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EXPEDITED PUBLICATION

Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program

Correlation With Outcomes

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Objectives The aim of this study was to assess the effects of serelaxin on short-term changes in markers of organ damage and congestion and relate them to 180-day mortality in patients with acute heart failure.

Background Hospitalization for acute heart failure is associated with high post-discharge mortality, and this may be related to organ damage.

Methods The Pre-RELAX-AHF (Relaxin in Acute Heart Failure) phase II study and RELAX-AHF phase III study were international, multicenter, double-blind, placebo-controlled trials in which patients hospitalized for acute heart failure were randomized within 16 h to intravenous placebo or serelaxin. Each patient was followed daily to day 5 or discharge and at days 5, 14, and 60 after enrollment. Vital status was assessed through 180 days. In RELAX-AHF, laboratory evaluations were performed daily to day 5 and at day 14. Plasma levels of biomarkers were measured at baseline and days 2, 5, and 14. All-cause mortality was assessed as a safety endpoint in both studies.

Results Serelaxin reduced 180-day mortality, with similar effects in the phase II and phase III studies (combined studies: N = 1,395; hazard ratio: 0.62; 95% confidence interval: 0.43 to 0.88; p = 0.0076). In RELAX-AHF, changes in markers of cardiac (high-sensitivity cardiac troponin T), renal (creatinine and cystatin-C), and hepatic (aspartate transaminase and alanine transaminase) damage and of decongestion (N-terminal pro–brain natriuretic peptide) at day 2 and worsening heart failure during admission were associated with 180-day mortality. Serelaxin administration improved these markers, consistent with the prevention of organ damage and faster decongestion.

Conclusions Early administration of serelaxin was associated with a reduction of 180-day mortality, and this occurred with fewer signs of organ damage and more rapid relief of congestion during the first days after admission. (J Am Coll Cardiol 2013;61:196–206) © 2013 by the American College of Cardiology Foundation

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Acute heart failure (AHF) is the most common cause of hospitalization in patients older than 65 years, with a mortality rate reaching 30% to 40% within 1 year (1–5). Recent studies have implicated organ damage and persistent or recurrent congestion during the first days after admission as contributors to this poor prognosis (3,6–8). Injury or end-organ dysfunction, including myocardial damage, worsening renal function, and hepatic impairment, is an independent predictor of increased mortality in patients with AHF (3,9–11). Signs of unresolved congestion and its most severe manifestation, episodes of worsening heart failure, are also strong predictors of poor outcomes (12–14). Therefore, it has been hypothesized that the prevention of organ damage and relief from congestion may be associated with lower mortality of patients with AHF (3,7,9,15).

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone that increases during pregnancy and mediates the maternal physiological cardiovascular and renal adaptations and has potential protective effects against organ damage (16–18). The RELAX-AHF (Relaxin in Acute Heart Failure) study examined the effects of serelaxin in patients with AHF. In this study, serelaxin improved 1 of the 2 primary endpoints, dyspnea measured using a visual analogue scale to day 5, but did not affect the other primary endpoint of dyspnea relief assessed using a Likert scale at 6, 12, and 24 h and did not reduce the rate of cardiovascular death or heart failure readmissions to day 60 or days alive and out of the hospital to day 60 (secondary endpoints). All-cause 180-day mortality, a pre-specified safety endpoint of the trial, was significantly reduced by serelaxin administration, and these results were similar to those of the Pre-RELAX-AHF phase II trial (19). In this report, we describe the effects of serelaxin on pre-specified markers of cardiac, renal, and liver damage, as well as signs and symptoms of congestion resolution. In a post hoc exploratory analysis, we explored the association of these changes with 180-day mortality in the RELAX-AHF trial.

Abbreviations and Acronyms

AHF = acute heart failure
ALT = alanine transaminase
AST = aspartate transaminase
CI = confidence interval
HR = hazard ratio
hs-cTnT = high-sensitivity cardiac troponin T
NT-proBNP = N-terminal pro–brain natriuretic peptide

Methods

Study design. Both the Pre-RELAX-AHF phase II and the RELAX-AHF phase III studies were randomized, double-blind, placebo-controlled, parallel-group, international trials comparing the intravenous administration of serelaxin for up to 48 h, started within 16 h of presentation, with placebo in patients hospitalized for AHF with dyspnea, congestion on chest radiography, increased natriuretic peptide levels, mild to moderate renal insufficiency, and systolic blood pressure >125 mm Hg. Background, design, and main results for both studies have been published (19–21).

Procedures. In the RELAX-AHF phase III study, blood samples were collected in all patients at baseline and at 24 h (day 1); 48 h (day 2); on days 3 and 4, if in hospital; and on days 5, 14, and 60 for standard hematology and chemistry at a central laboratory using commercially available, validated assays. Serum creatinine and transaminases were assessed as variables related to renal and liver function.

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Measurements of high-sensitivity cardiac troponin T (hs-cTnT), cystatin-C, and N-terminal pro–brain natriuretic peptide (NT-proBNP) were pre-specified in the protocol as biomarkers related to myocardial damage, kidney injury, and decongestion, respectively. These biomarkers were measured in all patients at baseline and on days 2, 5, and 14 at an independent central laboratory. All samples from the same patient were analyzed in the same batch by laboratory personnel blinded to subject treatment and study data. Plasma hs-cTnT was measured using the high-sensitivity Roche Elecsys assay (lot number 167345; Roche Diagnostics GmbH, Mannheim, Germany). The 99th-percentile upper reference limit was 0.014 μg/l, and the lowest concentration with a coefficient of variation ≤10% was 0.013 μg/l. NT-proBNP plasma levels were measured using the Roche Elecsys proBNP assay (Roche Diagnostics GmbH), which has a reporting range of 5 to 35,000 ng/l. Cystatin-C plasma levels were measured using the Gentian Cystatin C Immunoassay (Beckman Coulter, Brea, California), with a reporting range of 0.25 to 8.4 mg/l (18.7 to 629 nmol/l).

Definitions. Cutoff values to categorize plasma hs-cTnT, cystatin-C, and NT-proBNP changes were defined on the basis of previous studies and guidelines. Consistent with the universal definition of myocardial infarction, hs-cTnT concentration was defined a priori as elevated when its value exceeded the 99th percentile of the upper reference limit for the assay: 0.014 μg/l (22). Additional thresholds were chosen post hoc on the basis of current published recommendations. We defined substantial additional myocardial necrosis as a further increase in hs-cTnT level of at least 20% (23,24).

Worsening renal function was defined as increases in serum creatinine and plasma cystatin-C values of ≥0.3 mg/dl (27 μmol/l) and ≥0.3 mg/l (22 nmol/l), respectively, from the values measured at baseline, consistent with previously published studies (9,25,26). A decrease in NT-proBNP of ≥30% relative to baseline at day 2 was defined as clinically meaningful, according to previous studies (27,28). Evidence of hepatic damage was taken as 20% or greater increases from baseline to day 2 in aspartate transaminase (AST) and alanine transaminase (ALT).

Worsening heart failure was determined by the investigator using a scripted 1-page form and, similar to previous studies (12–14,29,30), and was defined as worsening signs and/or symptoms of heart failure requiring reinstitution or intensification of intravenous or mechanical therapy for heart failure.

Statistical analysis. Analyses were conducted on the intention-to-treat principle, with patients allocated according to randomized treatment. Analyses of plasma chemistry changes included patients treated with the study drug who had both baseline values and at least 1 follow-up value. Biomarkers (hs-cTnT, cystatin-C, and NT-proBNP) were analyzed in patients who had both baseline values and at least 1 follow-up value. Biomarker levels below the lower limit of quantification (or reporting range) were imputed as half the lower limit of quantification, and values above the upper limit of quantification were imputed as 1.5 times the upper limit of quantification. Values were log transformed for analysis, and treatment groups were compared using repeated-measures analysis of variance with adjustment for baseline values. Kaplan-Meier estimates of the cumulative risk for mortality through 180 days are presented, and groups were compared using log-rank tests. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from Cox regression models. A multivariable model for predicting 180-day all-cause mortality was constructed from baseline characteristics, including clinical and laboratory variables and biomarkers in the patients assigned to placebo, using backward selection, with the criterion for retaining in the model at $p < 0.10$. The association of serelaxin with 180-day all-cause mortality was then adjusted for the covariates included in this multivariate model in the full dataset. A post hoc analysis was performed in which the HR for 180-day all-cause mortality comparing serelaxin with placebo combined across Pre-RELAX-AHF and RELAX-AHF was estimated using Cox regression with stratification by study. Stratified Kaplan-Meier estimates were obtained using Mantel-Haenszel weighting of the results of the 2 studies, and treatments were compared using a stratified log-rank test. The number needed to treat to prevent 1 death by 180 days was estimated as the inverse of the absolute risk reduction (31).

Role of the funding source. The study was designed by the members of the executive committee, which included 2 Corthera clinical scientists, and was part of a phase II/III trial design (20). Data collection and analysis were performed by contract research organizations. The study databases were held by the sponsor. The authors had access to tables and listings supplied by the sponsor but did not have independent access to the study databases. The executive committee had full access to the final tables and figures. The authors not employed by the sponsor had ultimate editorial authority, with no interference by the sponsor on their final interpretation.

Results

The RELAX-AHF study examined the effect of serelaxin on dyspnea reduction and 60-day outcomes (21). One thousand one hundred sixty-one patients (placebo, n = 580; serelaxin, n = 581) in Eastern Europe (n = 562), Western Europe (n = 204), North America (n = 114), South America (n = 71), and Israel (n = 210) were enrolled in RELAX-AHF. One thousand one hundred thirty-eight patients (98%) received randomized study medication. Study drug infusion was maintained for the full 48 h in 929 of these patients (82%) (484 on placebo and 445 on serelaxin). Patients' characteristics are summarized elsewhere (21). A total of 1,126 randomized patients (97%) had both baseline and at least 1 follow-up standard chemistry result, and 1,102 (95%) had baseline and follow-up biomarker values.

The main results of the study have been published elsewhere (21). In short, serelaxin significantly reduced dyspnea, as

Table 1 Multivariable-Adjusted Association of Serelaxin With 180-Day Mortality in the Relaxin in Acute Heart Failure Study

Covariate*	HR for Continuous Variable is for an Increase of	HR 95% CI	p Value
Serelaxin treatment		0.64 (0.43–0.95)	0.026
Age (yrs)	1 yr	1.02 (1.00–1.04)	0.069
CHF 1 month previously		0.69 (0.44–1.06)	0.094
Stroke or other cerebrovascular event		1.68 (1.06–2.67)	0.028
Respiratory rate (breaths/min)	1 breath/min	1.02 (0.98–1.07)	0.24
Systolic BP (mm Hg)	10 mm Hg	0.83 (0.73–0.95)	0.0073
Edema‡	2/3 vs. 0/1	1.49 (1.00–2.22)	0.050
Orthopnea‡	2/3 vs. 0/1	2.68 (1.38–5.23)	0.0037
Lymphocytes (%)	5%	0.80 (0.69–0.93)	0.0037
Sodium (mmol/l)†	3 mmol/l	0.77 (0.67–0.88)	<0.0001
Creatinine (mg/dl)	1 mg/dl	1.97 (1.29–3.01)	0.0016
Log2 troponin T	Doubling	1.41 (1.21–1.64)	<0.0001

*Covariates considered but not included in the final model were male sex, white race, enrolled in United States, body mass index, heart rate, diastolic blood pressure, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, peripheral vascular disease, hyperlipidemia, hypertension, smoking, ejection fraction, baseline dyspnea visual analogue scale score, time from presentation to randomization, albumin, alanine transaminase, blood urea nitrogen, hemoglobin, rales, jugular venous pressure, N-terminal pro–brain natriuretic peptide, and cystatin-C. †Millimoles per liter are equivalent to milliequivalents per liter. ‡Edema was evaluated in any dependent area on a scale ranging from 0 to 3+; orthopnea was evaluated after the patient rested supine for 10 to 15 min and was rated on a scale ranging from 0 to 3: 0 = none, 1 = 1 pillow, 2 = 2 pillows, 3 = >30°.
BP = blood pressure; CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio.

measured by change from baseline on a 100-point visual analogue scale over 5 days, but did not affect dyspnea reduction as measured using a 7-point, Likert scale over the first 24 h (primary end-points). Serelaxin administration did not affect 60-day readmissions or death, largely because of the lack of an effect on readmissions (the secondary composite end-points). Serelaxin administration was associated with other beneficial effects on congestion, length of stay in the intensive care unit, and length of initial hospital stay as well as a reduction of 180-day all-cause mortality (21).

Effects of serelaxin on 180-day all-cause mortality. In RELAX-AHF, serelaxin significantly reduced 180-day all-cause mortality, and this result remained significant after adjustment for baseline characteristics found to be associated with 180-day all-cause mortality by multivariate analysis in the placebo group (HR: 0.64; 95% CI: 0.43 to 0.95) (Table 1). These results are consistent with those of the phase II Pre-RELAX-AHF study (Fig. 1) (19). In Pre-RELAX-AHF, the HR for all serelaxin dose groups combined versus placebo was 0.53 (95% CI: 0.22 to 1.30; p = 0.16). A combined analysis of these 2 trials confirmed the reduction in all-cause mortality at 180 days by serelaxin, with a combined HR of 0.62 (95% CI: 0.43 to 0.88; p = 0.0076), with a number needed to treat to save one life of 24. Survival curves in all analyses began to separate after day 5 onward through day 180.

Effects of serelaxin on organ damage. The risk for dying associated with incremental changes in hs-cTnT, NT-proBNP, cystatin-C, and creatinine from baseline to day 2, adjusted for baseline levels, in RELAX-AHF is shown in Table 2. Risks associated with changes in these biomarkers exceeding the clinically significant cutoffs defined a priori are given in Table 3. The effects of serelaxin on changes in biomarkers and standard markers of renal and liver function are shown in Table 4.

MYOCARDIAL DAMAGE. At baseline, hs-cTnT plasma levels were higher than the upper reference limit in 93% of patients. Baseline hs-cTnT levels were associated with 180-day all-cause mortality, with an HR of 1.41 (95% CI: 1.21 to 1.64) for any doubling of hs-cTnT levels. Increases from baseline in hs-cTnT levels at days 2, 5, and 14 were also associated with increased 180-day all-cause mortality (Table 2), and an increase of ≥20% over baseline at day 2 nearly doubled the risk (Table 3, Fig. 2A).

Baseline hs-cTnT levels were similar between the serelaxin and placebo groups (Table 4). Serelaxin administration was associated with significantly lower hs-cTnT levels at

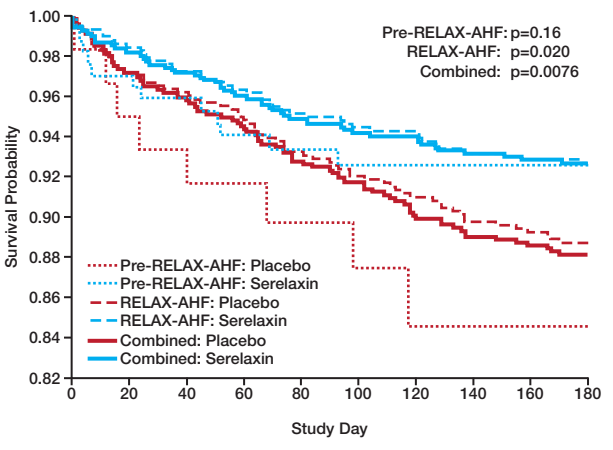

Figure 1 Risk for All-Cause Mortality in Pre-RELAX-AHF, RELAX-AHF, and Combined

The combined results represent stratified Kaplan-Meier estimates. p Values are for log-rank tests in the individual studies and for the stratified log-rank test for the combined studies. RELAX-AHF = Relaxin in Acute Heart Failure.

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Table 2 Association of Continuous Biomarker Changes From Baseline With 180-Day Mortality in the RELAX-AHF Study

Biomarker	HR (95% CI)*	p Value
Troponin (log2)		
Day 2	1.66 (1.24–2.02)	0.0002
Day 5	1.22 (1.01–1.47)	0.039
Day 14	1.68 (1.40–2.01)	<0.0001
Cystatin-C (log2)		
Day 2	2.28 (1.02–5.10)	0.046
Day 5	1.77 (0.87–3.59)	0.11
Day 14	1.34 (0.64–2.81)	0.44
Creatinine (log2)		
Day 2	1.64 (0.83–3.26)	0.15
Day 5	1.63 (0.88–3.00)	0.12
Day 14	1.12 (0.58–2.17)	0.74
NT-proBNP (log2)		
Day 2	1.73 (1.42–2.12)	<0.0001
Day 5	1.56 (1.30–1.88)	<0.0001
Day 14	1.48 (1.20–1.82)	0.0002

*Adjusted for baseline value of biomarker.
NT-proBNP = N-terminal pro–brain natriuretic peptide. Other abbreviations as in Table 1.

day 2 (p = 0.013) (Table 4) and no significant difference in levels at day 5 after enrollment (p = 0.18) (Fig. 3A) as well as with fewer patients having substantial further increases in hs-cTnT levels over baseline values at day 2 (Table 4).

Serelaxin-treated patients had a lower incidence of adverse events classified as cardiac disorders through day 5 (15.8% with placebo, 12.3% with serelaxin; odds ratio: 0.75; 95% CI: 0.54 to 1.05).

WORSENING RENAL FUNCTION AND LIVER DAMAGE. Worsening renal function, defined by a serum creatinine increase of ≥0.3 mg/dl (27 μmol/l) or a cystatin-C increase of ≥0.3 mg/l (22 nmol/l) at day 2, occurred in 167 of 1,086 (15.4%) and 212 of 1,081 (19.6%) patients, respectively. These measures of worsening renal function were associated with increased 180-day all-cause mortality (Table 3, Fig. 2B).

Patients assigned to serelaxin had similar values of serum creatinine and plasma cystatin-C at baseline, compared with those on placebo (Table 4). Serelaxin was associated with significantly lower serum creatinine and plasma cystatin-C values in the first 5 days after enrollment (Table 4, Figs. 3B and 4A) and, in the case of cystatin-C, also at day 14 (Fig. 3B). Serelaxin administration was associated with a lower incidence of worsening renal function at day 2 (Table 4). Patients on serelaxin also had lower levels of blood urea nitrogen and of uric acid at each day from day 1 to day 5 after enrollment (Figs. 4B and 4C). The incidence of adverse events classified as renal and urinary disorders was 5.6% on placebo and 4.6% on serelaxin (odds ratio: 0.81; 95% CI: 0.47 to 1.37).

Increases of ≥20% at day 2 in serum transaminases (AST and ALT) occurred in 99 of 1,005 (9.9%) and 99 of 1,069 (9.3%) patients, respectively. These changes in serum transaminases were associated with increased 180-day all-cause mortality (Table 3, Figs. 2C and 2D).

Serelaxin-treated patients had larger mean decreases in AST at days 1 and 2 and in ALT at days 2 and 3 (Figs. 4D and 4E), and lower proportions of patients had AST and ALT increases of ≥20% at day 2 (Table 4). Plasma bilirubin levels were not different between serelaxin and placebo (data not shown). Adverse events classified as hepatobiliary disorders through day 5 occurred less frequently in the serelaxin group (1.8% with placebo, 0.2% with serelaxin; odds ratio: 0.10; 95% CI: 0.01 to 0.77).

Reduction of congestion on serelaxin. The effects of serelaxin on symptoms and signs of heart failure related to congestion during the first days after randomization in RELAX-AHF have been described elsewhere (21). Patients on placebo received higher doses of intravenous diuretic agents over the first 5 days of the study. This difference was driven mostly by differences at days 3, 4, and 5, with no significant difference in doses of diuretic agents at days 1 and 2 of the study (p = 0.14 and p = 0.10, respectively).

Table 3 Association of Substantial Biomarker Changes at 48 h From Randomization With 180-Day Mortality in the Relaxin in Acute Heart Failure Study

	Death Through Day 180			
Biomarker Change From Baseline to Day 2	No	Yes	HR (95% CI)	p Value
Troponin (≥20% increase)	62/825	30/231	1.80 (1.16–2.777)	0.0076
	7.6 (6.0–9.6)	13.1 (9.3–18.2)		
Creatinine (≥27 μmol/l [0.3 mg/dl] increase)	75/919	23/167	1.76 (1.11–2.82)	0.016
	8.2 (6.6–10.2)	13.8 (9.4–20.0)		
Cystatin-C (≥22 nmol/l [0.3 mg/l] increase)	66/869	32/212	2.10 (1.38–3.20)	0.0004
	7.7 (6.1–9.7)	15.2 (11.0–20.7)		
AST (≥20% increase)	73/906	13/99	1.66 (0.92–3.00)	0.099
	8.1 (6.5–10.1)	13.4 (8.0–22.0)		
ALT (≥20% increase)	79/970	15/99	1.96 (1.13–3.40)	0.015
	8.2 (6.6–10.1)	15.3 (9.5–24.1)		
NT-proBNP (≥30% decrease)	53/395	45/686	0.47 (0.31–0.69)	0.0001
	13.5 (10.5–17.4)	6.6 (5.0–8.8)		

Values are n/N with Kaplan-Meier percentages and 95% CIs.
ALT = alanine transaminase; AST = aspartate transaminase. Other abbreviations as in Tables 1 and 2.

Table 4 Baseline Values and Changes From Baseline in Biomarkers Related to Organ Damage in the RELAX-AHF Study

Variable	Placebo (n = 580)	Serelaxin (n = 581)	Treatment Effect (95% CI)	p Value
Cardiac damage				
hs-cTnT (μg/l)				
Baseline geometric mean	0.036	0.034		
Below LLOQ (0.013 μg/l) at baseline	34/541 (6.3%)	40/533 (7.5%)		
Day 2 geometric mean	0.037	0.033		
Below LLOQ at day 2	32/534 (6.0%)	37/523 (7.1%)		
Relative change to day 2 (geometric mean change)	1.035	0.966	0.933 (0.883 to 0·985)*	0.013
≥20% increase at day 2	145/534 (27.2%)	86/522 (16.5%)	0.53 (0.39 to 0.71)†	<0.0001
Worsening renal function				
Serum creatinine (μmol/l)§				
Baseline mean	117	117		
Day 2 mean	123	113		
Mean change to day 2	6.2	−3.4	−9·5 (−12.4 to −6.6)‡	<0.001
≥0.3 mg/l (27 nmol/L) increase from baseline to day 2	108/545 (19.8%)	59/541 (10.9%)	0.50 (0.35 to 0.70)†	<0.0001
Cystatin C (nmol/l)‖				
Baseline geometric mean	109	109		
Day 2 geometric mean	118	112		
Relative change to day 2 (geometric mean change)	1.080	1.027	0.950 (0.931 to 0.970)*	<0.001
≥0.3 mg/l (22 nmol/l) increase from baseline to day 2	126/542 (23.2%)	86/539 (16.0%)	0.63 (0.46 to 0.85)†	0.0027
BUN (mmol/l)¶				
Baseline	9.8	9.7		
Day 2	10.7	9.9		
Change at day 2 (mmol/l)	0.8	0.2	−0.62 (−0.96 to −0.28)‡	<0.001
Uric acid (μmol/l)#				
Baseline	475	476		
Day 2	500	466		
Change at day 2 (μmol/l)	24.7	−8.5	−33 (−42 to −24)‡	<0.001
Liver function				
ALT (U/l)				
Baseline	28.4	31.1		
Day 2	25.5	24.6		
Change at day 2 (mg/dl)	−2.3	−6.4	−4.16 (−6.62 to −1·70)‡	<0.001
≥20% increase at day 2	61/537 (11.4%)	38/532 (7.1%)	0.60 (0.39 to 0.92)†	0.018
AST (U/l)				
Baseline	30.4	32.2		
Day 2	27.5	24.5		
Change at day 2 (mg/dl)	−2.2	−7.6	−5·33 (−9·04 to −1·62)‡	0.005
≥20% increase at day 2	64/502 (12.7%)	35/503 (7.0%)	0.51 (0.33 to 0.79)†	0.0024
Albumin (g/l)				
Baseline	40.0	40.5		
Day 2	38.5	39.1		
Change at day 2 (mg/dl)	−1.4	−1.3	0.15 (−0.23 to 0.53)‡	0.45
Decongestion				
NT-proBNP (ng/l)				
Baseline geometric mean	5,003.50	5,125.46		
Above ULOQ (35,000 ng/l) at baseline	6/551 (1.1%)	6/550 (1.1%)		
Day 2 geometric mean	3,037.50	2,544.23		
Above ULOQ at day 2	7/544 (1.3%)	1/538 (0.2%)		
Relative change to day 2 (geometric mean change)	0.607	0.492	0.812 (0.753 to 0.876)*	<0.001
≥30% decrease from baseline at day 2	315/543 (58.0%)	371/538 (69.0%)	1.61 (1.25 to 2.06)†	0.0002

*Ratio of geometric mean changes from repeated-measures analysis of covariance. †Odds ratio. ‡Mean difference. §Divide by 88.4 to convert from micromoles per liter to milligrams per deciliter. ‖Divide by 74.9 to convert from nanomoles per liter to milligrams per liter. No values were beyond the limits of quantitation at either baseline or day 2. ¶Multiply by 2.808 to convert from millimoles per liter to milligrams per deciliter. #Multiply by 0.168 to convert from micromoles per liter to milligrams per deciliter.

BUN = blood urea nitrogen; hs-cTnT = high-sensitivity cardiac troponin T; LLOQ = lower limit of quantification; ULOQ = upper limit of quantification. Other abbreviations as in Tables 1 to 3.

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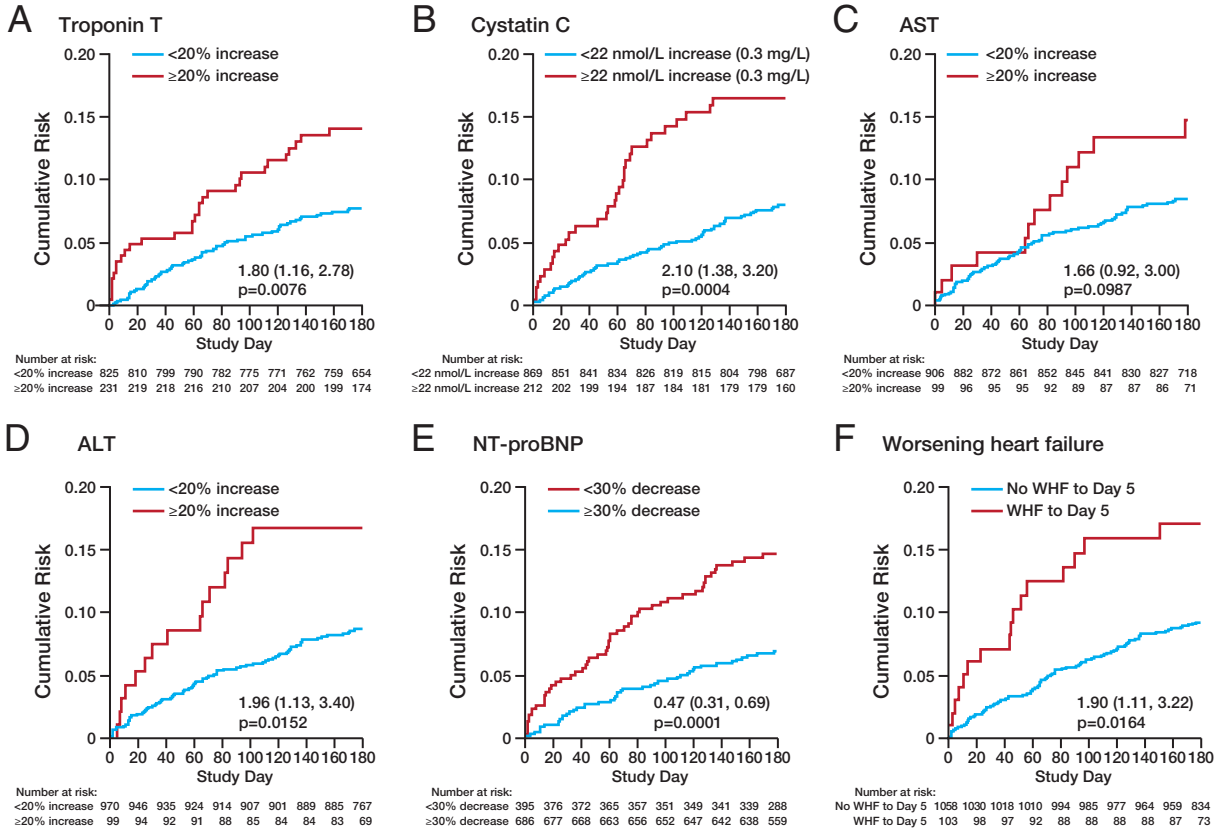

Figure 2 **Risk for Death by Early Changes in Markers of Organ Function, Damage, and Congestion**

All-cause death through day 180 in Relaxin in Acute Heart Failure study patients subdivided by percentage change in troponin T from baseline to day 2 **(A)**, absolute change in cystatin-C from baseline to day 2 **(B)**, percentage increases in serum aspartate transaminase (AST) **(C)** and serum alanine transaminase (ALT) **(D)** from baseline to day 2, decrease in N-terminal pro–brain natriuretic peptide (NT-proBNP) from baseline to day 2 **(E)**, and worsening heart failure (WHF) by day 5 **(F)**.

They also showed significantly greater early reductions in signs and symptoms of congestion (e.g., edema, rales, orthopnea, jugular venous pressure, and dyspnea on exertion) compared with patients on placebo.

NT-proBNP levels. Higher NT-proBNP levels were associated with increased 180-day all-cause mortality (Table 2), and their reduction during the first 2 days after enrollment predicted better prognosis (Tables 3 and 4, Fig. 2E).

Patients assigned to serelaxin had similar baseline values of plasma NT-proBNP compared with those on placebo (Table 4). Serelaxin was associated with significantly lower NT-proBNP levels at day 2 (Table 4, Fig. 3C), nonsignificantly different levels at day 5, and no difference thereafter (Fig. 3C). Serelaxin administration was also associated with a greater proportion of patients having 30% decreases in NT-proBNP from baseline to day 2 compared with placebo (Table 4).

Worsening heart failure. The 103 of 1,161 patients (8.9%) who developed worsening heart failure by day 5 had higher 180-day all-cause mortality (Fig. 2F). The risk for developing worsening heart failure through day 5 was lower in the serelaxin-treated patients (12.2% with placebo, 6.7% with serelaxin; HR: 0.53; 95% CI: 0.36 to 0.79; p = 0.0016).

Discussion

Hospitalizations for AHF are associated with high mortality. No major improvement in the early treatment of patients with AHF, and hence in their prognosis, has occurred in more than 20 years (3,4,32). In the RELAX-AHF study, serelaxin administration was associated with reduction in dyspnea but had no effect on the composite secondary endpoint, including 60-day readmission and death, because of the lack of an effect on readmissions. Serelaxin administration was associated with improvements in measures of congestion and with a reduced duration of the initial hospital stay. In the RELAX-AHF trial, consistent with the Pre-RELAX-AHF phase II study (19), the early administration of intravenous serelaxin was associated with a combined 38% decrease in 180-day all-cause mortality (p = 0.0076) (21), with the cumulative survival curves of

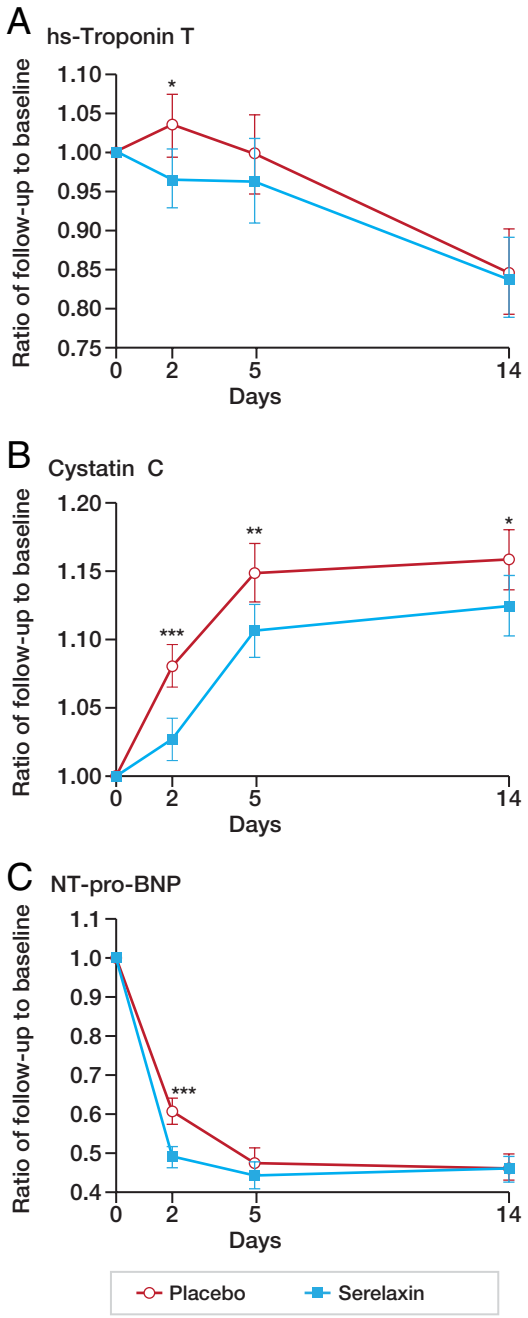

Figure 3 **Biomarker Changes From Baseline in the Placebo and Serelaxin Groups**

Changes from baseline to each study day in the Relaxin in Acute Heart Failure study in high-sensitivity (hs) troponin T **(A)**, cystatin-C **(B)**, and N-terminal pro–brain natriuretic peptide (NT-proBNP) **(C)**. *$p < 0.05$, **$p < 0.005$, and ***$p < 0.001$ by repeated-measures analysis of variance with adjustment for baseline value.

serelaxin versus placebo starting to separate at 5 days after enrollment in both studies. In the present study, we report that serelaxin had favorable effects on the short-term changes in multiple laboratory markers of cardiac, renal, and liver damage known to be associated with long-term mortality in AHF.

The role of ongoing myocardial injury in heart failure has been established with the advent of sensitive assays for myocardial necrosis (24,33). Multiple studies have demonstrated a strong association between elevated troponin levels in patients with heart failure and poor clinical outcomes. An increase in troponin during the hospital stay is more specific for myocardial damage associated with the acute episode and, accordingly, has been shown to have an independent relation with outcomes (23,34,35). It may therefore be hypothesized that preventing myocardial damage, as evidenced by acute increases in troponin, might favorably influence survival. Our study confirms that a rise in hs-cTnT level during the hospital stay, assessed either as a continuous measure or as a 20% increment, a cutoff chosen on the basis of current recommendations (23), is associated with increased 180-day all-cause mortality. Serelaxin administration was associated with reductions at day 2 from randomization, but not thereafter, in both overall levels of hs-cTnT and the proportion of patients who had ≥20% increases, providing a potential mechanism for the improved survival of serelaxin-treated patients.

The relationship between worsening renal function and poor outcomes in patients with heart failure has been established (25,36), although some uncertainty about the importance of transient worsening renal function persists (9,37). In the RELAX-AHF trial, creatinine levels at baseline and worsening renal function, as measured by increases in creatinine or cystatin-C, were associated with increased 180-day all-cause mortality. Serelaxin administration was associated with lower levels of markers of renal dysfunction as well as a reduced incidence of worsening renal function, consistent with the hypothesis that the prevention of renal dysfunction during AHF hospitalization favorably influences outcomes (3,9). Although some of this effect may be related to the use of greater doses of intravenous loop diuretic agents in the placebo-treated arm, most of the effect of serelaxin on renal function occurred early, during the first 2 days after randomization, when the difference in total doses of loop diuretic agents between the 2 groups was nonsignificant (21). It is also possible that the reduced need for loop diuretic agents in the serelaxin arm, compared with the placebo arm, is the result, rather than the cause, of improved kidney function. Patients treated with serelaxin had on average larger decreases in blood pressure, and hence the effect of serelaxin to reduce markers of renal impairment cannot be attributed to a lesser blood pressure decrease (21).

The role of liver damage in AHF and its relation to survival is incompletely studied (10,11,38). In AHF, either hepatic congestion or direct liver injury through the activation of inflammatory cascades, oxidative stress, or other mechanisms could result in hepatic damage. Serelaxin administration was associated with reduced levels of transaminases and with a trend toward higher levels of albumin, after randomization, and both these changes have been associated with better survival in AHF (10,11,30). Plasma levels of uric

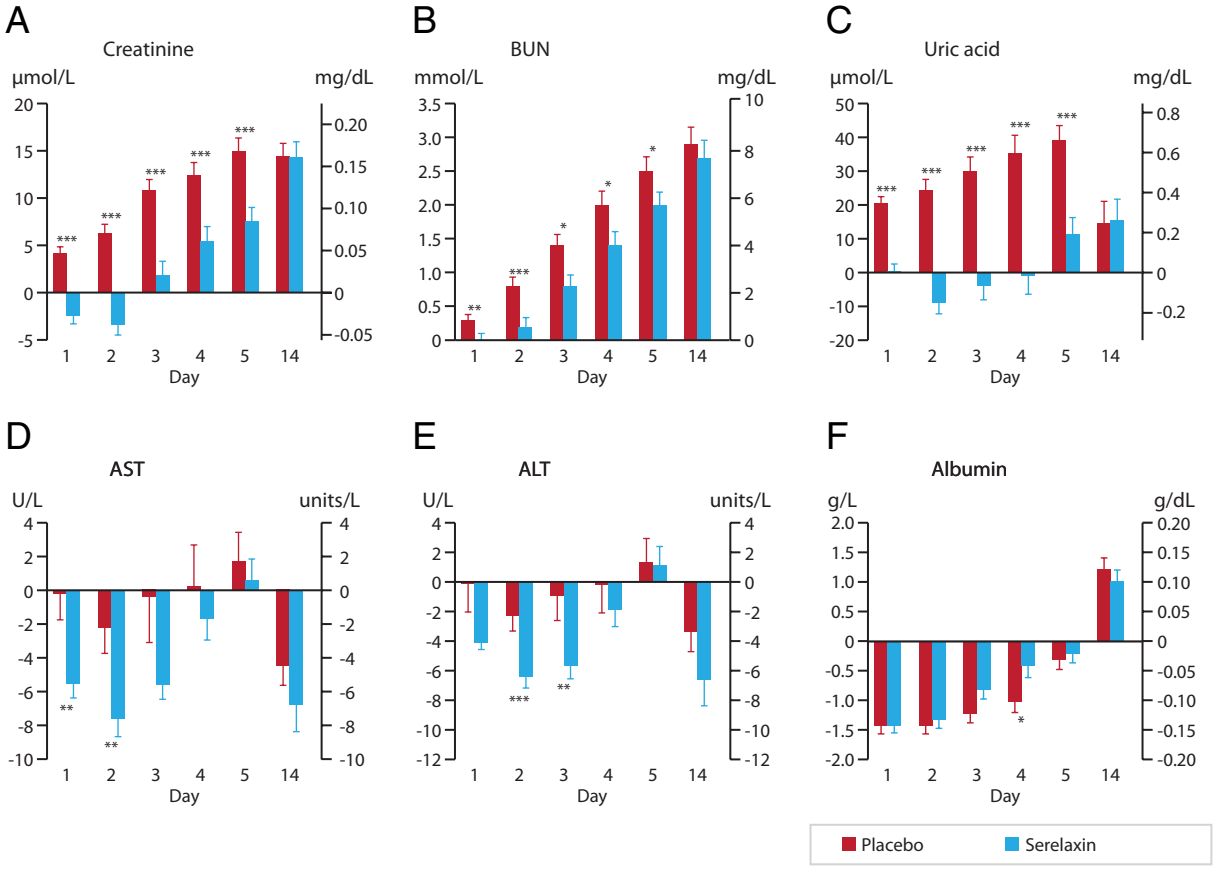

Figure 4 **Early Changes From Baseline in Laboratory Values**

Change from baseline in the Relaxin in Acute Heart Failure study in creatinine **(A)**, blood urea nitrogen (BUN) **(B)**, uric acid **(C)**, alanine transaminase (ALT) **(D)**, aspartate transaminase (AST) **(E)**, and albumin **(F)**. Changes are shown in Système International units on the left y-axis and in conventional units on the right y-axis. *$p <$ 0.05, **$p < 0.005$, and ***$p < 0.001$ by 2-sided, 2-sample *t* test for serelaxin versus placebo.

acid have also been related with mortality in heart failure (39), and serelaxin administration reduced them in RELAX-AHF.

Lack of, or slower, resolution of congestion during the first days of admission for AHF has been associated with more adverse outcomes (3,8,14). In its most extreme form, lack of decongestion manifests as worsening heart failure, and this event is associated with a 2-fold to 6-fold increase in mortality (12–14,30). Persistently elevated natriuretic peptide concentrations during the hospital stay have also been associated with a poor prognosis, independent of clinical signs (27,28). In the RELAX-AHF study, both worsening heart failure during the hospital stay and a lack of decrease in NT-proBNP levels during the hospital stay were associated with increased 180-day all-cause mortality, consistent with the hypothesis that persistent congestion may worsen patients' prognoses. Serelaxin administration significantly diminished signs and symptoms of congestion and reduced NT-proBNP levels at 2 days after randomization, but not thereafter, as well as the rate of worsening heart failure.

Thus, this post-hoc analysis shows that serelaxin is associated with significant reductions in markers of end-organ damage (cardiac, renal, and hepatic) and better relief from congestion. All of these changes have been associated with lower 180-day all-cause mortality in the present analysis as well as in previous studies (3,10,24,25,27,28,33,36). These findings suggest that organ damage and persistent congestion during the first days of admission are important mechanisms of the high mortality of patients with AHF and might be important treatment targets in AHF. Other mechanisms were likely present. Although treatment at days 5 and 14 was similar between the patients assigned to serelaxin or placebo (21), the administration of lower doses of diuretic agents and the lesser use of inotropes in the patients randomized to serelaxin may have contributed to their lower 180-day mortality (3). Last, mechanisms such as increased aortic impedance and afterload mismatch, inflammatory activation, and oxidative stress are likely related to the poor prognosis of the patients hospitalized for AHF and are potential targets of serelaxin (16–18). However, they are difficult to measure in current clinical practice.

Patients were enrolled in both the RELAX-AHF and Pre-RELAX-AHF studies early (the median time from presentation was about 6 h) and were required to have systolic blood pressures >125 mm Hg and elevated levels of natriuretic peptides at the time of screening. Therefore, the results of this study pertain to a subgroup of patients with AHF and cannot be extrapolated to other AHF subgroups, especially patients who present with low blood pressures. However, the patients included in the RELAX-AHF program may represent many patients with AHF, as demonstrated in the Acute Decompensated Heart Failure National Registry, in which 50% of the 186,805 patients enrolled had blood pressures >140 mm Hg at presentation (3). Importantly, the benefit of serelaxin administration given the potential improvement of dyspnea, length of stay, worsening heart failure, end-organ damage, and mortality should be balanced against the lack of effect on readmissions shown in this study.

Conclusions

Our results suggest that serelaxin reduced cardiac, renal, and liver damage and persistent congestion during the first few days after admission, and these beneficial effects may be associated with increased survival. The post hoc exploratory nature of our findings regarding the association between early biomarkers changes and 180-day mortality suggests that our study may be considered hypotheses generating and that further studies may be required to further explore the effects of serelaxin.

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Key Words: congestion ■ heart failure ■ organ protection ■ RELAX-AHF ■ serelaxin.

APPENDIX

For a list of the Study Personnel, please see the online version of this article.