Nature Reviews Cardiology **10**, 3 (2013); published online 20 November 2012; doi:10.1038/nrcardio.2012.174

HEART FAILURE

Promising data for serelaxin

Intriguing findings from the RELAX-AHF trial of serelaxin (recombinant human relaxin 2; RLX030, Novartis, Basel, Switzerland) in patients with acute heart failure were presented by John Teerlink at the 2012 AHA Scientific Sessions and published in the *Lancet*. Patients hospitalized with acute heart failure commonly have a dismal prognosis. Despite decades of clinical trials, no clearly safe and beneficial treatment options have emerged. The aetiology of acute heart failure can be multifactorial, and patient presentation is highly variable. Management of this diverse syndrome in patients admitted to hospital is an ongoing clinical challenge.

The naturally occurring form of relaxin 2 is important during pregnancy and birth, mediating haemodynamic changes including cardiac output, renal blood flow, and arterial compliance. Hypothetically, this hormone could exert similar effects in patients with acute heart failure who also experience haemodynamic perturbation.

The phase II/III RELAX-AHF trial was conducted as a follow-up to the phase II pre-RELAX-AHF study, which suggested that relaxin 30 μg/kg per day improved dyspnoea and clinical outcomes in the setting of acute heart failure. The RELAX-AHF investigators randomly assigned 1,161 patients to receive serelaxin 30 μg/kg per day or a placebo; 98% of the participants actually received treatment. The study population was predominantly male (62.4%) and of white ethnicity (94.4%), and the mean age was 72 years. Importantly, the enrolment criteria of RELAX-AHF required patients to have a systolic blood pressure >125 mmHg, but no specifications about left ventricular ejection fraction were made. The two primary end points of the study were change in patient-reported dyspnoea (visual analogue scale [VAS] score) from enrolment to day 5, and moderate or marked improvement in patient-reported dyspnoea during the study (Likert scale) at 6, 12, and 24 h after first administration of the study drug.

Patients in the placebo group required intravenous diuretic and vasoactive drugs more often than those receiving serelaxin. Serelaxin significantly improved VAS up to day 5 when compared with placebo ($P=0.007$). However, no difference between the two groups was observed in the other primary end point. Patients in the serelaxin group had a 30% reduction in the risk of worsening heart failure symptoms up to day 14, and greater improvements in the signs and symptoms of congestion by day 2 compared with individuals receiving the placebo. In addition, serelaxin reduced the average length of hospital stay by 0.9 days, and average length of time in intensive or coronary care units by 0.4 days, in comparison with placebo. Treatment with serelaxin did not reduce the incidence of readmission to hospital owing to heart failure, renal failure, or cardiovascular death, nor did it increase survival, up to 60 days after hospital discharge. However, serelaxin did reduce cardiovascular and all-cause mortality by 37% at 180 days ($P=0.028$ and $P=0.02$, respectively).

The rate of adverse events associated with renal impairment was higher in the placebo group than in the serelaxin group (9% vs 6%; $P=0.03$). The incidence of other adverse events, including hypotension, was similar between the two groups.

"RELAX-AHF … is arguably the first trial in acute heart failure to show both significant improvement in a clinically meaningful primary end point (dyspnoea) and adequate short-term and long-term safety," says Dr Marvin Konstam in an Editorial that accompanied the report in the *Lancet*. "However, the findings cannot be extrapolated to other populations, and scrutiny is needed to establish consistency across the trial's subpopulations." The RELAX-AHF investigators point out that the trial was neither designed nor powered to assess mortality as an end point. Therefore, the mortality data reported here should be viewed as hypothesis generating.

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Original article Teerlink, J. R. *et al*. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* doi:10.1016/S0140-6736(12)61855-8