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What can we learn from RELAX-AHF compared to previous AHF trials and what does the future hold?

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ABSTRACT

Each year in the USA there are over 1 million hospital admissions directly related to heart failure (HF). With similar rates across Europe, this places a huge economic burden on healthcare systems globally. Hospitalisation for HF is associated with poor clinical outcomes with 25% of patients being readmitted with signs and symptoms of HF within 1 month of discharge and 10–20% dying in the 6 months after discharge. Although hospital admission could be a sign of disease progression, it is also possible that some of the treatments given acutely for example, inotropic therapy, may result in neurohormonal, haemodynamic and other effects accelerating end-organ damage and contributing to these poor outcomes after discharge. In contrast to the treatment of chronic heart failure (CHF), clinical trials conducted over the past decade in patients with acute HF (AHF) have failed to show significant reductions in morbidity or mortality despite some agents causing beneficial changes in symptoms. As such, the current treatment of patients hospitalised with HF is mainly based on consensus rather than clinical evidence and has changed little over time. We review RELAX-AHF in the context of the other key, large-scale AHF trials conducted over the past 15 years and compare and contrast study design and outcomes in an attempt to determine which factors might be associated with a successful trial in the future.

INTRODUCTION

The reasons for the failure of acute heart failure (AHF) trials in demonstrating improvements in outcomes are likely multifactorial. One limitation may be the use of novel molecules with poorly described pharmacology in congested patients often with end-organ damage already. Frequently, phase I and II studies are conducted in patients with chronic heart failure (CHF) rather than AHF, and treatments may not demonstrate the same dose–response relationships in these two groups. Entry criteria and patient selection are also important as the presence of certain comorbidities may render patients more susceptible to adverse effects for example, renal toxicity. Finally, the importance of timing and duration of therapy should not be underestimated. For outcomes such as improvement in dyspnoea, only very early intervention is likely to be successful. On the other hand, reduction in readmission and postdischarge mortality might be best achieved using an early intravenous intervention with continuation of therapy orally postdischarge.

Until recently, attempts to produce an efficacious treatment for AHF had failed. It is important to consider why this trial was apparently successful, compared to previous attempts with alternative agents. Serelaxin was associated with a lower rate of renal adverse events compared with placebo. It resulted in improvements in measures of dyspnoea (albeit small and depending on imputation), reduction in early worsening HF events, reduction in troponin, shorter hospital admissions and reduction in CV and all-cause mortality. It did, however, fail to show reduction in hospital readmission rates for HF or renal failure. These positive outcomes were aided by: targeting a population of patients most likely to receive beneficial effects from a drug based on its properties and actions and by starting the initiation of therapy as early as possible.

In this review we discuss the drug itself, the patient population enrolled and the selection of end points. The 12 key AHF trials are summarised in tables 1–3.[1–12]

THE DRUG

The drug studied in RELAX-AHF was serelaxin, a recombinant form of human relaxin-2. The haemodynamic impact of serelaxin has recently been studied in AHF patients.[13] In this study it reduced pulmonary capillary wedge pressure and pulmonary artery pressure with concomitant reduction in systemic and pulmonary vascular resistance. It had no effect on cardiac index and

Table 1 Comparison of key inclusion/exclusion criteria and end points

	OPTIME CHF	SURVIVE	VERITAS	EVEREST	PROTECT	ASCEND-HF	RELAX-AHF
Clinicaltrials.gov Identifier	NK	NCT00348504	NCT00525707 and NCT00524433	NCT00071331	NCT00328692 and NCT00354458	NCT00475852	NCT00520806
Enrolment period	July 1997–November 1999	March 2003–December 2004	April 2003–January 2005	October 2003–February 2006	May 2007–January 2009	May 2007–August 2010	October 2009–February 2012
Randomised treatments	Milrinone: placebo (1:1)	Levosimendan: dobutamine (1:1)	Tezosentan: placebo (1:1)	Tolvaptan: placebo (1:1)	Rolofylline: placebo (2:1)	Nesiritide: placebo (1:1)	Serelaxin: placebo (1:1)
Inclusion criteria							
Age, years	≥18	≥18	≥18	≥18	≥18	≥18	≥18
Required history of HF	Yes*	NR	NR	Yes†	Yes‡	NR	NR
Time from presentation to randomisation, hours	<48	NR	<24	<48	<24	<48	<16
LVEF, %	<40	≤30	<40	≤40	NR	<40	Any LVEF
Dyspnoea requirements	Incorporated into 'HF score'§	At rest	At rest+RR ≥24/min	At rest or with minimal exertion¶	At rest or with minimal exertion	At rest or with minimal activity	At rest or with minimal exertion
Other evidence of HF (including symptoms, signs and objective measures)	≥3/10 on 'HF score'§	Insufficient response to IV diuretics and/or VD+ ≥1 of: dyspnoea at rest or mechanical ventilation for HF; oliguria not due to hypovolaemia; PCWP ≥18 mm Hg and/or cardiac index ≤2.2 L/min/m^2	≥2 of: elevated BNP or NT-proBNP; clinical evidence of pulmonary congestion/oedema; pulmonary congestion on CXR; LVSD (EF <40% or wall motion index ≤1.2)	≥2 of: dyspnoea; jugular venous distension; pitting oedema (>1+)	Requiring IV diuretic therapy+≥1 of: JVP >8 cm; pulmonary rales ≥1/3 above base; peripheral oedema (≥2 +); pre-sacral oedema	≥1 of: RR ≥20/min; pulmonary rales ≥1/3 above base+≥1 of pulmonary congestion on CXR; BNP ≥400 pg/mL (or NT-proBNP ≥1000); EF <40%; PCWP >20 mm Hg	Pulmonary congestion on CXR+BNP ≥350 pg/mL (or NT-proBNP ≥1400 pg/mL)
IV diuretic required before randomisation	No	No	Yes	No	Yes	No	Yes
Exclusion criteria							
Systolic BP, mm Hg	<80 or >150	<85	<100 (or <120 if after VD)	<90	<90 or ≥160	<100 (or <110 if after VD) or >180	≤125
Serum creatinine, mg/dL	>3.0	>5.0	≥2.5	>3.5	NR	NR	NR
eGFR, mL/min/1.73 m^2	NR	NR	NR	NR	<20 or >80 mL/min CC	NR	<30 or >75
Vasopressors/inotropes	Both	Inotropes**	None	None	Both	Both††	Both
Acute MI/ACS	Evidence of unstable angina, myocardial ischaemia, or MI within 3 months	NR	STEMI; On-going myocardial ischaemia or PCI/CABG during current admission	STEMI at time of hospitalisation	Evidence of ACS in 2 weeks before screening	ACS as primary diagnosis; ECG with new ST-elevation >1 mm in 2 consecutive leads	Diagnosis of ACS<45 days before screening; troponin >3 times upper limit of normal
Primary end point(s)							
	Cumulative days of hospitalisation for CV cause within 60 days after therapy	All-cause mortality in the 180 days after therapy	Change from baseline in dyspnoea over 24 h after therapy; Incidence of death or worsening HF at day 7	Composite score of changes from baseline in global clinical status and body weight at day 7 or discharge	Treatment success, treatment failure or no change in the patient's condition	Change in dyspnoea 6 and 24 h after therapy; rehospitalisation for HF and all-cause death after therapy to day 30	Change in dyspnoea from baseline to day 5; moderately or markedly improved dyspnoea from baseline at 6, 12 and 24 h

Continued

Table 1 Continued

	OPTIME CHF	SURVIVE	VERITAS	EVEREST	PROTECT	ASCEND-HF	RELAX-AHF
Secondary end point(s)‡‡	Proportion of treatment failures due to adverse events 48 h after therapy; proportion of patients achieving target doses of ACE-inhibitor therapy	All-cause mortality during the 31 days following therapy; mean change in plasma BNP level from baseline to 24 h	Incidence of death or major CV events at 30 days; length of initial hospital admission	Changes in dyspnoea at day 1 from baseline; global clinical status at day 7 or discharge	All-cause death and rehospitalisation for CV or renal causes through day 60; proportion of patients who developed persistent renal impairment	Self-reported overall well-being, measured 6 and 24 h after therapy; composite of worsening HF and all-cause mortality through index hospitalisation	Rate of combined end point of CV death or rehospitalisation for HF or renal failure to day 60; days alive and out of hospital to day 60
	REVIVE I	**REVIVE II**	**DOSE**	**CARRESS**	**ROSE**		
Clinicaltrials.gov Identifier	NCT00048425	NCT00048425	NCT00577135	NCT00608491	NCT01132846		
Enrolment period	December 2001–December 2004	December 2001–December 2004	March 2008–November 2009	June 2008–January 2012	September 2010–March 2013		
Randomised treatments	Levosimendan: placebo (1:1)	Levosimendan: placebo (1:1)	High-/low dose diuretic IV bolus/IV infusion diuretic (2×2 factorial)	Ultrafiltration medical therapy (1:1)	Dopamine: nesiritide: placebo (1:1:1)		
Inclusion criteria							
Age, years	>18	>18	≥18	≥18	≥18		
Required history of HF	No	No	Yes‡	No	No		
Time from presentation to randomisation, hours	≤48	NR	≤24	≤168	≤24		
LVEF, %	≤35	≤35	NR	NR	NR		
Dyspnoea requirements	At rest	At rest	Rest/exertion	NR	NR		
Other evidence of HF (including symptoms, signs and objective measures)	Can enrol >48 h if deteriorates after initial improvement with conventional therapy	Persisting dyspnoea at rest despite IV diuretic therapy	1 symptom and 1 sign of HF daily oral furosemide dose ≥80 ≤240 mg	Increase creatinine >0.3 mg/dL ≥2 +peripheral oedema, JVP >10 cm, radiological pulmonary congestion/oedema	eGFR ≥15 ≤60 mL/min/1.73 m^2 At least 1 sign and symptom of HF		
IV diuretic required before randomisation	Yes	Yes	Yes	Yes	NR		
Exclusion criteria							
Systolic BP, mm Hg	≤90	≤90	<90	<90	<90		
Serum creatinine, mg/dL	>5.0	>5.0	>3.0	>3.5	NR		
eGFR, mL/min/1.73 m^2	NR	NR	NR	NR	<15 or >60		
Vasopressors/inotropes	None	PDE V inhibitors	Both	Both	Both		
Acute MI/ACS	Angina in 6 h before randomisation	Angina in 6 h before randomisation	ACS within 4 weeks	ACS within 4 weeks	ACS within 4 weeks		
Primary end point(s)	Improved/unchanged/worse composite (24 h and 5 days)	Clinical composite (6 h, 24 h and 5 days)	1. Patient global assessment (VAS AUC) at 72 h 2. change in Cr at 72 h (safety)	Bivariate change in weight/change in creatinine (96 h)	1. Cumulative urine volume (72 h) 2. change cystatin C (72 h)		

Continued

Table 1 Continued

	REVIVE I	REVIVE II	DOSE	CARRESS	ROSE
Secondary end point(s)‡‡	Change in BNP at 24 h Change in PGA at 6 h Change in dyspnoea at 6 h DAOH Death or worsening HF NYHA class (day 5) Mortality (90 day)	Change in BNP at 24 h Change in PGA at 6 h Change in dyspnoea at 6 h DAOH Death or worsening HF NYHA class (day 5) Mortality (90 day)	Patient dyspnoea report Change in body weight Net fluid loss Proportion of patients congestion free (72 h) Increase serum Cr >0.3 mg/dL (72 h) Worsening/persistent HF Change in biomarkers (72 h/7 days/60 days) Death/hosp/ER visit (day 60) Days dead or hospitalised (day 60)	Primary end point days 1–3, day 7 Weight loss and renal function (96 h, 1 week) Treatment failure (7 days) Change in renal function (7 days, 30 days, 60 days); peak creatinine Change in electrolytes (96 h, 1 week) Change in weight (1 week, 30 days, 60 days) Proportion with clinical decongestion (96 h, 1 week, 30 days, 60 days) Total net fluid loss (96 h, 1 week) Change in biomarkers (96 h, 1 week, 60 days) Change in global assessment and VAS (96 h, 1 week) LOS, DAOH, HF hosp, ER visits, unscheduled office visits Change in diuretic dose from admission (discharge, 30 days, 60 days) Resource utilisation	Change in Cr (72 h) Cumulative urinary sodium excretion (72 h) PGA (72 h) Dyspnoea (72 h) Weight (72 h) Change in BUN/cystatin C ratio (72 h) Increase in serum Cr >0.3 mg/dL (72 h) Persistent or worsening HF (72 h) Treatment failure (72 h)

*Prior diagnosis of HF on any oral therapy for same.
†A history of CHF (defined as requiring treatment for a minimum of 30d before hospitalisation).
‡A history of HF ≥14 days for which diuretic therapy has been prescribed.
§HF Score: dyspnoea (exertional=1 point, nocturnal=2 points, orthopnoea=3 points, rest=4 points)—maximum of four points. HR (91-110 bpm=1 point, >110 bpm=2 points)—maximum of two points. rales (bases only=1 point, >bases=2 points)—maximum of two points. Right heart (JVP >6 cm=1 point, JVP >6 cm with oedema or hepatomegaly=2 points)—maximum of two points.
¶HF symptoms at rest or minimal exertion.
**Except dopamine ≤2 μg/kg/min or digitalis during the current hospitalisation.
††Excluded if: received first IV treatment of diuretics, VD or inotropes for HF >24 h before randomisation; treated with levosimendan or milrinone within 30 days before randomisation or anticipated need for these during current hospitalisation; treated with IV vasoactive medication where the dosage is not stable for 3 h before randomisation; treated with dobutamine ≥5 μg/kg/min at the time of randomisation.
‡‡Not exhaustive.
ACS, acute coronary syndrome; AHF, acute heart failure; ARB, angiotensin receptor blocker; AUC, area under the curve; ASCEND, acute study of clinical effectiveness of nesiritide in decompensated heart failure; BP, blood pressure; CV, cardiovascular; CABG, coronary artery bypass graft; CHF, heart failure; COPD, chronic obstructive pulmonary disease; CARRES, cardiorenal rescue study in acute decompensated heart failure; CXR, chest x-ray; DAOH, days alive and out of hospital; DOSE, diuretic optimization strategies evaluation; EF, ejection fraction; Egfr, estimated glomerular filtration rate; ER, days alive and out of hospital; EVEREST, the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan; Hosp, hospital; HF, heart failure; ICD, implantable cardiac defibrillator; IV, intravenous; JVP, jugular venous pressure; LVSD, left ventricular systolic dysfunction; LOS, length of stay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NK, not known; NT, n-terminal; NR, not required; NYHA, new york heart association; OPTIME, the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure; PDE, phosphodiesterase inhibitor; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PGA, patient global assessment; ProBNP, pro b-type natriuretic peptide; PROTECT, placebo-controlled randomised study of the selective A1 adenosine receptor antagonist rolofylline; Pts, patients; STEMI, ST-segment elevation myocardial infarction; SURVIVE, the survival of patients with acute heart failure in need of intravenous inotropic support; RELAX-AHF, the RELAXin in acute heart failure; RR, respiratory rate; REVIVIE, randomized evaluation of intravenous levosimendan efficacy; ROSE, renal optimization strategies evaluation; VAS, visual analogue score; VERITAS, the value of endothelin receptor inhibition with tezosentan in acute heart failure studies; VD, vasodilators.

Table 2 Baseline characteristics

Variable	OPTIME (n=949)	SURVIVE (n=1327)	VERITAS (n=1435)	EVEREST (n=4133)	PROTECT (n=2033)	ASCEND-HF (n=7007)	RELAX-AHF (n=1161)	REVIVE I (n=100)	REVIVE II (n=600)	DOSE (n=308)	CARRESS (n=188)	ROSE (n=360)
Demographic												
Mean age, years	66	67	70	66	70	67*	72	59	64	66	68*	70*
Female sex, %	29	28	40	26	32	34	38	23	27	27	25	27
White race, %	65	94	86	86	95	56	94	60	65	75	70	79
Black race, %	33	NK	8	8	NK	15	NK	NK	NK	25	30	21
Mean time from admission to randomisation, hours	15.3	NK	12.2	NK	NK	15.5*	7.9	NK	NK	14.6*	34*	24
Location, %												
USA/Canada	100	0	22	30†	NK	45†	10	NK	NK	100	100	100
Non-USA/Canada	0	100	78	70	NK	55	90	NK	NK	0	0	0
Physiological measures (mean)												
BMI (kg/m^2)	NK	28	29	29	29	28*	29	NK	NK	NK	NK	31*
RR, bpm	NK	NK	26	NK	21	24*	22	NK	NK	NK	NK	NK
HR, bpm	85	84	82	80	80	82*	80	84	82	78	NK	NK
Systolic BP, mm Hg	120	116	131	121	124	123*	142	115	116	120	NK	115*
Diastolic BP, mm Hg	71	70	72	73	74	74*	82	69	69	NK	NK	NK
Cardiac												
Mean LVEF, %	24	24	27	28	32	30*	39	20	24	35	33*	33*
LVEF ≥40%, %	NK	NK	53	NK	NK	20	49	0	0	NK	NK	NK
Mean BNP, pg/mL	NK	1624	1673	NK	1016*	992*	NK	NK	NK	NK	NK	NK
Mean NT-proBNP, pg/mL	NK	NK	11692	4263	3000*	4463*	5064‡	NK	NK	7439	4510	5017*
Ischaemic aetiology of HF, %	51	76	68	65	NK	48	NK	NK	NK	57	61	58
Prior HF hospitalisation, %	NK	NK	NK	79	NK	39§	34§	NK	NK	74	77	67
Biochemistry (mean)												
Blood urea nitrogen, mg/dL	11.4	NK	27.0	30.2	34.1	9.0*	27.2	NK	NK	37.5	49.6	36
Serum sodium, mEq/L	138	138	139	140	NK	139*	NK	NK	NK	138	NK	NK
Serum creatinine, mg/dL	1.4	1.6	1.3	1.4	1.5	1.2*	1.3	NK	NK	1.5	2.0	NK
eGFR, mL/min per 1.73 m^2	NK	NK	NK	NK	50.6 CC	NK	53.5	NK	NK	NK	NK	42*
Co-morbidity, %												
History of HF	NK	88	73	NK	NK	39¶	NK	NK	NK	NK	NK	NK
Hypertension	68	63	79	71	79	72	87	NK	NK	NK	85	83
Myocardial infarction	48	68	52	51	49	35	NK	NK	NK	NK	NK	NK
Atrial fibrillation	32	48**	37	43	55	38**	52**	NK	NK	53	NK	60
Mitral regurgitation	47	63	12	32	NK	NK	31	NK	NK	NK	NK	NK
PCI/CABG	18/31	NK	22	18/21	NK	NK	NK	NK	NK	NK	NK	NK
ICD	8	4	7	15	16	16	13	NK	NK	39	NK	43
Stroke	15	NK	16	11	NK	12	14	NK	NK	NK	NK	NK
Diabetes mellitus	44	32††	48	39	45	43	48	NK	NK	52	66	55
COPD/asthma	23/-	NK	19/-	10/-	20	16/-	16	NK	NK	NK	NK	NK

	OPTIME	SURVIVE	VERITAS	EVEREST	PROTECT	ASCEND-HF	RELAX-AHF	REVIVE I	REVIVE II	DOSE	CARRESS	ROSE
Pre-admission treatments, %												
ACE-inhibitor/ARB	70/13	69	NK	NK	76	NK	NK	74	77	64	54	50
MRA	NK	53	NK	NK	44	NK	NK	35	37	28	20	30

Continued

Table 2 Continued

	OPTIME	SURVIVE	VERITAS	EVEREST	PROTECT	ASCEND-HF	RELAX-AHF	REVIVE I	REVIVE II	DOSE	CARRESS	ROSE
β-blocker	22	50	NK	NK	76	NK	NK	44	69	83	79	82
Oral diuretic	90	NK	NK	NK	100	NK	NK	NK	NK	NK	94	94
Digoxin	73	NK	NK	NK	28	NK	NK	58	52	NK	NK	25
Treatment of acute episode, %												
IV diuretic	NK	79	99	97	100	95	99	100	100	100	89	100
Inotropes/vasopressors	NK	NK	NK	NK	7	NK	NK	25	25	NK	15	34
Vasodilator	NK	NK	NK	NK	11	NK	NK	7	13	NK	8	33

*Values given are median.
†North America.
‡Geometric mean (units are in ng/L).
§Within the past year.
¶One year before admission.
**Atrial fibrillation or flutter.
††Type II diabetes mellitus.
‡‡One month before admission.
AHF, acute heart failure; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; NK, not known.

caused only a slight decrease in systolic blood pressure (SBP).[13] These properties are of course, relevant when considering the underlying pathophysiology of AHF.

In a phase II, placebo-controlled dose-ranging study (Pre-RELAX-AHF) the potential therapeutic benefits of serelaxin were recognised.[14] In that pilot study, patients receiving the 30 µg/day dose experienced greater dyspnoea relief compared with placebo. These positive findings supported the undertaking of a larger-scale mortality/morbidity trial.

In comparison to other drugs that have been tested for use in AHF, serelaxin seems unique. Other drugs share its vasodilator actions (eg, nesiritide, tezosentan, milrinone and levosimendan) but none have reduced postdischarge mortality.[12] Several of these drugs (notably milrinone and levosimendan) have an inotropic action and this, in itself, may be associated with an increased risk of death. At the very least, doubts still remain regarding the overall safety of these agents. Even if the inotropic drugs are discounted, why did the other vasodilators such as nesiritide and tezosentan fail? One possibility is that previous AHF trials included patients unlikely to benefit from the effects of these drugs on account of on their AHF profile.

PATIENT POPULATION

The other trials did not fail because they were too small and underpowered. EVEREST and the ASCEND-HF trials, for example, were much larger.[9 10] The patients enrolled in RELAX-AHF were a specific subset of patients with AHF not previously included in other trials. This distinct cohort may have been more likely to benefit from the haemodynamic effects of serelaxin.[4]

The baseline characteristics of the patients enrolled in RELAX-AHF compared to those enrolled in other AHF trials are summarised in table 2. In RELAX-AHF, patients with a SBP of ≤125 mm Hg were excluded. In the 1161 patients included, the mean SBP was approximately 142 mm Hg—higher than equivalent values from previous studies. As demonstrated in the REVIVE II trial,[3] low SBP at baseline is associated with increased in-hospital and postdischarge mortality and to avoid this adverse outcome, RELAX-AHF enrolled a set of patients with a lower baseline risk.[4] In fact, as shown in table 2, 87% of patients in RELAX-AHF had a history of hypertension. Not only were potential participants excluded if their baseline SBP was too low, careful attention was also paid to any fall in SBP during the trial. If SBP decreased by more than 40 mm Hg from baseline, but remained greater than 100 mm Hg, the study drug infusion rate was halved for the remainder of the infusion period. The study drug infusion was discontinued if SBP dropped below 100 mm Hg. These additional measures may too have contributed to the overall tolerability of the study drug.

Another notable difference between RELAX-AHF and the other AHF trials was the inclusion of patients irrespective of left ventricular ejection fraction (LVEF).

Table 3 Comparison of dyspnoea assessment

	OPTIME—CHF	SURVIVE	VERITAS	EVEREST	PROTECT	ASCEND-HF	RELAX-AHF		REVIVE I	REVIVE II	DOSE	CARRESS	ROSE
Was dyspnoea an end point?	Secondary	Secondary	Co-primary	Secondary	Primary	Co-primary	Primary	Primary	Secondary	Secondary	Secondary	Secondary	Secondary
Instrument/scale used to measure dyspnoea	Composite HF score (not validated)	7-point Likert scale	VAS (quantified by AUC)	7-point Likert scale	7-point Likert scale	7-point Likert scale	VAS (quantified by AUC)	7-point Likert scale	7-point Likert scale	7-point Likert scale	VAS (quantified by AUC)	VAS (quantified by AUC)	VAS (quantified by AUC)
When was dyspnoea measured?	Baseline, day 3 and discharge	24 h	Baseline, 3, 6 and 24 h	24 h	24 h and daily until discharge	6 and 24 h	Baseline and days 1–5	6, 12 and 24 h	24, 48 h and days 3 and 5	6, 24, 48 h and days 3 and 5	Baseline to 72 h	Baseline, 96 h and 1 week	24 h and 48 h
Criteria for success?	Greater reduction in mean HF score for the active group compared to placebo	Greater % of pts reporting ≥mild improvement in active group compared to placebo	Mean difference of ≥150 mm×h for the active group compared to placebo	Greater % of pts showing improvement in dyspnoea score for active group compared to placebo	Greater % of pts reporting ≥moderate improvement compared to placebo	Greater % of pts reporting ≥moderate improvement compared to placebo	Mean difference of ≥468 mm×h for the active group compared to placebo	Greater % of pts reporting ≥moderate improvement compared to placebo	Greater % of pts reporting improvement in dyspnoea	Greater % of pts reporting Improvement in dyspnoea			
Improvement in dyspnoea?	No	No	No	Yes	No	Yes/no*	Yes	No	Yes	Yes	Yes†	No	No

*Depending on which statistical analysis plan considered.
†High-dose cohort.
CHF, chronic heart failure; HF, heart failure; VAS, visual analogue score.

Patients with HF and preserved ejection fraction (HF-PEF) represent up to half of all patients admitted with AHF. No HF treatment has been shown to be as effective in HF-PEF to date. With the exception of the PROTECT study, all other AHF trials excluded patients with HF-PEF (table 1). In RELAX-AHF ejection fraction was available for most patients with the mean being 39% and 45% of patients having a LVEF ≥40%. At presentation these patients had higher recordings of mean SBP and lower concentrations of NT-pro BNP, troponin T and serum creatinine.

Serelaxin induced a similar dyspnoea relief in both groups, according to visual analogue score (VAS)-AUC (mean AUC change, 461 vs 397 mm×h, respectively). It also exhibited similar effects on CV death or hospitalisation for heart or renal failure at day 60, days alive and out of hospital at day 60 and CV death at day 180.[15] Pathophysiological changes including increased LV afterload, pulmonary congestion and end-organ damage are common to HF-REF and HF-PEF. Although, this does not explain the failure of the other trials, it suggests that the beneficial effects seen with serelaxin may be explained by its systemic vascular effects.

While some of the other AHF trials analysed in this review excluded patients with varying degrees of renal dysfunction, RELAX-AHF included patients with an eGFR between 30 and 75 mL/min/1.73 m^2.[16] Worsening renal function (serum creatinine increase of ≥0.3 mg/dL (27 µmol/L) or cystatin-C increase of ≥0.3 mg/L (22 nmol/L) at day 2) occurred in 15.4% and 19.6% of patients, respectively.[17] These measures of worsening renal function were associated with higher 180 day all-cause mortality. Baseline values in serum creatinine were similar between the placebo and serelaxin groups, however, patients receiving serelaxin had significantly lower serum creatinine and cystatin-C levels at day 5. The serelaxin group had a lower incidence of worsening renal function at day 2 and lower levels of blood urea nitrogen and uric acid each day from day 1 to day 5. Serelaxin administration was therefore associated with lower markers of renal dysfunction and reduced incidence of worsening renal function, consistent with the hypothesis that the prevention of renal dysfunction during AHF hospitalisation, favourably influences outcomes.[17]

To reduce the chance of enrolling patients without pulmonary congestion, RELAX-AHF included raised baseline serum biomarkers (NT-pro BNP ≥1400 ng/L or BNP ≥350 ng/L) as part of the study inclusion criteria (mean NT-pro BNP 5064 ng/L). This is in contrast to the other AHF trials, none of which stipulated raised biomarker levels as being compulsory for inclusion. Of the other trials, only ASCEND-HF and VERITAS included raised BNP or NT-pro BNP as a potential route of enrolment. As this was optional, not all patients qualified for enrolment on this basis and in fact only 18% and 2% of patients in VERITAS had a raised BNP or NT-pro BNP, respectively, with the mean serum BNP at baseline being 590 pg/mL.[11 18] This may reflect a

potentially important difference between the populations studied.

A recent trial in *chronic* HF illustrates the potential value of using natriuretic peptides to select patients for trials. The TOPCAT investigators randomly assigned patients to receive either spironolactone or placebo and this randomisation was stratified according to whether patients were enrolled on the basis of prior hospitalisation within the previous 12 months (hospitalisation stratum) or an elevated natriuretic peptide level within 60 days before randomisation (BNP stratum).[19] They found that the study drug effects differed significantly according to randomisation stratum (p=0.01 for interaction). In the hospitalisation stratum, spironolactone had no effect on time to the composite outcome of death from CV causes, aborted cardiac arrest or hospitalisation for HF (HR, 1.01; 95% CI 0.84 to 1.21; p=0.92) whereas in the BNP stratum, spironolactone did show benefit (HR, 0.65; 95% CI, 0.49 to 0.87; p=0.003). These findings illustrate the potential importance of natriuretic peptide levels as a predictor of adverse outcomes in HF and their value as an inclusion and quality criterion in clinical trials—especially in the setting of HF-PEF which remains difficult to define.

The inclusion/exclusion criteria of RELAX-AHF also resulted in the selection of a relatively homogeneous population: older patients, with HF who were more likely to have hypertension than CAD. Other AHF trials may have enrolled a more heterogeneous population with subsets of patients that might not respond to therapy.

OTHER DESIGN ASPECTS OF TRIAL

RELAX-AHF was generally similar in terms of the elements of study design compared with previous AHF trials, as shown in table 1. The main similarities being: evidence of AHF, dyspnoea requirements, exclusion of patients receiving inotropes and exclusion of patients with on-going myocardial ischaemia.

However, there are some fundamental yet subtle differences. First, RELAX-AHF enrolled patients relatively early after presentation that is, within 16 h. We know that early intervention has the best chance of achieving symptomatic improvement as it is during this time that organ damage and congestion may exert long-term adverse effects. Other AHF trials have failed to recruit patients this early on. A shift from typical entry criteria and better communication between departments (eg, emergency and cardiology departments) may be necessary to streamline enrolment—allowing for early randomisation in future trials.

Although there was no difference in the effect of serelaxin according to time from admission to randomisation in RELAX-AHF,[20] patients assigned to serelaxin received a significantly lower average dose of intravenous loop diuretic (p=0.006) and fewer received other vasoactive drugs (p=0.01) up to day 5, compared with the placebo group. This may have reflected the overall rapid time to randomisation, with less need for escalation of conventional treatment in patients receiving serelaxin. Less use of conventional treatment in the serelaxin group may have contributed to the benefit of experimental therapy as higher doses of diuretics and the use of some vasoactive agents (ie, inotropes) is associated with worse outcomes.

The notion of initiating therapy as early as possible is not something that is new to cardiology. Most notably, this was demonstrated in reducing the time for patients receiving thrombolysis followed by PCI in the context of acute STEMI; the phrase 'time is muscle' being familiar to all cardiologists. As with acute coronary syndromes, we know that release of troponin in AHF represents myocardial injury and that elevated levels are associated with poorer long-term outcomes. A substudy of RELAX-AHF studied biomarkers representative of end organ damage including: high-sensitivity troponin (cardiac), serum creatinine and cystatin-C (renal), transaminases (liver), and NT-proBNP (congestion).[17]

This substudy first confirmed that elevated serum high-sensitivity troponin values at baseline were associated with increased 180-day all-cause mortality. Patients treated with intravenous serelaxin had reduction in their troponin levels at day 2 postrandomisation—potentially providing a mechanism for the improved long-term survival seen in the serelaxin treated group. However, to be valid, this hypothesis requires the myocardial injury sustained during admission to be substantial enough to lead to progressive worsening of ventricular function and HF status over time. It is perhaps easier to understand that recurrent admissions could lead to a downward spiral in this way. Markers of renal dysfunction, liver dysfunction and congestion were all reduced at day 2 in patients treated with intravenous serelaxin as was the other prespecified efficacy analysis looking at early worsening of HF. Significantly fewer patients in the serelaxin treated group experienced worsening of HF up to day 5 and there was a 30% reduction in the hazard of worsening HF in the first 14 days. Although worsening HF was not an adjudicated event in RELAX-AHF, the finding that serelaxin seemed to reduce the risk of this occurrence has led to a great deal of debate about the importance of worsening of HF (or persistence or worsening) during the patient's admission. Patients exhibiting worsening have a longer length of stay, higher in-patient and postdischarge mortality and an increased risk of readmission (compared those who do not experience worsening during their index admission). Whether in-patient worsening is a useful end point for future trials in AHF is presently the subject of regulatory discussion.[21 22]

END POINTS INCLUDING DYSPNOEA

Dyspnoea is the most commonly reported symptom in AHF. Despite this, its pathophysiology is poorly understood and there is no standardised assessment method. Although the use of dyspnoea as an end point in AHF

trials has become prominent over the years, there is subjectivity related to its evaluation and measurement. Typical assessments include a VAS, a Likert scale or both. Past studies suggest that the VAS better captures changes in dyspnoea over time although a number of factors (including patient positioning) during measurement affect responses.[23] Previous studies have also shown significant differences in patient responses between the two scales, suggesting poor inter-scale reliability. Dyspnoea improves rapidly in response to conventional therapy, making it difficult to show incremental benefit with novel treatments.[24 25]

Relief of dyspnoea is a key goal of treatment in patients with acute pulmonary oedema and historically is an accepted end point in acute HF trials.[26] However, it is clear that the use of dyspnoea as an end point is much more complex than originally thought. First, conventional therapy seems to lead to rapid relief of dyspnoea in most patients (at least as usually measured). It is difficult therefore, for any new treatment, added to usual therapy, to show more rapid or greater (or both) relief of dyspnoea (or greater relief in a larger proportion of patients more quickly). Certainly, starting a new treatment relatively late after presentation may 'miss the therapeutic boat'. Apart from trying to start the new intervention as early as possible, the other obvious approach would be to compare the new treatment to existing therapy (rather than add to it); however, there has been so much reluctance to withhold conventional treatment (ie, mainly intravenous diuretic) this has never been done in any large trial. We do not know why this convention has never been broken—we do not think to take such an approach is unethical and 'rescue therapy' could be permitted (and even be part of a study end point). It is also possible that a new therapy might not result in more rapid (or greater) dyspnoea relief but could achieve the same relief more safely—this is certainly a possibility given that there is concern among some that diuretics and other treatments (eg, inotropes) may be harmful in AHF, even if they relieve symptoms. Indeed, it is a pre-requisite that any new treatment shown to relieve dyspnoea must also demonstrate safety.

There is also uncertainty about how best to measure dyspnoea relief and simple provocation by placing the patient supine or using exercise may demonstrate that relief of dyspnoea may not be nearly as complete as when the patient is assessed in an upright or semirecumbent position.[27] Standardisation of the circumstances of measurement of dyspnoea has not been given the attention it deserves and it is still not clear to the authors which instrument is best for measurement of dyspnoea (eg, Likert scale or VAS). The measurement tools commonly used also create an additional problem; what is the clinical importance of a few mm difference in a VAS or half a point on a Likert scale? In particular, what is its economic value? So while dyspnoea relief is undoubtedly important to patients, showing a clinically and economically worthwhile benefit is an extremely challenging proposition and it is our view that while relief of this symptom will remain an end point in trials, 'harder' clinical end points (eg, worsening heart failure, readmission and death) and economic outcomes (eg, length of stay) are likely to become much more important in the future.

In RELAX-AHF both of the primary end points were related to dyspnoea. First, the change in dyspnoea from baseline to day 5 using the VAS (quantified by AUC) was measured. This primary end point proved to be successful, reaching statistical significance, with a mean difference of 448 mm×h in the AUC in serelaxin treated patients; however, improvement was largely driven by imputation of a worst (zero) score for patients treated for worsening HF. Second, dyspnoea was measured at 6, 12 and 24 h using a seven-point Likert scale. The improvement in this coprimary end point was non-significant, although positive findings were noted at each individual time interval in the active group.

Table 3 highlights the variation in dyspnoea assessment tools used in the other studies. In addition to RELAX-AHF, the only other study to show improvement in dyspnoea (as measured by the VAS) was the DOSE trial. Of the remaining studies which used the seven-point Likert scale to determine change in dyspnoea status, EVEREST, REVIVE and ASCEND-HF showed improvement (although this did not reach statistical significance in ASCEND-HF). It is difficult to interpret these results given the lack of a standardised tool. This may introduce unwanted variability and confound attempts to demonstrate efficacy of treatment.

MORTALITY

There was a puzzling divergence between the effect of serelaxin on mortality and heart failure/renal hospitalisation in RELAX-AHF. No satisfactory explanation has been found for this. However, a larger proportion of patients in the serelaxin group had a hospital admission for HF within a year prior to enrolment, compared with the placebo group—and recent HF hospitalisation is the single most powerful predictor of readmission. It should be noted, however, that the hospital readmission rates were only measured up to day 60 and different results may have been found if they were assessed at 180 days (as was the case with mortality alone). There is also the issue of competing risks, whereby the greater survival in the serelaxin group leaves more patients (and potentially sicker patients) in that group at risk of hospitalisation.

The most remarkable finding from RELAX-AHF was the possible 37% reduction in CV and all-cause mortality at 180 days in the serelaxin treated group compared to placebo. This finding, if true, is astonishing given that no other AHF trial ever showed a positive effect on long-term survival. This result raises an important question: how is it possible for a drug infusion given for 48 h to

have a positive effect on survival at 180 days? The answer to this is unclear. However, it is postulated that early intervention may ameliorate the 'neurohormonal storm' that is thought to characterise AHF. This intervention may prevent further damage to vital organs and, over a period of time, this is translated to long-term benefit in terms of improved survival.[4 17] The biomarker data alluded to above give some support for this hypothesis.

However, some have been sceptical of this mortality finding especially given that rehospitalisation rates were not reduced in the serelaxin group, compared with the placebo group. This concern is based on the evidence that other drugs shown to reduce mortality in HF also reduce HF hospital admissions (although we only know this from CHF trials).[28]

It has also been highlighted that the serelaxin treatment group, at baseline, were at higher risk of rehospitalisation compared to placebo due to a greater percentage of patients being admitted to hospital for HF in the past year (37% of patients in the serelaxin treatment group vs 31% of patients in the placebo group). Given the dispute surrounding this finding, RELAX-AHF 2 is currently underway in an attempt to replicate these results. This double-blind randomised trial is projected to enrol up to 6800 patients and will therefore be sufficiently powered to detect an effect on mortality.[29] It aims to confirm and expand the efficacy, safety and tolerability evidence of 48 h intravenous infusion of serelaxin (30 µg/kg/day) when added to standard care in patients admitted with AHF.[29]

CONCLUSIONS AND FUTURE IMPLICATIONS

While RELAX-AHF has demonstrated the possible efficacy of a novel therapeutic agent, these results were undoubtedly helped by adopting a more modern approach to study design. The concept of targeting a specific population is something that has been suggested before. By enrolling a more homogenous group with AHF, benefits from treatment with serelaxin—mediated by its predominantly vascular mode of action—were more likely to occur than in patients with AHF and other diverse clinical characteristics. This raises concerns regarding the generalisability of these results and emphasises the need for further evidence demonstrating its efficacy in other common clinical scenarios for example, the patient with AHF with hypotension. This trial has also highlighted the challenge of attempting to improve dyspnoea against standard therapy and has shown the need for future trials to move away from dyspnoea as an end point and to focus to harder outcomes such as long-term survival.

Ularitide (a synthetic analogue of urodilatin) has previously been trialled in two double-blind placebo-controlled, proof-of-concept pilot studies and demonstrated encouraging on haemodynamics and symptoms. TRUE-AHF is a phase III clinical trial examining the efficacy and safety of ularitide as a treatment for AHF.[30] The study has randomised over 2000 patients within 12 h of admission and the trial has two co-primary efficacy end points. One is a hierarchically constructed end point ranking patients as better, worse or unchanged over a fixed time period with the ranking dependent on patient global assessment, persistent or worsening HF requiring intervention and death. The other evaluates freedom from CV mortality during follow-up after randomisation for the duration of the trial.

Omecamtiv mecarbil (a selective cardiac myosin activator) enhances binding of actin to myosin and in so doing prolongs systole. Phase I and II testing has been completed and the compound was well tolerated (in the absence of tachycardia). These data were sufficient to proceed with the phase IIb trial (ATOMIC-AHF), the aim of which was to evaluate the effect of 48 h of intravenous omecamtiv mecarbil compared with placebo on dyspnoea in subjects with LVSD hospitalised for AHF.[31] Although this trial failed to achieve its primary end point, it did provide essential information to inform the dosing regimen for future phase III trials.

Completed trials in AHF with neutral or negative results, though disappointing, contribute to our overall knowledge regarding clinical characteristics and outcomes, and they can influence the design of future trials. We await the results of ongoing and new AHF trials to determine whether effective and safe therapies are on the horizon. In the future, attempts should be made to match patient characteristics with the expected pharmacological mechanism of action for new agents, rather than taking the traditional 'all comers' approach. Successful translation of this approach into a greater ability to demonstrate the effectiveness of therapies remains to be seen. Consideration must also be given to the timing of intervention to determine the optimal 'window of opportunity'. Although advances have been realised, many opportunities remain to reduce the burden of AHF.

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