RELAX-AHF: consistency across subgroups and new hypotheses generated

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This editorial refers to ‘Effects of serelaxin in subgroups of patients with acute heart failure: results from RELAX-AHF’, by M. Metra et al., on page 3128

The lifetime likelihood of developing heart failure (HF) is ~20% over 40 years of age, and acute heart failure (AHF) remains the most common cause of hospitalization in people older than 65 years, with increasing incidence, and substantial morbidity and mortality.1 Whereas success in treating chronic HF has been achieved throughout the last decades, treatment options for AHF have failed to demonstrate any substantial clinical benefit in randomized prospective trials.1

Serelaxin is a recombinant human relaxin-2 vasoactive peptide that causes systemic and renal vasodilation. The mechanism of action of serelaxin involves activation of the endothelin type B receptor (ETB-receptor) and stimulation of nitric oxide production, that mediate systemic and renal vasodilation and natriuresis.2 In a dose-finding study (Pre-RELAX-AHF), i.v. infusion of serelaxin over 24 h was associated with significant relief of dyspnoea and a reduction of cardiovascular death or readmission due to heart or renal failure at day 60.3 In the RELAX-AHF study enrolling 1161 patients admitted to hospital for AHF treatment, serelaxin was associated with dyspnoea relief, as evidenced by the visual analogue scale (VAS) area under the curve from baseline to day 5.4 For the two key secondary endpoints (cardiovascular death or readmission to hospital for HF or renal failure), no significant effect was found with serelaxin. However, in a longer follow-up, a significant reduction in cardiovascular deaths and all-cause deaths at 180 days was observed.4

Two distinctive peculiarities characterize the RELAX-AHF study: the selection of primary endpoint and the inclusion criteria of the patients. The RELAX-AHF focused on dyspnoea relief as a primary endpoint. More than 80% of patients admitted to hospital for AHF complain of dyspnoea, which is not relieved in ~50% of patients within 24 h or even in 25% of patients at the time of discharge.5 From a patient perspective, rapid and complete relief of dyspnoea is a clinically important goal of AHF treatment. The European Medicine Agency noted in their guidance on clinical investigation of new drugs for congestive HF that the preferred primary endpoint is mortality, but the Agency accepts symptom improvement, such as dyspnoea, with the provision that excess mortality is ruled out.6 Importantly, dyspnoea relief by using the VAS scales and Lickert scales was found to be associated with reduced risk of 30- and 60-day mortality.7

In contrast to previous AHF trials, key inclusion criteria of RELAX-AHF were increased brain natriuretic peptide (BNP) or N-terminal prohormones of BNP, mild to moderate renal insufficiency, and systolic blood pressure >125 mmHg, but not reduced left ventricular ejection fraction.8 By selecting this more homogeneous 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 clinical characteristics. As a consequence, the findings of RELAX-AHF should not be extrapolated to all patients presenting with AHF. In the future, we would like to see evidence that serelaxin is also effective in other common clinical scenarios, e.g. in hypotensive AHF patients.

The influence of clinical characteristics on the response to serelaxin treatment and prognosis has now been analysed.8 Subgroups were based on covariates pre-specified for regulatory reporting purposes (e.g. age, sex, race, and geographic region) and on pre-specified biomarkers (troponin, cystatin C, and NT-proBNP). For academic purposes, additional subgroups were analysed (e.g. baseline systolic blood pressure, left ventricular ejection fraction, estimated glomerular filtration rate, time from presentation to randomization, etc.). Finally, additional subgroups were defined post-hoc. This long list of subgroups (n = 23) was applied to primary and key secondary efficacy endpoints and cardiovascular and all-cause mortality through to day 180. The key finding of the subgroup analysis was that the two primary and key secondary efficacy endpoints did not disclose any significant interaction with respect of the effects of serelaxin.8 However, nominally significant (P < 0.05) treatment by subgroup interactions were observed in mortality at day 180: patients age >75 years, HF hospitalization in the previous year, lack of beta-blocker treatment at baseline, lymphocytes <12%, and estimated
glomerular filtration rate <50 mL/min/1.73 m² were associated with a more beneficial outcome with serelaxin.8 As correctly stated by the authors, the treatment by subgroup interactions with the two mortality endpoints at day 180 are hypothesis-generating and not more. Hopefully, these hypotheses are tested in the upcoming RELAX-AHF 2, comprising >6000 patients with AHF.

The obvious criticism of this paper is the large number of subgroups, in particular in relation to the population size and event rate. Admittedly, the authors state correctly this limitation in the manuscript, but the limitation of multiple testing remains.9 Somewhat disturbing is the definition of the subgroups. They did not follow one consistent concept, e.g. applying statistical approaches for dividing a study population into subgroups (e.g. above and below the median, or into tertiles).

In light of the putative mechanism of relaxin being a potent vasodilator in the HF setting with pre-constricted blood vessels, one might speculate that in patients with higher baseline blood pressure, infusion of serelaxin might be more potent to relieve dyspnoea and reduce cardiovascular and all-cause mortality. However, there was no treatment by subgroup interaction in the subgroups with baseline systolic blood pressure > and <140 mmHg. In a previous study, patients with higher blood pressure at time of admission also did not have improved rates of dyspnoea relief, worsening of HF, or admission for HF after discharge.10 Unfortunately, and despite the long list of subgroups, the association of the change in blood pressure with serelaxin (e.g. above/below the median) with respect to the outcome parameters was not analysed. In the Pre-RELAX-AHF, systolic blood pressure decreased by 4.9 mmHg more in the serelaxin than in the placebo group,3 and a greater early drop in systolic blood pressure was identified as an independent predictor of worsening renal function in AHF.11

Reduced renal blood flow emerged as a major driving force that explains the high frequency of impaired renal function in patients with HF.12 In the face of the strong vasodilatory effect of serelaxin on the renal vasculature, serelaxin is expected to be more effective in patients with reduced renal function. In RELAX-AHF, estimated glomerular filtration rate or cystatin C at baseline, both valid parameters of renal function, did not discriminate patients with a more favourable relief of dyspnoea, but were linked to lower mortality at day 180.8 The hypothesis that serelaxin may have beneficial effects in particular in patients with reduced renal function still needs to be proven. Worsening of renal function and prognosis in HF are closely related to each other,13 and the prevention of renal dysfunction by serelaxin might be one of the mechanisms that contributes to the reduced cardiovascular and all-cause mortality at day 180.8

Finally, the intriguing question remains of which are the pathogenic mechanisms that translate the effects of serelaxin infusion over 48 h into improved dyspnoea relief and potentially reduced mortality. In RELAX-AHF, early administratin of serelaxin was associated with fewer signs of organ damage and more rapid relief of congestion during the first days after admission, and changes in cardiac, renal, and hepatic damage and decongestion were associated with 100 day mortality.14 Thus, the short-term infusion of serelaxin may have a long-term effect on outcomes via beneficial effects of serelaxin on cardiac, renal, and hepatic injury in patients with AHF. Moreover, the vascular effect of serelaxin leading to decreased arterial compliance may exert beneficial effects on arterial compliance, wave reflection, and thereby unloading of the left ventricle and the renal vascular bed. Clinical data supporting this concept are scarce and awaited urgently, e.g. from the RELAX-AHF 2 trial.

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References