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REVIEW

Agents with vasodilator properties in acute heart failure: how to design successful trials

Alexandre Mebazaa[1,2,3]*, Dan Longrois[4], Marco Metra[5], Christian Mueller[6], Arthur Mark Richards[7,8], Lothar Roessig[9], Marie France Seronde[10], Naoki Sato[11], Norman L. Stockbridge[12], Wendy Gattis Stough[13], Angeles Alonso[14], Robert J. Cody[15], Nancy Cook Bruns[9], Mihai Gheorghiade[16], Johannes Holzmeister[17], Said Laribi[18]†, and Faiez Zannad[19]†

[1]University Paris Diderot, Sorbonne Paris Cité, Paris, France; [2]U942 INSERM, AP-HP, Paris, France; [3]APHP, Department of Anesthesia and Critical Care, Hôpitaux Universitaires Saint Louis-Lariboisière, Paris, France; [4]Département d'Anesthésie-Réanimation, Hôpital Bichat-Claude Bernard, University Paris Diderot, Sorbonne Paris Cité, Paris, U1148 INSERM, Paris, France; [5]Cardiology, University of Brescia, Brescia, Italy; [6]Department of Cardiology, University Hospital Basel, Basel, Switzerland; [7]Cardiovascular Research Institute, National University of Singapore, Singapore; [8]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [9]Global Clinical Development, Bayer Pharma AG, Berlin, Germany; [10]Department of Cardiology, University Hospital of Besançon, U942 INSERM, Besançon, France; [11]Internal Medicine, Cardiology, and Intensive Care Medicine, Nippon Medical School Musashi-Kosugi Hospital, Kanagawa, Japan; [12]Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [13]Campbell University College of Pharmacy and Health Sciences, NC, USA; [14]Scientific Advice Working Party European Medicines Agency, Madrid, Spain; [15]Janssen Research and Development, Raritan, NJ, USA; [16]Department of Medicine, Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [17]Cardiorentis AG, Zug, Switzerland; [18]APHP, Department of Emergency Medicine, Hôpitaux Universitaires Saint Louis-Lariboisière, INSERM U942, Paris, France; and [19]INSERM, Centre d'Investigation Clinique 9501 and Unité 961, Centre Hospitalier Universitaire, and the Department of Cardiology, Nancy University, Université de Lorraine, Nancy, France

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Agents with vasodilator properties (AVDs) are frequently used in the treatment of acute heart failure (AHF). AVDs rapidly reduce preload and afterload, improve left ventricle to aorta and right ventricle to pulmonary artery coupling, and may improve symptoms. Early biomarker changes after AVD administration have suggested potentially beneficial effects on cardiac stretch, vascular tone, and renal function. AVDs that reduce haemodynamic congestion without causing hypoperfusion might be effective in preventing worsening organ dysfunction. Existing AVDs have been associated with different results on outcomes in randomized clinical trials, and observational studies have suggested that AVDs may be associated with a clinical outcome benefit. Lessons have been learned from past AVD trials in AHF regarding preventing hypotension, selecting the optimal endpoint, refining dyspnoea measurements, and achieving early randomization and treatment initiation. These lessons have been applied to the design of ongoing pivotal clinical trials, which aim to ascertain if AVDs improve clinical outcomes. The developing body of evidence suggests that AVDs may be a clinically effective therapy to reduce symptoms, but more importantly to prevent end-organ damage and improve clinical outcomes for specific patients with AHF. The results of ongoing trials will provide more clarity on the role of AVDs in the treatment of AHF.

Keywords Acute heart failure • Vasodilator • Clinical trials

Introduction

Despite many therapeutic advances in the treatment of chronic heart failure (HF) over the past two decades, the number of hospitalizations for acute heart failure (AHF) has remained unchanged. In Europe, the approximate rate of AHF hospitalizations has been reported as 2 per 1000 persons.[1] In the USA, >1 million hospital discharges were reported in 2010, at an estimated cost of US$30.7 billion.[2]

Outcomes among patients with AHF remain poor. The in-hospital mortality rate ranges from 2% to 7%.[3] It was higher (12%) in the Acute Heart Failure Global Registry of Standard Treatment (ALARM-HF), but 11.7% of the enrolled patients had cardiogenic shock.[4] At 60–90 days, mortality ranges from 5%

*Corresponding author. University Paris Diderot, PRES Sorbonne Paris Cité, Department of Anesthesiology and Critical Care Medicine, Hôpitaux Universitaires Saint-Louis-Lariboisière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. Tel: +33 1 49958085, Fax: +33 1 49958073, Email: alexandre.mebazaa@lrb.aphp.fr
†These authors contributed as senior authors to the paper.

to 15%.[3,5] The 30-day rehospitalization rate for patients hospitalized for AHF ranges from 24% to 27%.[3] None of the new pharmacological therapies tested in clinical trials in the last two decades has improved clinical outcomes,[6–10] although the results of RELAX-AHF were hypothesis generating and suggested that a benefit on clinical outcomes might be possible.[11] In addition, with the possible exception of high-dose nitrates in patients with hypertensive AHF,[12,13] none of the pharmacological therapies routinely administered to patients with AHF is supported by data from a positive randomized controlled trial.

Data from clinical trials and observational registries have been central to advancing knowledge related to patient characteristics, clinical presentation, and outcomes in patients with AHF.[9,14–16] Hypothesis-generating subgroup and post-hoc analyses have pointed to effects such as hypotension [with some agents with vasodilator properties (AVDs)] or increased myocardial oxygen consumption (with positive inotropes) as major limitations of existing drug therapy, since these effects may negatively impact intermediate and long-term outcome [e.g. hypoperfusion of end-organs (AVDs) or the potential for ischaemia or arrhythmia (positive inotropes)].[14,17,18]

These data suggest that a paradigm shift is needed in the treatment approach to AHF, which to date has largely focused on improving symptoms and achieving haemodynamic stabilization.[19] Emerging data suggest that a more effective approach to influence clinical outcomes positively may be to select therapies that prevent end-organ damage as well as improve symptoms and haemodynamics.[20]

This topic was discussed during the 10th Global Cardiovascular Clinical Trialists Forum held in Paris, France, in December 2013 among a group of cardiovascular clinical trialists, biostatisticians, National Institutes of Health (NIH) scientists, European and US regulators, and pharmaceutical and device industry scientists. This paper summarizes the key outcomes from the CVCT session, updating previous CVCT reports,[6,7] and focuses on the current understanding of AHF pathophysiology and potential mechanisms by which AVDs might be beneficial when used appropriately. Optimal approaches to designing clinical trials of investigational AVDs are also presented throughout the paper (*Table 1*).

Table 1 Key considerations for designing clinical trials testing vasodilator agents

- The study population should reflect the expected action of the drug (e.g. patients with evidence of high left- or right-sided filling pressure, evidence of end-organ dysfunction, preserved blood pressure); successful studies are unlikely to be 'all-comer' trials
- Include procedures specified in the protocol to prevent and/or manage hypotension
- Achieve early randomization and study drug initiation
- Avoid dyspnoea as the primary endpoint
- An endpoint that assesses clinical outcome is preferred (e.g. cardiovascular mortality or clinical composite score) with adequately sized safety database

The pathophysiology of acute heart failure

One hypothesis to explain the poor patient outcomes after an AHF event is that each AHF event damages the heart (e.g. ischaemia, myocardial cell death)[21] or other organ systems, which adversely affects prognosis. Patients with AHF present most commonly with normal or high blood pressure (*Figure 1*),[22–25] high filling pressures, and preserved cardiac output. High left-sided filling pressure contributes to pulmonary oedema, while high right-sided filling pressure contributes to other organ damage, including acute kidney injury and liver damage, even in the absence of cardiogenic (low output) shock.

Central venous pressure was the strongest haemodynamic predictor of worsening renal function in a cohort of 145 patients hospitalized for acute decompensated HF.[26] In the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial, liver function tests were abnormal in 46% of patients. Systemic congestion and elevated filling pressures were associated with signs of cholestasis.[27] Furthermore, organ dysfunction such as myocardial ischaemia or kidney dysfunction worsens during the initial 2–5 days of AHF management in patients treated with standard of care.[20] In a recent observational study of patients undergoing cardiac surgery, echocardiographic indicators of right ventricular dysfunction and elevated central venous pressure were correlates of post-operative kidney dysfunction, whereas low cardiac output or mean arterial blood pressure were not.[28] These data are hypothesis generating and suggest that end-organ damage (i.e. renal injury in this example) occurs in the setting of AHF possibly because of venous congestion, especially when it is sustained. Therapies that reduce haemodynamic congestion while avoiding hypoperfusion might prevent end-organ damage and have a favourable impact on long-term outcomes.

It is important to note that symptoms of congestion and the existence of volume overload are not necessarily linked. Indeed, clinical evidence of volume overload may be absent in patients presenting with AHF and symptoms of congestion.[29] In normovolaemic patients, symptoms of congestion may result from a vascular mismatch, leading to fluid redistribution rather than volume overload. The aetiology of this vascular mismatch is complex and incompletely understood.[30] Systemic vascular resistance increases in response to many different stimuli, including neurohormonal or inflammatory activation, endothelial dysfunction, and increased oxidative stress.[30] Arterial vasoconstriction leads to increased afterload and eventually impaired cardiac function, especially diastolic relaxation and filling. Vasoconstriction in the venous system results in loss of capacitance and increased volume of venous return (preload).[31] Arterial stiffness due to ageing, collagen deposition, vasoactive substances especially in distal arteries, or other risk factors[32,33] also contributes to increased afterload (i.e. impaired arterial distensability)[31] and lower venous capacitance. Vascular congestion is characterized by abnormal haemodynamic

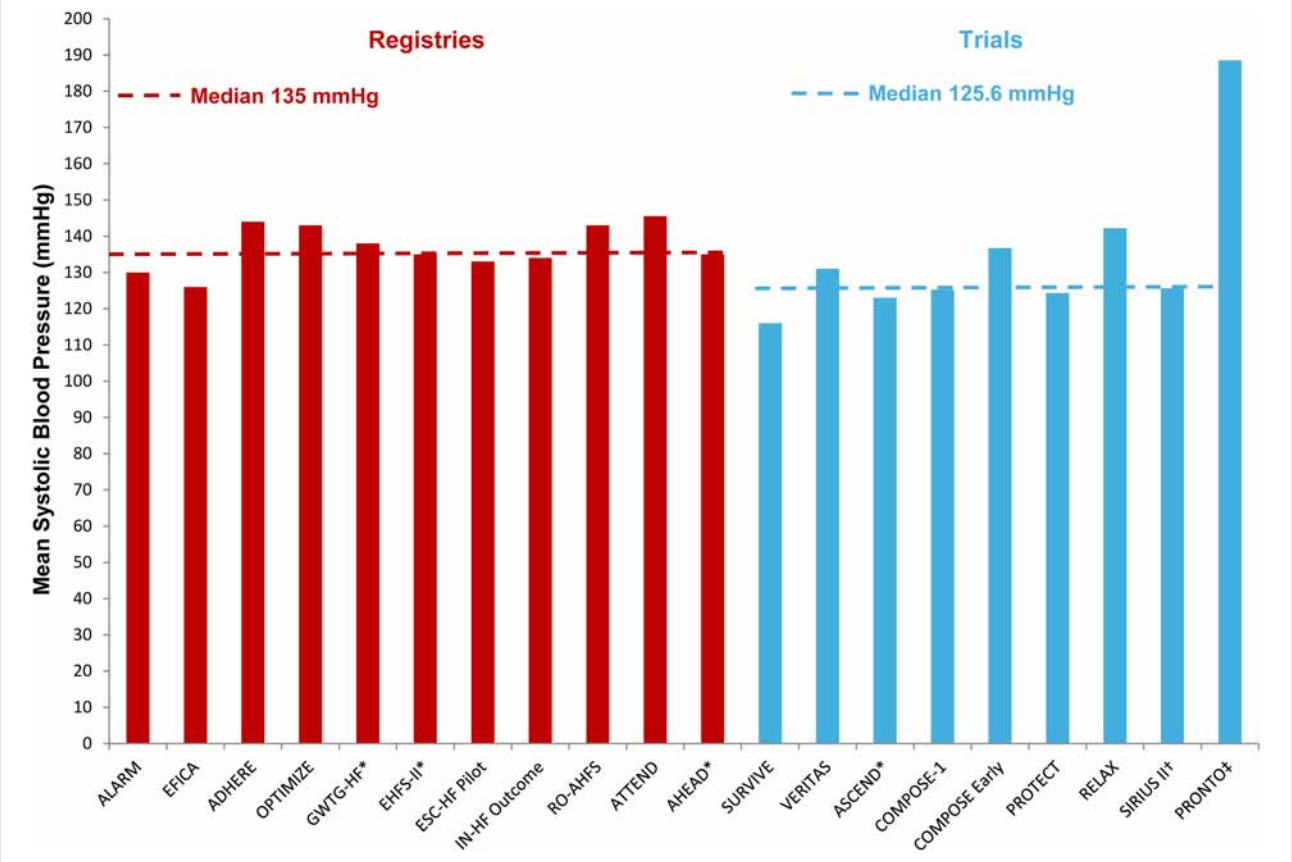

Figure 1 Mean systolic blood pressure in acute heart failure registries and clinical trials. Red bars denote registries, blue bars denote clinical trials. *ASCEND data are median values. †Systolic blood pressure is the average of placebo and three ularitide dosing groups. ‡Systolic blood pressure is the average of placebo and clevidipine.

parameters such as elevated LV diastolic pressure or PCWP, or decreased venous compliance,[34] and relatively preserved cardiac output.[35–38] In such patients, the standard approach of treating congestive symptoms with diuretics may be ineffective, but this pathophysiology may be well suited to treatments (e.g. AVDs) that can resolve the underlying vasoconstriction.[35]

Pharmacology of agents with vasodilator properties and relevance for acute heart failure

Agents with vasodilator properties are the second most frequently used treatment (after diuretics) for AHF in most parts of the world.[4,25,39–42] However, international guidelines accord limited support for their use, which is recommended only in specific patient subsets [e.g. nitroglycerin (Class IIa) or sodium nitroprusside (Class IIb) in patients with systolic blood pressure (SBP) >110 mmHg (both Level of Evidence B)[19] or as an adjuvant to diuretics in patients without symptomatic hypotension (Class IIb, Level of Evidence A)].[43] These limited guideline recommendations reflect a lack of robust evidence of efficacy on symptomatic or clinical outcomes from adequately powered, controlled randomized clinical trials.[44]

Prototypical AVDs (essentially nitrates) have not been shown to improve outcomes in randomized clinical trials,[9,37,38] although the results with newer agents are promising.[11] Non-randomized and observational studies, although clearly not definitive, suggest that AVDs may be associated with a clinical outcome benefit,[45] but it is clear that not all AHF patients benefit from these treatments.[9,37,38] The totality of evidence with AVDs suggests that research efforts should focus on determining the specific pathophysiological subset of AHF patients that will most probably benefit from AVD. For example, one such subset might include patients with abnormal haemodynamics consistent with vascular congestion in the setting of normal or high SBP.

It is unlikely that all AVDs have similar potency or act similarly on the same vascular beds. Future development programmes for AVDs ought to determine whether they act in specific vascular beds (e.g. kidney[46,47], liver, or coronary) but have less effect in others,[48–52] which could potentially minimize the problem of systemic vasodilation, hypotension, and organ hypoperfusion. In addition, although beneficial effects of AVDs might even result

Table 2 Clinical pharmacology of select agents with vasodilator properties

Drug	Mechanism of action	Haemodynamic effects
Nitroglycerin	Through formation of NO, activates guanylyl cyclase to increase cGMP and promote vascular smooth muscle relaxation	Reduces LVEDP, PCWP, SVR, SBP, MAP; relatively selective for venous capacitance vessels[84]
Nitroprusside	Direct acting vasodilator, activates guanylyl cyclase to increase cGMP in vascular smooth muscle	Reduces LVEDP, PCWP, SVR, SBP, MAP; increases renal blood flow (except with excessive hypotension); stronger arterial vasodilatory effect than nitroglycerin[84]
Nesiritide	Binds to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of cGMP and smooth muscle relaxation	Reduces PCWP, MAP, SVR; increases CI and SVI
Levosimendan	Calcium-dependent binding to cardiac troponin C, increasing the sensitivity of myocardial contractile proteins to calcium and accelerating formation of the actin–myosin cross-bridge and slowing its dissociation; activates opening of ATP-sensitive sarcolemma potassium channels of smooth muscle cells and myocytes; selective phosphodiesterase III inhibition	Increases CO, LVEF, SV; reduces PCWP, MAP, mPAP, mRAP, TPR
Ularitide	Synthetic form of endogenous urodilatin; binds to specific natriuretic peptide receptors (NPR-A, NPR-B, and others) and increases intracellular cGMP to cause smooth muscle relaxation and increased renal blood flow[81,85]	Increases CI; reduces RAP, PCWP, SVR.[86] Dilation of renal, pulmonary, and coronary arterial vessels; diuresis and natriuresis from inhibition of sodium resorption in the renal tubules[87]
Serelaxin	Recombinant form of relaxin-2; peptide hormone; activates a wide range of signalling pathways;[88] haemodynamic effects may be mediated indirectly by increased production of NO, matrix metalloproteinases, vascular endothelial growth factor, endothelin type B receptor, and ANP; may inhibit endothelin and angiotensin II vasoconstriction.[89,90]	No change in CI; decreases RAP, PCWP, mPAP, PVR, SVR. Possibly stimulates increase in renal blood flow (unclear whether GFR is increased).[89,90] Evidence from RELAX-AHF: serelaxin associated with less myocardial cell loss, less worsening of renal function (except possibly in the setting of hypotension[16]), less liver damage, and more decongestion vs. placebo[20]
Clevidipine	Arterial selective dihydropyridine L-type calcium channel blocker	Decreases SVR, PVR, MAP; increases SV
Cinaciguat	Haem-independent activator of soluble guanylate cyclase	Vasodilator and antiplatelet activity, potent antihypertensive effect, haemodynamic profile similar to nitrates[91,92]
CXL-1020, CXL-1427	Decomposes to produce pure nitroxyl (HNO); provides direct positive cAMP-independent lusitropic and inotropic effects, and combined venous and arterial dilation;[93] activates sGC; increases circulating neuropeptide calcitonin-related peptide; activates vascular smooth muscle potassium channels.	Increases myocardial contractility, LVEF, CI, SVI; decreases PCWP, LVEDP, RAP, MVO_2, SVR
TRV 120027	β-Arrestin ligand of the AT1R[94,95]	Decreases PCWP, SVR, PVR, MAP, ANP; increases CO
Cenderitide	NPR-A and NPR-B agonist[96]	Decreases PCWP, RAP; increases CO

ANP, atrial natriuretic peptide; AT1R, angiotensin II type I receptor; CI, cardiac index; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; MVO_2, myocardial oxygen consumption; NO, nitric oxide; NPR, natriuretic peptide receptor; PVR, pulmonary vascular resistance; SAP, systolic arterial pressure; SBP, systolic blood pressure; sGC, soluble guanylate cyclase; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; TPR, total peripheral resistance.

from the reduction in blood pressure, haemodynamic-independent effects of the specific mode of action may contribute to organ protection by individual compounds. Furthermore, interesting work in the field of pulmonary arterial hypertension has used homing peptides to deliver drugs precisely to the target vascular bed.[53,54] Whether such an approach might be feasible, efficacious, and result in better safety in AHF has yet to be investigated to our knowledge.

Agents with vasodilator properties rapidly reduce preload and afterload, improve left ventricle to aorta[55–57] as well as right ventricle to pulmonary artery coupling,[58] and improve symptoms (*Table 2*). Interestingly, several AVDs showed a reduction in plasma

natriuretic peptides in the first days after administration, suggesting beneficial effects on cardiac stretch and possibly vascular tone and renal function.[10,20,59,60] Indeed, levosimendan (an inodilator),[10,59] serelaxin,[20] and high-dose nitrate[60] all markedly reduce plasma BNP or NT-proBNP within a few days after the onset of therapy. Decreases in NT-proBNP with serelaxin were further associated with prevention of kidney dysfunction.[20]

There is growing evidence to suggest that when AHF patients (without cardiogenic shock) first present to the hospital, efforts should be directed towards (i) reducing dyspnoea and episodes of in-hospital worsening HF; (ii) prevention of the worsening organ dysfunction that is typically seen early after admission; and (ii) improving post-discharge outcomes, probably through better relief from congestion and protection from end-organ damage. In contrast to vasopressors, AVDs might be effective in preventing worsening organ dysfunction.[61]

Importance of blood pressure in trials of agents with vasodilator properties

Hypotension induced by agents with vasodilator properties

Multiple factors may contribute to the development of hypotension in AHF, including use of high-dose diuretics or guideline-directed therapies that also lower blood pressure (e.g. ACE inhibitors, ARBs, beta-blockers, or hydralazine). Therefore, it is difficult to differentiate, in a particular instance, hypotension caused by AVDs from that resulting from other factors related to AHF or its management (*Table 3*). Blood pressure decreases even with traditional therapy in the first hours after admission to the emergency room. This response has been repeatedly shown in the placebo arms of randomized trials (RITZ[62] and VERITAS[37]), and it is probably caused by decongestion, the mild direct vasodilator effects of furosemide, and relief from anxiety. It is therefore difficult to discriminate between the vasodilator effects of the study drug and the 'spontaneous' changes occurring with traditional therapy in randomized, placebo-controlled, double-blind trials.

Potential harm from hypotension induced by agents with vasodilator properties

Hypotension may promote end-organ damage through tissue hypoperfusion, thereby contributing to worse clinical outcomes. A study of sodium nitroprusside in acute myocardial infarction (AMI) patients with elevated LV filling pressures first supported the hypothesis that excess vasodilator-induced hypotension may worsen outcome in this population.[63] Patients who received sodium nitroprusside <9 h after symptom onset had higher mortality than those receiving placebo, whereas mortality was lower for the sodium nitroprusside group compared with placebo when the infusion was started later than 9 h. One hypothesis for this finding proposed by the authors was that a reduction in arterial pressure might have reduced blood flow to the areas of ischaemia, which might have contributed to worse outcomes.[63] Of note, the CONSENSUS-II trial of intravenous enalapril early after myocardial infarction was prematurely stopped due to concerns of a possible adverse effect on mortality, hypothesized to be related to hypotension, particularly in the elderly.[64]

Optimal systolic blood pressure prior to initiation of agents with vasodilator properties

As the field evolved, trials began excluding patients with low SBP, although with different thresholds across studies (*Table 3*). There are no data to support the concept that higher SBP at inclusion will prevent all AVD-induced hypotensive events, although it is a logical approach. Importantly, in a trial specifically studying hypertensive AHF, patients with the highest SBP at inclusion have been observed to experience the greatest drop in SBP after treatment with an AVD[65] (*Table 3*). Both the magnitude of change in SBP and the end-resulting SBP are important.

In the Pre-RELAX-AHF study, a greater early drop in SBP was an independent predictor of worsening renal function [adjusted odds ratio (OR) 1.45, 95% confidence interval (CI) 1.04–2.00, $P = 0.0267$].[16] Worsening renal function was also associated with higher mortality at 60 and 180 days.[16] In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, 21.8% of patients had an episode of in-hospital hypotension, and it was associated with increased risks of 30-day mortality [hazard ratio (HR) 2.03, 95% CI 1.57–2.61, $P < 0.001$], 30-day HF hospitalization or mortality (HR 1.58, 95% CI 1.34–1.86, $P < 0.001$), and 30-day all-cause hospitalization or mortality (HR 1.40, 95% CI 1.22–1.61, $P < 0.001$).[18] Of note, in the Randomized Evaluation of Intravenous Levosimendan Efficacy I and II trials (REVIVE), an increased risk for death was observed in patients with SBP below 110 mmHg randomized to receive the inodilator levosimendan.[14]

These data raise the hypothesis that AVD-induced hypotension negatively impacts end-organ function such that subsequent mortality is increased.[66] It is plausible that this adverse effect may have obscured potential benefits of AVD in completed clinical trials.[66] These data also add support to the hypothesis that excessive dilation of the vasculature is not desirable, but attention should be paid to identifying the specific vascular abnormalities present in AHF and target those vascular beds with AVDs. New pivotal clinical trials are targeting patients with normal to elevated SBP and have stringent protocol procedures in place to respond to hypotensive events.[10,11,14,37,67] Earlier AHF studies had less specific protocol procedures for responding to low SBP. In ASCEND-HF, no protocol-specific procedures were stated in the study design publication, except that the loading dose of nesiritide could be omitted for patients with SBP <110 mmHg.[68] In the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Studies (VERITAS), the infusion rate could be decreased or stopped for symptomatic hypotension or SBP <90 mmHg.[69] The REVIVE trials

Table 3 Blood pressure entry criteria and effect of tested vasodilators on blood pressure in acute heart failure trials

Trial	Study drug	SBP enrolment requirements	Mean SBP (mmHg) at baseline in treatment arm	SBP change (mmHg) from baseline in treatment arm	Hypotension recorded as adverse event in treatment arm	Hypotension recorded as adverse event in standard of care or placebo arm (*P*-value vs. treatment arm)
SURVIVE[10]	Levosimendan	≥85 mmHg	116 ± 18	Approximately −4 mmHg at 6 h	15.5% levosimendan	13.9% dobutamine ($P = 0.48$)
REVIVE[14]	Levosimendan	>90 mmHg	115 ± 17	−4 mmHg during 24 h infusion	50%	36% ($P < 0.05$)
VERITAS[37]	Tezosentan	≥100 mmHg (or ≥120 mmHg if receiving a vasodilator)	131 ± 22	−14.6 ± 18.33 mmHg at 24 h	Stopped study drug due to hypotension: 8.3% Reported hypotension up to 5 days after initiation: 22.7%	Stopped study drug due to hypotension: 4.7% ($P = 0.003$) Reported hypotension up to 5 days after initiation: 14.5%
ASCEND[9]	Nesiritide	≥100 mmHg (or ≥110 mmHg if receiving i.v. NTG)	Median (IQR) 123 (110–140)	Median (IQR) SBP during the hypotensive episode 80 mmHg (70–87) NES vs. 80 mmHg (70–85) PL	Any hypotension: 26.6% Symptomatic: 7.2%	Any hypotension: 15.3% ($P < 0.001$) Symptomatic: 4% ($P < 0.001$)
COMPOSE[97]	Cinaciguat	≥120 mmHg	125 ± 5 (COMPOSE 1) 137 ± 12 (COMPOSE EARLY)	−12.3 to −15.3 mmHg (depending on dose) at 8 h (COMPOSE 1)	Any hypotension: 22.2% (COMPOSE 1), 27.9% (COMPOSE EARLY) Treatment-emergent hypotension: 11.1% (COMPOSE 1), 4.7% (COMPOSE EARLY)	
PROTECT[98]	Rolofylline	≥95 mmHg	124 ± 18	Not reported	7.3%	6% ($P = 0.27$)
RELAX[11]	Serelaxin	>125 mmHg	142 ± 16	Greater decreases from baseline in SBP in SER vs. PL group, ~4–6 mmHg difference	BP-related study drug adjustment: 29% BP reduction requiring treatment (predominantly i.v. fluids): 12%	BP-related study drug adjustment: 18% ($P < 0.0001$) BP reduction requiring treatment (predominantly i.v. fluids): 8%
SIRIUS II[99]	Ularitide	>90 mmHg	124 ± 22 to 126 ± 25 (depending on arm)	Approximately −7 to −14 mmHg at 6 h depending on dose	Any hypotension during infusion: 8.3–16.4% (depending on dose) Symptomatic hypotension: 5.7–7.3% (depending on dose)	Any hypotension during infusion: 1.9% Symptomatic hypotension: 0%
PRONTO[65]	Clevidipine	≥160 mmHg	190 ± 26	Approximately −30–40 mmHg	SBP <90 mmHg: 3 (6%) Symptomatic hypotension: 1 (2.3%)	SBP <90 mmHg: 1 (2%) Symptomatic hypotension: 0
TRUE-AHF[67]	Ularitide	≥116 and ≤180 mmHg	Ongoing	Ongoing	Ongoing	Ongoing
RELAX-AHF-2[71]	Serelaxin	≥125 mmHg	Ongoing	Ongoing	Ongoing	Ongoing
GALACTIC[83]	Nitrates, hydralazine, ACE inhibitors, ARBs	≥100 mmHg	Ongoing	Ongoing; treating to target SBP 90–110 mmHg	Ongoing	Ongoing

IQR, interquartile range; NES, nesiritide; NTG, nitroglycerin; PL, placebo; SBP, systolic blood pressure; SER, serelaxin.

also allowed for a reduction in the study drug infusion rate if the standard dose was not tolerated.[70]

In the Relaxin in Acute Heart Failure study (RELAX-AHF), more stringent rules were adopted. The study drug infusion was halved if SBP decreased by ≥40 mmHg from baseline and remained >100 mmHg; the study drug was discontinued if SBP was <100 mmHg.[11] Serelaxin was discontinued in 107 (19%) patients who met this protocol-defined blood pressure threshold.[11] In RELAX-AHF-2, patients are required to have an SBP ≥125 mmHg at the start and end of screening,[71] and tight rules are applied to deal with hypotension. If the patient's SBP decreases by >40 mmHg from baseline but remains >100 mmHg, the study drug infusion rate is halved for the remainder of the infusion period, whereas the study drug is discontinued if the patient's SBP falls to <100 mmHg.[72] In the Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF) study, SBP must be ≥116 and ≤180 mmHg at the time of randomization.[67] If symptomatic hypotension or SBP <100 mmHg occurs, the protocol requires specific procedures for blood pressure management. This specific approach of reducing study drug dose according to threshold drops in SBP might be a more effective means of optimally using and testing these agents in patients with AHF. The exclusion of patients with low SBP should minimize the problem of hypotension, but it does not solve the clinical problem of the lack of effective therapies for patients with SBP below 120 mmHg, a group that accounts for half of the AHF population. Effective and safe drug development is needed for this subset of AHF patients.

Importance of early randomization in acute heart failure trials

Early randomization is important in AHF trials to maximize the likelihood of detecting a treatment effect if one exists (e.g. on dyspnoea endpoints), to allow administration of lower doses of diuretics, when the study drug is also effective on congestion, and, perhaps more importantly, to prevent or minimize injury to the myocardium and other end-organs. Experimental evidence from animal models and normal human volunteers suggests that activation of neurohormones and inflammatory cytokines occurs after a short period (60–75 min) of venous congestion.[30,73,74] These findings lend support to the hypothesis that early intervention might provide the greatest magnitude of benefit, but this concept needs to be tested in clinical trials.

Most patients respond quickly (within 6 h) to standard therapy,[75] and those patients who do not are more likely to be refractory to therapy. Thus, trials that allowed enrolment up to 48 h after hospitalization may have had difficulty detecting an incremental benefit of the investigational therapy above standard care with the dyspnoea endpoint. Recognition of this fact has led newer trials to randomize patients as quickly as possible. In RELAX-AHF, the mean time from presentation to randomization was 7.8 ± 4.6 h.[11] Significantly fewer patients randomized to serelaxin experienced the threshold of early (within 2 days post-randomization) biomarker changes that were associated with increased 180-day mortality [i.e. ≥20% increase in high sensitivity cardiac troponin T (hs-cTnT), aspartate aminotransferase (AST), or alanine aminotransferase (ALT); or a ≥0.3 mg/L increase in serum creatinine or cystatin C], and more serelaxin patients exhibited a ≥30% decrease in NT-proBNP.[20] It is plausible that the early randomization achieved in RELAX-AHF provided an opportunity for serelaxin to exert end-organ protective effects, as evidenced by the lower proportion of patients with adverse biomarker changes. Whether the same effects on biomarkers would have occurred if serelaxin had been started later is unknown. RELAX-AHF achieved the shortest time to randomization of major AHF trials conducted to date (*Table 4*). It is possible that the time to randomization may account, at least in part, for the promising results of this study and the disappointing results of past trials, particularly if the mechanism of benefit proves to be prevention of early end-organ damage by resolving venous congestion. Ongoing trials have early randomization targets, within 16 h for RELAX-AHF-2[71] and 12 h for TRUE-AHF (*Table 4*).[67] Although these targets are improvements over previous trials, 12–16 h might still be suboptimal, and even faster enrolment should be studied in future trials to identify the optimal time to treatment in this population. Having stated the likely importance of early introduction of treatment, if novel agents are beneficial in trials with early introduction of the experimental therapy, supplementary trials with later introduction of treatment will

Table 4 Mean time to randomization in trials of agents with vasodilator properties in acute heart failure

Trial	Mean time from presentation to randomization
SURVIVE[10]	>24 h
VERITAS[37]	11 h (to start of study drug)
ASCEND[9]	15.3 h
COMPOSE[97]	COMPOSE Early: within 12 h after initial clinical assessment, mean time to study drug not reported
PROTECT[98]	Enrolment within 24 h of admission, mean time to study drug not reported
RELAX[11]	7.8 h
SIRIUS II[99]	2–3 days
PRONTO[65]	3.2 ± 1.9 (door-to-study drug)
TRUE-AHF[67]	Ongoing, within 12 h after initial clinical assessment
RELAX-AHF-2[71]	Ongoing, randomized within 16 h from presentation to hospital
GALACTIC[60,83]	Within 2 h of admission

still be necessary to define properly the time window of possible efficacy.

Endpoint considerations for clinical trials assessing benefits of agents with vasodilator properties

Dyspnoea has been a component of the primary endpoint of all the major AVD trials in AHF (*Table 5*), but it is difficult for any new agent to demonstrate improvement on this endpoint because diuretics are generally given early to all patients, they are effective, and work quickly. Dyspnoea is a relevant endpoint from the patient perspective, and it is accepted by regulatory authorities provided adequate assurance of safety is demonstrated.[76] However, consensus has not been reached on the optimal assessment methodology. Both the visual analogue scale (VAS) and the Likert 7-point scale have been used in clinical trials, but these scales may not be equally sensitive to changes in dyspnoea. In RELAX-AHF, serelaxin improved dyspnoea scores compared with placebo when measured using the VAS, but Likert scale scores did not differ significantly from placebo.[11]

All-cause mortality is generally accepted as the most clear-cut, scientifically rigorous, and clinically relevant endpoint for cardiovascular clinical trials, but drugs given for short periods of time are generally unlikely to influence long-term mortality, unless a safety problem exists.[76] In RELAX-AHF, the Kaplan–Meier mortality estimate of all-cause mortality was 10–12% in the placebo arm at 6 months. Cardiovascular mortality was an additional efficacy endpoint, whereas all-cause mortality was a pre-specified safety endpoint.[11] Serelaxin reduced all-cause mortality (HR 0.63, 95% CI 0.43–0.93, $P = 0.02$) and cause-specific cardiovascular mortality (HR 0.63, 95% CI 0.41–0.96, $P = 0.028$) vs. placebo.[11] Most of the deaths were cardiovascular, and the serelaxin treatment effect was most evident on deaths classified as 'other cardiovascular' or sudden.[77] As impressive as this unplanned finding was, its slow evolution long after the drug treatment ended undermined confidence in this being a reliable finding. Thus, the RELAX-AHF-2 trial was designed with the primary endpoint of time to cardiovascular death within 6 months and time to worsening HF through day 5 (also considering death) to evaluate these findings further.

Regulators will generally accept any demonstration of clinical improvement that is accompanied by a correspondingly reassuring safety database. A larger safety database would be needed for small effects on fast-resolving symptoms, and an adequate but lesser sized safety database for a major reduction in hospitalization.[78–80] The acceptance of non-clinical endpoints (e.g. biomarkers or measures of organ function) is complicated by the history in HF of poor correlations between plausible biomarkers and clinical outcomes. Nevertheless, demonstration of sustained beneficial effects on biomarkers merits discussion.

Table 5 Primary endpoints of select trials of agents with vasodilator properties in acute heart failure

Trial	Study drug	Phase	Primary endpoint
SURVIVE[10]	Levosimendan	III	All-cause mortality at 180 days.
REVIVE[14]	Levosimendan	III	Clinical composite of improved (patient global assessment of moderate or marked improvement at 6 h, 24 h, and 5 days without evidence of clinical deterioration), unchanged, or worsened (death within 5 days, persistent or unresponsive HF symptoms after 24 h, worsening HF during 5 days, or patient global assessment of moderately or markedly worsened at 6 h, 24 h, or 5 days).
VERITAS[37]	Tezosentan	III	Change from baseline in dyspnoea over first 24 h of treatment, measured at 3, 6, and 24 h by the patient using a VAS
ASCEND[9]	Nesiritide	III	Co-primary change in dyspnoea at 6 and 24 h as measured on a 7-point Likert scale, and the composite of rehospitalization for HF or death within 30 days
COMPOSE[97]	Cinaciguat	II	Haemodynamics and dyspnoea
PROTECT[98]	Rolofylline	III	Treatment success (patient-reported improvement in dyspnoea at 24 and 48 h measured by 7-point Likert scale), failure, or no change in patient's condition
RELAX[11]	Serelaxin	III	Change in patient-reported dyspnoea quantified by the AUC of the VAS at day 5; and moderately or markedly improved patient-reported dyspnoea relative to the start of study drug using the 7-point Likert scale at 6, 12, and 24 h
SIRIUS II[99]	Ularitide	II	Change in PCWP, and change in patient's self-assessed dyspnoea score using the 7-point Likert scale
PRONTO[65]	Clevidipine	II	Co-primary median time to and percentage of patients attaining SBP within a target blood pressure range within 30 min
GALACTIC[83]	Nitrates, hydralazine, ACE inhibitors, and ARBs	III	Death or rehospitalization from HF within 180 days

AUC, area under the curve; HF, heart failure; SBP, systolic blood pressure; VAS, visual analogue scale.

Drugs in development and ongoing trials

Serelaxin

The Efficacy, Safety, and Tolerability of Serelaxin When Added to Standard Therapy in Acute Heart Failure trial (RELAX-AHF-2) (NCT01870778, is a randomized, double-blind, placebo-controlled phase III study. The planned enrolment is 6800 patients with AHF defined by hospitalization for AHF with expected intravenous therapy for at least 48 h, persistent dyspnoea at rest or with minimal exertion, pulmonary congestion on chest X-ray, and BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL (BNP ≥750 pg/mL or NT-proBNP ≥3000 pg.mL for patients ≥75 years of age or with AF at the time of randomization), who received ≥40 mg of i.v. furosemide between presentation and study screening. As mentioned, patients are required to have SBP ≥125 mmHg and will be randomized within 16 h from the time of hospital presentation to serelaxin or placebo. The primary endpoint is time to confirmed cardiovascular death through 180 days and time to worsening HF through 5 days (also considering death), with all-cause mortality through 180 days pre-specified as a safety endpoint.[71]

Ularitide

The TRUE-AHF study (NCT01661634) is a phase III multicentre, double-blind, placebo-controlled trial in patients with acute decompensated HF.[81,82] Patients are randomized to a continuous infusion of ularitide 15 ng/kg/min for 48 h or matching placebo, and receive other standard treatments at the investigator's discretion. The target enrolment is up to 4304 patients in an adaptive design, with dyspnoea at rest (semi-recumbent, 30–40°) that has worsened within the past week despite standard background therapy, radiological evidence of HF on chest X-ray, BNP >500 pg/mL or NT-pro BNP >2000 pg/mL, and persistent dyspnoea at rest despite treatment that must include ≥40 mg of i.v. furosemide or equivalent (but not within 2 h prior to randomization). Baseline SBP ≥116 and ≤180 mmHg is required. Study drug is commenced within 12 h of the initial assessment. One primary efficacy endpoint is improvement in a hierarchical clinical composite endpoint (assessed at 6, 24, and 48 h after start of study drug) including patient global assessment of symptomatic improvement, lack of improvement, or worsening; persistent or worsening HF requiring pre-specified mechanical or pharmacological interventions; and all-cause death. The second primary efficacy endpoint is freedom from cardiovascular death throughout the duration of the trial.[67]

Clevidipine

The Study of Blood Pressure Control in Acute Heart Failure Pilot Study (PRONTO) was a randomized, open-label active control study of the i.v. dihydropyridine calcium channel blocker clevidipine vs. standard care in 104 patients presenting to the emergency department with hypertensive AHF (SBP ≥160 mmHg required for entry; mean SBP of those enrolled was 189.5 ± 26.4 mmHg).[65] The primary endpoints were the percentage of patients achieving SBP in the target range (defined as a 15% reduction from baseline with a range of 20–40 mmHg) and the median time to achieve the target. Dyspnoea measured by a 100 mm VAS was the secondary endpoint. More clevidipine patients achieved the target blood pressure, and the target was achieved more rapidly in the clevidipine group than in the standard of care group.[65] Patients randomized to clevidipine also had a greater improvement in VAS scores compared with the active control. These data are encouraging, but not definitive, because of the relatively small sample size, open-label design, and short duration of follow-up.

Transdermal nitrates and oral hydralazine

Early initiation (within 2 h of admission) of high-dose transdermal nitrates was shown to lower serum BNP levels faster and to a greater extent than standard care in an open-label, non-randomized pilot study.[60] These data supported further investigation of this strategy, and led to the design of The Goal-Directed Afterload Reduction in Acute Congestive Cardiac Decompensation (GALACTIC) study.[83] GALACTIC is an ongoing randomized trial comparing standard treatment for AHF based on European Society of Cardiology (ESC) guidelines with an early goal-directed strategy of reducing preload and afterload to a target SBP of 90–110 mmHg using transdermal nitrates and oral hydralazine, followed by rapid up-titration of ACE inhibitors and/or ARBs.[83] Enrolment of 700 patients with AHF and BNP ≥500 pg/mL is planned; patients with SBP <100 mmHg, cardiogenic shock, or who require intensive care unit admission are excluded. The primary endpoint is death or HF rehospitalization within 180 days.[83]

Conclusion

Agents with vasodilator properties continue to be used for the treatment of AHF, but whether or not they improve clinical outcomes remains to be determined. A strong pathophysiological rationale for their use exists, from the standpoint of acute symptomatic improvement as well as the potential to reduce or prevent end-organ damage that occurs in the setting of haemodynamic congestion and elevated filling pressures. Furthermore, organ dysfunction worsens in the first days after admission for AHF despite standard of care. The extent to which end-organ protection may impact clinical outcomes is a working hypothesis that requires confirmation in clinical trials. It is clear that a fine balance exists between prevention of end-organ damage by AVDs and end-organ damage that may occur in the setting of organ hypoperfusion. Thus, ongoing clinical trials are specifically focusing on this issue by limiting enrolment to patients with preserved SBP and diligently managing hypotension should it occur. Ongoing pivotal phase III trials have slightly different inclusion SBP thresholds, which may provide an opportunity to learn about optimal thresholds for baseline SBP. These trials also have implemented early randomization strategies, enabling the concept of early randomization to be tested. Whether the 12–16 h time frame is early enough remains to be determined. The developing body of evidence

from completed and ongoing clinical trials suggests that AVD may be a clinically effective therapy to reduce symptoms, but more importantly to prevent end-organ damage, and improve clinical outcomes for specific patients with AHF. The results of ongoing trials will provide more clarity on the role of individual AVD in the treatment of AHF.

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