RELAX-AHF: rising from the doldrums in acute heart failure

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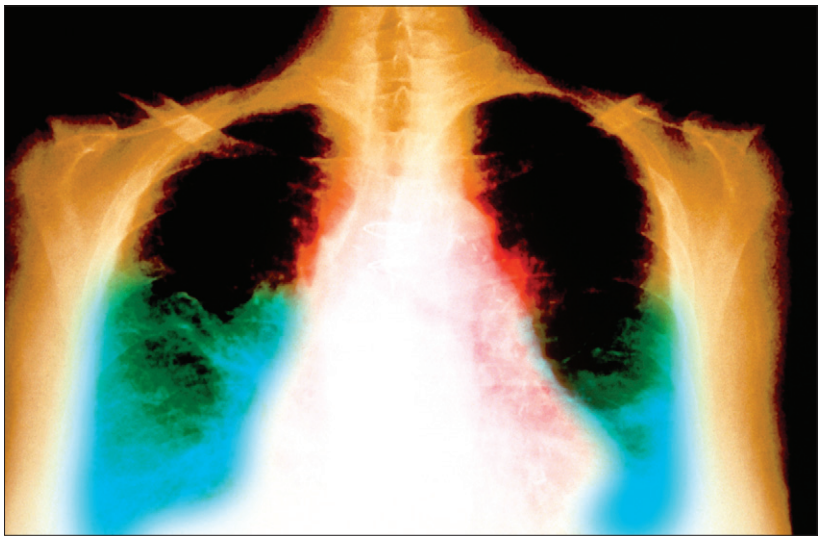
After a decade of acute heart failure trials,[1–4] clinicians are left with an array of drugs without hard evidence of clinical benefit and with nagging concerns over safety. In this setting, the RELAXin in Acute Heart Failure (RELAX-AHF) trial,[5] reported in *The Lancet*, represents an important step forward.

By contrast with patients with acute ST-segment elevation myocardial infarction, for whom lysis of a coronary thrombosis halts an acute disease process and confers long-term outcome benefit, the acute heart failure population is characterised by a constellation of inciting factors contributing to diverse clinical syndromes, and with admission to hospital driven by the subjective judgment of individual clinicians. In this setting, the prospect for long-term outcome benefit through short-term drug treatment seems remote. Instead, investigators have sought to document short-term symptom benefit, combined with long-term safety. However, even this goal is elusive, in view of the subjectivity and variability of available metrics and the diverse, unstable nature of acute heart failure populations, for whom post-randomisation imbalances are the rule.

RELAX-AHF, investigating recombinant human relaxin-2, is arguably the first trial in acute heart failure to show both significant improvement in a clinically meaningful primary endpoint (dyspnoea) and adequate short-term and long-term safety. But the report raises several crucial issues: (1) the population studied; (2) statistical and clinical significance of the dyspnoea finding; (3) interpretation of the mortality signal; (4) underlying mechanisms; and (5) clinical applicability.

Entry criteria differed from those in previous acute heart failure trials, with enrolment requiring a systolic blood pressure (SBP) greater than 125 mm Hg and not requiring a low left ventricular ejection fraction (LVEF). The resulting population was exceptional for clinical trials in this disorder, with a mean age of 72 (SD 11) years, baseline SBP of 142 (17) mm Hg, 45% having LVEF 40% or higher, and 30-day mortality of only 3·3%. In many ways, these demographic characteristics better resemble the broad acute heart failure population, except for the absence of patients with lower SBP. Compared with other trials in acute heart failure, the population is selected for more patients with hypertensive heart disease, fewer with dilated cardiomyopathy, and, importantly, avoidance of patients with more marginal blood pressure. Prevalence was probably higher for acute pulmonary oedema and lower for right heart failure. The investigators should be applauded for targeting a population with increased likelihood of efficacy and reduced likelihood of adverse effects from a vasodilator. However, the findings cannot be extrapolated to other populations, and scrutiny is needed to establish consistency across the trial's subpopulations.

The investigators are justified in regarding this trial as positive, despite significance in only one of two primary endpoints, since they achieved the appropriately adjusted p-value target for improvement of dyspnoea at day 5 measured by visual analogue scale (VAS). Rejection of the null hypothesis is further supported by a favourable trend for improvement of dyspnoea during the first 24 h assessed by Likert scale, benefit in the general wellbeing VAS, and favourability for the endpoint of worsening heart failure, a competing risk for dyspnoea assessment. However, the clinical relevance of a 448 mm × h VAS area under the curve between-group difference is obscure. This value falls below the 468 mm × h mark denoted as the target driving the sample size assignment. Despite statistical non-significance, the Likert scale is easier to interpret. The 12-h 50% versus 45% difference seems small



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for serelaxin versus placebo group patients showing markedly or moderately improved dyspnoea. But scepticism regarding the clinical relevance of these findings should be tempered by the challenging nature of showing positivity for the dyspnoea endpoint in acute heart failure. A significant reduction in dyspnoea, with several supportive short-term findings, sets serelaxin apart from most other drugs currently in clinical use.

I applaud the investigators for restraining their zeal in interpreting the favourable mortality trends. The findings, with a fairly small number of events, can only be regarded as hypothesis-generating. The associated p values reside among a multitude of exploratory endpoints and therefore have no validity for rejecting the null hypothesis. Several previous small studies in heart failure, including one designed to compare renal effects of losartan versus captopril,[6] displayed nominally significant mortality reductions, which later proved spurious.[7] All previous drugs proven to reduce mortality in heart failure were also shown to reduce admissions to hospital for heart failure.[8–11] The adverse trend in readmission to hospital in RELAX-AHF therefore generates further scepticism that the mortality findings will be reproduced. Nevertheless, the favourable mortality signals provide strong support for safety. Efforts should be undertaken to replicate them in an appropriately powered trial.

Among multiple potential mechanisms, combined systemic and renal vasodilation probably contributed to both the efficacy findings and reduction in renal adverse events, despite baseline renal impairment and drug-induced SBP reduction, with more interventions for hypotension. Although this favourable constellation has not always been observed with vasodilators,[12] similar results might be achievable with other available agents. Serelaxin reduced average SBP by up to 6 mm Hg, with greater individual effects, within this relatively hypertensive acute heart failure population, in which nitroglycerin and nitroprusside are often regarded as first-line treatments. Nitroglycerin and nitroprusside could achieve the same efficacy and safety observed here, although it should be acknowledged that such evidence does not exist.

For the clinician, there are several key caveats. None of the findings necessarily apply to unstudied populations, particularly those with SBP 125 mm Hg or lower. Further, internal consistency should be explored to identify subgroups that are either more or less likely to benefit. For example, do patients with acute pulmonary oedema respond similarly to those with right heart failure? Finally, safety was promoted through rigorous monitoring and dose adjustment, which might be difficult to replicate in clinical practice. With these caveats in mind, and assuming that regulatory approval is achieved, based on RELAX-AHF, clinicians will have a new treatment option with a uniquely documented combination of significant clinical efficacy and a strong safety profile.

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Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

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Summary

Background **Serelaxin, recombinant human relaxin-2, is a vasoactive peptide hormone with many biological and haemodynamic effects. In a pilot study, serelaxin was safe and well tolerated with positive clinical outcome signals in patients with acute heart failure. The RELAX-AHF trial tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo.**

Methods **RELAX-AHF was an international, double-blind, placebo-controlled trial, enrolling patients admitted to hospital for acute heart failure who were randomly assigned (1:1) via a central randomisation scheme blocked by study centre to standard care plus 48-h intravenous infusions of placebo or serelaxin (30 μg/kg per day) within 16 h from presentation. All patients had dyspnoea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP, mild-to-moderate renal insufficiency, and systolic blood pressure greater than 125 mm Hg. Patients, personnel administering study drug, and those undertaking study-related assessments were masked to treatment assignment. The primary endpoints evaluating dyspnoea improvement were change from baseline in the visual analogue scale area under the curve (VAS AUC) to day 5 and the proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale during the first 24 h, both analysed by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00520806.**

Findings **1161 patients were randomly assigned to serelaxin (n=581) or placebo (n=580). Serelaxin improved the VAS AUC primary dyspnoea endpoint (448 mm×h, 95% CI 120–775; p=0·007) compared with placebo, but had no significant effect on the other primary endpoint (Likert scale; placebo, 150 patients [26%]; serelaxin, 156 [27%]; p=0·70). No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure (placebo, 75 events [60-day Kaplan-Meier estimate, 13·0%]; serelaxin, 76 events [13·2%]; hazard ratio [HR] 1·02 [0·74–1·41], p=0·89] or days alive out of the hospital up to day 60 (placebo, 47·7 [SD 12·1] days; serelaxin, 48·3 [11·6]; p=0·37). Serelaxin treatment was associated with significant reductions of other prespecified additional endpoints, including fewer deaths at day 180 (placebo, 65 deaths; serelaxin, 42; HR 0·63, 95% CI 0·42–0·93; p=0·019).**

Interpretation **Treatment of acute heart failure with serelaxin was associated with dyspnoea relief and improvement in other clinical outcomes, but had no effect on readmission to hospital. Serelaxin treatment was well tolerated and safe, supported by the reduced 180-day mortality.**

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Introduction

Heart failure is a major worldwide health problem and the most frequent cause of admission to hospital in patients older than 65 years.[1–4] Although existing treatments substantially improve the clinical course and prognosis of ambulatory patients with chronic heart failure, treatment of patients admitted to hospital for acute heart failure has not changed in recent decades[3,5] with no treatments showing safe improvement in outcomes. Despite a favourable response to initial treatment, most patients remain symptomatic at 24 h and up to 25% develop worsening symptoms during the hospital stay.[6–8] Sustained relief of these signs and symptoms remains an important goal of treatment.[9–11]

Admission to hospital for heart failure portends an increased risk of poor outcomes, with a 5–15-times increase in the risk of death compared with ambulatory patients and a mortality rate of 10–20% in the 6 months after hospital discharge.[12,13] Although hospital admission could simply herald disease progression, this event and the related interventions might also directly contribute to poor outcomes through increased neurohormonal and inflammatory activation, haemodynamic compromise, and consequent end-organ damage.[12,14] Drugs that prevent or treat these factors might favourably affect the clinical course and prognosis of these patients, even if given for a short time during the acute episode.

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Serelaxin is recombinant human relaxin-2, a naturally occurring peptide that regulates maternal adaptations to pregnancy[15] with several effects potentially relevant to the treatment of acute heart failure, including increased arterial compliance, cardiac output, and renal blood flow.[16,17] Pre-RELAX-AHF,[18] a phase 2, dose-finding study with 234 patients, suggested beneficial effects of serelaxin on both dyspnoea and post-discharge clinical outcomes in patients admitted for acute heart failure, with evidence of congestion, normal-to-raised blood pressure, and mild-to-moderate renal dysfunction. The RELAXin in Acute Heart Failure (RELAX-AHF) trial was done in the same targeted patient population to evaluate the effects of serelaxin on dyspnoea relief and post-discharge clinical efficacy outcomes, as well as its safety and tolerability.[19]

Methods

Study design

RELAX-AHF was a prospective, randomised, double-blind, placebo-controlled, parallel-group trial comparing serelaxin with placebo in patients admitted to hospital for acute heart failure. Patients were enrolled at 96 sites in 11 countries. Centres included cardiology units and emergency medicine departments. The study background and design have been published[19] and the protocol and statistical analysis plan are available in the appendix. The ethics committee at each centre approved the study, and patients provided written informed consent. An independent data safety monitoring board reviewed accumulated safety data throughout the trial. A masked, independent clinical events committee adjudicated hospital admissions and deaths within 60 days and deaths up to 180 days after randomisation. Statistical analyses were done independently of the sponsor by Accovion GmbH (Frankfurt, Germany), and were subsequently confirmed by the sponsor.

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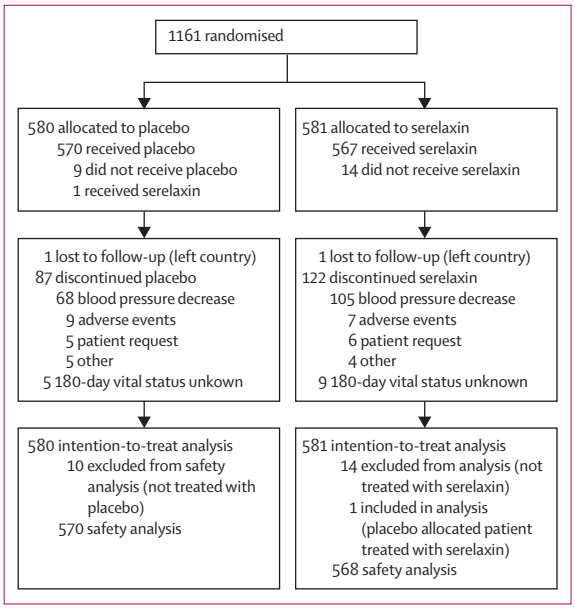

Figure 1: **Trial profile**

Participants

Patients eligible for enrolment presented for acute heart failure within the previous 16 h with dyspnoea at rest or with minimum exertion, pulmonary congestion on chest radiograph, and brain natriuretic peptide (BNP) 350 ng/L or higher or N-terminal prohormone of BNP (NT-proBNP) 1400 ng/L or higher, as well as mild-to-moderate renal dysfunction (simplified Modification of Diet in Renal Disease estimated glomerular filtration rate of 30–75 mL/min per 1·73 m^2), systolic blood pressure greater than 125 mm Hg, and treatment with at least 40 mg intravenous furosemide or its equivalent before screening. Exclusion criteria included treatment with other intravenous heart failure drugs (except intravenous nitrate ≤0·1 mg/kg per h in patients with systolic blood pressure at screening of >150 mm Hg) or mechanical support within 2 h before screening, signs of active infection, known significant pulmonary or valvular disease, acute heart failure due to significant arrhythmias, acute coronary syndrome diagnosed within 45 days, or a troponin concentration three times or more higher than the level diagnostic of myocardial infarction.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio according to a central randomisation scheme blocked by study centre to one of the two treatment groups (serelaxin 30 μg/kg per day or placebo). Serelaxin and matching placebo were supplied to study sites in identical masked kits. The randomisation scheme and the kit list consisting of kit numbers randomly assigned to treatment were generated by an independent supplier (Almac Clinical Technologies, Souderton, PA, USA) and verified by an independent unmasked statistician from another supplier (Statistics Collaborative Inc, Washington, DC, USA). Once an eligible patient was identified, trained study staff (principal investigator, subinvestigator, or study coordinator) called a central interactive voice response system to request assignment of study drug kits for each 24-h period of dosing. Qualified clinical research personnel, who were masked to the contents of the kits, prepared study drug by mixing the contents of the vials to achieve the proper concentration of serelaxin or to prepare placebo according to the patient's weight. Patients, and all other site personnel, including those administering study drug, and those undertaking study-related assessments, were masked to treatment assignments. All study personnel involved in the operations of the study or with any potential site contact, such as medical monitors, remained masked to treatment assignments from the time of randomisation until after the day 180 database lock.

Procedures

After randomisation, patients received either serelaxin 30 µg/kg per day or placebo administered intravenously for up to 48 h continuously. If systolic blood pressure decreased by more than 40 mm Hg from baseline but was greater than 100 mm Hg, the study drug infusion rate was halved for the remainder of the infusion period. The study drug was discontinued if systolic blood pressure fell to less than 100 mm Hg or if a serious or intolerable adverse event or clinically significant laboratory abnormality occurred. Other drugs or treatments were left to the treating physician's discretion including titration, discontinuation or introduction of intravenous loop diuretic drugs, nitrates, or inotropes. Other study procedures are described in the appendix.

The two primary efficacy endpoints were: (1) change in patient-reported dyspnoea as quantified by the area under the curve (AUC) of visual analogue scale (VAS) scores (0–100 mm scale) from baseline to day 5; and (2) moderately or markedly improved patient-reported dyspnoea relative to the start of study drug using the

	Placebo (n=580)	Serelaxin (n=581)
Age (years)	72·5 (10·8)	71·6 (11·7)
Men	357 (62%)	368 (63%)
White	552 (95%)	544 (94%)
Weight (kg)	82·8 (18·7)	81·9 (18·5)
Body-mass index (kg/m²)	29·5 (6·1)	29·1 (5·3)
Region*		
Eastern Europe	282 (49%)	280 (48%)
Western Europe	101 (17%)	103 (18%)
USA	55 (9%)	59 (10%)
Argentina	37 (6%)	34 (6%)
Israel	105 (18%)	105 (18%)
Systolic blood pressure (mm Hg)	142·1 (17·0)	142·2 (16·2)
Diastolic blood pressure (mm Hg)	81·7 (13·2)	82·2 (14·2)
Heart rate (beats per min)	80·4 (14·9)	78·9 (15·0)
Respiratory rate (breaths per min)	22·0 (4·6)	21·8 (4·6)
Admitted to hospital for heart failure in past year	181 (31%)	216 (37%)
Number of admissions for heart failure in past year	1·5 (1·1)	1·7 (1·5)
Most recent ejection fraction (%)	38·6% (14·3)	38·7% (14·8)
Ejection fraction <40%	295 (55%)	303 (55%)
New York Heart Association class 30 days before admission		
Class I	11 (3%)	12 (3%)
Class II	140 (33%)	164 (38%)
Class III	198 (47%)	191 (44%)
Class IV	72 (17%)	63 (14%)
Medical history		
Hypertension	510 (88%)	496 (85%)
Hyperlipidaemia	313 (54%)	304 (52%)
Stroke or other cerebrovascular event	84 (14%)	73 (13%)
Cigarette smoking	81 (14%)	72 (12%)
Peripheral vascular disease	82 (14%)	73 (13%)
Mitral regurgitation	182 (31%)	179 (31%)
Ischaemic heart disease	307 (53%)	296 (51%)
Pacemaker	58 (10%)	63 (11%)
Biventricular pacing	52 (9%)	61 (10%)
Implantable cardiac defibrillator	75 (13%)	79 (14%)
Atrial fibrillation or flutter	305 (53%)	297 (51%)
Atrial fibrillation at screening	246 (42%)	233 (40%)
Asthma, bronchitis, or chronic obstructive pulmonary disease	88 (15%)	96 (16%)
Diabetes mellitus	272 (47%)	279 (48%)
Concomitant heart failure drugs at baseline		
Angiotensin-converting enzyme inhibitors	320 (55%)	313 (54%)
Angiotensin receptor blockers	97 (17%)	88 (15%)
β blocker	407 (70%)	387 (67%)
Aldosterone antagonist	173 (30%)	193 (33%)
Digoxin	108 (19%)	120 (21%)
Intravenous loop diuretic	580 (100%)	578 (99%)
Time from presentation to randomisation (h)	7·9 (4·7)	7·8 (4·6)
Intravenous nitrates at randomisation	42 (7%)	39 (7%)
NT-proBNP (ng/L)	5003 (4633–5404)	5125 (4772–5506)
Troponin T (µg/L)	0·036 (0·034–0·039)	0·034 (0·032–0·037)
eGFR (mL/min per 1·73 m²)†	53·3 (12·9)	53·7 (13·1)

Data are mean (SD), n (%), or geometric mean (95% CI). NT-proBNP=N-terminal prohormone of brain natriuretic peptide. *Eastern Europe (Hungary, Poland Romania), western Europe (France, Germany, Italy, Netherlands, Spain). †Estimated glomerular filtration rate (eGFR) calculated by the simplified Modification of Diet in Renal Disease formula.

Table 1: **Baseline characteristics of the patients in the intention-to-treat population**

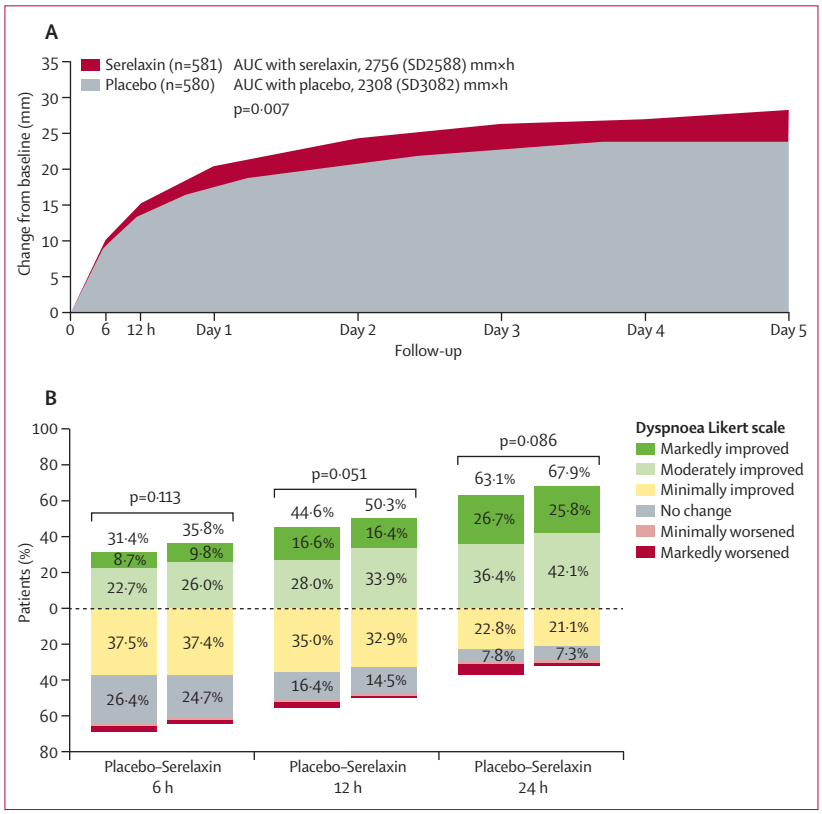

Figure 2: **Patient-reported change in dyspnoea**
(A) The primary endpoint of patient-reported change in dyspnoea measured with the use of a visual analogue scale (VAS) and quantified as the area under the curve (AUC) of serial assessments from baseline to day 5, where increasing values represent improvements in dyspnoea. Mean AUCs are shown for the placebo and serelaxin treatment groups. (B) The patient-reported change in dyspnoea relative to baseline during the initial 24 h was measured with a seven-level scale. Results for each individual timepoint are shown with percentages of patients reporting each level of change. There were fewer than 0·6% of patients with moderately worsened dyspnoea at each timepoint and data for this group consequently could not be shown.

seven-level Likert scale at 6, 12, and 24 h, where a responder was a patient with moderate or marked improvement at all three of those timepoints. Patients were asked to report their absolute current degree of both dyspnoea and general wellbeing on 100-mm VAS and their current level of both dyspnoea and general wellbeing relative to baseline using seven-level Likert scales. The VAS scales were administered at baseline, and both the Likert and VAS scales were administered at 6, 12, and 24 h and on days 2, 3, 4, 5, and 14. Worsening heart failure was defined as worsening signs or symptoms of heart failure necessitating intensification of intravenous or mechanical heart failure treatment. Symptom and sign scores are imputed after worsening heart failure onset or death.

The study had two secondary efficacy endpoints: (1) days alive and out of the hospital to day 60 and (2) cardiovascular death or readmission to hospital for heart failure or renal failure before day 60 as adjudicated by the clinical events committee. Readmission to hospital was defined as an unplanned hospital admission lasting for at least 24 h.

The protocol-specified additional efficacy analyses are listed in the appendix and included symptoms and signs at different timepoints; total dose of intravenous loop diuretic drugs before day 5; time to worsening heart failure up to days 5 and 14; length of hospital and intensive care unit or coronary care unit stay; all-cause or cardiovascular death or readmissions to hospital for heart failure or renal failure, individually, at 60 days; and cardiovascular death before day 180. Vital status was recorded at all scheduled follow-up visits or contacts up to day 180, and 180-day all-cause mortality was a prespecified safety endpoint.

	Placebo	Serelaxin	Treatment effect (95% CI)	p value
Change from baseline in dyspnoea VAS score (mm)				
Hour 6	8·9 (16·1)	10·2 (16·9)	1·3 (–0·6, 3·2)*	0·173†
Hour 12	13·2 (19·7)	15·2 (18·9)	1·9 (–0·3, 4·2)*	0·089†
Day 1	17·1 (25·0)	20·3 (21·7)	3·2 (0·5, 5·9)*	0·021†
Day 2	20·5 (28·9)	24·2 (23·9)	3·8 (0·7, 6·8)*	0·016†
Day 5	23·6 (33·3)	28·2 (27·8)	4·6 (1·1, 8·1)*	0·011†
Day 14	21·0 (36·5)	24·4 (32·4)	3·4 (–0·6, 7·4)*	0·093†
Dyspnoea VAS AUC (mm × h)				
Baseline to day 14	7131 (10112)	8442 (8443)	1311 (238, 2384)*	0·017†
Day 1 to day 5	2033 (2772)	2436 (2290)	403 (111, 696)*	0·007†
Day 1 to day 14	6855 (9846)	8122 (8199)	1266 (223, 2310)*	0·017†
Patients with markedly or moderately improved dyspnoea per Likert scale				
Hour 6	180 (31%)	205 (36%)	1·22 (0·95, 1·56)‡	0·113§
Hour 12	256 (45%)	288 (50%)	1·26 (1·00, 1·59)‡	0·051§
Day 1	362 (63%)	389 (68%)	1·24 (0·97, 1·58)‡	0·086§
Day 2	412 (72%)	438 (76%)	1·28 (0·98, 1·67)‡	0·064§
Day 5	446 (77%)	469 (82%)	1·31 (0·98, 1·75)‡	0·064§
Day 14	424 (73%)	433 (75%)	1·10 (0·84, 1·43)‡	0·479§

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	Placebo	Serelaxin	Treatment effect (95% CI)	p value
(Continued from previous page)				
Change from baseline in general wellbeing VAS score (mm)				
Hour 6	8·5 (16·6)	9·8 (16·4)	1·3 (–0·6, 3·2)*	0·187†
Hour 12	12·6 (19·2)	14·6 (18·5)	2·1 (–0·1, 4·2)*	0·063†
Day 1	16·0 (24·2)	20·3 (20·9)	4·3 (1·7, 6·9)*	0·001†
Day 2	18·8 (27·9)	23·6 (23·3)	4·8 (1·8, 7·8)*	0·001†
Day 5	22·1 (32·8)	27·5 (27·6)	5·4 (1·9, 8·9)*	0·003†
Day 14	19·3 (35·7)	23·4 (31·4)	4·0 (0·2, 7·9)*	0·042†
General wellbeing Likert score¶				
Hour 6	0·9 (1·19)	1·0 (1·02)	0·1 (0·0, 0·2)*	0·170‖
Hour 12	1·2 (1·26)	1·4 (1·07)	0·2 (0·0, 0·3)*	0·087‖
Day 1	1·5 (1·52)	1·7 (1·17)	0·2 (0·1, 0·4)*	0·091‖
Day 2	1·6 (1·65)	1·9 (1·32)	0·2 (0·1, 0·4)*	0·110‖
Day 5	1·7 (1·92)	2·0 (1·59)	0·3 (0·1, 0·5)*	0·103‖
Day 14	1·5 (2·17)	1·7 (1·97)	0·2 (0·0, 0·4)*	0·427‖
Study day of moderately or markedly improved dyspnoea before day 5**	1·9 (2·1)	1·5 (1·9)	–0·4 (–0·6, –0·2)*	0·002‖
Study day of worsening heart failure before day 5††	5·5 (1·4)	5·8 (0·9)	0·3 (0·1, 0·4)*	0·0009‖
Worsening heart failure before 14 days	91 (KM 15·7%)	66 (KM 11·4%)	0·70 (0·51, 0·96)‡‡	0·024§§
Total intravenous loop diuretic dose before day 5 (mg)¶¶	213 (358)	161 (265)	–52 (–88, –15)*	0·006†
Total oral loop diuretic dose before day 5 (mg)††	183 (189)	193 (195)	10 (–12, 32)*	0·382†
Change in bodyweight from baseline (kg)				
Day 1	–1·4 (1·9)	–1·5 (2·1)	–0·1 (–0·3, 0·2)*	0·540†
Day 2	–2·1 (2·3)	–2·0 (2·6)	0·1 (–0·2, 0·4)*	0·567†
Day 5	–3·0 (3·3)	–2·7 (3·4)	0·3 (–0·1, 0·7)*	0·167†
Day 14	–3·6 (4·4)	–3·0 (4·1)	0·6 (0·1, 1·1)*	0·023†
Length of initial hospital stay (days)	10·5 (9·6)	9·6 (9·1)	–0·9 (–1·9, 0·2)*	0·039‖
All-cause death or readmission to hospital for heart or renal failure before day 60	77 (KM 13·4%)	77 (KM 13·4%)	1·01 (0·74, 1·38)‡‡	0·959§§
Days alive out of hospital before day 30	20·4 (6·83)	20·9 (6·44)	0·5 (–0·3, 1·3)*	0·293‖
Cardiovascular death before day 180‖‖	55 (KM 9·6%)	35 (KM 6·1%)	0·63 (0·41, 0·96)‡‡	0·028§§
Days in intensive care unit or cardiac care unit	3·9 (7·0)	3·5 (7·1)	–0·3 (–1·1, 0·5)*	0·029‖
Death before day 30	19 (KM 3·3%)	12 (KM 2·1%)	0·63 (0·30, 1·29)‡‡	0·202§§
Death or worsening heart failure or readmission to hospital for heart failure before day 30	110 (KM 19·0%)	90 (KM 15·6%)	0·79 (0·60, 1·04)‡‡	0·089§§
Cardiovascular death or readmission to hospital for heart or renal failure before day 30	40 (KM 6·9%)	43 (KM 7·5%)	1·08 (0·70, 1·66)‡‡	0·726§§
Cardiovascular death or readmission to hospital for heart or renal failure before 30 days after discharge	42 (KM 7·4%)	50 (KM 8·9%)	1·21 (0·80, 1·82)‡‡	0·360§§

Data are mean (SD), n (%), or n (Kaplan Meier [KM] %). Statistical tests not adjusted for multiple comparisons. VAS=visual analogue scale. AUC=area under the curve. *Mean difference. †Two-sample *t* test. ‡Odds ratio. §χ^2 test. ¶General wellbeing scored as markedly improved (+3), moderately improved (+2), mildly improved (+1), unchanged (0), mildly worsened (–1), moderately worsened (–2), and markedly worsened (–3). ‖Wilcoxon rank sum test. **Patients who did not report moderately or markedly improved dyspnoea by day 5 were assigned a value of day 6. ††Patients for whom the investigator did not report any worsening heart failure by day 5 were assigned a value of day 6. ‡‡Hazard ratio. §§Log-rank test. ¶¶Calculation of furosemide equivalents (mg) for torasemide, bumetanide, and etacrynic acid are actual dose (mg) multiplied by constant 2, 20, or 0·8, respectively. ‖‖Clinical events committee adjudication of cause of death before day 180 resulted in 54 cardiovascular deaths in the placebo group (9·4% KM) and 34 cardiovascular deaths in the serelaxin group (5·9% KM) with a hazard ratio of 0·62 (95% CI 0·40–0·95; p=0·027).

Table 2: **Protocol-specified additional efficacy outcomes**

Statistical analysis

SAS (version 9.2) was used for all analyses. Efficacy analyses were done according to the intention-to-treat (ITT) principle. The dyspnoea VAS AUC primary endpoint means were compared with a *t* test, and the proportions with moderately or markedly improved dyspnoea were compared with a χ^2 test. The false-positive error rate was controlled at the two-sided 0·05 level for the two primary efficacy endpoints with the Hochberg approach;[20] serelaxin was judged effective in relieving dyspnoea if the statistical tests comparing serelaxin versus placebo were significant either at the two-sided 0·05 significance level for both endpoints, or at the 0·025 significance level for one endpoint. With 1100 patients, estimated power was roughly 81% to detect a mean difference on the dyspnoea VAS AUC of 468 mm×h (assuming an SD of 2700 mm×h) or a

relative risk of 1·3 in the proportion with moderately or markedly improved dyspnoea (estimated placebo response of 25%). 1160 patients were to be enrolled to obtain 1100 patients evaluable for efficacy. Outcomes were compared with *t* tests if continuous, Wilcoxon rank sum tests if ordered, and χ^2 tests if binary. Kaplan-Meier estimates of cumulative risks of time-to-first event are presented and groups compared with log-rank tests; hazard ratios (HRs) and confidence intervals were estimated with Cox regression. There were no adjustments for multiple comparisons in the analyses of the additional efficacy endpoints. Safety analyses included patients who received study drug in the treatment actually received.

This trial is registered at ClinicalTrials.gov, NCT00520806.

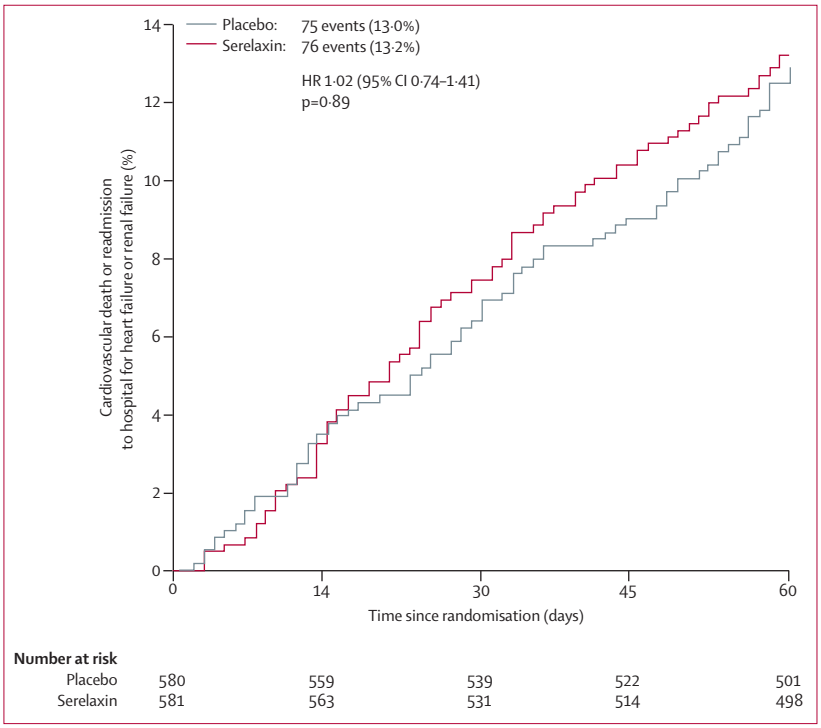

Figure 3: **Cardiovascular death or readmission to hospital for heart failure or renal failure during 60-day follow-up**
Kaplan-Meier curves are shown for the secondary endpoint of cardiovascular death or readmission to hospital for heart failure or renal failure during the 60-day follow-up, for the intention-to-treat population. HR=hazard ratio.

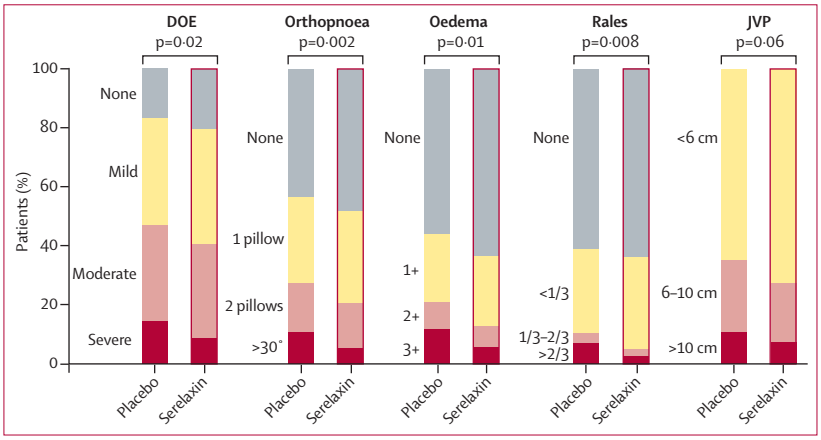

Figure 4: **Signs and symptoms of congestion at day 2**
The signs and symptoms of congestion present on study day 2 (after scheduled completion of study drug infusion) are shown for placebo-treated and serelaxin-treated patients. p values are for the Wilcoxon rank sum test of the change from baseline. DOE=dyspnoea on exertion. JVP=jugular venous pressure.

Role of the funding source

The study was designed by the members of the executive committee in collaboration with two Corthera clinical scientists and was part of a phase 2/3 trial design.[19] Data collection and analysis was done by an independent contract research organisation. The executive committee had full access to the final data 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

From Oct 11, 2009 to Feb 14, 2012, 1161 patients were enrolled (placebo, 580; serelaxin, 581), of whom 1138 (98%) received randomised study treatment (figure 1). Vital status at 180 days was ascertained for all but 14 patients (two lost to follow-up; 12 withdrew consent); baseline variables are shown in table 1.

Serelaxin significantly improved the primary dyspnoea efficacy endpoint compared with placebo, as evaluated by the VAS AUC (448 mm×h, 95% CI 120–775; p=0·007), fulfilling the prespecified criterion for efficacy of one primary endpoint with p<0·025. Mild improvement was noted in dyspnoea starting at 6 h and persisting through all 5 days (figure 2A; table 2). As a competing risk for the evaluation of dyspnoea and a component of the dyspnoea endpoint, worsening of heart failure events was also significantly reduced by serelaxin (table 2). There was no significant difference in the other primary efficacy endpoint of the proportion of patients with dyspnoea relief, which required the patient to report moderate or marked dyspnoea improvement at all three timepoints of 6, 12, and 24 h (Likert scale; placebo, 150 patients [26%]; serelaxin, 156 [27%]; p=0·70), although there were numerical improvements at each individual timepoint through to day 5 (figure 2B; table 2).

Treatment with serelaxin did not significantly increase the days alive out of hospital up to day 60 (placebo, 47·7 [SD 12·1] days; serelaxin, 48·3 [11·6]; p=0·37). There was no difference in cardiovascular death or readmission to hospital because of heart failure or renal failure up to day 60 between the serelaxin and placebo groups (figure 3). There were 27 cardiovascular deaths and 50 hospital readmissions for heart failure or renal failure up to day 60 in the placebo group and 19 cardiovascular deaths and 60 hospital readmissions in the serelaxin group.

Patients treated with serelaxin reported improvements in general wellbeing by VAS, but there were no such benefits evident with the Likert scale (table 2). Although the primary Likert dyspnoea endpoint was not improved in the first 24 h, serelaxin-treated patients reported moderate or marked dyspnoea improvement more

rapidly (p=0·002; table 2) than those receiving standard of care and placebo. Early worsening of heart failure was reduced in serelaxin-treated patients, with significantly fewer patients experiencing worsened heart failure by each study assessment up to day 5 (p=0·0009) and a 30% reduction in the hazard of worsening heart failure in the first 14 days (p=0·02; table 2). Despite no difference in change in bodyweight, and a significantly increased use of intravenous diuretic drugs (p=0·006; table 2) and vasoactive drugs (placebo, 95 patients [16%]; serelaxin, 66 [11%]; p=0·01) up to day 5 in placebo-treated patients, there were significantly greater early reductions in signs and symptoms of congestion (eg, oedema, rales, orthopnoea, jugular venous pressure, and dyspnoea on exertion) in serelaxin-treated patients by day 2 (figure 4; appendix). The average index length of hospital stay was significantly reduced in the serelaxin-treated group by 0·9 days (p=0·04) and time in the intensive care or coronary care unit was reduced by 0·4 days (p=0·03; table 2). There were no improvements in the composite endpoints that included readmission to hospital at day 30 or day 60.

Serelaxin reduced cardiovascular death at 180 days (ITT population; placebo, 55 cardiovascular deaths; serelaxin, 35; HR 0·63, 95% CI 0·41–0·96; p=0·028; number needed to treat, 29; figure 5), with the Kaplan-Meier curves separating after day 5 through to day 180. An analysis of all-cause mortality showed a similar 37% reduction (ITT population; placebo, 65 deaths; serelaxin, 42; HR 0·63, 95% CI 0·43–0·93; p=0·02; figure 5). All-cause mortality up to day 30 was reduced to a similar extent, but was not significant (37% hazard reduction; p=0·20; table 2).

There were significantly greater decreases from baseline in systolic blood pressure during infusion (up to 48 h) and after infusion (24 h after discontinuation) in the serelaxin group compared with the placebo group (roughly 4–6 mm Hg difference; appendix). More patients on serelaxin (167 patients; 29%) than on placebo (103; 18%) had a protocol-defined blood-pressure-related study drug dose adjustment (p<0·0001), resulting in a 50% dose reduction (placebo, 43 patients [7%]; serelaxin, 75 [13%]), discontinuation of study drug (placebo, 71 patients [12%]; serelaxin, 107 [19%]), or both (placebo, 12 patients [2%]; serelaxin, 16 [3%]). Although most resolved spontaneously (placebo, 91 patients; serelaxin 141), the blood pressure decreases required treatment (predominantly intravenous fluids) in 19 (12%) serelaxin-treated patients compared with nine (8%) patients in the placebo group. There was no evidence of rebound hypertension after study drug discontinuation, as reflected in adverse events of hypertension up to day 5 (placebo, 18 patients [3%]; serelaxin, five [1%]; p=0·006).

More patients on placebo had adverse events related to renal impairment compared with serelaxin (placebo, 51 patients [9%]; serelaxin, 32 [6%]; p=0·03). Otherwise, the adverse event profile after study drug exposure was comparable between the two treatment groups (appendix). Hypotension-related adverse events up to day 5 were generally infrequent and comparable (placebo, 25 patients [4%]; serelaxin, 28 [5%]; p=0·78), suggesting that the protocol-specified rules for dose adjustment limited serelaxin-induced hypotensive adverse events. Fewer patients (41) in the serelaxin group died by day 180 (safety population; appendix;

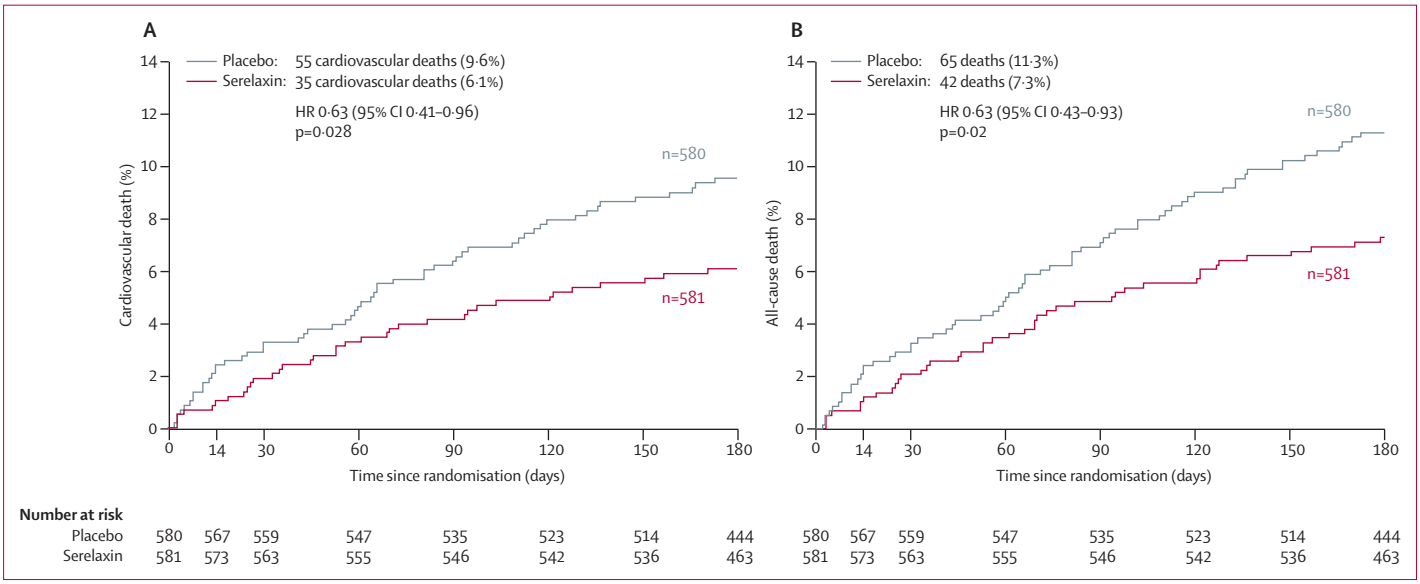

***Figure 5*: Kaplan-Meier analysis of death**

(A) Cardiovascular and (B) all-cause death during 180 days of follow-up in the placebo-treated group compared with the group that received serelaxin in the intention-to-treat (ITT) population. The additional efficacy analysis of cardiovascular death in the ITT population was protocol-specified, whereas all-cause death in the ITT population is a post-hoc sensitivity analysis presented for comparison. A Kaplan-Meier analysis of the protocol-specified, all-cause death up to day 180 in the safety population is shown in the appendix (placebo, 64 deaths [11·3%]; serelaxin, 41 [7·3%]; HR 0·63 [95% CI 0·42–0·93]; p=0·02). HR=hazard ratio.

p=0·02; number needed to treat, 25) compared with placebo (64 patients).

Discussion

In RELAX-AHF, a 48-h infusion of serelaxin resulted in mild improvements in measures of dyspnoea, associated with significant reductions in early worsening heart failure events, signs and symptoms of congestion, initial length of hospital stay, and duration of intensive care (panel). However, there was no improvement in readmission to hospital for heart failure or renal failure. A 37% reduction in cardiovascular and all-cause mortality was also noted in the serelaxin-treated patients. Serelaxin mildly reduced blood pressure, and was well tolerated with no notable difference in the overall adverse event profile and a lower rate of renal adverse events compared with placebo.

There are some limitations of the trial. RELAX-AHF enrolled a specific group of patients with acute heart failure and the results might not be generalisable to other patient populations. The efficacy, tolerability, and safety of serelaxin were shown in the setting of specific guidance for titration and discontinuation in response to changes in the patient's blood pressure. Additionally, RELAX-AHF was not prospectively designed or powered as a mortality trial and had a moderate number of death events.

The patients enrolled in RELAX-AHF were similar to many patients in the community population who present with acute heart failure,[25] representing elderly patients with normal-to-increased blood pressure and multiple comorbidities, including mild-to-moderate renal dysfunction, presenting with dyspnoea and signs of congestion. Patients with other acute diseases that could interfere with the clinical course of acute heart failure (eg, acute coronary syndromes, pneumonia or other systemic infections) were excluded. Patients enrolled in RELAX-AHF also were required to have objective findings of congestion with positive chest radiograph findings and BNP or NT-proBNP concentrations above threshold levels. The thresholds selected were based on the biomarker literature in acute heart failure, are consistent with those used in other trials,[10,23] and resulted in mean and median concentrations above 5000 ng/L of NT-proBNP measured in a core laboratory. However, this criterion also enriched the patient population for patients with atrial fibrillation (RELAX-AHF, 41%; compared with VERITAS, 35%;[10] PROTECT, 55%[23]). Additionally, these thresholds might have excluded patients with heart failure who also had factors known to reduce BNP concentrations, including obesity, acute mitral regurgitation, and very early acute heart failure.

The inclusion criterion of systolic blood pressure greater than 125 mm Hg was a central element of the trial design, enrolling patients whom we believed would derive the most benefit while avoiding the potential for harm of hypotension with serelaxin treatment. Although limiting hypotension-related adverse events to a rate similar to placebo, this criterion also resulted in a mean systolic blood pressure (142 mm Hg) that is greater than that of other trials that enrolled patients with much lower blood pressure (eg, VERITAS, 131 mm Hg;[10] ASCEND-HF, 124 mm Hg;[11] DOSE, 120 mm Hg[26]). However, we also note that patients in RELAX-AHF were enrolled on average many hours to a full day earlier than patients in those trials, so direct comparisons could be misleading. In the ADHERE registry of 187 565 patients presenting with acute heart failure to US hospitals,[25] 186 805 patients had blood pressure measured on presentation and 50% of them had systolic blood pressure greater than 140 mm Hg, suggesting that the patients enrolled in RELAX-AHF are representative of a large proportion of the acute heart failure population. However, this patient population might also represent a group at lower risk for in-hospital and post-discharge mortality, compared with those much rarer patients with low blood pressures.[27] The 180-day mortality of the placebo group was 11%, which is at the lower end of the 10–20% range previously reported. Of note, the 30-day all-cause mortality of placebo-treated patients in the VERITAS trial was 5%, compared to 4% in ASCEND-HF and 3% in RELAX-AHF.

Dyspnoea, the most prominent symptom in patients with acute heart failure, causes profound discomfort via neural signalling pathways triggering pain and anxiety centres,[28] driving patients to seek care and physicians to urgently intensify treatment. The RELAX-AHF trial met the primary objective of improving dyspnoea as quantified by the VAS instrument. The dyspnoea VAS AUC endpoint was developed on the basis of experience from VERITAS[10] and Pre-RELAX-AHF,[18] but the minimum clinically important difference (MCID) for the dyspnoea VAS AUC has not been established. A small study of 74 patients presenting to one centre for acute heart failure[29] suggested that the MCID for VAS dyspnoea relief from presentation to the emergency department before treatment during a median 2-h ascertainment period was 21·1 mm, but the investigators found a significant difference in MCID based on the index dyspnoea VAS, such that patients with less dyspnoea at presentation had an MCID of 5·7 mm compared with those with greater dyspnoea (MCID of 30·9 mm). This difference in dyspnoea response was also seen in the URGENT-HF study.[6]

Although these studies provide important insight into the very early dyspnoea response, there are several aspects that limit their applicability to RELAX-AHF. In RELAX-AHF, the mean difference in the dyspnoea VAS AUC of 448 mm×h represents a 19% increase in the VAS AUC over the observed placebo response, a magnitude of clinical benefit that is greater than that typically regarded as clinically meaningful. In the DOSE study,[26] in which a significant improvement in the VAS AUC over 72 h for dyspnoea was observed, the effect size was a difference of 210 mm×h, substantially less than that shown in RELAX-AHF, even when adjusted for the different time windows. Serelaxin-treated patients had improvement in dyspnoea

in the context of decreased intravenous diuretic and other vasoactive heart failure treatments, and less frequent worsening heart failure. Worsening heart failure not only reflects an even more dramatic and clinically significant reflection of the extreme of the symptom continuum of a patient's course, but is also associated with a greater risk of subsequent death or readmission to hospital.[7,8,30–32] The Likert assessment of dyspnoea improvement, moderate or marked improvement at all timepoints (6, 12, and 24 h) up to 24 h, was not significantly different in serelaxin-treated patients compared with those receiving standard of care and placebo. However, the greater proportion of serelaxin-treated patients reporting moderate or marked improvement in dyspnoea at the individual timepoints of 6, 12, or 24 h as assessed by the Likert scale, and earlier achievement of moderate or marked dyspnoea relief within the first 5 days, provides support for symptomatic improvement in serelaxin-treated patients.

Serelaxin did not improve the secondary endpoints of the composite of death and hospital admission up to day 60, and showed no beneficial effect on readmission. Non-significant decreases in the number of deaths and increases in the number of readmissions to hospital in the serelaxin versus the placebo group offset each other. The numerically higher readmission rates in the serelaxin group could have been related to the larger proportion of patients with a recent heart failure hospital admission within a year of enrolment in the serelaxin compared with the placebo group, a factor known to increase the incidence of readmission to hospital.[33] Additionally, the reduced number of deaths with serelaxin could have increased the patients at risk of needing hospital admission. However, early readmission to hospital might also be precipitated by processes independent of the effect of serelaxin on mortality.[34]

The reduction in mortality up to day 180 with serelaxin is an intriguing finding. No previous intervention outcome trial in patients with acute heart failure has shown a beneficial effect on post-discharge mortality.[9–11,23,35,36] RELAX-AHF selected a patient population with characteristics believed to be specifically targeted by serelaxin's effects: patients with evidence of vasoconstriction, vascular congestion, and renal impairment who were early in their clinical course, probably with significant neurohormonal and inflammatory activation. The early separation of the serelaxin and placebo group survival curves after 5 days from enrolment suggests a protective effect of serelaxin during the early in-hospital phase that persisted for the subsequent 180 days. However, in the setting of several previous negative trials with other drugs and the absence of a beneficial effect on readmission to hospital, this finding of a potential intermediate-term (180 day) survival benefit for a drug given for 48 h with a moderate number of death events (107 total) raises the question of whether this benefit is due to chance and whether another, confirmatory trial should be done. The observed improved survival in serelaxin-treated patients is consistent with its effects on other outcomes such as dyspnoea, congestion, the need for other intravenous vasoactive treatments (including inotropes, which are independently associated with increased mortality),[37,38] worsening heart failure, length of the initial hospital stay, and duration of intensive care. Treatment with serelaxin was also associated with fewer adverse events related to renal impairment, consistent with the results of experimental models,[17] as well as with the use of lower doses of diuretic drugs in the

Panel: Research in context

Systematic review

There are few new treatments for acute heart failure. In the USA, the phosphodiesterase inhibitor milrinone was approved in 1988 on the basis of small, haemodynamic studies. Since that time, there have been few approvals for new intravenous agents. The US Food and Drug Administration approved nesiritide in 2001 on the basis of the 489-patient Vasodilation in the Management of Acute CHF trial (VMAC[21]). In Europe, levosimendan was first approved in Sweden in 2000, and since then is available in about 40 countries (south European countries, Scandinavia, Russia, and several markets in South America), but major European Union countries did not accept the Swedish marketing authorisation. A systematic review of PubMed (accessed Oct 26, 2012) was done with the MeSH search term of "heart failure/*drug therapy" which revealed 19 154 articles. Addition of the search terms "randomised controlled trial (publication type)" limited the results to 2176 articles, and subsequent addition of the term "acute disease" resulted in 61 articles. These articles were manually reviewed for primary reports of phase 3 trials of novel, intravenous treatments for acute heart failure, excluding design or concept papers. This search resulted in articles on the novel drugs levosimendan, nesiritide, rolofylline, and tezosentan.

Interpretation

All these drugs have phase 3 clinical trials with efficacy endpoints in acute heart failure populations. Levosimendan has been studied in the 700-patient, placebo-controlled REVIVE I and II trials, in which the primary endpoint of a clinical composite based on the patient global assessment during the first 5 days of treatment was positive, but increases in ventricular and atrial arrhythmias, symptomatic hypotension, and early mortality were also evident. The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE[22]) trial compared intravenous levosimendan and dobutamine in 1327 patients and did not achieve the primary endpoint of reducing all-cause mortality at 180 days; although it did decrease brain natriuretic peptide, levosimendan did not improve any of the other secondary endpoints (all-cause mortality at 31 days, number of days alive and out of the hospital, patient global assessment, patient assessment of dyspnoea at 24 h, and cardiovascular mortality at 180 days). In a placebo-controlled, post-approval trial (ASCEND-HF[11]) nesiritide did not meet the prespecified primary endpoints of dyspnoea relief and had no beneficial effect on readmission to hospital, all-cause mortality, or worsening renal function. The A_1 adenosine receptor antagonist rolofylline was studied in the 2033-patient PROTECT trial,[23] failing to meet its primary clinical composite endpoint with no reduction in readmission to hospital or worsening renal failure, but complicated by increases in seizures and stroke.[24] In a series of trials, culminating in the 1448-patient VERITAS program,[10] tezosentan did not show an improvement in dyspnoea, using a similar endpoint as in RELAX-AHF, nor in worsening of heart failure or death at 7 days, and had no effect on worsening renal function, readmission to hospital, or mortality. In this context, the results of the RELAX-AHF trial are interesting. Similar to all the previous studies, there was no reduction in readmission to hospital. However, RELAX-AHF was able to show a significant although mild improvement in dyspnoea relief, as well as in several other additional endpoints, and was well tolerated with a safe profile, supported by fewer deaths in the serelaxin-treated patients compared with placebo.

serelaxin-treated patients.[26] Worsening renal function has been associated with a poorer outcome in some studies,[39–41] although not all,[42,43] and the prevention of renal dysfunction by serelaxin might also be a mechanism contributing to reduced mortality. In a study of 1007 propensity-matched pairs, patients admitted with acute heart failure treated with vasodilator therapy and diuretic drugs had a 27% reduction in in-hospital mortality compared with those treated with diuretic drugs alone.[37] The improved survival in RELAX-AHF is similar to that previously suggested in the Pre-RELAX-AHF study, in which there was a 16% all-cause mortality in the placebo group compared with 9% for the 30 µg/kg per day serelaxin-treated patients.[18] There were no significant differences in baseline characteristics or in post-discharge heart failure treatments to confound this difference in survival.

On the basis of the hypothesis-generating findings of Pre-RELAX-AHF,[18] RELAX-AHF tested the effects of serelaxin on symptoms and outcomes. Serelaxin improved dyspnoea relief to a mild extent, while significantly preventing worsening of heart failure and improving other additional efficacy outcomes. The observed reduction in mortality with serelaxin compared with placebo is consistent with the emerging concept that acute heart failure is associated with damage to multiple organ systems, and that protection from the harmful effects of these episodes can have favourable effects on survival. The results from the RELAX-AHF trial provide supportive evidence for a beneficial effect of serelaxin improving symptoms and other clinical outcomes in selected patients with acute heart failure.

Contributors

JRT contributed to the conception, design, and implementation of the study; enrolment and follow-up of patients; interpretation of results; statistical analysis plan; and drafting of the first version of the report and its following versions. MM contributed to the conception, design, and implementation of the study; enrolment and follow-up of patients; interpretation of results; statistical analysis plan; and drafting of the first version of the report and its following versions. GC contributed to the conception, design, and implementation of the study; design and implementation of the statistical analysis; interpretation of results; drafting of the report; statistical expertise; administrative, technical, or logistic support; and collection and assembly of data. BAD contributed to the conception, design, and implementation of the study; design and implementation of the statistical analysis; interpretation of results; drafting of the report; statistical expertise; administrative, technical, or logistic support; and collection and assembly of data. GMF, GF, BHG, PP, and AAV contributed to the conception, design, and implementation of the study, enrolment of patients, interpretation of results, and drafting of the report. KFA, MID, LRG, GJ, AM, JM, PSP, and KW contributed to the conception and implementation of the study, enrolment of patients, interpretation of results, and drafting of the report. CAB contributed to the statistical analysis; interpretation of results; statistical expertise; administrative, technical, or logistic support; and collection and assembly of data. EU contributed to the conception, design, and implementation of the study; design and implementation of the statistical analysis; interpretation of results; obtaining of funding; administrative, technical, or logistic support; and collection and assembly of data. SLT contributed to the conception, design, and implementation of the study. CS, TMS, AT, and RS contributed to the implementation of the study, its statistical analysis, technical or logistic support, interpretation of results, obtaining of funding, administrative, technical, or logistic support, and drafting of the report. All authors have reviewed the Article and agree with its contents.

Conflicts of interest

JRT has received research grants or consulting fees from Amgen, Bayer, Corthera, Cardio3 Bioscience, Cytokinetics, Merck, Novartis, Takeda, Teva, and Trevena. GC and BAD are employees of Momentum Research, which has provided consulting and trial management services to NovaCardia, Merck, Corthera, Novartis, Nile Therapeutics, Bioheart, Cardio3 Biosciences, Amgen, Celadon, Targegen, Trevena, Sorbent Therapeutics, and NIH. GMF reports consulting income from Novartis, Medpace, Amgen, Otsuka, Trevena, Roche Diagnostics, Merck, BG Medicine, Medtronic, and St Judes and grant fundings from Amgen, Otsuka, Roche Diagnostics, and NHLBI. GF is an executive committee member and consultant to Corthera (a Novartis company), Bayer, Cardiorentis, and has received research grants from Amgen, Nanosphere, European Union. BHG served as a consultant for Corthera and Novartis. PP was a consultant for Astellas, Bayer, EKR Therapeutics, J&J, the Medicines Company, Medtronic, Novartis, Otsuka, Palatin Technologies, PDL BioPharma, Pericor Therapeutics, SigmaTau, Solvay Pharmaceuticals, and Trevena; has received honoraria from Alere, Beckman-Coulter, BiogenIdec, Corthera, Ikaria, Nile Therapeutics, Momentum Research, and Overcome; has received research support from Abbott, Merck and PDL BioPharma; and has received travel support from MyLife and equipment support from Sonosite. EU is employed by the sponsor, Corthera (a Novartis company). AAV has received consultancy fees and/or research grants from Alere, Bayer, Cardio3Biosciences, Celladon, Ceva, European Committee, Dutch Heart Foundation, Novartis, Servier, Torrent, and Vifor. KFA has received research grants and consulting fees from Corthera, Merck, Roche Diagnostics, and Duke Clinical Research Institute; research grants from Novartis and Amgen; and consulting fees from Momentum Research. MID, LRG, JG, AM, JM, and KW have received research grants from Corthera (a Novartis affiliate company). KW received personal support for travel to meetings for the RELAX-AHF trial. KW's institution received honorarium for patient enrolment in the RELAX-AHF trial and honorarium for national coordinatorship of KW for the RELAX-AHF trial. PSP has been a consultant for Astellas, Bayer, EKR Therapeutics, J&J, the Medicines Company, Medtronic, Novartis, Otsuka, Palatin Technologies, PDL BioPharma, Pericor Therapeutics, SigmaTau, Solvay Pharmaceuticals, Trevena; received honoraria from Alere, Beckman-Coulter, BiogenIdec, Corthera, Ikaria, Nile Therapeutics, Momentum Research, and Overcome; received research support from Abbott, Merck, and PDL BioPharma; and received travel support from MyLife and equipment support from Sonosite. SLT was an employee of the sponsor, Corthera (a Novartis affiliate company). AT, CAB, RS, CS, and TMS are Novartis employees and receive salary, benefits, and stock options from Novartis Pharmaceuticals Corporation (CAB, RS, AT) or Novartis Pharma (CS, TS). MM has received consulting income from Abbott Vascular, Bayer, Corthera, and Novartis, as well as travel support and honoraria from Servier and Novartis.

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with non-TNFi biologics cannot be addressed. In the ORAL Step study specifically, patients were required to have failed at least one TNFi, and consequently there were no patients included who had failed a non-TNFi biological DMARD only.

To strengthen the evaluation of tofacitinib in rheumatoid arthritis subpopulations, data from phase 2 and 3 studies were pooled, within which the demographic and baseline rheumatoid arthritis disease characteristics were comparable.[2] Similar efficacy was noted across primary efficacy endpoints for patients who were positive for anticitrullinated protein antibodies (ACPA) or rheumatoid factor, or both, compared with patients who were negative for ACPA or rheumatoid factor, or both, and in patients with a body-mass index (BMI) of <30 relative to patients with a BMI of ≥30. The effect of baseline disease activity on efficacy was assessed by comparing the efficacy results in patients with a baseline disease activity score DAS28-4(ESR) ≤5·1 to those with a baseline value >5·1; similar results were noted in both populations. In conclusion, tofacitinib efficacy is consistent across rheumatoid arthritis subpopulations.

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Not time to RELAX in acute heart failure

The RELAX-AHF investigators should be commended for matching the mechanism of serelaxin to a unique and appropriately selected population of patients (Jan 5, p 29).[1] However, it should be emphasised that dyspnoea is challenging to quantify,[2] subjective,[3] and might still be easily provoked even when absent at rest.[4] Additionally, dyspnoea responds rapidly and substantially to early initiation of standard therapy,[4] as shown by the comparable response in the proportion of patients with moderate and marked dyspnoea relief at 24 h, one of the coprimary endpoints.

Despite improving nearly all other endpoints for short-term efficacy and requiring a lower cumulative dose of intravenous diuretics during hospitalisation, serelaxin is associated with a smaller decrease from baseline in bodyweight beginning at day 5 and reaching the threshold for statistical significance by day 14. This finding is clinically relevant, because post-discharge bodyweight increases are important predictors of rehospitalisation,[5] possibly explaining the non-significant increase in readmission due to heart or renal failure noted in patients randomised to serelaxin.

Finally, as the authors point out, the signal towards lower mortality should be deemed supportive of safety but not long-term efficacy since the study was underpowered to detect a mortality difference, serelaxin (or placebo) was only infused for a maximum of 48 h, and no approved heart failure therapies have been shown to improve mortality without simultaneously reducing readmissions.

Thus, there remains an unmet therapeutic need in hospitalised heart failure to reduce the unacceptably high post-discharge morbidity and mortality.

We declare that we have no conflicts of interest.

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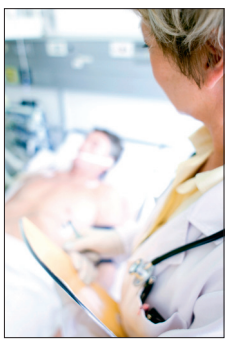
Authors' reply

We thank Andrew Ambrosy and Ronald Witteles for their comments on the RELAX-AHF trial.[1]

We agree that dyspnoea remains the most prominent presenting symptom leading to hospitalisation in patients with acute heart failure (AHF), and is challenging to measure. For these reasons, RELAX-AHF had two primary dyspnoea endpoints and accounted for the competing risk of worsening heart failure. However, in RELAX-AHF only 26% of patients achieved moderate or marked dyspnoea improvement at 6, 12, and 24 h; as reported in other studies, the early response to therapy remains far from satisfactory.

In RELAX-AHF, serelaxin administration caused better dyspnoea relief, reduction in signs of congestion, and shorter hospital stay with slightly less bodyweight reduction, compared with placebo. We maintain that these effects are consistent with serelaxin's additional mechanisms of action, such as fluid redistribution, in addition to volume loss. The analysis of EVEREST cited by Ambrosy and Witteles showed an association between an increase in bodyweight of 2 kg and rehospitalisation,[2] whereas in RELAX-AHF, serelaxin-treated



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patients had 3 kg bodyweight loss at day 14 (only 0·6 kg less than patients receiving placebo). We are committed to understanding serelaxin's effects on rehospitalisation, beyond the confounding effects of the greater proportion of patients with a history of previous hospitalisation for heart failure, the shorter length of stay and the improved survival in the serelaxin-treated patients. Short-term rehospitalisations might also be more related to non-modifiable factors (eg, social support, geographic location, and socioeconomics) so that there is a disconnect between early readmissions and post-discharge mortality.[3]

The RELAX-AHF trial reported a 37% reduction in mortality, but it was not prospectively powered to assess mortality, so the concept of the study power for this endpoint is problematic. The ability of a short-term infusion to have long-term effect on outcomes has already been clearly shown in the area of thrombolytics, and AHF, for which short-term infusions of inotropes result in both early and late increases in mortality.[4] AHF is a syndrome in which end organ damage occurs early and is related to subsequent mortality. We hypothesise that early treatment with serelaxin might prevent or reduce this end organ damage and might reduce mortality. Secondary analyses of RELAX-AHF provide additional support for this hypothesis,[5] and a clinical trial with mortality as the prospectively defined primary endpoint is being planned.

Additional analyses are required to better understand the role of serelaxin in the treatment of patients with AHF.

We have received consulting fees and clinical research grants from Corthera, a Novartis affiliated company (the sponsor of the RELAX-AHF trial).

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Cognitive behavioural therapy for treatment-resistant depression

If a trial is designed with pill X added to ongoing drug treatment in depressed, non-responding patients, clear-cut improvement should be expected in those receiving X, rather than standard care, even if X is a placebo.[1] If X is replaced by a psychotherapy Y, the outcome should be equally easy to predict. Undoubtedly, larger symptom reduction would be obtained in patients receiving this extra dose of attention, whatever its nature is.

This talk-induced improvement could be attributable to the non-specific support provided, or to the fact that patients meeting regularly with a kind therapist might find it impolite to deny any improvement. Also, being regularly reminded of the nature of their disorder might increase patients' adherence to their medication.

To claim that Y, in addition to such non-specific factors, exerts a specific effect, one would have to show superiority versus some other treatment. The fact that psychotherapy studies are difficult to blind does not preclude the inclusion of a credible control.

If a paper were submitted to *The Lancet* in which a drug had been evaluated as described above, it would have been mercilessly rejected, the reviewers harshly pointing out that a comparison with standard care permits no conclusion whatsoever regarding true efficacy. But for studies of cognitive behavioural therapy (CBT), the journal applies very different standards, as shown by the publication of the report by Nicola Wiles and colleagues (Feb 2, p 375),[2] as well as other papers.[3-5]

Why is a design precluding conclusions less of a problem for CBT trials than for drug trials?

I declare that I have no conflicts of interest.

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Authors' reply

Elias Eriksson raises the question of the need for an attention control in trials of psychological interventions. We can provide some background to this question with regards to our recent publication of the CoBalT trial.[1]

As outlined in our paper, we asked a pragmatic question about the value of addition of psychological therapy (specifically, cognitive behavioural