European Heart Journal Supplements (2016) **18**(Supplement G), G33–G42
The Heart of the Matter
doi:10.1093/eurheartj/suw043

What is on the horizon for improved treatments for acutely decompensated heart failure?

Javier Díez[1]* and Antoni Bayés-Genis[2,3]

[1]*Department of Cardiology and Cardiac Surgery, Program of Cardiovascular Diseases, and Centre for Applied Medical Research, University of Navarra Clinic, University of Navarra, Av. Pio XII 55, 31008 Pamplona, Spain*
[2]*Cardiology Service and Heart Failure Unit, Universitari Germans Trias i Pujol, Ctra. de Canyet, s/n, 08, 08916 Badalona, Spain*
[3]*Department of Medicine, Autonomous University of Barcelona, 08193, Cerdanyola del Vallès, Barcelona, Spain*

KEYWORDS
Acute heart failure;
Unmet need;
Novel therapies;
Biomarkers;
Organ damage;
Clinical management

Patients hospitalized with acutely decompensated heart failure (ADHF) are often critically ill and require immediate treatment to stabilize their haemodynamic status. Despite improving the signs and symptoms of ADHF, currently available therapies have failed to demonstrate improvements in post-discharge outcomes, such as mortality and rehospitalization, and to address the impact of end-organ damage. Furthermore, attempts to develop therapies to treat patients with ADHF over the past 10 to 20 years have been largely unsuccessful, further compounding the problem. Recent evidence supporting a variety of novel therapies, such as serelaxin and natriuretic peptides, may signal a new hope on the horizon for patients with ADHF.

Introduction

Acutely decompensated heart failure (ADHF) is the rapid worsening of the symptoms and signs of heart failure (HF).[1] Most cases of ADHF occur in patients with underlying chronic HF, which can present as HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] $<40\%$), heart failure with preserved ejection fraction (HFpEF; LVEF $\geq 50\%$) or heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%).[1] ADHF is a growing healthcare problem; increases in risk factors for cardiovascular (CV) disease have resulted in a rise in HF-related hospitalizations.[2] Recent estimates, based on health service records from a number of European countries, suggest that hospitalizations with a primary diagnosis of HF account for 1–2% of all hospitalizations.[3] Patients admitted to hospital for ADHF are critically ill with serious and often life-threatening symptoms; therefore the immediate focus for treatment is stabilizing the patient's haemodynamic status, improving organ perfusion and relieving the signs of systemic and pulmonary congestion (e.g. dyspnoea, oedema, elevated blood pressure [BP] and irregular heart rhythm).[1] These short-term outcomes can be achieved through treatment with currently available therapies, which include administration of oxygen, diuretics, nitrates, inotropes, and β-blockers.[1,3] However, it is critical for the patient's overall prognosis that long-term outcomes, such as end-organ protection, prevention of hospital readmission, reduction of length of hospital stay and reduction in mortality, are also improved.[1,4]

Despite improving the initial signs and symptoms of ADHF during hospitalization, current therapies have failed to reduce post-discharge event rates and may have detrimental effects on organs, contributing to increased morbidity and mortality.[2,4,5] Further, heterogeneity in the underlying pathophysiology of HF may help to explain the lack of evidence for unequivocal benefit with current treatments.[6] Hence, there is significant unmet need in ADHF for novel agents that relieve both the early signs and symptoms of ADHF and have a beneficial effect on long-term outcomes, as well as reducing rehospitalizations and length of hospital stay.[2]

In this article, we provide an overview of the key data supporting therapies currently in development for the treatment of ADHF. We discuss how these treatments have

* Corresponding author. Tel: +34 948 194700, Fax: +34 948 194716, Email: jadimar@unav.es

the potential to affect current clinical management practices aiming not only to relieve symptoms, but also to provide end-organ protection of multiple organs, and thus, improve in-hospital, post-discharge and long-term patient outcomes. Furthermore, we highlight the importance and utility of biomarkers as valuable tools which can aid diagnosis, evaluate organ damage and guide clinical decision making.

Treatment options for acute heart failure in advanced development stage

Despite a considerable effort, few clinical trials have demonstrated significant improvements in long-term outcomes for patients with ADHF.[6] Mortality remains high and patients are likely to experience frequent hospital readmissions[3]; therefore, the development of new therapies is warranted. Below, we review the currently available data for several promising investigational agents in advanced stages of clinical development for the management of ADHF.

Serelaxin

Serelaxin is a recombinant form of the naturally occurring human relaxin-2 peptide hormone, which is involved in the regulation of haemodynamic and renal changes during pregnancy.[7,8] Recent clinical studies suggest that serelaxin acts through multiple pathways to improve haemodynamics and relieve congestion in the short-term, as well as providing organ protection to enhance patients' long-term outcomes, distinguishing this potential treatment from traditional vasodilator therapies.[4]

Serelaxin induces vasorelaxation by binding to the relaxin family peptide 1 receptor in the heart, blood vessels and kidneys, leading to modulation of multiple signalling pathways, including nitric oxide synthase activation, antagonism of vasoconstrictors (e.g. endothelin-1, angiotensin II), prostacyclin production, induction of vascular endothelial growth factor transcription, and inhibition of transforming growth factor β transcription.[4,7]

Evidence from pre-clinical and clinical studies suggests that serelaxin alleviates haemodynamic imbalance and relieves congestion through multiple pathways, including increasing arterial compliance and decreasing systemic vascular resistance (SVR).[9] Importantly, serelaxin is also thought to interfere with systemic and local mechanisms that mediate end-organ damage, including inhibition of the inflammatory response, protection of endothelial cells against oxidative stress, inhibition of apoptotic and necrotic cell death, and inhibition of fibrosis and hypertrophy.[4] Serelaxin also appears to have pro-angiogenic effects that may facilitate tissue repair and minimize organ damage.[4]

Evidence from clinical trials supports the hypothesis that serelaxin may improve both short- and long-term outcomes in patients with ADHF.[10,11] In the preliminary RELAXin in Acute Heart Failure (pre-RELAX-AHF) phase IIb dose-finding study ($n = 234$), serelaxin 30 μg/kg/day administered as a 48-h intravenous (IV) infusion significantly improved dyspnoea vs. placebo (assessed with the Likert scale) and was associated with improvements in clinical outcomes such as length of stay, days alive out of hospital and CV death or readmission due to heart or renal failure.[11]

In the RELAXin in Acute Heart Failure (RELAX-AHF) phase III clinical trial ($n = 1161$), patients were randomized to serelaxin (30 μg/kg/day via 48-h IV infusion) or placebo, both in addition to standard of care.[12] Serelaxin significantly improved the primary endpoint, relief from dyspnoea, as assessed by the visual analogue scale (VAS) area under the curve (AUC) from baseline to Day 5, compared with placebo. No significant effect was observed on the other primary endpoint, relief from dyspnoea as assessed with the Likert scale during the first 24 h (*Figure 1*).[10] Treatment with serelaxin was not associated with improvements in the secondary endpoints of days alive out of hospital, and CV death or hospital readmission for HF or renal failure through Day 60 compared with placebo.[10] Serelaxin was associated with significant improvements in a number of other clinical outcomes which included greater reductions in the early signs and symptoms of congestion, reduced risk of worsening HF in the first 14 days, and reduced length of hospitalization, compared with placebo.[10] Serelaxin demonstrated significant improvements

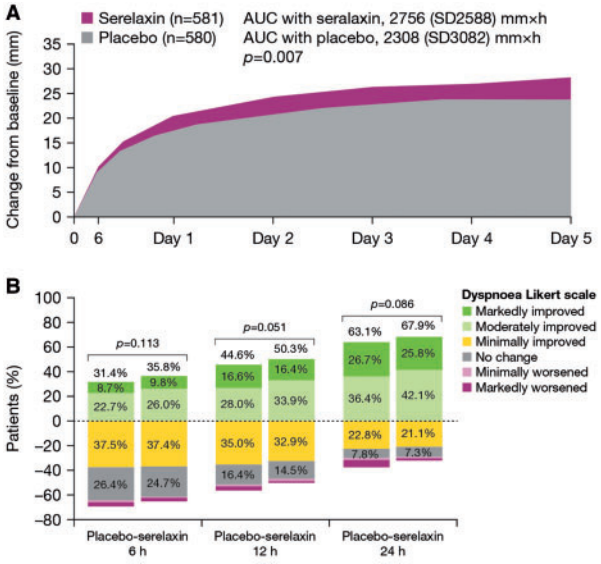

Figure 1 Patient-reported change in dyspnoea with serelaxin vs. placebo in the RELAX-AHF study.[10]

AUC, area under the curve; h, hour; VAS, visual analogue scale

(*A*) The primary endpoint of patient-reported change in dyspnoea measured using the VAS and quantified as the 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 (Likert 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.

Reprinted from The Lancet **381**, Teerlink *et al*. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomized, placebo-controlled trial, pages 29–39, Copyright 2013 with permission from Elsevier.

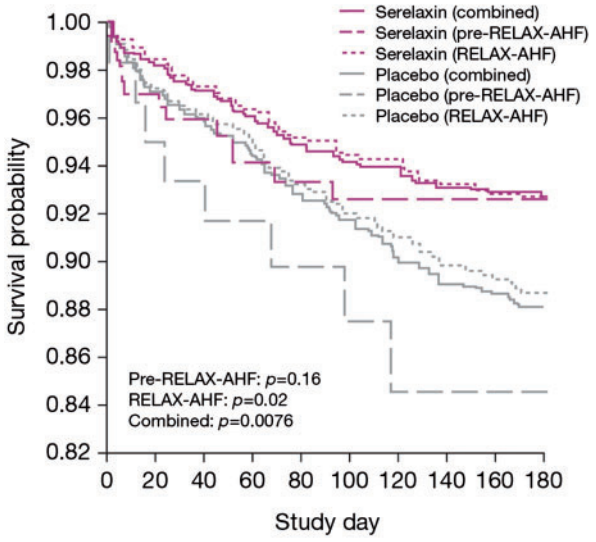

Figure 2 Risk for all-cause mortality following treatment with serelaxin vs. placebo in the Pre-RELAX-AHF and RELAX-AHF studies, and for both studies combined.[13]

RELAX-AHF, Relaxin in Acute Heart Failure.

The combined results represent stratified Kaplan–Meier estimates. *P* values are for log-rank tests in the individual studies and for the stratified log-rank test for the combined studies.

on longer term outcomes which included reductions in 180-day CV and all-cause mortality, compared with placebo.[10] Analysis of combined data from pre-RELAX-AHF and RELAX-AHF studies confirmed the beneficial effect of serelaxin, vs. placebo, on 180-day all-cause mortality (*Figure 2*).[13]

In a *post-hoc* analysis of RELAX-AHF, substantial changes of markers of cardiac (troponin T, N-terminal pro-B-type natriuretic peptide [NT-proBNP]), renal (cystatin-C) and hepatic (aspartate transaminase [AST] and alanine transaminase [ALT]) damage at Day 2 were associated with an increased risk of all-cause mortality at Day 180.[13] Treatment with serelaxin reduced levels of these biomarkers at Day 2 compared with placebo, suggesting that early treatment with serelaxin may prevent organ damage in patients following hospitalization.[4,13] In a recent *post-hoc* analysis of patients ($n = 1132$) enrolled in RELAX-AHF, patients with renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) who were treated with serelaxin had lower CV and all-cause mortality vs. placebo, supporting a protective role of serelaxin in this highly vulnerable patient population.[14] Overall, data from pre-RELAX-AHF and RELAX-AHF studies indicate that serelaxin was well tolerated with a favourable safety profile, compared with placebo.[10,11,13–16]

The impact of serelaxin on the prognosis of patients with ADHF is being evaluated in several large phase III studies (>10 000 participants).[17–19] RELAX-AHF-2 ($n = \sim 6800$) is evaluating the efficacy and safety of serelaxin (30 μg/kg/day via 48-h IV infusion) vs. placebo, in addition to standard therapy, with co-primary endpoints of CV death at 180 days and worsening HF at Day 5.[19,20] RELAX-AHF-ASIA ($n = 1520$) is assessing the safety and efficacy of serelaxin (30 μg/kg/day via 48-h IV infusion) in patients from several Asian countries with a trichotomous primary endpoint of treatment success, treatment failure or no change evaluated through Day 5 after randomization.[18,20] Evaluation of the safety of serelaxin treatment in the RELAX-AHF-2 and RELAX-AHF-ASIA trials will include analysis of total adverse events, serious adverse events and death.[18,19] Finally, RELAX-AHF-EU ($n = 2685$) is a 2:1 randomized open-label study which will confirm and extend the evidence for serelaxin (30 μg/kg/day via 48-h IV infusion) in addition to standard of care, vs. current standard of care alone.[17]

Natriuretic peptides

Natriuretic peptides, which include atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and urodilatin, are known to promote a diverse set of physiological actions which include stimulating vasodilation, natriuresis, diuresis, and reducing fibrosis, proliferation and inflammation, thus protecting against organ damage.[20,21] As such, the natriuretic peptide system and its role in the development and progression of HF has been extensively investigated.[21] Two novel natriuretic peptides currently being studied include ularitide and cenderitide. It should be noted that the clinical development of ularitide is currently at a more advanced stage than that of cenderitide.

Ularitide

Ularitide is a chemically synthesized form of the human natriuretic peptide urodilatin.[22] Urodilatin, a differentially processed peptide of ANP, is produced in the distal tubule cells of the kidney and is secreted into the urine in response to increased serum levels of sodium.[20,22,23] Secreted urodilatin binds to natriuretic peptide receptor (NPR)-A in the renal collecting duct, leading to inhibition of sodium uptake and induction of natriuresis and diuresis.[20,22,23]

In the phase IIa dose-finding Safety and efficacy of an IV placebo-controlled Randomized Infusion of Ularitide in a prospective double-blind Study (SIRIUS) I trial in patients requiring hospitalization for ADHF ($n = 24$), ularitide (7.5, 15, and 30 ng/kg/min via 24-h IV infusions) significantly reduced pulmonary capillary wedge pressure (PCWP) and improved dyspnoea at 6 h, vs. baseline, compared with placebo. At 24 h, plasma NT-proBNP levels were reduced in patients receiving ularitide, compared with placebo.[24] In the SIRIUS II study in patients with ADHF ($n = 221$), ularitide (15 and 30 ng/kg/min via 24-h IV infusions) was associated with significantly lowered cardiac filling pressures (*Figure 3*), reduced SVR, and increased cardiac index at 6 h, compared with placebo.[25] At 6 and 24 h, more patients in the ularitide groups (7.5, 15, and 30 ng/kg/min) reported that their dyspnoea was moderately or markedly better, compared with patients receiving placebo who more frequently reported no change in dyspnoea.[25] During

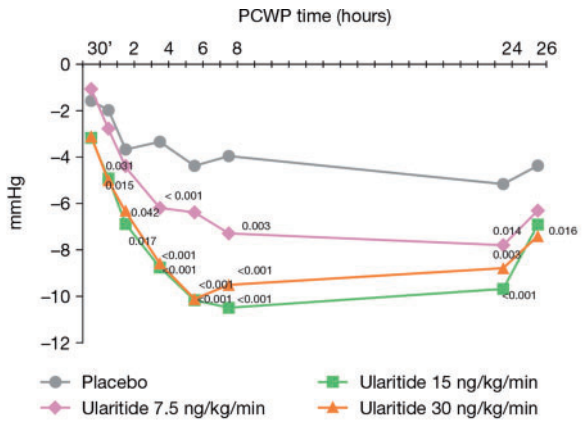

Figure 3 Changes from baseline in pulmonary capillary wedge pressure in patients receiving ularitide vs. placebo in the SIRIUS II study.[25]

h, hour; IV, intravenous; PCWP, pulmonary capillary wedge pressure; SIRIUS, Safety and efficacy of an IV placebo-controlled Randomized Infusion of Ularitide in a prospective double-blind Study.

The change from baseline in PCWP over time (0.5, 1, 2, 4, 6, 8, and 24 h of dosing, and 2 h post-dosing [26 h]) in patients receiving placebo or ularitide (7.5, 15, or 30 ng/kg/min). *P* values for the difference in ularitide treatment vs. placebo at individual time points are indicated.

a 2-day follow up analysis of SIRIUS II, treatment with ularitide did not affect eGFR, serum creatinine, creatinine clearance and blood urea nitrogen, compared with placebo.[26] The most frequent treatment-related adverse events (AEs) associated with ularitide were hypotension, a dose-dependent reduction in BP, confusional state, restlessness and dyspnoea.[24,25] The possible effects of ularitide on long-term outcomes such as impact on mortality and rehospitalization have not yet been published.

The Phase III TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure (TRUE-AHF) is currently being conducted to explore the effectiveness of ularitide in a larger population of patients with ADHF ($n = 2157$).[22,27] This trial enrolled patients with a systolic BP 116-180 mmHg and administered an intermediate dose of ularitide (15 ng/kg/min via 48-h IV infusions)[27] in an attempt to minimize the risk of hypotension. The key objectives are to evaluate the effect of ularitide on clinical status (symptom improvement, worsening HF, clinical intervention) up to 48 h post-randomization, and CV mortality for the duration of the trial. [27]

Cenderitide

Cenderitide is a chimeric natriuretic peptide that is able to interact with NPR-A and NPR-B and is resistant to degradation.[28-30] In pre-clinical studies in normal canines, infusion of cenderitide significantly increased GFR and was associated with reduced hypotensive effect, compared with equimolar doses of nesiritide.[29]

In healthy volunteers ($n = 10$), cenderitide activated cyclic guanosine monophosphate (cGMP), suppressed aldosterone production and promoted natriuresis and diuresis with minimal effects on BP.[31] In a phase II dose-ranging study in patients with symptomatic ADHF and renal compromise (a creatinine clearance of 30-80 mL/min) ($n = 66$), cenderitide 1.25 and 2.5 ng/kg/min (IV infusion for at least 48 h) improved serum creatinine and cystatin-C levels, compared with placebo.[32,33] Patients receiving the maximum dosage of cenderitide (5 ng/kg/min) were withdrawn from treatment due to clinically relevant reductions in BP, however, cenderitide appeared to be well-tolerated by the remaining treatment groups.[33] A further study to assess the haemodynamic and renal effects of cenderitide (3 ng/kg/min for 8 h further increased to 10 ng/kg/min) in patients with stabilized ADHF ($n = 11$) reported a significant decrease in PCWP (the primary outcome) compared with baseline in patients who received both dosages.[34,35] Trends towards increased cardiac output and decreased right atrial pressure were also reported in patients receiving cenderitide; however, these trends did not reach statistical significance.[20,34] Furthermore, urine output increased significantly from baseline in patients receiving cenderitide, and serum creatinine levels were unchanged, suggesting that cenderitide may preserve renal function.[20,34] The full study results are, as yet, unpublished.

Other emerging therapeutic approaches for acute heart failure

Cardiac-specific myosin activators

Cardiac-specific myosin activators directly target the diminished cardiac contractility that is central to HF with reduced ejection fraction.[36,37] Omecamtiv mecarbil is a novel, small-molecule, selective cardiac myosin activator that binds to the catalytic domain of myosin, increasing the probability of the transition from a weakly actin-bound to a strongly actin-bound, force-producing state. Hence, omecamtiv mecarbil prolongs systolic ejection time and increases cardiac contractility.[38]

In the phase II Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) trial, the first study of omecamtiv mecarbil in patients with ADHF and LVEF $\leq$40% ($n = 606$), there was no significant difference in improvement of dyspnoea at 48 h (primary endpoint). However, treatment with the highest total dose of omecamtiv mecarbil (0.67 mg/mL) provided greater dyspnoea relief at 48 h and through 5 days, compared with placebo. In an echocardiographic sub-study ($n = 89$), omecamtiv mecarbil significantly increased left ventricular systolic ejection time and decreased left ventricular end-systolic dimension, compared with placebo.[39] Furthermore, a numerical reduction in incidence of death or worsening HF within 7 days in patients receiving omecamtiv mecarbil was observed.[39] Plasma troponin concentrations were slightly higher in patients receiving omecamtiv mecarbil vs. placebo; however, no relationship between omecamtiv mecarbil exposure and the maximal increase in troponin from baseline was observed.[39] Omecamtiv mecarbil was generally well tolerated. Further clinical trials of this novel therapy are required to determine its place in the management of ADHF.[39]

Direct soluble guanylate cyclase modulators

Targeting soluble guanylate cyclase (sGC) activity to increase cGMP synthesis is a novel mechanistic approach for the treatment of ADHF.[40] In patients with HF, reduced nitric oxide bioavailability resulting from decreased generation as a result of endothelial dysfunction and increased degradation by reactive oxygen species leads to inadequate sGC activity and reduced production of cGMP, which is vital for normal cardiac and vascular function.[40]

The sGC stimulator vericiguat has been evaluated for the treatment of worsening chronic HF in the phase II Soluble Guanylate Cyclase Stimulator in Heart Failure Studies (SOCRATES) programme, which consists of two randomized, placebo-controlled, parallel-group, dose-finding trials.[40] In SOCRATES-REDUCED, clinically stable patients ($n = 456$) with LVEF <45%, within 4 weeks of a worsening chronic HF event (requiring hospitalization or outpatient IV diuretic) were randomized to vericiguat (1.25, 2.5, 5, or 10 mg) or placebo for 12 weeks.[41] In the primary analysis, NT-proBNP levels were not significantly different in patients treated with vericiguat vs. placebo. However, greater reductions in NT-proBNP were associated with higher vericiguat doses in an exploratory analysis.[41] The results of the similar SOCRATES-PRESERVED study (stable patients with LVEF ≥45%) remain to be published.[40,42] Further investigations are needed to explore the potential role for vericiguat in patients with ADHF.[41]

The sGC activator, cinaciguat, has recently been investigated in a phase II dose-ranging study (NCT00559650) of patients with ADHF ($n = 139$). In this study, treatment with cinaciguat (50–600 μg/h) was associated with significant improvements in several haemodynamic parameters (e.g. PCWP, right arterial pressure and cardiac index) but was terminated early due to an increase in hypotension at cinaciguat dosages ≥200 μg/h.[43] For this reason, three further phase II trials, COMPOSE 1, COMPOSE 2, and COMPOSE EARLY investigated cinaciguat at dosages <200 μg/h (50, 100, and 150 μg/h) in patients with ADHF.[44] However, as a result of recruitment difficulties, excessive hypotension and a lack of effect on dyspnoea and cardiac index in patients receiving cinaciguat, these trials were terminated prematurely[44] and cinaciguat is no longer being pursued as a potential treatment option for patients with ADHF.[43,44]

Dual SERCA2 stimulation and Na-K ATPase inhibition

Sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase-2a (SERCA2a) has a vital role in the regulation of Ca^{2+} in the cardiomyocyte and its expression and function is diminished in HF.[45] SERCA2a has therefore been identified as a potential therapeutic target for HF.

Istaroxime is a luso-inotropic, small-molecule, Na-K ATPase inhibitor that stimulates SERCA2a-ATPase activity and accelerates calcium cycling in HF by relieving phospholamban inhibition.[46] In the phase II Hemodynamic Effects of Istaroxime in Patients With Worsening HF and Reduced LV Systolic Function (HORIZON-HF) trial ($n = 120$), istaroxime significantly reduced PCWP and increased systolic BP vs. placebo in patients with ADHF who had not received IV inotropes and had serum creatinine levels ≤3.0 mg/dL.[47] Furthermore, istaroxime-treated patients showed significant improvements in several parameters of left ventricular diastolic stiffness, compared with placebo.[47] An additional phase II trial evaluating the efficacy and safety of istaroxime in patients with ADHF is planned.[48]

An alternative approach to SERCA2a stimulation has been pioneered by the Hajjar laboratory. Recent investigations assessing the effects of vector-mediated gene transfer of SERCA2a have led to the successful completion of phase I and II trials in patients with severe chronic HF.[49-51] However, in the Calcium Upregulation by Percutaneous Administration of Gene Therapy in Patients with Cardiac Disease (CUPID-2) study, a double-blind, placebo-controlled, phase 2b trial in patients with HFrEF ($n = 250$), SERCA2a gene therapy did not reduce the time to recurrent HF events (defined as hospital admission for HF or treatment for worsening HF), compared with placebo.[52] Further studies are required to fully demonstrate the potential of this possible treatment option in HF.[51,53]

β-arrestin-biased angiotensin II type 1 receptor ligands

Inhibition of angiotensin II signalling via blockade of angiotensin II type 1 receptor (AT1R) is a common therapeutic approach in the treatment of HF. Recent mechanistic investigations on the selective activation of AT1R, mediated through the actions of β-arrestin, have suggested an alternative approach to the modulation of AT1R-signalling in HF.[20,54] In contrast to currently available unbiased AT1R blockers that decrease cardiac contractility, pre-clinical studies in mice showed that β-arrestin-biased-signalling resulted in enhanced cardiac contractility while decreasing myocardial oxygen consumption.[55]

TRV027 (also known as TRV120027) is a novel β-arrestin-biased ligand that has been shown to improve cardiac performance and preserve renal function in several pre-clinical studies.[56-58] Results from a randomized, double-blind, placebo-controlled, titration study in patients with stable chronic HF ($n = 32$) indicate that TRV027 (3–10 μg/kg/min) decreased mean arterial pressure and PCWP in patients with high vs. low plasma renin activity receiving TRV027, or vs. patients receiving placebo.[59] TRV027 was investigated further in the Biased-Ligands of the Angiotensin receptor Study in Acute Heart Failure (BLAST-AHF), a phase IIb dose finding study; however, the development of TRV027 has since been discontinued due to failure to achieve the primary or secondary endpoints.[60,61]

Nitroxyl donors

Nitroxyl (HNO) is a reactive nitrogen species that improves myocardial function, via direct cyclic adenosine monophosphate-independent, lusitropic and inotropic effects, and by venous and arterial dilation partially attributable to sGC activation.[62] CXL-1020, a novel synthetic compound which decomposes to produce HNO, was assessed in patients hospitalized for haemodynamic

assessment of HF prior to heart transplantation, or for ADHF ($n = 31$).[62] Positive haemodynamic effects were recorded with CXL-1020 (10 and 20 μg/kg/min via IV infusion) vs. placebo; PCWP and right arterial pressure decreased, and cardiac and stroke indexes increased. In general, CXL-1020 was well tolerated with few AEs; however, longer infusions of high dosages (20 μg/kg/min) were associated with inflammatory irritation at the infusion site, thus development was terminated.[62] Further studies investigating CXL-1427, a second generation HNO donor, are underway.[63,64]

Short-acting calcium blockers

Clevidipine is a short-acting L-type calcium channel blocker with vasodilatory properties that is approved for the treatment of severe hypertension.[20,65] Results from a sub-study of patients with ADHF ($n = 19$) enrolled in the Evaluation of the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients with Severe Hypertension (VELOCITY) trial suggested that clevidipine was safe and well tolerated in this patient population.[66] In a subsequent open-label trial assessing the efficacy and safety of clevidipine vs. current standard of care in patients with hypertensive ADHF ($n = 104$), patients treated with clevidipine had significant improvements in dyspnoea and were more likely to obtain a pre-specified systolic BP target, compared with patients receiving standard of care.[67] Further studies are required to demonstrate the long-term safety and efficacy of clevidipine in patients with ADHF.[20]

Potassium channel activators

Nicorandil is a potassium channel activator with vasodilatory properties currently used for the treatment of angina pectoris.[20] In a phase II titration study assessing the haemodynamic properties of nicorandil in patients with ADHF ($n = 99$), IV bolus administration followed by continuous infusion of nicorandil over 6 h resulted in improvements to PCWP, cardiac index and right arterial pressure, compared with baseline.[68] Of note, there was a significant reduction in systolic BP in patients receiving nicorandil who had a baseline systolic BP >160 mmHg, while there was no significant change in systolic BP when the baseline systolic BP was <120 mmHg.[68] The impact of nicorandil (an initial bolus injection followed by continuous IV injection for 3 days) on longer term outcomes was assessed in patients ($n = 408$) hospitalized for ADHF.[69] Over a follow-up period of 180 days, death or hospitalization for HF (co-primary endpoint) was significantly less likely to occur in patients who received nicorandil compared with patients who did not.[69] A meta-analysis of 20 nicorandil studies in patients with chronic HF or ADHF ($n = 1222$) further underlined the potential therapeutic effects of nicorandil in these patient populations.[70]

If-channel inhibitors

Ivabradine, the first sinus node inhibitor to be marketed, inhibits the I*f*-channel to reduce heart rate, and was initially investigated and approved for the treatment of chronic stable angina.[71] In the Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial (SHIFT) in patients with symptomatic HFrEF (LVEF ≤35%), in sinus rhythm, with a heart rate ≥70 beats per minute (b.p.m.), who were hospitalized for HF within 12 months and receiving evidence-based therapies, ivabradine treatment was associated with a reduction in the combined endpoint of CV mortality and hospitalization for worsening HF.[72] Subsequently, ivabradine was approved by the European Medicines Agency for the treatment of patients with HFrEF (LVEF ≤ 35%), in sinus rhythm, with a resting heart rate ≥75 b.p.m.[1,73] The United States Food and Drug Administration approved ivabradine for the treatment of patients with stable HF, with a resting heart rate ≥70 b.p.m. who are receiving maximum tolerated doses of beta-blockers.[74]

The role of ivabradine in the treatment of patients with ADHF is unclear; however, in a recently published retrospective analysis of patients hospitalized with ADHF ($n = 29$), ivabradine treatment resulted in a reduction in heart rate, without incidence of bradycardia or hypotension.[75] Ivabradine may therefore represent a useful treatment to reduce heart rate, while maintaining BP, in patients with ADHF, although randomized trials are needed to characterize the efficacy and safety of ivabradine treatment in larger numbers of patients.[75]

Central role of biomarkers in acute heart failure management

The identification of physiological or biochemical surrogate markers that can be used for guiding management, as well as determining the effects of treatment on them, is a key area of research.[76,77] Biomarkers should meet a number of criteria, including high sensitivity (e.g. diagnosis) and specificity (e.g. when assessing treatment response). In addition, biomarkers should ideally be indicative of abnormal physiology or biochemistry, correlate with prognosis, and be used to guide treatment.[77] As such, effective biomarkers may potentially allow personalization of ADHF treatment based on the probability of response to specific therapies.[77]

The usefulness of natriuretic peptides, such as BNP and NT-proBNP, in establishing the diagnosis and prognosis of HF has been widely studied,[76,78-81] leading to their inclusion in current HF guidelines.[1] A *post-hoc* analysis of data from RELAX-AHF clearly showed that substantial increases in biomarkers of liver and kidney dysfunction from baseline to Day 2 were associated with increased risk of all-cause mortality at Day 180.[13] Recent evidence supports a role for the use of additional biomarkers, including troponins, soluble neprilysin, soluble ST2, galectin, cystatin-C and procalcitonin in the management of ADHF and assessment of organ function (*Table 1*).[76,79,82-86] Furthermore, preliminary studies indicate that mid-regional pro-atrial natriuretic peptide and D-dimer may be of diagnostic and prognostic value in patients with ADHF.[87,88] Like NT-proBNP, the inclusion of additional biomarkers in future HF guidelines will depend on the quality of clinical evidence generated from multiple studies; however, in the future, it is likely that physicians will use a variety of biomarkers to

Table 1 The value of individual biomarkers in the diagnosis, stratification and guided management of acutely decompensated heart failure[77,79,80]

Biomarker	Diagnostic capability	Risk stratification	Biomarker-guided treatment
Natriuretic peptides	+++[a]	+++	+++
Hs-troponins	+++[a]	+++	+++
ST2	++[a]	+++	+++
sNEP	-	++	-
Procalcitonin	+++[b]	+++	++
NGAL	++[c]	++	++
Cystatin C	+++[c]	++	+
MR-proADM	-	+++	+
Copeptin	-	+++	++

Hs-troponins, high-sensitivity troponins; sNEP, soluble neprilysin; NGAL, Neutrophil gelatinase-associated lipocalin; MR-proADM, Mid-regional pro Adrenomedullin.
[a]Heart failure.
[b]Pulmonary infection.
[c]Acute kidney injury.

aid diagnosis, assess organ damage and dysfunction, and guide treatment in patients with ADHF.

Overall conclusions and summary

Current therapies for ADHF effectively relieve the presenting signs and symptoms of systemic and pulmonary congestion, thus stabilizing the patient; however, they have minimal impact on the underlying organ damage and long-term clinical outcomes associated with ADHF. New therapeutic strategies that address the acute symptoms of HF, prevent damage to multiple organs and thus, target both short- and long-term treatment goals are urgently needed. Furthermore, the successful implementation of improved biomarkers alongside new therapies in daily clinical practice has the potential to transform the way physicians diagnose and manage patients admitted to hospital with ADHF. Data from recent clinical trials highlights the promise of several novel therapeutic approaches for the treatment of ADHF; however, further adequately designed studies are required to fully demonstrate the safety and efficacy of these treatments in larger patient populations. Continued and significant investment into the research and development of new therapies is necessary to realize the full potential of these novel treatments and to tackle the rapidly growing global ADHF pandemic.

Acknowledgements

The authors were assisted in the preparation and editorial content of the manuscript by Derek Lavery (CircleScience, an Ashfield company, part of UDG Healthcare plc), a service that was funded by Novartis Pharma AG, Basel, Switzerland. The authors designed, jointly reviewed and revised the initial draft and subsequent versions of the manuscript, and both agreed on the final version submitted for publication.

Funding

The EHJ Supplement, containing this article, and Open Access to readers was sponsored by Novartis Pharma AG, Basel, Switzerland. The sponsor reviewed the drafts of the manuscript for proprietary evaluation and own study data accuracy.

Conflicts of interest: J.D. has served as an advisor and as a speaker for Novartis, Merck Sharp and Dohme, Abbvie and Bayer. A.B-G. has served as an advisor and speaker for Novartis, Roche Diagnostics, and Critical Diagnostics.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**18**:891–975.
2. Hsiao R, Greenberg B. Contemporary Treatment of Acute Heart Failure. *Prog Cardiovasc Dis* 2016;**58**:367–378.
3. Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, López-Sendón J. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Failure* 2014;**1**:110–145.
4. Díez J, Ruilope LM. Serelaxin for the treatment of acute heart failure: a review with a focus on end-organ protection. *Eur Heart J* 2016;**2**:119–130.
5. Pang PS, Komajda M, Gheorghiade M. The current and future management of acute heart failure syndromes. *Eur Heart J* 2010;**31**:784–793.
6. McDonagh TA, Komajda M, Maggioni AP, Zannad F, Gheorghiade M, Metra M, Dargie HJ. Clinical trials in acute heart failure: simpler solutions to complex problems. Consensus document arising from a European Society of Cardiology cardiovascular round-table think tank on acute heart failure, 12 May 2009. *Eur J Heart Fail* 2011;**13**:1253–1260.
7. Bathgate RA, Halls ML, van der Westhuizen ET, Callander GE, Kocan M, Summers RJ. Relaxin family peptides and their receptors. *Physiol Rev* 2013;**93**:405–480.
8. Díez J. Serelaxin: A novel therapy for acute heart failure with a range of hemodynamic and non-hemodynamic actions. *Am J Cardiovasc Drugs* 2014;**14**:275–285.
9. Leo CH, Jelinic M, Ng HH, Tare M, Parry LJ. Serelaxin: A Novel Therapeutic for Vascular Diseases. *Trends Pharmacol Sci* 2016;**37**:498–507.
10. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF, Jr., Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;**381**:29–39.
11. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, Marmor A, Katz A, Grzybowski J, Unemori E, Teichman SL, Cotter G. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009;**373**:1429–1439.
12. Ponikowski P, Metra M, Teerlink JR, Unemori E, Felker GM, Voors AA, Filippatos G, Greenberg B, Teichman SL, Severin T, Mueller-Velten G, Cotter G, Davison BA. Design of the RELAXin in acute heart failure study. *Am Heart J* 2012;**163**:149–155.
13. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF, Jr., Dorobantu MI,

Grinfeld L, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Prescott MF, Edwards C, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol* 2013;**61**:196–206.
14. Liu LC, Voors AA, Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Chen Y, Greenberg BH, Ponikowski P, Pang PS, Prescott MF, Hua T, Severin TM, Metra M. Effects of serelaxin in acute heart failure patients with renal impairment: results from RELAX-AHF. *Clin Res Cardiol* 2016;**105**:727–737.
15. Filippatos G, Teerlink JR, Farmakis D, Cotter G, Davison BA, Felker GM, Greenberg BH, Hua T, Ponikowski P, Severin T, Unemori E, Voors AA, Metra M. Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial. *Eur Heart J* 2014;**35**:1041–1050.
16. Metra M, Ponikowski P, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Hua TA, Severin T, Unemori E, Voors AA, Teerlink JR. Effects of serelaxin in subgroups of patients with acute heart failure: results from RELAX-AHF. *Eur Heart J* 2013;**34**:3128–3136.
17. Clinicaltrials.gov. NCT02064868. Effect of serelaxin versus standard of care in acute heart failure (AHF) patients (RELAX-AHF-EU). https://clinicaltrials.gov/ct2/show/NCT02064868?term=NCT02064868&rank=1. (29 September 2016).
18. Clinicaltrials.gov. NCT02007720. Efficacy, safety and tolerability of serelaxin when added to standard therapy in AHF (RELAX-AHF-ASIA). https://clinicaltrials.gov/ct2/show/NCT02007720?term=NCT02007720&rank=1. (29 September 2016).
19. Clinicaltrials.gov. NCT01870778. Efficacy, safety and tolerability of serelaxin when added to standard therapy in AHF (RELAX-AHF-2). https://clinicaltrials.gov/ct2/show/NCT01870778?term=NCT01870778&rank=1. (29 September 2016).
20. Singh A, Laribi S, Teerlink JR, Mebazaa A. Agents with vasodilator properties in acute heart failure. *Eur Heart J* 2016;Feb 4. pii: ehv755. [Epub ahead of print].
21. Volpe M, Carnovali M, Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clin Sci (Lond)* 2016;**130**:57–77.
22. Anker SD, Ponikowski P, Mitrovic V, Peacock WF, Filippatos G. Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies. *Eur Heart J* 2015;**36**:715–723.
23. Forssmann W, Meyer M, Forssmann K. The renal urodilatin system: clinical implications. *Cardiovasc Res* 2001;**51**:450–462.
24. Mitrovic V, Luss H, Nitsche K, Forssmann K, Maronde E, Fricke K, Forssmann WG, Meyer M. Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: a double-blind, placebo-controlled, ascending-dose trial. *Am Heart J* 2005;**150**:1239.
25. Mitrovic V, Seferovic PM, Simeunovic D, Ristic AD, Miric M, Moiseyev VS, Kobalava Z, Nitsche K, Forssmann WG, Luss H, Meyer M. Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006;**27**:2823–2832.
26. Luss H, Mitrovic V, Seferovic PM, Simeunovic D, Ristic AD, Moiseyev VS, Forssmann WG, Hamdy AM, Meyer M. Renal effects of ularitide in patients with decompensated heart failure. *Am Heart J* 2008;**155**:1012 e1011–1018.
27. Clinicaltrials.gov. NCT01661634. Efficacy and safety of ularitide for the treatment of acute decompensated heart failure (TRUE-AHF). https://clinicaltrials.gov/ct2/show/NCT01661634?term=NCT01661634&rank=1. (29 September 2016).
28. Dickey DM, Potter LR. Dendroaspis natriuretic peptide and the designer natriuretic peptide, CD-NP, are resistant to proteolytic inactivation. *J Mol Cell Cardiol* 2011;**51**:67–71.
29. Lisy O, Huntley BK, McCormick DJ, Kurlansky PA, Burnett JC. Jr., Design, synthesis, and actions of a novel chimeric natriuretic peptide: CD-NP. *J Am Coll Cardiol* 2008;**52**:60–68.
30. Martin FL, Sangaralingham SJ, Huntley BK, McKie PM, Ichiki T, Chen HH, Korinek J, Harders GE, Burnett JC. Jr., CD-NP: a novel engineered dual guanylyl cyclase activator with anti-fibrotic actions in the heart. *PLoS One* 2012;**7**:e52422.
31. Lee CY, Chen HH, Lisy O, Swan S, Cannon C, Lieu HD, Burnett JC. Jr., Pharmacodynamics of a novel designer natriuretic peptide, CD-NP, in a first-in-human clinical trial in healthy subjects. *J Clin Pharmacol* 2009;**49**:668–673.
32. Clinicaltrials.gov. NCT00839007. Study to Assess the Safety and Efficacy of CD-NP in the Treatment of Patients With Acute Decompensated Heart Failure. https://clinicaltrials.gov/ct2/show/NCT00839007?term=NCT00839007&rank=1 (29 September 2016).
33. Lieu HD, Young J, Elkayam U, Katz A, Darius H, Goldstein S, Massie B, Costello-Boerrigter LC, Burnett J. A Phase II, dose-ranging study with CD-NP, a chimeric natriuretic peptide, in acute decompensated heart failure patients with renal compromise. *J Am Coll Cardiol* 2011;**57**:(Abstract-E2029).
34. Nile Therapeutics Inc. press release, 'Nile Therapeutics announces positive interim data from Phase 2a study of CD-NP in patients with heart failure' issued on 14 October, 2008. http://www.biospace.com/News/nile-therapeutics-inc-announces-positive-interim/112859 (29 September 2016).
35. Clinicaltrials.gov. NCT00699712. Study to Assess Hemodynamic Effects, Safety and Tolerability of Chimeric Natriuretic Peptide (CD-NP) in Patients With Stabilized Acute Heart Failure (AHF) (PreCONDITION). https://clinicaltrials.gov/ct2/show/NCT00699712?term=NCT00699712&rank=1. (29 September 2016).
36. Garg V, Frishman WH. A new approach to inotropic therapy in the treatment of heart failure: cardiac myosin activators in treatment of HF. *Cardiol Rev* 2013;**21**:155–159.
37. Starling RC. Cardiac myosin activators for the treatment of heart failure: stop now or push ahead?. *J Am Coll Cardiol* 2016;**67**:1456–1458.
38. Malik FI, Hartman JJ, Elias KA, Morgan BP, Rodriguez H, Brejc K, Anderson RL, Sueoka SH, Lee KH, Finer JT, Sakowicz R, Baliga R, Cox DR, Garard M, Godinez G, Kawas R, Kraynack E, Lenzi D, Lu PP, Muci A, Niu C, Qian X, Pierce DW, Pokrovskii M, Suehiro I, Sylvester S, Tochimoto T, Valdez C, Wang W, Katori T, Kass DA, Shen YT, Vatner SF, Morgans DJ. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science* 2011;**331**:1439–1443.
39. Teerlink JR, Felker GM, McMurray JJ, Ponikowski P, Metra M, Filippatos GS, Ezekowitz JA, Dickstein K, Cleland JG, Kim JB, Lei L, Knusel B, Wolff AA, Malik FI, Wasserman SM. Investigators A-A. Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure: The ATOMIC-AHF Study. *J Am Coll Cardiol* 2016;**67**:1444–1455.
40. Pieske B, Butler J, Filippatos G, Lam C, Maggioni AP, Ponikowski P, Shah S, Solomon S, Kraigher-Krainer E, Samano ET, Scalise AV, Muller K, Roessig L, Gheorghiade M. Investigators S, Coordinators. Rationale and design of the SOluble guanylate Cyclase stimulatoR in heArT failurE Studies (SOCRATES). *Eur J Heart Fail* 2014;**16**:1026–1038.
41. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET, Muller K, Roessig L, Pieske B. Investigators S-R, Coordinators. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA* 2015;**314**:2251–2262.
42. Clinicaltrials.gov. NCT01951638. Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients With Heart Failure and Preserved Ejection Fraction Suffering From Worsening Chronic Heart Failure (SOCRATES-PRESERVED). https://clinicaltrials.gov/ct2/show/NCT01951638?term=NCT01951638&rank=1. (29 September 2016).
43. Erdmann E, Semigran MJ, Nieminen MS, Gheorghiade M, Agrawal R, Mitrovic V, Mebazaa A. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. *Eur Heart J* 2013;**34**:57–67.
44. Gheorghiade M, Greene SJ, Filippatos G, Erdmann E, Ferrari R, Levy PD, Maggioni A, Nowack C, Mebazaa A. Investigators C, Coordinators. Cinaciguat, a soluble guanylate cyclase activator: results from the randomized, controlled, phase IIb COMPOSE programme in acute heart failure syndromes. *Eur J Heart Fail* 2012;**14**:1056–1066.
45. Fragoso-Medina J, Zarain-Herzberg A. SERCA2a: its role in the development of heart failure and as a potential therapeutic target. *Res Rep Clin Cardiol* 2014;**5**:43–55.
46. Ferrandi M, Barassi P, Tadini-Buoninsegni F, Bartolommei G, Molinari I, Tripodi MG, Reina C, Moncelli MR, Bianchi G, Ferrari P. Istaroxime stimulates SERCA2a and accelerates calcium cycling in heart failure by relieving phospholamban inhibition. *Br J Pharmacol* 2013;**169**:1849–1861.

47. Shah SJ, Blair JE, Filippatos GS, Macarie C, Ruzyllo W, Korewicki J, Bubenek-Turconi SI, Ceracchi M, Bianchetti M, Carminati P, Kremastinos D, Grzybowski J, Valentini G, Sabbah HN, Gheorghiade M. Investigators H-H. Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: results from the Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) trial. *Am Heart J* 2009;**157**:1035–1041.
48. ClinicalTrials.gov. NCT02617446. The Clinical Study of the Safety and Efficacy of Istaroxime in Treatment of Acute Decompensated Heart Failure. https://clinicaltrials.gov/ct2/show/NCT02617446?term=NCT02617446&rank=1. (29 September 2016).
49. Jaski BE, Jessup ML, Mancini DM, Cappola TP, Pauly DF, Greenberg B, Borow K, Dittrich H, Zsebo KM, Hajjar RJ. Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease Trial I. Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID Trial), a first-in-human phase 1/2 clinical trial. *J Card Fail* 2009;**15**:171–181.
50. Jessup M, Greenberg B, Mancini D, Cappola T, Pauly DF, Jaski B, Yaroshinsky A, Zsebo KM, Dittrich H, Hajjar RJ. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease I. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID): a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. *Circulation* 2011;**124**:304–313.
51. Zsebo K, Yaroshinsky A, Rudy JJ, Wagner K, Greenberg B, Jessup M, Hajjar RJ. Long-term effects of AAV1/SERCA2a gene transfer in patients with severe heart failure: analysis of recurrent cardiovascular events and mortality. *Circ Res* 2014;**114**:101–108.
52. Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, Barnard D, Bouchard A, Jaski B, Lyon AR, Pogoda JM, Rudy JJ, Zsebo KM. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet* 2016;**387**:1178–1186.
53. Kho C, Lee A, Jeong D, Oh JG, Gorski PA, Fish K, Sanchez R, DeVita RJ, Christensen G, Dahl R, Hajjar RJ. Small-molecule activation of SERCA2a SUMOylation for the treatment of heart failure. *Nat Commun* 2015;**6**:7229.
54. Reiter E, Ahn S, Shukla AK, Lefkowitz RJ. Molecular mechanism of beta-arrestin-biased agonism at seven-transmembrane receptors. *Annu Rev Pharmacol Toxicol* 2012;**52**:179–197.
55. Zhai P, Yamamoto M, Galeotti J, Liu J, Masurekar M, Thaisz J, Irie K, Holle E, Yu X, Kupershmidt S, Roden DM, Wagner T, Yatani A, Vatner DE, Vatner SF, Sadoshima J. Cardiac-specific overexpression of AT1 receptor mutant lacking G alpha q/G alpha i coupling causes hypertrophy and bradycardia in transgenic mice. *J Clin Invest* 2005;**115**:3045–3056.
56. Boerrigter G, Lark MW, Whalen EJ, Soergel DG, Violin JD, Burnett JC. Jr., Cardiorenal actions of TRV120027, a novel ss-arrestin-biased ligand at the angiotensin II type I receptor, in healthy and heart failure canines: a novel therapeutic strategy for acute heart failure. *Circ Heart Fail* 2011;**4**:770–778.
57. Boerrigter G, Soergel DG, Violin JD, Lark MW, Burnett JC. Jr., TRV120027, a novel beta-arrestin biased ligand at the angiotensin II type I receptor, unloads the heart and maintains renal function when added to furosemide in experimental heart failure. *Circ Heart Fail* 2012;**5**:627–634.
58. Violin JD, DeWire SM, Yamashita D, Rominger DH, Nguyen L, Schiller K, Whalen EJ, Gowen M, Lark MW. Selectively engaging beta-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. *J Pharmacol Exp Ther* 2010;**335**:572–579.
59. Soergel D, Subach RA, James IE, Cowan CL, Gowen M, Lark M. TRV 027, a Beta-Arrestin Biased Ligand at the Angiotensin 2 Type 1 Receptor, Produces Rapid, Reversible Changes in Hemodynamics in Patients with St able Systolic Heart Failure. *J Am Coll Cardiol* 2013;**61**:(Abstract-E683).
60. Felker GM, Butler J, Collins SP, Cotter G, Davison BA, Ezekowitz JA, Filippatos G, Levy PD, Metra M, Ponikowski P, Soergel DG, Teerlink JR, Violin JD, Voors AA, Pang PS. Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor. Rationale and design of the BLAST-AHF study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). *JACC Heart Fail* 2015;**3**:193–201.
61. TRV027 development: Phase 2b proof of concept study in AHF. http://www.trevena.com/TRV027-development.php. (29 September 2016).
62. Sabbah HN, Tocchetti CG, Wang M, Daya S, Gupta RC, Tunin RS, Mazhari R, Takimoto E, Paolocci N, Cowart D, Colucci WS, Kass DA. Nitroxyl (HNO): A novel approach for the acute treatment of heart failure. *Circ Heart Fail* 2013;**6**:1250–1258.
63. Clinicaltrials.gov. NCT02157506 A Dose Ranging Phase IIa Study of 6 Hour Intravenous Dosages of CXL-1427 in Patients Hospitalized With Heart Failure. https://clinicaltrials.gov/ct2/show/NCT02157506?term=NCT02157506&rank=1 (29 September 2016).
64. Cowart D, Venuti R, Guptill J, Noveck R, Foo S. A Phase 1 Study of the Safety and Pharmacokinetics of the Intravenous Ni troxyl Prodrug, CXL -1427A876. *J Am Coll Cardiol* 2015;**65**:(Abstract-A876).
65. Gradman AH, Vivas Y. New therapeutic perspectives with clevidipine: an ultra-short-acting intravenous Ca2+ channel blocker. *Expert Opin Investig Drugs* 2007;**16**:1449–1457.
66. Peacock F, Varon J, Ebrahimi R, Dunbar L, Pollack CV. Jr., Clevidipine for severe hypertension in acute heart failure: a VELOCITY trial analysis. *Congest Heart Fail* 2010;**16**:55–59.
67. Peacock WF, Chandra A, Char D, Collins S, Der Sahakian G, Ding L, Dunbar L, Fermann G, Fonarow GC, Garrison N, Hu MY, Jourdain P, Laribi S, Levy P, Mockel M, Mueller C, Ray P, Singer A, Ventura H, Weiss M, Mebazaa A. Clevidipine in acute heart failure: Results of the A Study of Blood Pressure Control in Acute Heart Failure-A Pilot Study (PRONTO). *Am Heart J* 2014;**167**:529–536.
68. Tanaka K, Kato K, Takano T, Katagiri T, Asanoi H, Nejima J, Nakashima M, Kamijo T, Sakanashi M. Acute effects of intravenous nicorandil on hemodynamics in patients hospitalized with acute decompensated heart failure. *J Cardiol* 2010;**56**:291–299.
69. Ishihara S, Koga T, Kaseda S, Nyuta E, Haga Y, Fujishima S, Ishitsuka T, Sadoshima S. Effects of intravenous nicorandil on the mid-term prognosis of patients with acute heart failure syndrome. *Circ J* 2012;**76**:1169–1176.
70. Zhao F, Chaugai S, Chen P, Wang Y, Wang DW. Effect of nicorandil in patients with heart failure: a systematic review and meta-analysis. *Cardiovasc Ther* 2014;**32**:283–296.
71. Doig C. Ivabradne: first of a new class of treatments for angina. *Prescriber* 2006;**15**:14–17.
72. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
73. European Medicines Agency. Procoralan (ivabradine) Summary of Product Characteristics. July 6, 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000597/WC500043590.pdf Accessed 16 August 2016 (29 September 2016).
74. FDA. FDA approves Corlanor to treat heart failure. FDA, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm442978.htm (29 September 2016).
75. Pascual Izco M, Alonso Salinas GL, Sanmartín Fernández M, Del Castillo Carnevalli H, Jiménez Mena M, Camino López A, Zamorano Gómez JL. Clinical Experience with Ivabradine in Acute Heart Failure. *Cardiology* 2016;**134**:372–374.
76. Cohen-Solal A, Laribi S, Ishihara S, Vergaro G, Baudet M, Logeart D, Mebazaa A, Gayat E, Vodovar N, Pascual-Figal DA, Seronde MF. Prognostic markers of acute decompensated heart failure: the emerging roles of cardiac biomarkers and prognostic scores. *Arch Cardiovasc Dis* 2015;**108**:64–74.
77. Maisel A. Biomonitoring and biomarker-guided therapy: the next step in heart failure and biomarker research. *J Am Coll Cardiol* 2011;**58**:1890–1892.
78. Felker GM, Hasselblad V, Hernandez AF, O'connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. *Am Heart J* 2009;**158**:422–430.
79. Gaggin HK, Januzzi JL. Jr., Biomarkers and diagnostics in heart failure. *Biochimica Et Biophysica Acta* 2013;**1832**:2442–2450.
80. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure:

an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006;**27**:330–337.
81. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ, Mant J. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ* 2015;**350**:h910.
82. Bayes-Genis A, Barallat J, Pascual-Figal D, Nunez J, Minana G, Sanchez-Mas J, Galan A, Sanchis J, Zamora E, Perez-Martinez MT, Lupon J. Prognostic value and kinetics of soluble Neprilysin in acute heart failure: a pilot study. *JACC Heart Fail* 2015;**3**:641–644.
83. Choudhary R, Gopal D, Kipper BA, De La Parra Landa A, Aramin H, Lee E, Shah S, Maisel AS. Cardiorenal biomarkers in acute heart failure. *J Geriatr Cardiol* 2012;**9**:292–304.
84. Llibre C, Zamora E, Caballero A, Lupon J, Ros A, Benito N, de Antonio M, Galan A, Domingo M, Bayes-Genis A. The real-life value of ST2 monitoring during heart failure decompensation: impact on long-term readmission and mortality. *Biomarkers* 2016;**21**:225–232.
85. Maisel AS, Choudhary R. Biomarkers in acute heart failure-state of the art. *Nat Rev Cardiol* 2012;**9**:478–490.
86. Pang PS, Teerlink JR, Voors AA, Ponikowski P, Greenberg BH, Filippatos G, Felker GM, Davison BA, Cotter G, Kriger J, Prescott MF, Hua TA, Severin T, Metra M. Use of high-sensitivity Troponin T to identify patients with acute heart failure at lower risk for adverse outcomes: an exploratory analysis from the RELAX-AHF trial. *JACC Heart Fail* 2016;**4**:591–599.
87. Minami Y, Haruki S, Jujo K, Itani R, Shimazaki K, Arashi H, Watanabe E, Hagiwara N. Elevated D-dimer levels predict an adverse outcome in hospitalized patients with acute decompensated heart failure. *Int J Cardiol* 2016;**204**:42–44.
88. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. *J Am Coll Cardiol* 2010;**55**:2062–2076.