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REVIEW

Novel therapeutic concepts

Agents with vasodilator properties in acute heart failure

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Millions of patients worldwide are admitted for acute heart failure (AHF) each year and physicians caring for these patients are confronted with the short-term challenges of reducing symptoms while preventing end organ dysfunction without causing additional harm, and the intermediate-term challenges of improving clinical outcomes such as hospital readmission and survival. There are limited data demonstrating the efficacy of any currently available therapies for AHF to meet these goals. After diuretics, vasodilators are the most common intravenous therapy for AHF, but neither nitrates, nitroprusside, nor nesiritide have robust evidence supporting their ability to provide meaningful effects on clinical outcomes, except perhaps early symptom improvement. Recently, a number of novel agents with vasodilating properties have been developed for the treatment of AHF. These agents include serelaxin, natriuretic peptides (ularitide, cenderitide), β-arrestin-biased angiotensin II type 1 receptor ligands (TRV120027), nitroxyl donors (CXL-1020, CXL-1427), soluble guanylate cyclase modulators (cinaciguat, vericiguat), short-acting calcium channel blockers (clevidipine), and potassium channel activators (nicorandil). These development programmes range from the stage of early dose-finding studies (e.g. TRV120027, CXL-1427) to large, multicentre mortality trials (e.g. serelaxin, ularitide). There is an urgent need for agents with vasodilating properties that will improve both in-hospital and post-discharge clinical outcomes, and these novel approaches may provide opportunities to address this need.

Keywords Acute heart failure • Vasodilators • Clinical trials • Outcomes • Haemodynamics

Introduction

Acute heart failure (AHF) may be defined as the new onset or recurrence of symptoms and signs of heart failure (HF) requiring urgent or emergent therapy. Despite the word 'acute,' many patients may have a more sub-acute course, with gradual worsening of symptoms that ultimately reach a level of severity sufficient to seek unscheduled medical care. These events can occur in patients with a known history of HF (either with reduced or preserved left ventricular systolic function) or *de novo* in patients with no prior history of HF. Physicians caring for patients with AHF are confronted with the short-term challenges of reducing symptoms, predominantly dyspnoea, and preventing end organ dysfunction without causing harm, and the intermediate-term challenge of improving clinical outcomes such as hospital readmission and survival. Unfortunately, there are limited data demonstrating the efficacy of any currently available therapies to meet these goals, except perhaps early symptom improvement. Several observational studies show that >85% of patients with AHF receive intravenous diuretics, regardless of the continents on which they receive care.[1] The second most commonly used agents for AHF are intravenous vasodilators. While the term vasodilator encompasses a class of agents, it is clear that there may be important distinctions between the traditional direct-acting vasodilators, such as nitroglycerin and nitroprusside, and those that work through receptor-based mechanisms, such as natriuretic, relaxin, angiotensin or other receptors, or have alternative mechanisms of action, such as nitroxyl. This review will describe data on current vasodilators and ongoing trials of promising agents with vasodilator properties in AHF with the exclusion of cardiogenic shock. However, this review will not discuss inodilators, such as phosphodiesterase inhibitors or levosimendan, as they combine inotropic effects with vasodilator properties, or prostacyclins which have been shown to be associated with increased mortality.[2]

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Current vasodilators

Data from registries such as the Acutely Decompensated Heart Failure National Registry (ADHERE)[3] and Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF)[4] have shown that traditional vasodilators, especially nitrates, are the second most frequently given class of medication after diuretics in AHF patients (*Table 1*).[5–12] Depending on surveys, nitrates are used in 9–51.3% of studied population in patients admitted for AHF.[4] Of note, the use of vasodilators exhibits substantial geographic variation and appears less prominent in AHF management in North America compared with other regions. Despite the importance of such observational studies, one of their main limitations is that most of the published registries have been performed in Western countries, thus not representing the global population. Furthermore, the use of these agents is still based on limited evidence, generally from small, single centre studies focused on their acute haemodynamic effects. Interestingly, those observational studies show that the main indication of vasodilators is AHF associated with high blood pressure at presentation.[1]

Nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and sodium nitroprusside) had long been considered first-line agents for acute hypertensive HF. As a class, these drugs act by providing an exogenous source of nitric oxide (NO) which binds to soluble guanylate cyclase (sGC), producing cyclic GMP and vascular smooth muscle relaxation. At low doses, this effect occurs predominantly in the venous circulation, resulting in increased capacitance and a marked reduction in systemic preload, as well as venous back pressure on the kidney and other perfused organs. Nitrates may also modulate effects of vasocontrictive hormones released during AHF crisis on venous beds. At higher doses (≥150–250 μg/min), nitrates dilate arteries, including those from the coronary vasculature.

Randomized controlled trial evidence comparing clinical outcomes of traditional vasodilators, especially nitrates, in AHF patients is limited and of relatively low methodological quality. A study in patients with severe pulmonary oedema suggested that high-dose intravenous nitrates reduced the need for mechanical ventilation and may have decreased myocardial infarctions,[13] while a pilot study of non-invasive high-dose nitrate administration in patients with AHF suggested a more rapid decrease in B-type natriuretic peptide (BNP) and a trend to fewer ICU admissions, but no difference in other outcomes.[14] However, an extensive review on vasodilator use in AHF patients by the Cochrane library only identified four randomized controlled trials comparing nitrates (isosorbide dinitrate and nitroglycerin) with alternative interventions over the last decades in adult population.[15] Two of the four studies only included patients with AHF following acute myocardial infarction. Authors of this review conclude that they found no evidence to support a difference in the rapidity of symptom relief between intravenous nitrates and alternative interventions in patients with AHF. This review also found no evidence to support a difference in AHF patients receiving intravenous nitrates or alternative interventions with regard to the following outcome measures: requirement for mechanical ventilation, progression to MI, or change in systolic or diastolic blood pressure (SBP), heart rate, pulmonary capillary wedge pressure (PCWP), and cardiac output. These findings are consistent with the neutral effect of vasodilators on mortality in a *post hoc* analysis of ESCAPE trial.[16]

A more recent systematic review of treatment with intravenous nitrovasodilators used in emergency department (ED) and ED-like settings suggested that they do improve short-term symptoms and appear safe to administer, but no evidence for longer-term outcomes.[17] The Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation Study (GALACTIC; NCT00512759) is a 770 patient trial testing the hypothesis that early treatment to a target SBP of 90–110 mmHg by aggressive vasodilatation in patients with AHF is safe, and improves clinical and healthcare economic outcomes.

Nesiritide is a recombinant form of human BNP that acts as a balanced arterial and venous vasodilator when infused intravenously.

Table 1 Current management of acute heart failure

	Publication year	Diuretics	Nitrates	Inotropes	NIV
ADHERE	2005	92	9	15	NA
EFICA	2006	87	50	53	24
OPTIMIZE-HF	2008	NA	NA	15	NA
EHFS II	2010	84.4	38.7	29.8	8.8
ESC-HF pilot	2010	84.6	18.5	10.5	NA
RO-AHFS	2011	79.9	33.4	17.7	NA
AHEAD	2011	88.9	24.5	10.6	NA
ATTEND	2011	76.3	44.9	18.5	24.4
ALARM-HF	2011	89.7	41.1	39	9.6
HEARTS	2011	89	27.8	30.1	NA
Korean HF registry	2011	68.1	35.8	21.7	NA
Sub-Saharan Africa Survey	2012	92.9	7.9	5	NA
Italian survey on acute heart	2012	95.3	51.3	24.6	NA

Values are expressed as the per cent of patients of the survey who received the treatment during hospital management.
NIV, non-invasive ventilation; NA, not applicable.

Nesiritide was the first potential challenger to nitrates to be developed and had been subject to extensive study before and after its approval in the United States in 2001. VMAC, the first large nesiritide study, showed a greater reduction of filling pressure with nesiritide vs. nitrates and improvements in early dyspnoea relief compared with placebo, but there were some concerns regarding safety.[18] Research involving nesiritide culminated in 2011 with publication of results from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), the largest investigation of AHF treatment that compared nesiritide ($n = 3496$) with placebo ($n = 3511$) in a prospective, randomized trial.[19] Median time to patient randomization was relatively short in both arms (~15 h). Patients treated with nesiritide experienced a modest improvement in self-reported dyspnoea at 6 and 24 h; however, this improvement did not meet the pre-specified statistical significance and it was not considered clinically meaningful. Moreover, there was no difference in the co-primary end-point of 30-day mortality or rehospitalization (9.4 vs. 10.1%; $P = 0.31$) with equivalent rates of renal impairment through 30 days (31.4 vs. 29.5%; $P = 0.11$), signifying that nesiritide is safe but lacking in clinical efficacy. Of note, mean BP was not particularly high in either group (123 mmHg for nesiritide, 124 mmHg for placebo) suggesting that perhaps the wrong patient population (i.e. one for whom afterload was not a major component of the acute pathophysiology) was targeted for the trial.

Although levels of evidence for most of the medications used in patients with AHF are poor, many national and international guidelines recommend the use of nitrates in certain circumstances (*Table 2*). The 2012 European Society of Cardiology (ESC) guidelines on HF state that intravenous infusion of a nitrate should be considered in patients with pulmonary congestion/oedema and a SBP over 110 mmHg, who do not have severe mitral or aortic stenosis, to reduce PCWP and systemic vascular resistance (SVR). European Society of Cardiology guidelines also advise that symptoms and blood pressure should be monitored frequently during administration of intravenous nitrates.[20] The 2013 ACCF/AHA guidelines on HF management state that intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as adjuvant to diuretic therapy for relief of dyspnoea in hospitalized HF patients, if symptomatic hypotension is absent (class of recommendation, IIb; level of evidence A).[21] In a more recent, exhaustive review of the evidence base for AHF management by the National Institute for Health and Care Excellence of the UK,[22] the specific recommendations regarding current vasodilators are: (i) do not routinely offer nitrates to people with AHF and (ii) do not offer sodium nitroprusside to people with AHF. These recommendations reflect the poor evidence base for existing vasodilators. The recognition of the need to target therapies to specific pathophysiologic profiles has led to the development of new vasodilator agents in recent years.

Table 2 Class of recommendation and levels of evidence for selected treatments for patients with acute heart failure without cardiogenic shock

	Class of recommendation, level of evidence	
	ESC (2012)[20]	ACC/AHA (2013)[21]
Diuretics for fluid overload	I,B	I,B
Intravenous nitrates for dyspnoea relief	IIa,B	IIb,A
Inotropes	III,C	III,B
Non-invasive ventilation	IIa,B	NA

NA, not applicable, if the topic was not addressed. European Society of Cardiology definitions of class of recommendation: I = evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; IIa = weight of evidence/opinion is in favour of usefulness/efficacy; III = evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. European Society of Cardiology definitions of level of evidence: A = data derived from multiple randomized clinical trials or meta-analyses; B = data derived from a single randomized clinical trial or large non-randomized studies; C = consensus of opinion of the experts and/or small studies, retrospective studies, and registries. American College of Cardiology/American Heart Association (ACC/AHA) definitions of class of recommendation and level of evidence: I, B = recommendation that procedure or treatment is useful/effective and evidence from single randomized trial or non-randomized studies; IIb,A = recommendation's usefulness/efficacy less well established and greater conflicting evidence from multiple randomized trials or meta-analyses; III,B = recommendations that procedure or treatment is not useful/effective and may be harmful and evidence from single randomized trial or non-randomized studies.

New agents with vasodilator properties

Serelaxin

Serelaxin is a recombinant form of human relaxin-2. Relaxin[23,24] is a 53 amino acid peptide that shares structural similarities with insulin, including the removal of a C-peptide to yield a two-chain molecule with conserved disulfide bonds, and is believed to play a central role in the cardiovascular and renal adaptations to pregnancy in humans. Relaxin binding to the G-protein-coupled receptor RXFP1, previously known as LGR7, in the myocardium, renal, and systemic vasculature leads to downstream effects on NO via cAMP, endothelin type B receptor and subsequent NO production via upregulation of matrix metalloproteinases, atrial natriuretic peptide, and vascular endothelial growth factor. Relaxin also has antifibrotic properties through its regulation of fibroblast collagen synthesis and effect on matrix metalloproteinase. Finally, relaxin decreases SVR and increases arterial compliance. Due to these properties, relaxin gained interest as a potential therapeutic in AHF.[25]

Favourable early clinical studies supported a potential role of serelaxin in patients with AHF.[26] The dose-finding study, Pre-RELAX-AHF,[27] enrolled 234 patients admitted with AHF, dyspnoea with minimal exertion or at rest, normal-to-elevated SBP (SBP > 125 mmHg), and mild-to-moderate renal dysfunction and randomized within 16 h to a 48 h intravenous infusion of either serelaxin (10, 30, 100, or 250 mcg/kg/day) or placebo. This Phase II study suggested that patients receiving the 30 mcg/kg/day dose of serelaxin had improvements in dyspnoea, signs and symptoms of congestion, worsening HF and perhaps even survival, and consequently, this dose was selected for further study.

The RELAX-AHF trial was a Phase III, multicentre, double-blind, placebo-controlled trial that randomized 1161 patients with a mean age of 72 years with almost a 50:50 mix of patients with left ventricular ejection fraction (LVEF) <40% and >40% to serelaxin 30 μg/kg/day vs. placebo for 48 h continuous infusion. Patients admitted for AHF were enrolled within 16 h of presentation if they had a SBP > 125 mmHg, renal dysfunction, and elevated BNP.[28] A primary end-point that solely assessed early dyspnoea relief in the first 24 h by Likert scale was not statistically improved by serelaxin. However, serelaxin significantly improved the other primary end-point of dyspnoea relief from baseline to Day 5 on the VAS as compared with placebo ($P = 0.007$) driven predominantly by a nearly 50% reduction in in-hospital worsening of HF. Hospital length of stay was decreased by 0.9 days in the treatment group ($P = 0.04$), although there was no decrease in hospital readmission rates through Day 60. The serelaxin treated group had a statistically significant decline in cardiovascular death (HR = 0.63, 95% CI 0.41–0.96; $P = 0.028$) and all-cause mortality (HR = 0.63, 95% CI 0.42–0.93; $P = 0.02$) at 180 days compared with placebo. More patients treated with serelaxin required study-drug dose adjustment due to protocol-defined blood pressure rules (29 vs. 18%, $P < 0.0001$), with most episodes resolving spontaneously.

In a subsequent analysis of biomarkers from the RELAX-AHF trial, serelaxin reduced markers indicative of cardiac (cardiac troponin T), renal (creatinine and cystatin-C), and hepatic (aspartate transaminase and alanine transaminase) damage or dysfunction, as well as NT-pro-BNP.[29] Another analysis noted that there were similar clinical benefits of serelaxin among multiple subgroups in RELAX-AHF.[30] One specific subgroup analysis of the patients with HFpEF (LVEF > 50%), present in 26% of patients in RELAX-AHF, showed similar results as the combined study,[31] providing some of the first evidence-based benefit in HFpEF patients admitted for AHF. Small randomized studies have demonstrated serelaxin's beneficial systemic and pulmonary haemodynamic effects,[32] as well as improvements in renal haemodynamics in patients with HF.[33] The RELAX-AHF trial, its subgroup analyses, and these haemodynamic studies provide compelling evidence for a new treatment option in patients with preserved blood pressure and AHF.

The potential improvement in survival with serelaxin treatment seen in Pre-RELAX and RELAX-AHF is being tested in a second Phase III trial, RELAX-AHF-2 (NCT01870778; *Table 3*). This trial is randomizing ~6800 patients who were admitted to hospital requiring IV therapy for AHF with normal to elevated SBP (≥125 mmHg) to a 48-h infusion of either serelaxin or placebo, both in addition to

Table 3 Selected on-going trials of novel agents with vasodilating properties

Trial (clinicaltrials.gov registration)	Projected sample size	Treatment groups	Patient population	Primary endpoint(s)	Estimated projected completion
RELAX-AHF-2 (NCT01870778)	6800	Serelaxin 30 mcg/kg/day × 48 h Placebo × 48 h	Aged 18–85 years Admitted for ADHF Dyspnoea at rest or minimal exertion SBP ≥ 125 and ≤ 180 mmHg Randomized within 16 h	CV death through 180 days Worsening HF through 5 days	August 2016
RELAX-AHF-ASIA (NCT02007720)	1520	Serelaxin 30 mcg/kg/day × 48 h Placebo × 48 h	Aged 18–85 years Admitted for AHF Dyspnoea at rest or minimal exertion SBP ≥ 125 and ≤ 180 mmHg Renal impairment (eGFR 25–75 mL/min/1.73 m^2). Randomized within 16 h	Trichotomous clinical composite end-point of treatment success, treatment failure, or no change through 5 days	September 2016
TRUE-AHF (NCT01661634)	2152	Ularitide 15 ng/kg/min × 48 h Placebo × 48 h	Aged 18–85 years Admitted for AHF Dyspnoea at rest SBP ≥ 116 and ≤ 180 mmHg Randomized within 12 h	Hierarchical clinical composite at 48 h CV mortality through duration of trial	October 2015
BLAST-AHF (NCT01966601)	500	TRV027 1 mg/h × 48–96 h TRV027 5 mg/h × 48–96 h TRV027 25 mg/h × 48–96 h Placebo × 48–96 h	Aged 21–85 years History of HF Admitted for AHF Dyspnoea at rest or minimal exertion SBP ≥ 120 and ≤ 200 mmHg Randomized within 16 h	Composite *Z* score of: (1) Death through Day 30 (2) HF re-hospitalization through Day 30 (3) Worsening HF through Day 5 (4) Change in dyspnoea VAS AUC score from baseline through Day 5 (5) Length of initial hospital stay	June 2016

standard therapy. The co-primary endpoints of RELAX-AHF-2 are cardiovascular mortality at 180 days and worsening of HF within 5 days. A third Phase III trial, RELAX-AHF-ASIA (NCT02007720) will enrol ~1520 patients with similar criteria to RELAX-AHF-2 from at least 8 Asian countries, and randomizing them to a 48-h infusion of either serelaxin or placebo, both in addition to standard therapy. The primary end-point for RELAX-AHF-ASIA is a trichotomous clinical composite end-point of treatment success, treatment failure, or no change, evaluated through 5 days after randomization. In addition, RELAX-REPEAT (NCT01982292) will assess the safety of repeat doses of serelaxin in ~300 patients with chronic HF, while markers of efficacy will also be collected as exploratory measures.

The natriuretic peptide system

The natriuretic peptide hormone family includes atrial (ANP), brain or b-type (BNP), C-type (CNP), D-type (DNP) natriuretic peptides, and urodilatin. ANP and BNP are primarily synthesized and secreted in the atria and ventricles, respectively, in response to wall stress, while CNP is produced in vascular endothelial cells.[34] D-type natriuretic peptide was first isolated from the venom of the green mamba snake and has not been found in human DNA. There are three main natriuretic peptide receptors (NPR), NPR-A, NPR-B, and NPR-C (*Figure 1*). NPR-A is primarily located on the endothelial surface of large vessels, kidneys, and adrenal glands, while NPR-B is located in vascular smooth muscle cells and the brain. In contrast, NPR-C serves as a clearance receptor to remove natriuretic peptides from circulation. The physiological effect of activation of the NPRs is shown in *Figure 1*. Plasma concentrations of BNP are elevated in AHF, and initially may serve to counteract the adverse effects of vasoconstrictive neurohormones. However, down-regulation and/or desensitization of the NPRs leads to decreased beneficial effect, which make them an attractive target for pharmacologic therapy.[35] Two of the novel natriuretic peptides

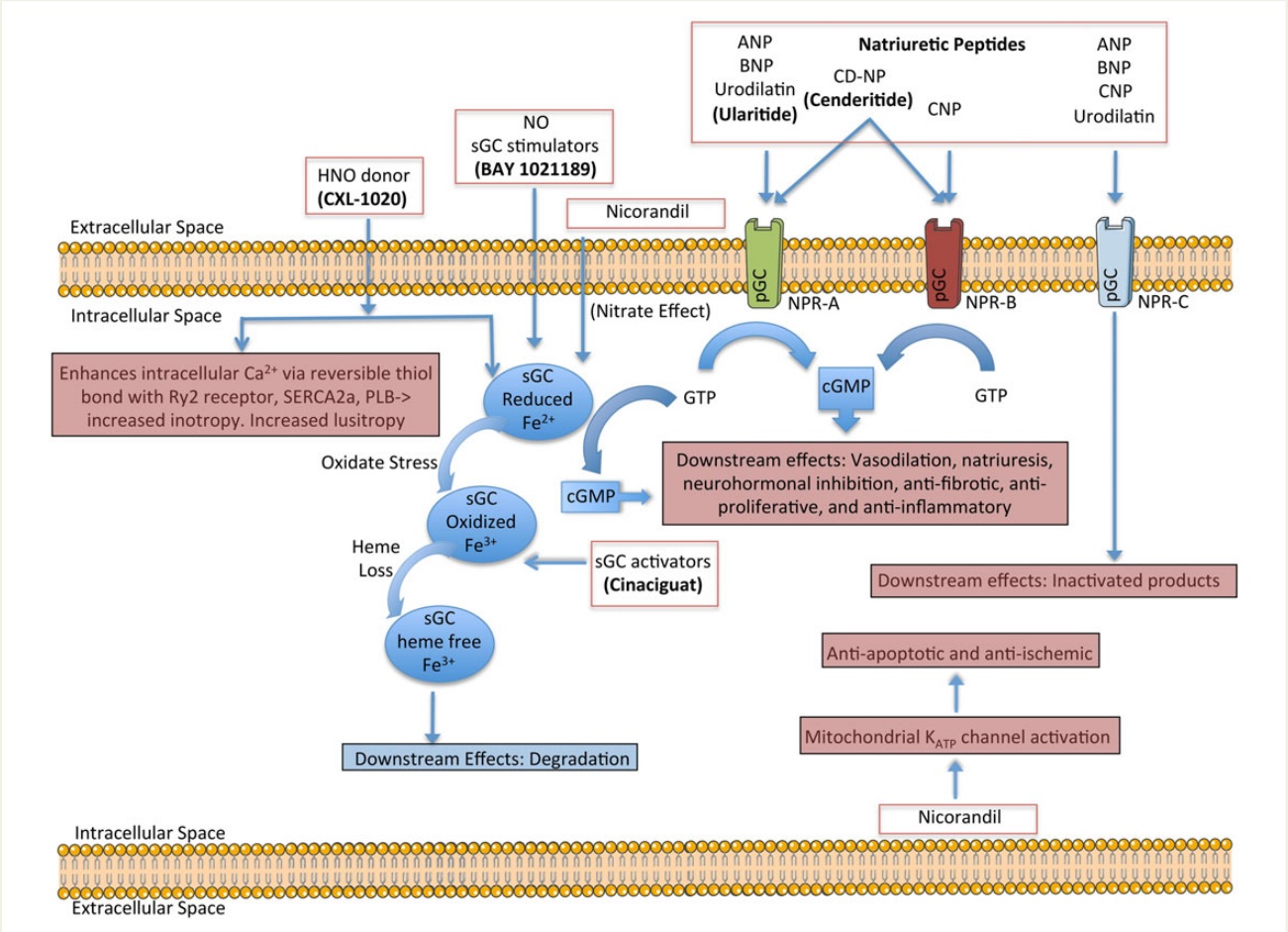

Figure 1 Schematic of mechanisms of action of some agents with vasodilating properties (1). All of these agents also have significant vasodilating effects. soluble guanylate cyclase is a heterodimer of an α- and a heme-containing β-subunit. The heme moiety of soluble guanylate cyclase exists in three forms: a reduced (Fe^{2+})-heme bound form, an oxidized (Fe^{3+})-heme bound form, and an oxidized (Fe^{3+})-heme-free form. NO can only induce soluble guanylate cyclase upon binding to its reduced form. In the oxidized state, the affinity for the heme prosthetic group is markedly reduced, increasing the probability of loss of the heme group. Its loss makes the enzyme insensitive to endogenous or exogenous NO, e.g. nitrates. Oxidative stress and subsequent generation of reactive oxygen species in cardiovascular disease and heart failure lead to decreased bioavailability of NO and oxidation of the soluble guanylate cyclase heme moiety. Nicorandil acts as both a nitric oxide donor and a K_{ATP} channel activator. For further details, please see text. Adapted from Tamargo and Lopez-Sendon.[87]

currently under development include ularitide and cenderitide (CD-NP).

Ularitide

Ularitide[36] is a synthetic form of urodilatin. Urodilatin is a 32 amino acid peptide that is formed via alternative splicing of the ANP prohormone in the kidney and secreted in response to increased pressure by the cells of the distal tubule and collecting duct, and ultimately binding to NPR-A receptors, especially in the renal collecting duct. This locally specific binding leads to sodium and water excretion and it is this theoretical specificity that is thought to distinguish ularitide from nesiritide.[37] Randomized Phase II trials of ularitide (SIRIUS I and SIRIUS II) have shown improvement in hemodynamic parameters (reduction in PCWP), reduction of NT-proBNP, and an improvement in dyspnoea in patients treated with urodilatin compared with placebo without adversely affecting renal function.[38]

The SIRIUS II study was a randomized, placebo-controlled, and double-blind study of ularitide in addition to standard therapy for acute decompensated HF.[39] Based on the inclusion criteria, patients were enrolled 2–3 days after hospitalization with a mean age of 61 years, SBP $>$ 90 mmHg, 95% of patients had an LVEF $<$ 40%, CI of 1.9 L/min/m^2, and a mean PCWP of 25 mmHg. Two hundred and twenty-one patients were randomized to 24-h infusions of ularitide 7.5, 15, or 30 ng/kg/min or placebo. The co-primary endpoints were changes in PCWP and changes in the patient assessed dyspnoea scores at 6 h using a seven-level Likert scale. At 6 h, all of the ularitide groups showed dose-dependent statistically significant decreases in PCWP and dyspnoea scores. In addition, the 15 and 30 ng/kg/min groups evidenced statistically significant reductions in SVR and increased cardiac index (CI) at 6 h. At 24 h, in the two higher dose groups the reduction in PCWP, improved dyspnoea scores, reduction in SVR, and increased CI persisted. As with other natriuretic peptides, there was a dose-dependent reduction in SBP with 10% of treated patients experiencing an SBP $<$ 80 mmHg. As in SIRIUS I, there was no significant change in renal function in SIRIUS II.

A multicentre, randomized, double-blind, and phase III event-driven trial (TRUE-AHF; NCT01661634; *Table 3*) that completed enrolment of 2157 patients to evaluate the efficacy and safety of ularitide 15 ng/kg/min infused over 48 h vs. placebo for the management of acute decompensated HF. This trial enrolled patients with SBP 116–180 mmHg and uses an intermediate dose in an attempt to avoid hypotension, an adverse effect that has resulted in termination of multiple other development programs. There are two co-primary end-points. The first evaluates improvement in a hierarchical clinical composite comprised of elements associated with: patient global assessment using a 7-point scale of symptomatic improvement, the lack of improvement, or worsening; persistent or worsening HF requiring an intervention (initiation or intensification of IV therapy, circulatory or ventilatory mechanical support, surgical intervention, ultrafiltration, haemofiltration or dialysis). The second co-primary end-point is assessed by freedom from cardiovascular mortality during follow-up after randomization, for the entire duration of the trial.

Cenderitide

Cenderitide, CD-NP, is an engineered natriuretic peptide that fuses the C-terminal portion of DNP with CNP. This fusion peptide has two advantages compared with CNP alone. First, fusion of CNP with the 15 amino acid C-terminal portion of DNP increases its resistance to degradation, allowing for a longer therapeutic half-life.[40] Second, DNP is a potent NPR-A agonist, while CNP is a potent NPR-B agonist, resulting in dual activation of NPR-A with attendant aldosterone suppression and NPR-B with anti-proliferative and anti-fibrotic effects (*Figure 1*).[41] In pre-clinical studies, infusion of equimolar quantities of CD-NP vs. nesiritide in normal canines showed that CD-NP was less hypotensive and increased GFR, whereas BNP infusion did not change GFR.[42] This result supports the potential mechanistic benefit for dual activation of NPR-A and NPR-B by CD-NP, including cardiac unloading, renal enhancing properties, and a favourable neurohumoral profile.

Two phase II studies have been completed for CD-NP in AHF. In the first (NCT00839007), 66 patients with symptomatic AHF, NT-pro-BNP level $\geq$1400 pg/mL, SBP $\geq$105–180 mmHg, and renal compromise with Cr clearance of 30–80 mL/min were randomized to receive an intravenous infusion of CD-NP (1.25, 2.5, 3.75, or 5 ng/kg/min) or placebo for at least 48 h. CD-NP infusion at 1.25 and 2.5 ng/kg/min appeared to preserve renal function relative to placebo. Dose-dependent maximum SBP reductions compared with placebo were observed and the 5 ng/kg/min dose of CD-NP was aborted due to clinically relevant blood pressure reduction.[43]

In the second investigation (NCT00699712), 11 of a planned 30 patients with stabilized AHF were infused for 8 h with open-label CD-NP at 3 ng/kg/min, followed by a 14 h washout period, and then another 8 h infusion of CD-NP at 10 ng/kg/min ($n = 9$). There was a dose-dependent statistically significant reduction in PCWP with a trend towards decreased RAP and increased cardiac output. There was a concomitant rise in CD-NP dose-dependent urine output of 48 and 93 mL/h during the 3 and 10 ng/kg/min infusion, respectively (both $P = 0.01$ compared with pre-dose baseline), but no effect on serum creatinine levels and increased hypotension was once again noted.[44] At this time, development of cenderitide has shifted to chronic HF patients.

β-Arrestin-biased angiotensin II type 1 receptor blocker: TRV120027

Angiotensin II plays an important role in the pathogenesis of HF, with many of its adverse effects mediated by the angiotensin II type I receptor (AT1R), a member of the G-protein-coupled seven transmembrane helical receptor family.[45] Recent studies show that the AT1R also signals via an independent β-arrestin pathway (*Figure 2*).[46,47] In pre-clinical studies on mice β-arrestin-biased-signalling resulted in enhanced cardiac contractility while decreasing myocardial oxygen consumption as assessed by ventricular systolic pressure–volume loops.[48] In contrast, the currently available unbiased AT1R blockers antagonize the G-protein-coupled pathway leading to vasodilatory effects and block the β-arrestin pathway resulting in decreased cardiac contractility. Sar1,D-Ala8 angiotensin II (TRV120027 or TRV027) is a novel β-arrestin-biased ligand that reduces PCWP, systemic and pulmonary vascular resistance, mean arterial pressure, and atrial natriuretic peptide while increasing cardiac

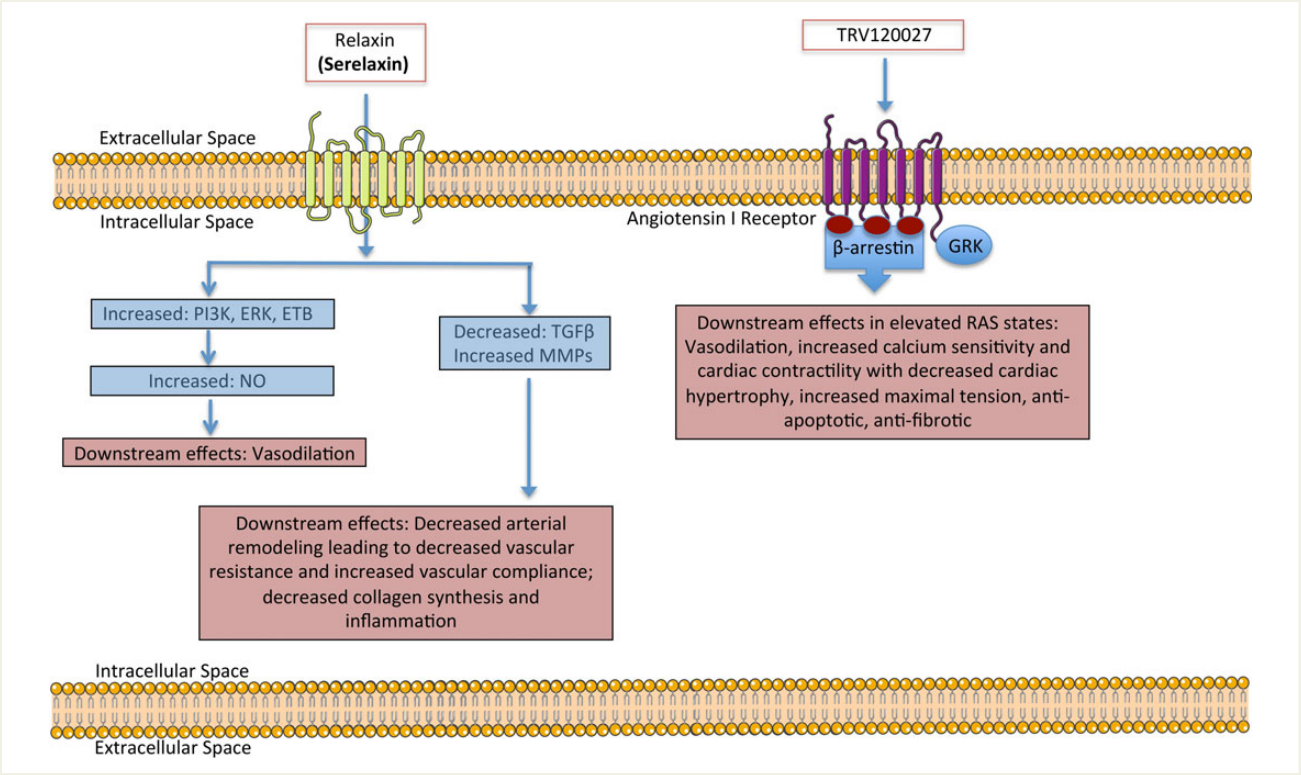

Figure 2 Schematic of mechanisms of action of some agents with vasodilating properties (2). Adapted from Du *et al.*[24] and Violin *et al.*[88]

output in rats and canines.[49,50] Also in canines, when added to furosemide, TRV027 preserves furosemide-mediated natriuresis and diuresis, while preserving renal function and reducing cardiac preload and afterload.[51] These promising pre-clinical results have led to human studies.

A randomized, double-blind, and placebo-controlled titration study evaluated TRV027 in stable HF patients.[52] Thirty-two patients with HFrEF (LVEF $<$ 35%) with SBP $\geq$100 mmHg, PCWP $\geq$20 mmHg were randomized 1:3 to receive either placebo or one of three maintenance doses of TRV027, 1, 3, or 10 μg/kg/min. Other HF medications were held for 6 h. The drug was administered IV for 14 h with a 4 h dose escalation phase and a 10 h maintenance phase, followed by a 4 h washout phase. Mean arterial pressure decreased during all phases for patients with elevated plasma renin activity (PRA), but not in patients with normal PRA or placebo. Pulmonary capillary wedge pressure decreased during drug treatment and returned to baseline during washout in those with elevated PRA. Cardiac index did not change. These results were consistent with the prior study in healthy volunteers[53] and provided the basis for the Biased-Ligands of the Angiotensin receptor STudy in Acute Heart Failure (BLAST-AHF; NCT01966601; *Table 3*), a phase IIb dose-finding study currently recruiting patients to determine safety and efficacy of TRV120027 when administered in addition to standard of care.[54]

Nitroxyl (HNO) donors: CXL-1020 and CXL-1427

CXL-1020 is a novel synthetic compound, which non-enzymatically decomposes to produce nitroxyl (HNO) and an inactive organic by-product that is renally cleared. HNO is related to NO, but displays many unique pharmacological actions in blood vessels and myocytes (*Figure 1*).[55] In contrast to NO, HNO targets selective cysteine residues resulting in new covalent bonds or reversible disulfide bonds. In the myocyte, HNO enhances sarcoplasmic reticular calcium transients via SERCA2a, phospholamban, and the ryanodine receptor and also improves myofilament calcium sensitivity. HNO improves myocardial function by direct positive cAMP-independent lusitropic and inotropic effects.[56] The potent vasodilatory effects of HNO are partially attributable to sGC activation, but also relate to increased circulating neuropeptide calcitonin-related peptide levels and activation of vascular smooth muscle potassium channels. Compared to nitrates and vasodilators there is less chance for tolerance development or tachyphylaxis. Beyond these potential vascular effects, the lustropic and inotropic effects may be the most intriguing.

Progress was initially limited due to the poor pharmacologic properties of available HNO donors. CXL-1020 was developed to address these issues.[57] While a 6-hour forced titration study showed that CXL-1020 treated patients had a statistically significant decline in PCWP and SVR, and at higher dose an increase in CI and stroke volume index, a subsequent study with an infusion rate of 20 μg/kg/min for 12–24 h was found to produce inflammatory irritation at the intravenous insertion site. As a result, further development of CXL-1020 as a human therapeutic has been abandoned. However, second generation HNO donor compounds are currently in development, including CXL-1427. In a dose-finding, ascending dose cohort Phase I trial in 70 healthy volunteers, CXL-1427 improved CI with some decreased blood pressure without increases

in heart rate at the maximally tolerated dose of 10 μg/kg/min.[58] A 48 patient dose-ranging Phase IIa study in patients hospitalized with HF is enrolling (NCT02157506).

Soluble guanylate cyclase modulators: cinaciguat and vericiguat

The GC family includes both membrane bound (particulate GC) and cytosolic soluble isoforms that are expressed in most cell types. The biological messenger NO activates sGC. In AHF, endothelial dysfunction leads to impairment in the formation and responsiveness to NO, thereby affecting both of the GC pathways.[59] Traditional therapy with nitrates and vasodilators have focused on replacing these depleted NO stores; however, treatment leads to a dose-related tolerance with decreased effectiveness. Novel sGC modulators are being developed that can stimulate sGC in the absence of NO. The difference between the mechanisms of action of the traditional and novel therapies is explained by the oxidation state of sGC where oxidized sGC is insensitive to induction by NO.[60] Unlike traditional nitrates, sGC modulators can induce sGC in its NO insensitive state. There are currently two classes of sGC modulators[61]; sGC activators, like cinaciguat, induce sGC in its NO-insensitive oxidized (Fe3+)-heme-free state, whereas the sGC stimulators, like BAY 1021189 (vericiguat), enhance the affinity of sGC to the low levels of NO.

Cinaciguat (BAY 58−2667) is the best studied of the sGC activators and illustrates the difficulty in developing a vasodilator therapeutic. While Phase I and II studies showed dose-dependent benefit with improved haemodynamic paramaters (PCWP), there were clinically significant episodes of hypotension at fixed doses >200 μg/h and increase in plasma renin and noradrenaline levels.[62−64] For this reason, the COMPOSE program (COMPOSE III and COMPOSE EARLY; NCT01064037), in patients with ADHF were initiated to investigate the safety and efficacy of cinaciguat at fixed doses <200 μg/h; however, these studies were terminated due to hypotension and recruitment difficulties. To our knowledge, there are no further plans to develop cinaciguat as a drug to improve haemodynamics in ADHF. Vericiguat (BAY 1021189) is an oral sGC stimulator currently undergoing phase II trials [SOCRATES-REDUCED (NCT01951625) and SOCRATES-PRESERVED (NCT01951638)] in patients after clinical stabilization from AHF.[65]

Short-acting calcium channel blocker: clevidipine

Intravenous clevidipine is a short-acting dihydropyridine L-type calcium channel blocker that mediates the influx of calcium in smooth muscle leading to arterial dilation.[66] Currently, it is approved for the acute management of severe hypertension. Unlike other members of the dihydropyridine family, clevidipine has a rapid onset with high clearance, is arterial selective, and has no effect on myocardial contractility or central venous pressure.[67] As a result, clevidipine is being evaluated for the treatment of patients with AHF presenting with elevated blood pressure.

An analysis of a subset of the 126 patient, open-label, uncontrolled Evaluation of the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients With Severe Hypertension (VELOCITY) trial was done to assess the safety and efficacy of clevidipine for the treatment of severe hypertension in the 19 patients who presented with AHF.[68] Among these 19 patients, 94% achieved the initial target BP range with no hypotension or increase in heart rate, suggesting that clevidipine may be safe and well tolerated in these patients.

A subsequent randomized, open-label, active control study of clevidipine vs. standard of care intravenous antihypertensive therapy (PRONTO) enrolled 104 patients to determine the efficacy and safety of clevidipine in hypertensive AHF.[69] Patients were enrolled if their SBP ≥160 mmHg with a dyspnoea visual analogue score (VAS) ≥50 mm (out of 100 mm). Coprimary end-points were median time to, and percent attaining, a systolic BP within a prespecified target BP range (TBPR) at 30 min. Dyspnoea reduction was the main secondary end-point. Baseline SBP and VAS were 186.5 ± 23 mmHg and 64.8 ± 19.6 mm, respectively. A greater percentage of clevidipine-treated patients achieved TBPR (71 vs. 37%, $P = 0.002$), achieved TBPR faster, and had statistically significant improvement in mean VAS dyspnoea scores compared with standard of care. However, there is the possibility for bias when evaluating symptom scores in open-label studies, especially since the study drug is a white lipid emulsion.[70] These studies suggest that clevidipine is safe during treatment; however, the longer-term safety profile needs to be evaluated given the brief follow-up (12 h) and prior reports of reflex tachycardia and atrial fibrillation with clevedipine.[71]

Potassium channel activator: nicorandil

Nicorandil is a member of the potassium channel (K_{ATP}) activator family characterized by vasodilator properties. In addition to arterial vasodilation, nicorandil has venodilating properties attributable to a nitrate group in its chemical structure. Due to this dual mechanism of action, the drug acts as a balanced venous and arterial (coronary, pulmonary, and systemic) vasodilator, reducing both preload and afterload.[72] It is currently used for the treatment of angina pectoris with multiple clinical trials ongoing to assess its role in the treatment of myocardial ischemia. Studies in mice and rats show that nicorandil has a cardioprotective effect on mitochondrial function and SERCA2 gene expression.[73,74] As a result of its favourable hemodynamic effects and other possible beneficial effects, nicorandil is being evaluated in the treatment of AHF.

A phase II study of nicorandil randomized 99 patients with AHF with PCWP ≥18 mmHg to three treatment groups with the same bolus injection followed by increasing continuous infusion doses.[69] Nicorandil reduced preload and afterload immediately after initiation of treatment and rapidly improved haemodynamics (PCWP, TPR, SVI, and CI) in a dose-dependent manner. There was a mean change in SBP in patients with a baseline SBP > 160 mmHg of −22.7 ± 20.3 mmHg ($P = 0.003$) while there was no significant change in SBP when the baseline SBP was <120 mmHg. Of note, diastolic blood pressure decreased across all blood pressure ranges, but there was no hypotension or significant change in heart rate during administration.

A comparison of nicorandil with carperitide suggested that they were differentially effective in improving haemodynamics in AHF. Thirty-eight patients were assigned to receive 48 h continuous infusions of carperitide ($n = 19$; 0.0125−0.05 μg/kg/min) or nicorandil ($n = 19$, 0.05−0.2 mg/kg/h).[75] Based on transthoracic

echocardiogram and blood pressure measurements, the carperitide group showed a greater decrease in SBP (carperitide, 22.1% from baseline of 141 ± 26 mmHg vs. nicorandil, 5.3% from baseline of 131 ± 31 mmHg, $P = 0.003$) and estimated PCWP (38.2 vs. 26.5% for nicorandil, $P = 0.036$) at 48 h after drug administration, while the nicorandil group showed a greater increase in estimated cardiac output (52.1 vs. 11.4%, $P = 0.001$). Of note, the urine output in the carperitide group was higher over 24 h with lower diuretic doses, but this did not reach statistical significance.[76]

New insights on potential beneficial effects of novel vasodilators

There is increasing evidence that organ dysfunction associated with AHF is related in many patients to congestion. Pulmonary congestion is related to increased pulmonary venous pressure upstream of the left ventricle. Similarly, the cardio-renal syndrome in HF is predominantly related to venous congestion upstream of the right ventricle. Indeed, creatinine clearance is related to the level of venous congestion in chronic HF and worsening renal function in AHF patients admitted in ICU is also related to venous congestion, precisely to central venous pressure but not to cardiac output or blood pressure.[77] Recently, liver dysfunction in the setting of AHF has also been related to poor clinical outcomes.[78] Thus, novel agents with vasodilator properties, especially those acting on venous bed, might reduce central venous pressure, decrease organ backpressure, and improve organ perfusion.

Recent evidence suggests that the beneficial effects of some agents with vasodilator properties exceed their haemodynamic effects. Serelaxin rapidly prevented organ dysfunction and end organ damage when administered early after hospital admission for AHF, and these changes were associated with reductions in early worsening of HF, as well as possible improvements in 180-day survival.[29] Some of those beneficial effects might be related to alteration of inflammatory activation and/or oxidative stress that are potential targets of serelaxin. Many of the new agents with vasodilator properties also act on the cellular (inflammation, apoptosis, and fibrosis) and/or subcellular level (calcium handling, mitochondrial activation, and oxidative stress). The promise of these new agents is that intermediate-term morbidity and mortality can be beneficially affected by reducing the end organ damage during AHF. Furthermore, acute worsening HF is increasingly being recognized as an entity associated with poor clinical outcomes,[29,79–83] and both TRUE-AHF and RELAX-AHF-2 have acute worsening HF as a primary end-point to assess early benefits of both novel therapies.

In parallel with the development of these novel vasodilators, there has been an evolution in the design of clinical trials for AHF therapies. Early studies had very broad entry criteria that were not optimized for the therapy's mechanism of action. Many of these trials did not have objective diagnostic criteria for AHF (e.g. natriuretic peptides), potentially allowing the enrolment of patients with less severe or even without AHF. An anticipated side effect of vasodilators is hypotension and multiple trials have demonstrated a relationship between hypotension and subsequent adverse events, as well as poor clinical outcomes [84–86] While some of the novel vasodilators may actually act selectively in a manner that reduces the incidence of hypotension, contemporary development programs have also emphasized careful dose selection and have protocol-defined down-titration and stopping rules to limit hypotensive episodes. In addition, the two largest ongoing trials in AHF, namely TRUE-AHF and RELAX-AHF-2, do not include AHF patients with low blood pressures (<116 or 125 mmHg, respectively) before the administration of studied drug. Thus, advances in clinical trial design have complemented the development of these novel vasodilator therapies for AHF. Indeed, those programmes need to be successful (i) to ascertain the use of agents with vasodilator properties in AHF and (ii) to demonstrate that intravenous agent(s) administered during the hospital stay may alter mid-term outcome.

In summary, nitrates have been used in patients with AHF throughout the world, despite the absence of evidence of beneficial effects on clinical outcomes. Several large ongoing trials are evaluating the potential of novel vasodilators to address this significant unmet need with the hope that as they rapidly relieve congestion, and more importantly exert some direct beneficial effects at the cellular level, these new therapies may also improve clinical outcomes, including survival.

Authors' contributions

A.S., S.L., J.R.T., A.M. acquired the data. A.S., S.L., J.R.T., A.M. conceived and designed the research. A.S., S.L., J.R.T., A.M. drafted the manuscript. A.S., S.L., J.R.T., A.M. made critical revision of the manuscript for key intellectual content.

Conflict of interest: S.L. received fees as a member of advisory board from Servier. J.T. has received research grants and consulting fees from Actelion, Amgen, Bayer, Cytokinetics, Novartis, Sevier and Trevena. A.M. received speaker's honoraria from Abbott, Novartis, Orion, Roche et Servier. A.M. received fee as member of advisory board and/or Steering Committee from Cardiorentis, Adrenomed, MyCartis, ZS Pharma and Critical Diagnostics.

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