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Extended abstract

New heights in acute heart failure syndrome: focus on new inotropes and vasodilators

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Acute heart failure (ADHF) remains a major healthcare problem as hospitalization rates continue to increase and outcome remains poor with a one-year rate of cardiovascular mortality or heart failure hospitalization of 30-40% (1).

Current therapies for ADHF include loop diuretics to reduce intravascular volume, vasodilators to reduce vascular resistance and inotropic agents/calcium sensitizers to increase cardiac contractility (2). However, little has happened in drug therapy for several decades. There is an urgent unmet need for new drug therapies, with attention recently focussing on the myosin activator omecamtiv mecarbil and the maternal hormone relaxin.

Myosin activator omecamtiv mecarbil

Omecamtiv mecarbil is a novel small molecule that increases cardiac contractility by selectively and directly activating the enzymatic domain of cardiac myosin heavy chain, the force generating motor protein of the cardiac sarcomere (3). In vitro experiments demonstrated that omecamtiv mecarbil augments contractility without changing the intracellular calcium transient in isolated cardiac myocytes. In animal studies with heart failure, omecamtiv mecarbil significantly improved LV systolic function and cardiac output by increasing the left ventricular systolic ejection time without a change of dP/dt or heart rate.

In clinical studies in humans (five phase 1 and 4 phase 2 studies), omecamtiv mecarbil showed a significant prolongation of LVET associated with an improvement of fractional shortening and wall thickness, an increase of cardiac output and stroke volume and a decrease of left and right atrial filling pressures without a change of blood pressure (4). Heart rate significantly decreased due to an improvement of the hemodynamic situation. Recently, the proof of concept study with the acronym ATOMIC-AHF was finalized. The primary aim of the trial was to evaluate the safety and efficacy of omecamtiv mecarbil in patients with acute decompensation over a period of 48 hours. The results will be presented on the occasion of ESC 2013.

Vasodilator serelaxin

Serelaxin is a recombinant form of human relaxin-2, a naturally occurring peptide hormone that mediates maternal systemic hemodynamic and renal adaptations to an increase in intravascular volume in pregnant women (5). In previous clinical studies, relaxin showed numerous hemodynamic and renal effects such as an increase in arterial compliance, a concomitant decrease in systemic and pulmonary vascular resistance, an increase in renal blood flow and GFR and an improvement of cardiac output (6). In the pilot Pre-Relax-AHF study, treatment with serelaxin resulted in beneficial effects on both dyspnoea and clinical outcome in ADHF patients. These results were recently confirmed in the large

RELAX-AHF phase 3 study. Here, early treatment with serelaxin was well tolerated and associated with a significant improvement in dyspnoea and a 37% reduction in 108-day mortality.

KEYWORDS: acute heart failure, hemodynamics, omecamtiv mecarbil, serelaxin

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