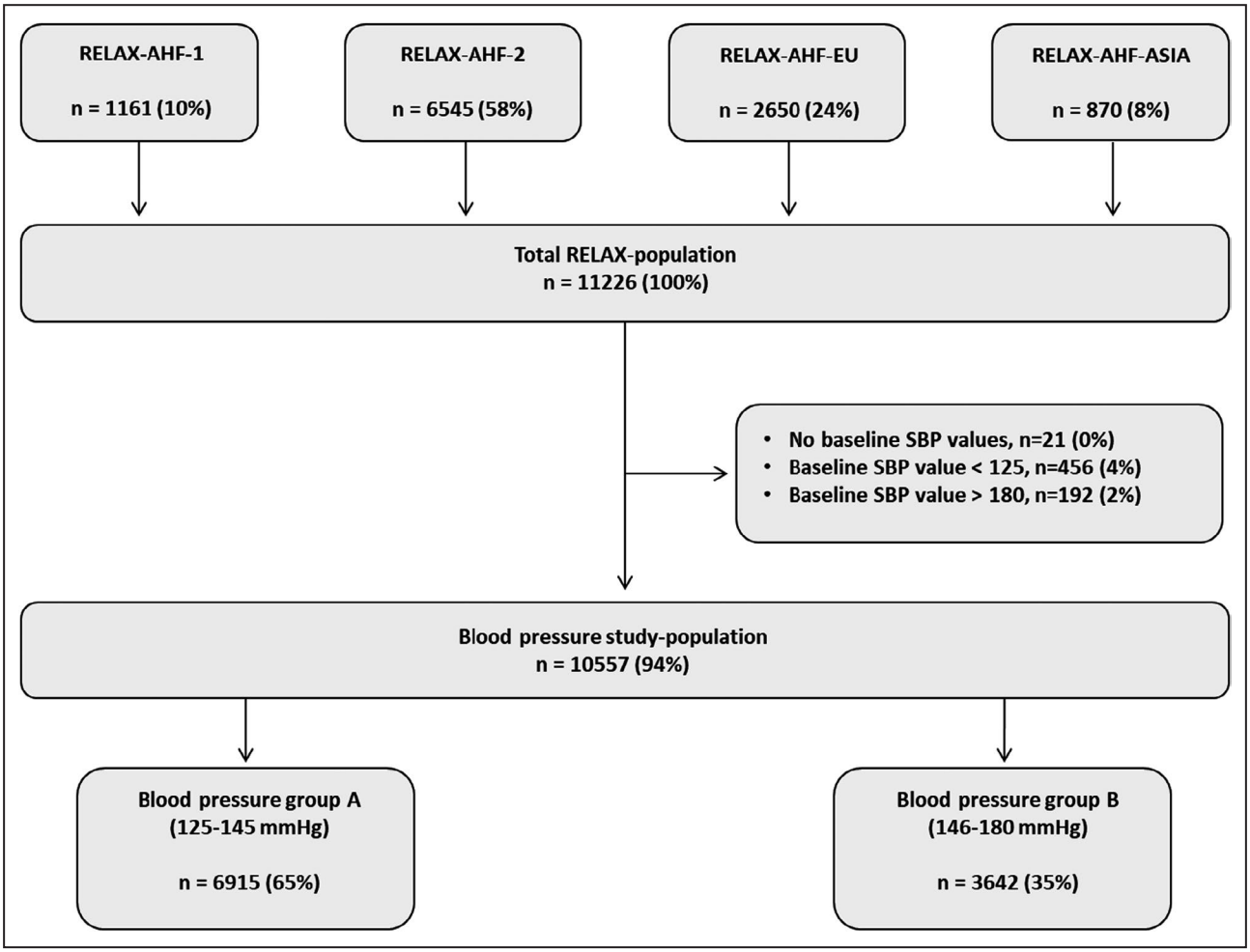

Figure 1. Flowchart of study population.
SBP indicates systolic blood pressure. Relax-AHF-1, effects of serelaxin in patients with acute heart failure; RELAX-AHF-2, serelaxin, recombinant human relaxin-2, for treatment of acute heart failure: a randomised, placebo-controlled trial; RELAX-AHF-ASIA, the efficacy, safety, and tolerability of additional serelaxin administration to standard therapy in Asian patients with acute heart failure; RELAX-AHF-EU, efficacy and safety of serelaxin when added to standard of care in patients with acute heart failure: results from a PROBE study.

Table 1. Demographics and Baseline Characteristics of Study Population by Blood Pressure Groups A and B

	Blood pressure group A, 125–145 mm Hg; n=6915 (65%)	Blood pressure group B, 146–180 mm Hg; n=3642 (35%)	*P* value
Demography			
Age, y	73±11	73±12	0.01*
Male sex	4270 (66)	2029 (56)	<0.0001*
Body mass index, kg/m²	28±6	29±7	<0.0001*
Randomization			
Allocated to serelaxin	3714 (54)	1969 (54)	0.73
Clinical status			
Systolic blood pressure, mm Hg	134±6	158±9	<0.0001*
Diastolic blood pressure, mm Hg	79±13	85±15	<0.0001*
Heart rate, beats per min	83±17	82±17	0.01*
Atrial fibrillation at screening	3138 (45)	1459 (40)	<0.0001*
Ejection fraction, %	39±14	44±14	<0.0001*
Ejection fraction <40%	3471 (50)	1266 (35)	<0.0001*
Ejection fraction ≥40%	3010 (44)	2116 (58)	
Ejection fraction unknown	434 (6)	260 (7)	
Time from presentation to randomization	7.1 (4.8–11.4)	6.9 (4.9–10.7)	0.04*
Intravenous nitrates at randomization	182 (3)	395 (11)	<0.0001*
NT-proBNP, ng/L	5609 (3112–9006)	5345 (3000–9000)	0.02*
eGFR, mL/min per 1.73 m²	53 (41–67)	50 (38–64)	0.03*
New York Heart Association class before admission			
Class I	230 (4)	127 (5)	0.09
Class II	1893 (36)	940 (39)	
Class III	2455 (47)	1064 (45)	
Class IV	650 (12)	262 (11)	
Medical history			
History of heart failure	3511 (51)	1567 (43)	<0.0001*
Hypertension	5979 (88)	3423 (90)	<0.0001*
Cigarette smoking	2664 (39)	1425 (40)	0.83
Ischaemic heart disease	3511 (51)	1567 (43)	<0.0001*
Atrial fibrillation or flutter	3873 (56)	1764 (48)	0.42
Previous TCI/stroke	1016 (15)	563 (15)	0.29
Diabetes	2846 (41)	1649 (45)	<0.0001*
Asthma/COPD	1059 (15)	504 (14)	0.05
Concomitant heart failure drugs at baseline			
Angiotensin-converting enzyme inhibitors	4304 (62)	2092 (57)	<0.0001*
β-blockers	5784 (84)	2919 (80)	<0.0001*
Aldosterone antagonists	4430 (64)	1930 (53)	<0.0001*
Loop diuretics	5794 (84)	2839 (78)	<0.0001*
Including study			
Relax-AHF-1	693 (10)	369 (10)	
Relax-AHF-2	4100 (59)	2091 (57)	0.11
Relax-AHF-EU	1652 (24)	894 (25)	
Relax-AHF-ASIA	470 (7)	288 (8)	

Data are provided as mean±SD, number (percentage), or median (quartile 1–quartile 3). COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–brain natriuretic peptide; Relax-AHF-1, effects of serelaxin in patients with acute heart failure; Relax-AHF-2, serelaxin, recombinant human relaxin-2, for treatment of acute heart failure: a randomised, placebo-controlled trial; Relax-AHF-ASIA, the efficacy, safety, and tolerability of additional serelaxin administration to standard therapy in Asian patients with acute heart failure; Relax-AHF-EU, efficacy and safety of serelaxin when added to standard of care in patients with acute heart failure: results from a PROBE study; and TCI, transitory cerebral ischemia.

*Statistical significans ($P<0.05$).

Table 2. HRs from Univariable and Multivariable Cox Regression Models for a Composite End Point (Worsening Heart Failure, Hospital Readmission for Heart Failure, or All-Cause Mortality Through Day 14) and 180-Day Mortality

	HR for death after 180 days				HR for composite end point			
	Univariable, HR (95% CI)	*P* value	Multivariable, HR (95% CI)	*P* value	Univariable, HR (95% CI)	*P* value	Multivariable, HR (95% CI)	*P* value
BP group A, 125–145 mm Hg	1.21 (1.06–1.39)	0.0063*	1.16 (1.00–1.33)	0.04*	1.26 (1.10–1.45)	0.0008*	1.28 (1.11–1.47)	0.0006*
BP group B, 146–180 mm Hg	Reference		Reference		Reference		Reference	
Age, y	1.03 (1.02–1.03)	<0.0001*	1.03 (1.02–1.03)	<0.0001*	1.01 (1.01–1.02)	0.0003*	1.01 (1.01–1.02)	<0.0001*
Female sex	1.05 (0.92–1.19)	0.47	0.92 (0.80–1.05)	0.19	0.93 (0.81–1.05)	0.23	0.86 (0.75–0.98)	0.03*
BMI	0.98 (0.97–0.99)	0.0005*	1.01 (0.99–1.02)	0.07	1.02 (1.01–1.03)	0.0019*	1.02 (1.01–1.04)	<0.0001*
Atrial fibrillation/flutter at admission	0.79 (0.69–1.89)	0.0002*	1.14 (1.01–1.31)	0.04*	0.98 (0.86–1.11)	0.72	0.97 (0.86–1.11)	0.69
eGFR baseline	0.97 (0.97–0.98)	<0.0001*	0.98 (0.97–0.98)	<0.0001*	0.98 (0.98–0.99)	<0.0001*	0.98 (0.98–0.99)	<0.0001*
LVEF <40% at baseline, reference=LVEF≥40%	1.03 (0.90–1.19)	0.64	1.17 (1.02–1.35)	0.03*	0.90 (0.76–1.07)	0.22	1.081 (0.94–1.24)	0.29
No LVEF at baseline, reference=LVEF≥40%	1.54 (1.27–1.86)	<0.0001*	1.56 (1.27–1.88)	<0.0001*	1.18 (0.99–1.39)	0.06	1.37 (1.09–1.70)	0.006*
History of heart failure	1.38 (1.19–1.59)	<0.0001*	1.16 (0.98–1.36)	0.07	1.19 (1.04–1.38)	0.01*	1.16 (0.99–1.36)	0.07
History of diabetes	1.26 (1.11–1.43)	0.0004*	1.20 (1.05–1.38)	0.008*	1.31 (1.16–1.49)	<0.0001*	1.20 (1.20–1.37)	0.005*
History of ischemic heart disease	1.25 (1.09–1.42)	0.0008*	1.13 (0.99–1.29)	0.06	1.12 (0.99–1.27)	0.07	0.91 (0.87–1.14)	0.91
Allocated to serelaxin	0.90 (0.79–1.02)	0.10	0.89 (0.79–1.02)	0.08	0.85 (0.75–0.97)	0.02*	0.86 (0.75–0.97)	0.01*
Relax-AHF-1	0.79 (0.79–0.98)	0.03*	0.82 (0.66–1.02)	0.07	1.45 (1.21–1.76)	<0.0001*	1.53 (1.27–1.85)	<0.0001*
Relax-AHF-EU	1.33 (1.33–1.68)	0.02*	1.22 (0.96–1.09)	0.10	1.01 (0.87–1.54)	0.89	1.12 (0.95–1.31)	0.18
Relax-AHF-ASIA	0.76 (0.58–0.98)	0.03	0.83 (0.63–1.09)	0.17	1.17 (0.89–1.54)	0.25	1.42 (1.07–1.89)	0.02*
Relax-AHF-2	Reference		Reference		Reference		Reference	

BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; Relax-AHF-1, effects of serelaxin in patients with acute heart failure; Relax-AHF-2, serelaxin, recombinant human relaxin-2, for treatment of acute heart failure: a randomised, placebo-controlled trial; Relax-AHF-ASIA, the efficacy, safety, and tolerability of additional serelaxin administration to standard therapy in Asian patients with acute heart failure; and Relax-AHF-EU, efficacy and safety of serelaxin when added to standard of care in patients with acute heart failure: results from a PROBE study.

*Statistically significant.

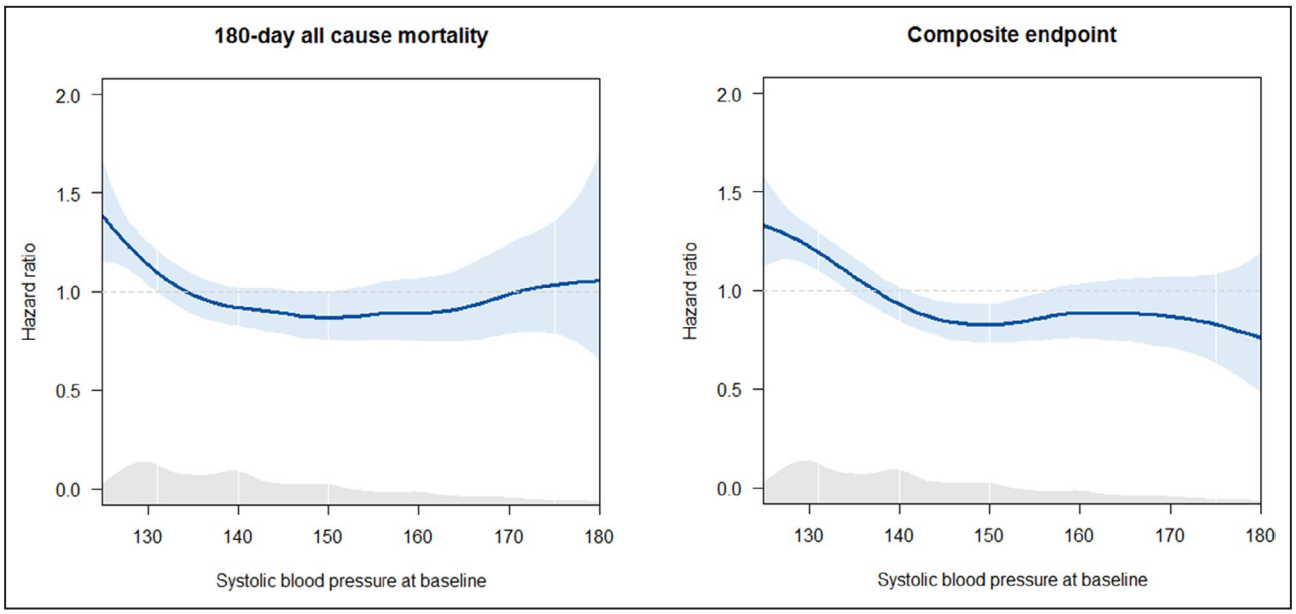

Figure 2. Risk of 180-day all-cause mortality (left) and short-term composite end point (right; worsening heart failure, hospital readmission for heart failure, or all-cause mortality through day 14) and as a function of systolic blood pressure at baseline as illustrated by a Cox regression model with cubic smoothing splines.
The mountain plot on top of the *x* axis shows the density of the population along the spline variable. Multivariable Cox models are adjusted for age, sex, baseline body mass index, left ventricular ejection fraction, serum estimated glomerular filtration rate, allocated treatment (placebo/serelaxin), diabetes, ischemic heart disease, and atrial fibrillation/flutter. The blue line shows the hazard ratios with their 2-sided 95% CIs (light blue area).

HF drugs at baseline were being taken more often in group A (Table 1).

Associations Between Baseline SBP and Outcomes

The lower blood pressure group A was associated with a significantly higher risk of 180-day mortality compared with group B in univariate analyses (Figure S1) and after adjusting for known confounders in multivariable analyses ($HR_{adjusted}$, 1.16; 95% CI, 1.01–1.33; Table 2). Older age, diabetes, atrial fibrillation at admission, LVEF<40%, and lower eGFR were also associated with higher 180-day mortality rates.

Group A was also associated with a higher risk of the short-term composite end point compared with group B in univariate analyses and after adjusting for known confounders in multivariable analyses ($HR_{adjusted}$, 1.28; 95% CI, 1.11–1.47; Table 2). Older age, higher BMI, male sex, LVEF<40%, lower eGFR, and inclusion in Relax-AHF-1 or Relax-AHF-EU (compared with inclusion in Relax-AHF-2) were also associated with the short-term composite end point. Allocation to serelaxin was associated with less risk of the short-term composite end point (Table 2).

Of the individual components of the composite outcome, WHF occurred in 831 patients (8%), rehospitalization for HF occurred in 127 patients (1%), and

Table 3. HRs Assessing the Association between Systolic Blood Pressure in Intervals and a Composite End Point (Worsening Heart Failure, Hospital Readmission for Heart Failure, or All-Cause Mortality Through Day 14) and 180-Day Mortality

	HR for death after 180 days		HR for composite end point	
	Multivariable,* HR (95% CI)	*P* value	Multivariable,* HR (95% CI)	*P* value
SBP 125–135, n=4104; 39%	1.28 (1.09–1.51)	0.0025†	1.32 (1.13–1.55)	0.0007†
SBP 136–145, n=2792; 27%	Reference		Reference	
SBP 146–155, n=1760; 17%	0.98 (0.79–1.20)	0.80	0.87 (0.70–1.07)	0.21
SBP 156–165, n=1050; 10%	0.92 (0.71–1.20)	0.57	1.00 (0.78–1.29)	0.90
SBP 166–180, n=827; 8%	1.19 (0.91–1.54)	0.19	0.97 (0.74–1.27)	0.84

A total of 24 participants are missing from the analyses because of missing values. HR indicates hazard ratio; and SBP, systolic blood pressure.
*Adjusted for the variables presented in Table 2.
†Statistically significant.

death occurred in 179 patients (2%) within 15 days. In multivariable analyses, group A was associated with WHF (HR, 1.22; 95% CI, 1.05–1.42), rehospitalization for HF (HR, 1.5; 95% CI, 1.01–2.29), and mortality (HR, 1.66; 95% CI, 1.17–2.35). The prevalence of outcomes in each study is shown in Table S2.

SBP as a continuous variable was significantly associated with a higher 180-day mortality ($HR_{adjusted}$, 0.93; 95% CI, 0.88–0.98; per 10 mm Hg increase) incidence of the short-term composite end point ($HR_{adjusted}$, 0.90; 95% CI, 0.86–0.95; per 10 mm Hg increase; Figure 2).

A sensitivity analysis revealed that SBPs of 125 to 135 mm Hg were especially associated with worse short-term and long-term outcomes (Table 3). There were no interactions of SBP groups on the association between allocation to serelaxin and the 2 outcomes.

Interaction Between SBP and Left Ventricular Systolic Myocardial Function

In group A, 50% of patients had LVEF<40%, and 35% patients in group B had LVEF<40% (Table 1). Crude 180-day mortality of patients with LVEF<40%, LVEF 40% to 49%, and LVEF≥50% stratified according to blood pressure at baseline is illustrated in the Kaplan–Meier plot in Figure 3. The prevalence of end points according to LVEF is shown in Table S3.

A significant association between baseline SBP and 180-day mortality was present in patients with LVEF<40% ($HR_{adjusted}$, 0.84; 95% CI, 0.77–0.92; per 10 mm Hg increase), but not in patients with LVEF≥40% ($HR_{adjusted}$, 0.98; 95% CI, 0.91–1.04; per 10 mm Hg increase; Figure 3 and Figure S2).

Baseline SBP and 180-day mortality were not associated in patients with LVEF≥50% ($HR_{adjusted}$, 0.97; 95% CI, 0.90–1.05; per 10 mm Hg increase) or in patients with LVEF 40% to 49% ($HR_{adjusted}$, 0.96; 95% CI, 0.83–1.11; per 10 mm Hg increase; Figure 4). For the group of patients with LVEF<50%, there was a statistically significant association between SBP and 180-day mortality ($HR_{adjusted}$, 0.86; 95% CI, 0.79–0.93; per 10 mm Hg increase). A statistically significant interaction between LVEF, SBP group, and 180-day mortality was found ($P_{interaction}$=0.0003).

Baseline SBP was inversely associated with the incidence of the short-term composite end point in patients with LVEF≥40% ($HR_{adjusted}$, 0.91; 95% CI, 0.85–0.9697; per 10 mm Hg increase) and patients with LVEF<40% ($HR_{adjusted}$, 0.85; 95% CI, 0.78-0.93; per 10 mm Hg increase; Figure 4).

However, there was no significant interaction of LVEF, SBP group, or the short-term composite end point.

Serelaxin had a similar effect in the 2 blood pressure groups, and there was no interaction of SBP group on the association between allocation to serelaxin and incidence of the short-term composite end point (P=0.24) or 180-day mortality (P=0.56; Figure 5).

DISCUSSION

In this post hoc analysis of a large sample of adult patients with AHF without cardiogenic shock, we examined the association between baseline SBP and clinical outcomes. We found that a normal baseline SBP compared with a moderately elevated SBP was significantly associated with a higher incidence of both 180-day mortality and short-term outcome.

In our predefined subgroup analysis, we found that baseline SBP was not associated with mortality in patients with LVEF≥40%, but was strongly associated

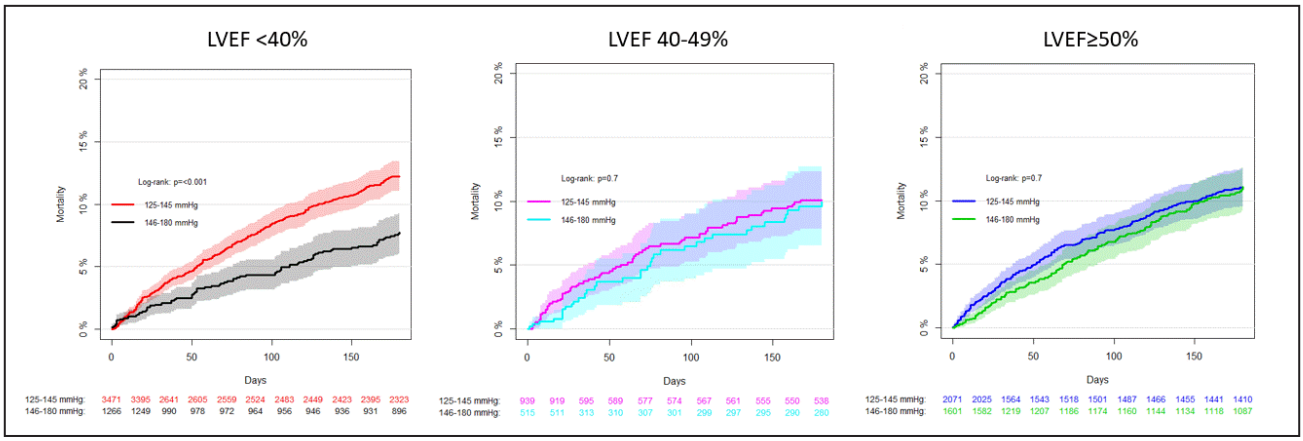

Figure 3. Kaplan–Meier survival curves for specified subgroups showing the cumulated mortality rate through day 180 for the 2 blood pressure groups.

Left, Kaplan–Meier survival curve illustrates the subgroup with LVEF<40%. **Middle**, Kaplan–Meier survival curve illustrates the subgroup with LVEF 40% to 49%. **Right**, Kaplan–Meier survival curve shows the subgroup with LVEF≥50%. LVEF indicates left ventricular ejection fraction.

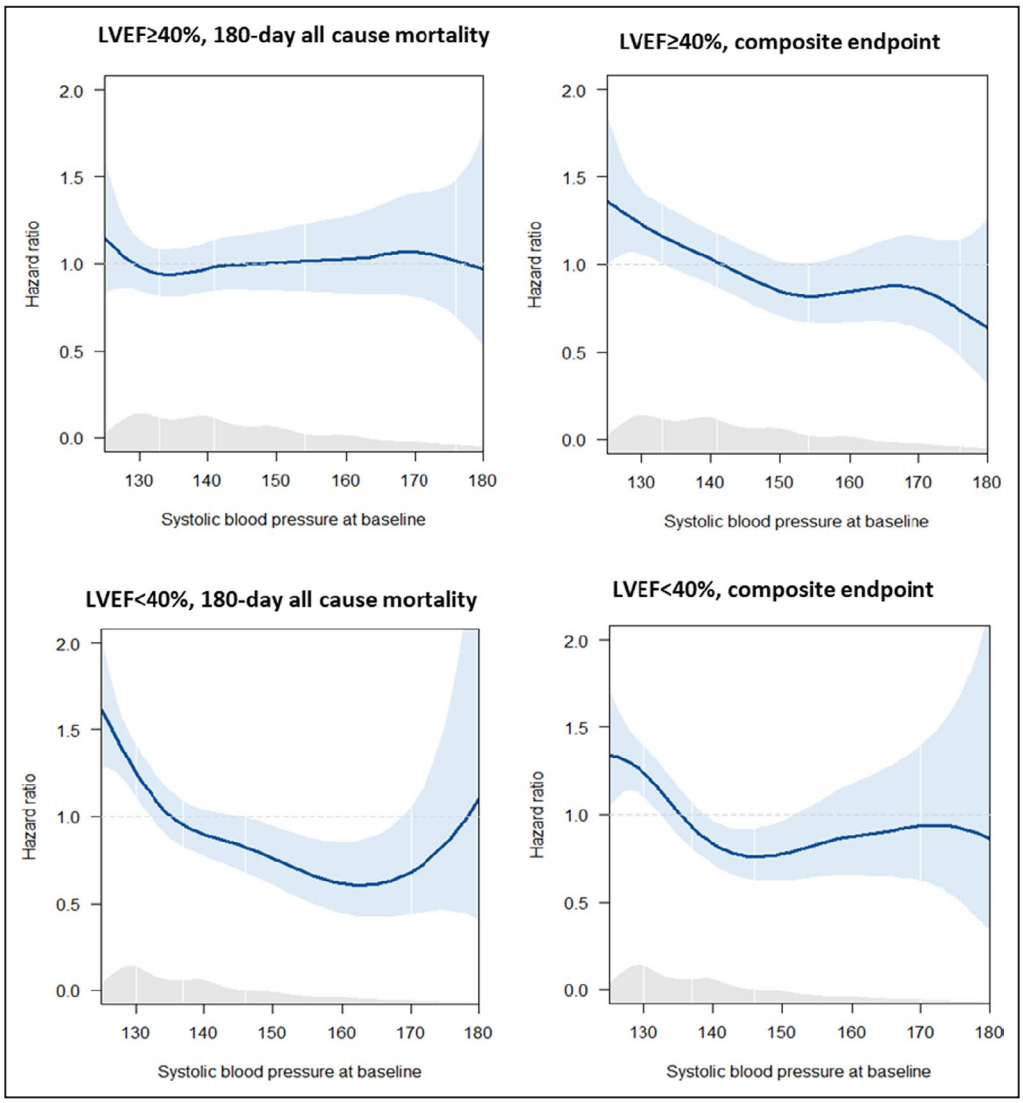

Figure 4. Risk of 180-day mortality (left) and risk of a short-term composite end point (right; worsening heart failure, hospital readmission for heart failure, or all-cause mortality through day 14) as a function of systolic blood pressure at baseline illustrated by a multivariable Cox regression model with cubic smoothing splines.
The mountain plot on top of the *x* axis shows the density of the population along the spline variable. Multivariable Cox models are adjusted for age, sex, baseline body mass index, LVEF, serum estimated glomerular filtration rate, allocated treatment (placebo/serelaxin), diabetes, ischemic heart disease, and atrial fibrillation/flutter. The blue line shows the hazard ratios with their 2-sided 95% CIs (light blue area). LVEF indicates left ventricular ejection fraction.

with mortality in patients with LVEF<40%. The results indicate that even without hypotension, low SBP is an independent risk factor for poor outcome compared with moderately elevated SBP.

Although numerous register studies previously have examined associations between SBP and outcomes,[22,23] the present study is unique because of the large clinical population of consecutively enrolled and strictly monitored patients with AHF. Blood pressure measurements were protocolized and registered with several measurements at rest, providing a more valid estimate of hemodynamic function than values deduced from a registry. Furthermore, the present multicenter, randomized controlled clinical trial design is likely to have provided a more valid and strict registration of LVEF. These 2 factors may increase the likelihood of demonstrating a significant prognostic interaction with LVEF.

In a registry study of 56 942 patients aged >65 years hospitalized for HF, Vidán et al found that higher SBP on admission was associated with significantly lower 1-year mortality.[24] Unlike the present study, the study by Vidán et al included patients in the whole spectrum

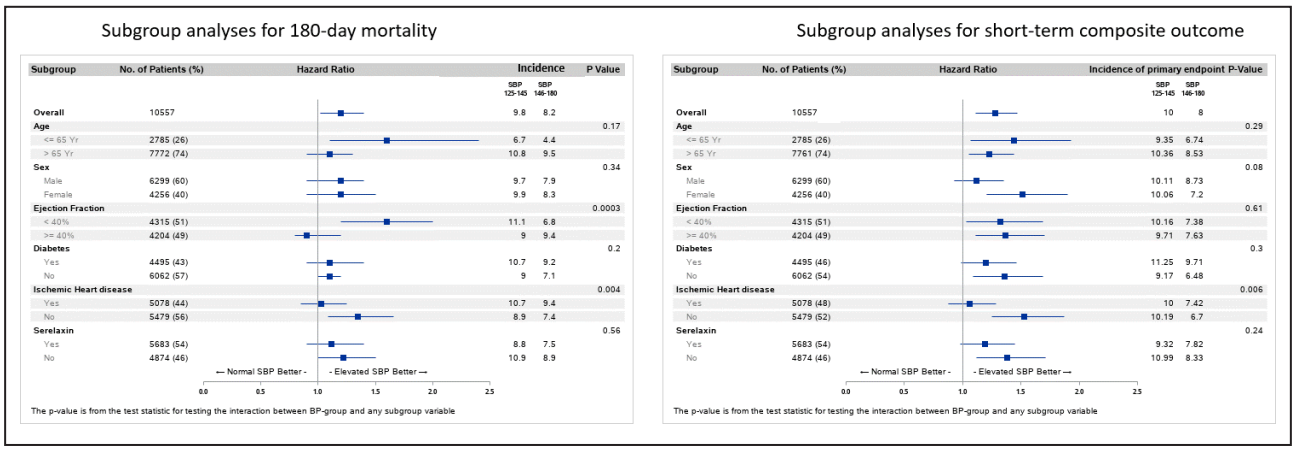

Figure 5. Subgroup analyses of a short-term composite end point (left; worsening heart failure, hospital readmission for heart failure, or all-cause mortality through day 14) and 180-day mortality (right).
Hazard ratios with 95% CIs are from multivariable Cox regression models with the following prespecified covariates: age, sex, baseline body mass index, left ventricular ejection fraction, serum estimated glomerular filtration rate, allocated treatment (placebo/serelaxin), diabetes, ischemic heart disease, and atrial fibrillation/flutter. BP indicates blood pressure; and SBP, systolic blood pressure.

of blood pressures, including patients with very low blood pressure and shock. They report an association between SBP and mortality for all degrees of LVEF. In another register study of 4848 patients with AHF, Al-Lawati et al found that the prognosis consistently improved with higher SBP, regardless of LVEF.[9] In alignment with our findings, a study of 525 Japanese patients with HF with preserved ejection fraction by Sato et al found that admission SBP was not associated with all-cause death or rehospitalization.[15] A 2010 study of 1049 patients with AHF found an inverse association between SBP and mortality in HF with reduced ejection fraction, but not in HF with preserved ejection fraction.[25] Our results supports these previous findings (Figure 4 and 5).

In most studies, including patients with low SBP, patients deteriorating to cardiogenic shock may very well drive the adverse outcome in the hypotensive subgroup. In contrast, our study included patients without initial low blood pressure or vasopressor requirements, excluding patients in cardiogenic shock. Interestingly, despite excluding patients who were high risk and hypotensive at baseline, we found a highly significant association of a "normal" (ie, 125-135 mm Hg) SBP with adverse short-term and long-term outcomes (Table 3). It is unclear why elevated SBP in HF with reduced ejection fraction is associated with a better prognosis.[26] One explanation may be that the hemodynamic capability to raise SBP and at the same time withstanding an increased afterload may be a marker of a preserved myocardial reserve and therefore inversely associated with severity of heart failure. In HF with preserved ejection fraction, which is a heterogeneous condition characterized by preserved systolic myocardial function, we did not find any association between SBP and mortality.

Another explanation for the favorable outcome in patients with elevated SBP could be a confounding-by-indication effect linked to the initial treatment because patients with low blood pressure were more frequently treated with HF drugs. Treatment options in AHF, disregarding randomization, are well-known preload-reducing and afterload-reducing drugs, such as loop diuretics and vasodilators, with significant blood pressure–lowering effects.[6]

Low blood pressure may simply be a marker for more severe disease, which is not accounted for by the variables adjusted for in the multivariable models. Possibly, the patients with highest SBP are more often hospitalized because of hypertensive pulmonary edema rather than having been within the context of chronic HF with the full syndrome of other organ-associated and neurohormonal-associated changes.[27] When high blood pressure is a trigger for AHF, it is straightforward to treat with well-known effective drugs and the favorable prognosis in elevated SBP could simply be attributed to this fact. In this pooled analysis, allocation to serelaxin administration was associated with a significant reduction in the short-term composite end point and a nonsignificant reduction in 180-day all-cause mortality. A study-level meta-analyses by Teerlink et al found an estimated HR of 0.87 (95% CI, 0.77–0.98).[19] Because serelaxin first and foremost is a vasodilator, this suggests that vasodilation confers a potential benefit in patients with AHF. Surprisingly, we did not find a greater effect of seralaxin in patients with elevated SBP at baseline.

The current analysis is from a database, which to our knowledge is one of the largest clinical databases with detailed information on admission, in-hospital, and follow-up variables. This data collection in the trials was uniform because of the fact that the

protocols were coordinated by the same sponsor (Novartis) and designed explicitly to be largely identical with subtle variations, making the pooled analysis possible.

Another strength of this database compared with registry studies is that patient blood pressure was monitored intensely to secure a precise measurement. Furthermore, data were collected prospectively and consecutively in each trial. Limitations to this study include the post hoc and observational nature, which is why the results should at best be considered as hypothesis generating. Blinding was only present in the larger trials, whereas 2 trials were open label with risk of bias. Also, and perhaps most important, patients were included based on strict criteria, including a need for high levels of natriuretic peptides, and patients with significant comorbidities were excluded, making the study population selected and limiting external validity. Notably, patients with SBP <125 mm Hg and >180 mm Hg were excluded. This population was relatively low risk, and the results do not necessarily apply to patients with more hemodynamic instability. Furthermore, we used a single time point for the SBP value, which was at randomization, and although SBP was measured multiple times at rest to acquire an accurate measurement, fluctuations and changes in SBP the following hours were not accounted for. Our results reflect the prognostic value of SBP obtained after the initial stabilization of patients with AHF, and the patients had varying times from admission to randomization, which may confound results. If the admission SBP value was used, the results might be different. We used a binary definition of LVEF<40% versus LVEF≥40%, including patients with mid-range ejection fraction[28] in the LVEF>40% group.

In conclusion, elevated SBP is independently associated with improved short-term and long-term outcomes in patients hospitalized for AHF without shock. This association was pronounced in patients with LVEF<40%; however, in patients with LVEF≥40%, there was no association of SBP and mortality.

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Disclosures

Dr Maggioni received personal fees for the participation in committees of studies sponsored by Novartis, Fresenius, and Bayer. Dr Nielsen received personal fees for the participation in committees of studies sponsored by Novartis and advisory boards sponsored by Astra-Zeneca and Novo Nordisk. Dr López-Sendón received personal fees and institutional grants for the participation in committees of studies sponsored by Novartis, Bayer, Sanofi, Merck, and Pfizer. Dr Ertl received personal fees for the participation in committees of studies sponsored by Novartis and Bayer. Dr Metra received personal fees from Actelion, Amgen, Astra-Zeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Livanova, Vifor Pharma, WindTree Therapeutics, and as a member of trials' committees or for speeches at sponsored meetings. Dr Holbro is an employee and shareholder of Novartis Pharma AG. Dr Teerlink reports research support from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cytokinetics, Medtronic, Novartis, and Windtree Therapeutics and personal fees for consulting from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cytokinetics, Medtronic, Merck, Novartis, Servier, and Windtree Therapeutics. Dr Gimpelewicz is a Novartis employee.

Supplementary Material

Tables S1–S3
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Data of study population stratified according to initial AHF-study. *LVEF was assessed prior to randomization only.

	Relax-AHF 1 n=1161 (10%)	**Relax-AHF 2** n=6544 (59%)	**Relax-AHF EU** n=2650 (24%)	**Relax-AHF Asia** n=870 (8%)	**p-value**
Demography:					
- Age - year (±SD)	72 (±11)	73 (±11)	76 (±11)	70 (±14)	**<0.0001**
- Male sex - n (%)	725 (62%)	3908 (59%)	1507 (57%)	556 (64%)	**0.0004**
- Body-mass index (kg/m²)	29 (±6)	29 (±6)	29 (±6)	26 (±5)	**<0.0001**
Randomization:					
- Allocated to Serelaxin - n (%)	581 (50%)	3274 (50%)	1756 (66%)	435 (50%)	**<0.0001**
Clinical status					
- Systolic blood pressure – mmHg (±SD)	143 (±16)	142 (±15)	144 (±16)	142 (±16)	**<0.0001**
- Diastolic blood pressure – mmHg (±SD)	79 (±14)	82 (±14)	81 (±14)	81 (±16)	**<0.0001**
- Heart rate – beats per min (±SD)	80 (±15)	84 (±17)	83 (±17)	85 (±17)	**<0.0001**
- Atrial fibrillation at screening	479 (41%)	2723 (42%)	1425 (54%)	242 (28%)	**0.0004**
- Ejection fraction* <40% - n (%)	598 (52%)	3180 (49%)	482 (18%)	354 (41%)	**<0.0001**
- Ejection fraction* >=40% - n (%)	493 (43%)	2948 (45%)	698 (26%)	301 (35%)	
- Ejection fraction unknown - n (%)	70 (6%)	417 (6%)	1470 (55%)	215 (25%)	
- Ejection fraction - % (±SD)	39±15%	40±14%	41±14%	40±15%	**<0.0001**
- Time from presentation to randomisation (h)	7.8 (±4.4)	8.2 (±4.7)	8.1 (±4.2)	8.9 (±4.2)	**<0.0001**
- Intravenous nitrates at randomization	81 (7%)	360 (6%)	127 (5%)	64 (7%)	**0.003**
- NT-proBNP (ng/L)	3000 (2690-5761)	6086 (3541-9890)	5461 (2934-9000)	6007 (3217-9301)	**<0.0001**
- eGFR (mL/min per 1·73 m²)	53 (±16)	51 (±14)	52 (±15)	51 (±14)	0.57
New York Heart Association class before admission					
- Class I	23 (3%)	210 (4%)	91 (5%)	55 (10%)	**<0.0001**
- Class II	304 (26%)	1848 (39%)	651 (33%)	213 (39%)	
- Class III	389 (46%)	2184 (46%)	963 (49%)	203 (37%)	
- Class IV	135 (16%)	507 (11%)	245 (14%)	74 (14%)	
Medical history					
- History of Heart failure - n (%)	861 (74%)	4854 (74%)	1955 (74%)	556 (64%)	**<0.0001**
- Hypertension - n (%)	1006 (87%)	5856 (89%)	2397 (91%)	718 (83%)	0.39
- Cigarette smoking - n (%)	153 (13%)	2983 (46%)	840 (32%)	408 (47%)	**<0.0001**
- Ischaemic heart disease - n (%)	403 (56%)	3217 (49%)	1375 (52%)	350 (40%)	**<0.0001**
- Atrial fibrillation or flutter - n (%)	602 (50%)	3465 (53%)	1568 (59%)	354 (41%)	**<0.0001**
- Previous TCI/stroke - n (%)	157 (13%)	1004 (15%)	429 (16%)	91 (10%)	**<0.0001**
- Diabetes - n (%)	551 (28%)	3013 (46%)	1189 (45%)	38 (4%)	**<0.0001**
- Asthma/COPD - n (%)	184 (16%)	1039 (16%)	394 (15%)	46 (5%)	0.54

Table S2. Protocol-Specified Efficacy Endpoints stratified according to initial AHF-study.

	Relax-AHF 1 n=1161 (10%)	**Relax-AHF 2** n=6544 (59%)	**Relax-AHF EU** n=2650 (24%)	**Relax-AHF Asia** n=870 (8%)	**p-value**
Primary efficacy end points — no. (%)					
- Death from any cause at 180 days*	108 (9%)	755 (12%)	108 (4%)	74 (9%)	**<0.0001**
- Worsening heart failure, rehospitalization for heart failure or death from all causes at 15 days	157 (14%)	593 (9%)	244 (9%)	74 (9%)	**<0.0001**
Key secondary efficacy end points					
- Worsening heart failure at 15 days — no. (%)	145 (12%)	479 (7%)	201 (8%)	70 (8%)	**<0.0001**
- Rehospitalization for heart failure at 15 days — no. (%)	22 (2%)	91 (1%)	22 (1%)	-	**<0.0001**
- Death from any cause at 15 days — no. (%)	18 (2%)	108 (2%)	50 (2%)	24 (3%)	0.12
- Median length of index hospital stay (IQR) — days	8 (6-11)	7 (5-10)	8 (6-14)	8 (5-13)	**<0.0001**
- SBP decrease event** — no. (%)	408 (35%)	1456 (22%)	442 (17%)	215 (25%)	**<0.0001**

RELAX-AHF-EU had only follow-up for 30 days after admission.

**Systolic blood pressure decreased by more than 40 mm Hg from baseline and the absolute value was 100 mm Hg or more in two consecutive measurements 15 minutes apart, the infusion rate was decreased by 50% (as detailed in the protocol). If the systolic blood pressure was below 100 mm Hg in two consecutive measurements 15 minutes apart, the infusion was permanently discontinued.

Table S3. Population divided in LVEF <40% (heart failure with reduced ejection fraction, HFrEF), LVEF 40-49% (heart failure with mid-range ejection fraction, HFmrEF) and LVEF≥50%. (heart failure with preserved ejection fraction, HFpEF).

	HFrEF n=4737 (45%)	**HFmrEF** n=1454 (14%)	**HFpEF** n=3672 (35%)	**No LVEF** n=694 (7%)	**p-value**
Primary efficacy end points — no. (%)					
- Death from any cause at 180 days	288 (9%)	109 (8%)	158 (8%)	417 (11%)	**0.0003**
- Worsening heart failure, rehospitalization for heart failure or death from all causes at 15 days	311 (10%)	136 (9%)	204 (10%)	341 (9%)	0.21
Blood pressure group					
- Group A (SBP 125-145 mmHg) — no. (%)	3471 (73%)	939 (65%)	2071 (56%)	434 (63%)	**<0.0001**
- Group B (SBP 146-180 mmHg) — no. (%)	1266 (27%)	515 (35%)	1601 (44%)	260 (37%)	**<0.0001**

Figure S1. Kaplan–Meier survival curves for specified subgroups, showing the cumulated mortality rate through day 180 for the two blood pressure groups. The left Kaplan–Meier survival curve illustrates the subgroup with left ventricular ejection fraction (LVEF) <40%. The right Kaplan–Meier survival curve shows the subgroup with LVEF ≥40%.

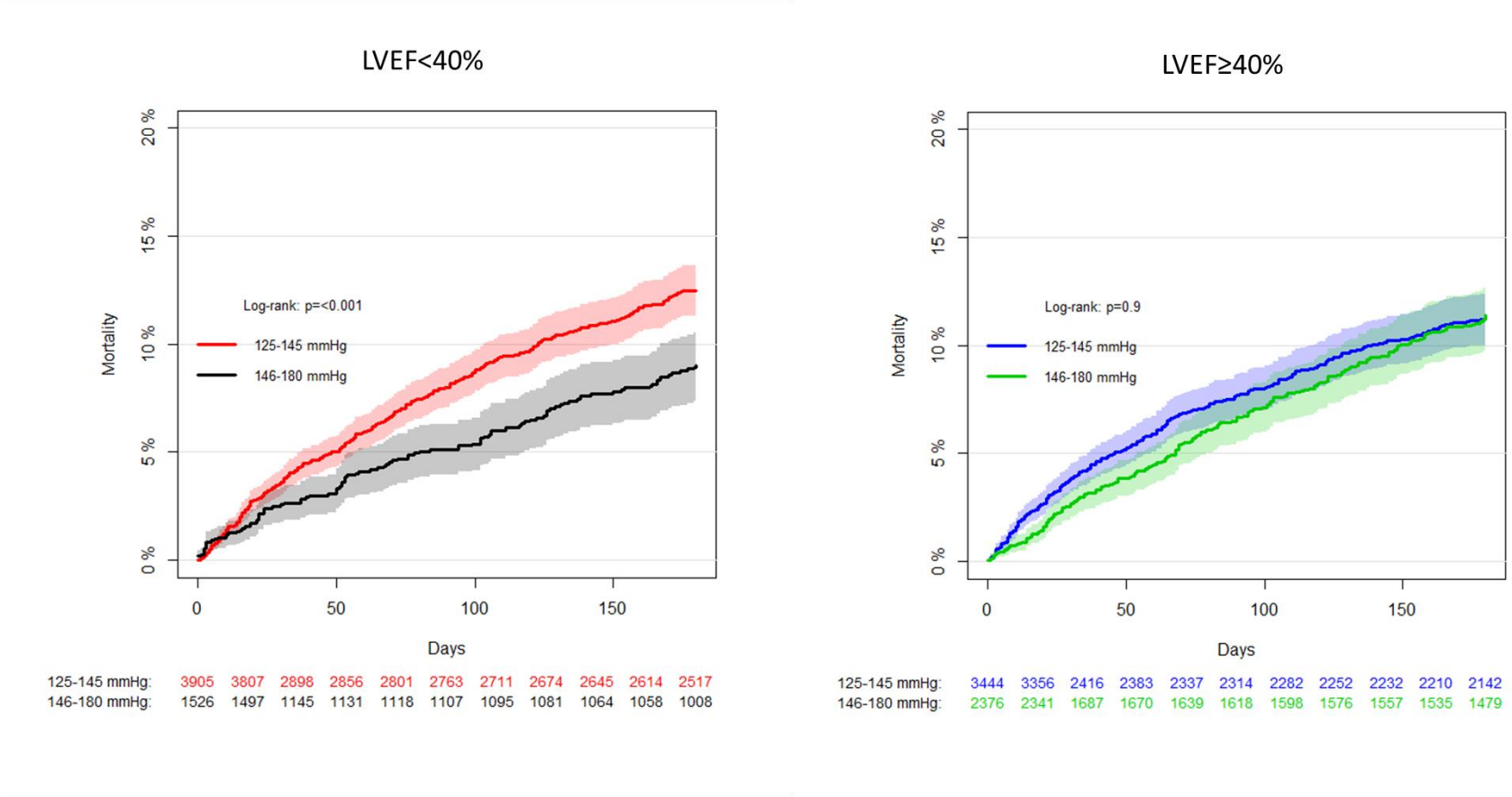

Figure S2. Kaplan–Meier survival curves for study population divided in blood pressure groups.