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**POSITION PAPER**

# Pathophysiology and clinical use of agents with vasodilator properties in acute heart failure. A scientific statement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

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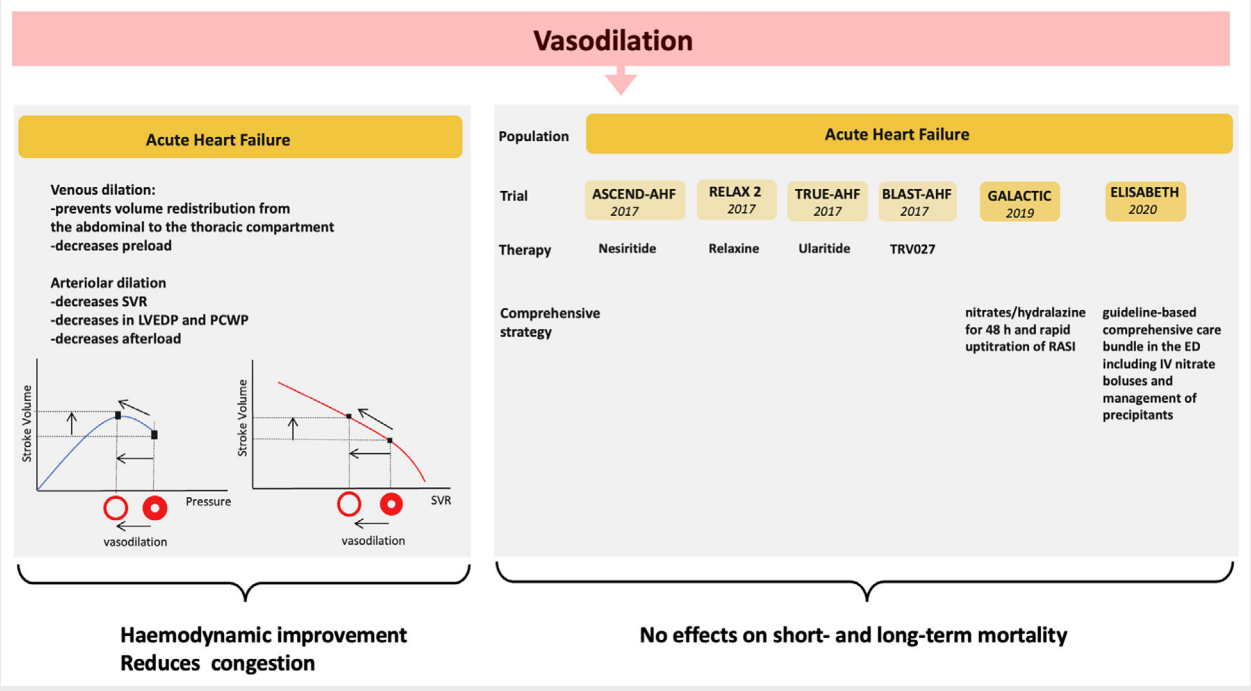
Acute heart failure (AHF) affects millions of people each year and vasodilators have been a central part of treatment for over 25 years. The haemodynamic effects of vasodilators vary considerably among individual agents. Some vasodilators, such as nitrates, primarily act on the venous system by redistributing the circulating blood volume away from the heart towards the venous capacitance system. Other vasodilators, such as nesiritide, lead to balanced vasodilatation in the arteries and veins, decreasing left ventricular afterload and preload. Considering mechanisms of action, intravenous vasodilators are thought to be effective in patients with AHF, particularly in those with acute pulmonary oedema, where increased cardiac filling pressures and elevated systemic blood pressures occur in the absence of, or with minimal systemic fluid accumulation. However, the 2021 European heart failure guidelines have downgraded the use of vasodilators due to two recent studies and several contemporary meta-analyses failing to show benefit in terms of survival. Thus, there remains no firm recommendation suggesting the use of vasodilator treatment over usual care. In addition, despite repeated efforts to develop new vasodilatory agents, no novel therapy has outperformed traditional AHF management. In parallel with the development of novel vasodilators, changing the design of clinical trials for AHF to consider phenotype diversity of AHF patients remains an unmet need. New randomized clinical trials should particularly focus on subgroups that may mechanistically derive benefit from vasodilators, which may entail moving enrolment of patients to clinical settings close to moment of decompensation, such as the emergency department.

## Graphical Abstract




Vasodilators in acute heart failure: disconnection between beneficial pathophysiological and haemodynamic effects and clinical effects in randomized clinical trials. AHF, acute heart failure; ASCEND-AHF, A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure; BLAST-AHF, Biased Ligand of the Angiotensin receptor STudy in Acute Heart Failure; ED, emergency department; ELISABETH, Effect of an Emergency Department Care Bundle on 30-Day Hospital Discharge and Survival Among Elderly Patients With Acute Heart Failure; GALACTIC, Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation Study; IV, intravenous; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; RASI, renin–angiotensin system inhibitor; RELAX-AHF-2, Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF; SVR, systemic vascular resistance; TRUE-AHF, Trial of Ularitide Efficacy and Safety in Acute Heart Failure; TRV027, biased ligand of the angiotensin II type 1 receptor (AT1R).

**Keywords** Acute heart failure • Vasodilators • Prognosis

# Introduction

Acute heart failure (AHF) constitutes a broad spectrum of disease states, with heterogeneous clinical presentations, various ejection fraction (EF) categories, diverse non-cardiac comorbidities, but commonly characterized by high rates of mortality and readmissions.[1] Physicians taking care of patients with AHF are confronted with the short-term challenges of reducing symptoms and preventing end-organ dysfunction, and the long-term challenge of improving clinical outcomes such as hospital readmission and survival.[1] However, despite many clinical trials conducted to date in these patients, there is not any approved agent that has been found to improve clinical outcomes in patients with AHF.[1] Although many of these therapies may have acute haemodynamic benefits that consolidate pathophysiological background, this has not been followed by improving clinical outcomes.

There is a strong pathophysiological rationale suggesting that early administration of an intravenous (IV) vasodilator can be of benefit in AHF. IV vasodilators dilate venous and arterial vessels leading to a reduction in preload and afterload, with subsequent increase in stroke volume (SV) and decongestion, finally leading to relief of symptoms (*Graphical Abstract*). Previous studies have consistently shown that the administration of sodium nitroprusside (SNP) or angiotensin-converting enzyme inhibitors (ACEI) is associated with early haemodynamic benefits, including increase in cardiac index (CI) and decrease in left-sided filling pressures.[2,3]

Vasodilator therapy is the second most used IV medication in AHF in real-world clinical practice (*Table 1*),[4–21] but it remains among the most controversial issues, as the recommendation for its use has been downgraded in the 2021 European Society of Cardiology (ESC) heart failure (HF) guidelines.[1]

It is therefore the aim of the present scientific statement to focus on vasodilator mechanisms, the clinical settings where they may be used, and to review the evidence from randomized clinical trials (RCTs), in order to better inform and support clinical practice, with respect to vasodilator use in AHF.

# Mechanisms of congestion and rationale for vasodilators in acute heart failure

## Congestion: volume overload and redistribution

Congestion is the hallmark of AHF. Abrupt or progressive elevation of filling pressures is detected prior to an episode of AHF,[22] and many patients do not gain significant weight prior to a worsening HF episode, particularly those presenting with acute pulmonary oedema (APO).[23–25] Thus, fluid accumulation alone cannot explain the development of congestion in all AHF patients. The mechanism of APO was described as a consequence of acutely increased afterload in patients with decreased systolic and diastolic capacity to adapt to changes in loading conditions[26] (*Figure 1*). Patients with APO respond to increased afterload with an increase in heart rate and systemic vasoconstriction rather than an acute adaptation in cardiac dimensions.[27] Increases in afterload can be the primary mechanism responsible for pulmonary congestion (as seen in patients with significantly elevated blood pressure) or can be the result of the intense neurohormonal activation secondary to significant cardiac dysfunction (as seen in APO after large myocardial infarction). Because of their mechanisms of action, IV vasodilators may be more effective than diuretics in those patients whose APO is caused by increased afterload and fluid redistribution to the lungs, in the absence of, or with minimal fluid accumulation.

In a landmark article, Fallick *et al.*[28] described the alternate model of fluid redistribution for HF decompensation: the decrease in capacitance of the venous reservoir, mediated by sympathetic drive, causes the shifting of volume out of the splanchnic vessels and increases effective circulating blood volume. In the splanchnic venous system, alpha 1 and alpha 2-adrenergic receptor stimulation leads to venoconstriction, which decreases venous capacitance and increases venous return[28,29] (*Figure 2*). Splanchnic organs constitute 10% of the body weight, but they contain 25% of the total blood volume. Nearly two thirds of the splanchnic blood (i.e. 800 ml) can be transferred into the systemic circulation within seconds.[29] This explains the clinical relevance of venous dilators in AHF and does question the use of isolated volume reduction strategies in these patients with 'redistributed volume'. It also provides the theoretical basis for other therapies addressing modulation of splanchnic circulation.[28]

## Congestion patterns in heart failure with reduced and preserved ejection fraction

The HF categories stratified by EF share a similar 1-year all-cause mortality,[30] but HF-related hospitalizations seem to be fewer in HF with preserved EF (HFpEF),[30,31] although that may vary by region.[32] During HF hospitalization, the congestion patterns appear similar, though N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are consistently lower in HFpEF patients.[32–34] Invasive evaluations show a similar magnitude of elevated filling pressures.[35] In the MEDIA-DHF study, pulmonary rales and venous congestion (as assessed by enlarged inferior vena cava, left and right atria) were similar between acute HFpEF and HF with reduced EF (HFrEF) patients.[33] In the ESC HF Long-Term Registry, pulmonary congestion, as reflected by the presence of pulmonary rales, was similar, irrespective of EF category.[34]

## Relevance of afterload on ventricular–arterial coupling in heart failure with reduced versus preserved ejection fraction

Cardiovascular performance is reflected by the time variation of left ventricular (LV) volume and pressure, as depicted by the conceptual framework of pressure–volume loops[36,37] (online supplementary *Figure S1*). Effective arterial elastance [E(a)] represents the best measure of total arterial afterload and can be well

**Table 1** Rate of use of intravenous vasodilators, diuretics and inotropes during hospitalization in various acute heart failure registries

| Registries, year of publication, sample size | Sample size | Vasodilators (%) | Diuretics (%) | Inotropes (%) |
|---|---|---|---|---|
| ADHERE,[4] 2005 | 107 362 | 9 | 92 | 15 |
| EHFS II,[5] 2006 | 3580 | 38.7 | 84.4 | 29.8 |
| EFICA,[6] 2006 | 599 | 50 | 87 | 53 |
| OPTIMIZE-HF,[7] 2008 | 48 612 | NA | NA | 15 |
| ATTEND,[8] 2010 | 1110 | 44.9 | 76.3 | 18.5 |
| HEARTS,[9] 2011 | 1090 | 27.8 | 89 | 30.1 |
| RO-AHFS,[10] 2011 | 3224 | 33.4 | 79.9 | 17.7 |
| Korean HF Registry,[11] 2011 | 2572 | 35.8 | 68.1 | 21.7 |
| ALARM-HF,[12] 2011 | 4953 | 41.1 | 89.7 | 39 |
| AHEAD,[13] 2011 | 4153 | 24.5 | 88.9 | 10.6 |
| Sub-Saharan Africa Survey,[14] 2012 | 1006 | 7.9 | 92.9 | 5 |
| IN-HF Outcome,[15] 2012 | 5610 | 29.9 | 98.1 | 19.4 |
| OFICA,[16] 2013 | 1658 | NA | 84 | 6.9 |
| ESC-HF Pilot,[17] 2010 | 5118 | 18.5 | 84.6 | 10.5 |
| ESC HF LT Registry,[18] 2017 | 6629 | 21.2 | 81.7 | 12.3 |
| ESC HF LT Registry,[19] 2019 | 7865 | 19.3 | 81.1 | 11.7 |
| EAHFE Registry,[20] 2019 | 11 261 | 13.5 | 84.6 | 1.8 |
| REPORT-HF,[21] 2020 | 18 553 | 15.7 | 76.3 | 8.8 |

NA, not available.

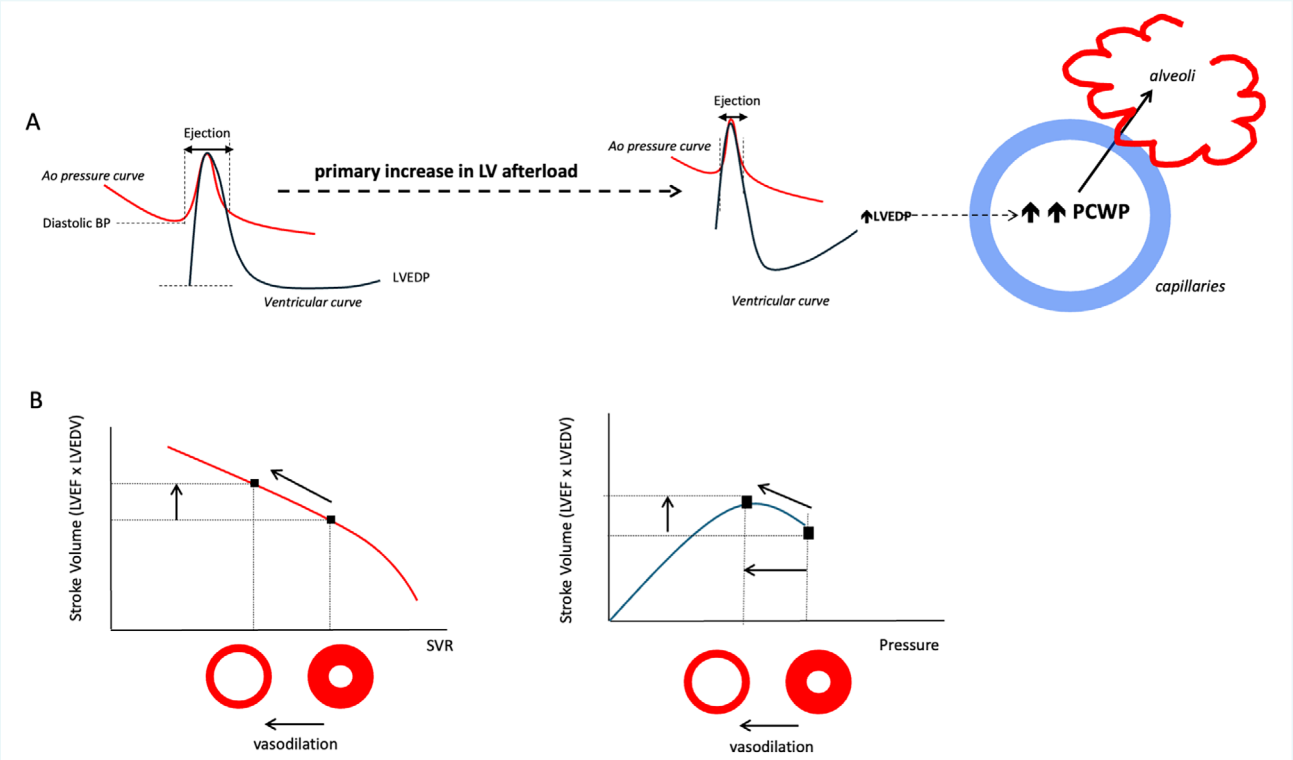



**Figure 1** (*A*) Haemodynamic effects of acute increase in afterload. An increase in afterload causes shortening of ejection time and a decrease in stroke volume. At the end of diastole there is a high left ventricular end-diastolic pressure (LVEDP). A high LVEDP as a result of acute increase in afterload increases fluid transfer across alveolo-capillary membrane resulting in pulmonary congestion. (*B*) Effects of vasodilatation in patients with acute heart failure. Vasodilatation decreases systemic vascular resistance (SVR) and LVEDP leading to an increase in stroke volume. Ao, aorta; BP, blood pressure; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.

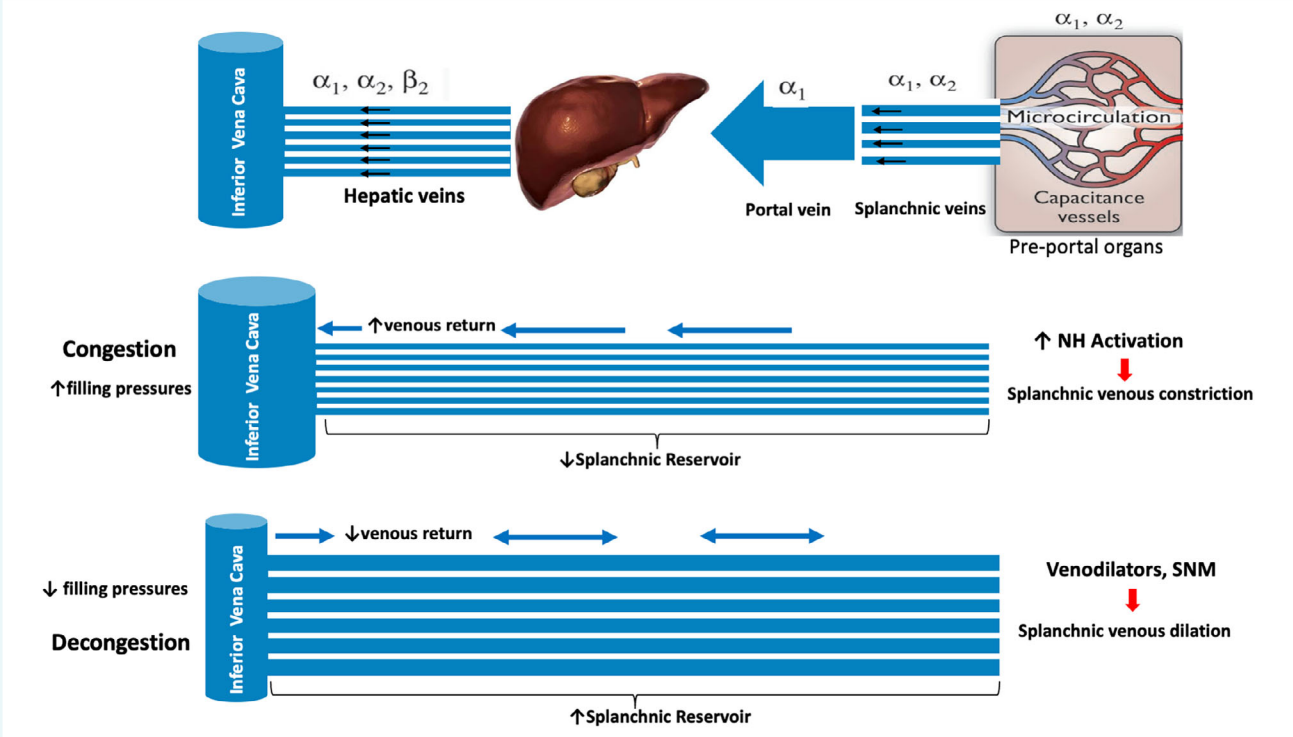



**Figure 2** Contribution of the splanchnic venous system to fluid redistribution in acute heart failure. The splanchnic circulation is very sensitive to sympathetic tone because it contains a large concentration of alpha- adrenergic receptors in the vein's walls. The sympathetic nervous system modulates the capacitance of the splanchnic venous circulation, and stimulation of adrenoreceptors produces venoconstriction and rapid functional shifts of blood volume, which ultimately result in physical translocation of blood from the splanchnic bed to the central circulation. Dysregulation of volume redistribution plays a significant role in acute heart failure. Since the splanchnic vascular compartment holds the largest pool of intravascular blood volume, neurohormonal (NH) imbalance with increased sympathetic tone causes an effective volume redistribution from the abdominal to the thoracic compartment that finally induces or worsens congestion. $\alpha_1$, alpha 1 adrenergic receptor; $\alpha_2$, alpha 2 adrenergic receptor; $\beta_2$, beta 2 adrenergic receptor; SNM, splanchnic nerve modulation.

approximated by the formula E(a) = ESP/SV (ESP: end-systolic pressure).[38] When LV function is reduced, the left ventricle is uncoupled to the elevated E(a).[39] In HFrEF, the most important component of E(a) is the non-pulsatile load, given by the systemic vascular resistances (SVR). Decreasing E(a) improves the coupling of the left ventricle to the arterial system, making the system more efficient, as less potential energy is lost. Also SV will be directly increased. The model operates very well in HFrEF and provides the physiological rationale for the use of conventional vasodilators or inodilators, such as levosimendan/milrinone in AHF.[35]

The pressure–volume loop model for HFpEF is different (online supplementary *Figure S1*). With increasing age, as E(a) becomes elevated, ventricular elastance [E(es)], considered the closest measure of the contractile state of the left ventricle, is similarly increased, thus giving normal values to the ventricular–arterial coupling (VAC) and making more relevant the nominal values of E(a) and E(es), rather than their ratio.[35,40–42] In the middle aged, the elderly and especially in hypertensive individuals, the pulsatile load represented by the reflected aortic wave becomes relevant as it occurs earlier, in mid to late systole, thus adding to the late afterload of the left ventricle and widening pulse pressure.[41,43] These alterations are even more pronounced in HFpEF.[40,41,44] In a study comparing baseline haemodynamics and acute responses to vasodilatation with IV SNP in patients with HFrEF and HFpEF, patients with HFpEF had higher systolic blood pressure (SBP), higher pulse pressure and lower arterial compliance as compared to HFrEF patients, at any value of E(a).[35] With IV SNP, filling pressures decreased to a similar extent in both forms of HF, but patients with HFpEF experience greater blood pressure reduction, less enhancement in cardiac output, and greater likelihood of SV drop with vasodilators, suggesting greater vulnerability to venodilator effects and an excessive drop in preload.[35] This model (online supplementary *Figure S1*) demonstrates that with increasing E(es), there is limited SV reserve, increased blood pressure lability and increased preload sensitivity, as compared to HFrEF.[40,41,43,45]

## Haemodynamic effects of vasodilators

Each vasodilator has specific haemodynamic effects. Invasive haemodynamic studies in HF were performed in the '70s and the '80s for prazosin,[46] phentolamine,[47] nifedipine,[48] hydralazine,[49] isosorbide dinitrate[50] and the combination of the last two (hydralazine-isosorbide dinitrate [H-ISDN]).[51] All

these vasodilators decreased filling pressures, but with differential magnitudes of change for CI or SVR, depending on their individual mechanism of action, the underlying cardiovascular abnormality and the dose.[52] At lower doses, nitrates produce predominantly venous dilatation, while at higher doses (≥150–250 μg/min), nitrates dilate arteries.[52] Dihydropyridine-type calcium-channel blockers can effectively decrease blood pressure having benefits in hypertensive emergencies but are less adequate for HF. Right atrial pressure, pulmonary capillary wedge pressure (PCWP) and LV end-diastolic pressure were not decreased by nifedipine (as opposed to the consistent response after IV SNP) and in addition, nifedipine decreased inotropism.[48]

Sodium nitroprusside has significant haemodynamic benefits in a variety of HF clinical settings that extend from improving venous capacitance vessels to lowering filling pressures and increasing CI, especially when associated with LV dysfunction.[53–56] The balanced mechanism of action (both arterial and venous dilatation) gives SNP the best rationale for use in the acute setting, especially in critically ill patients with hypertension and hypoxia.[57]

Haemodynamic benefit of ACEI were described for captopril that significantly decreased PCWP (by an average of 48%) and increased SV index (by an average of 26%).[58] Enalapril, as well, acutely and significantly decreased PCWP and increased CI.[3] Clinical benefits were observed when ACEI were administered long term and this translated to survival benefit in the SOLVD and CONSENSUS trials[3,59–61] although interestingly not when given early in acute myocardial infarction.[61]

In a meta-analysis of 35 studies performed in the AHF setting, vasodilators reduced left- and right-sided filling pressures, within 24 h of treatment.[62] Interestingly, a similar short-term effect was demonstrated with the use of inotropes, but the latter agents showed a trend towards higher mortality.[62]

## Differences in heart failure with reduced versus preserved ejection fraction

The haemodynamic effect of vasodilators in HF depend upon whether LVEF is preserved or reduced.[35,48] HFrEF patients can tolerate vasodilators easier compared to HFpEF, as even a small drop of SBP will efficiently lower E(a), enhance VAC and immediately improve SV.[35,45] Considering the already elevated E(es) with 'normalized' VAC, HFpEF patients will go through more profound decrease of SBP but with absence of haemodynamic benefit, or even decrease in SV[35,40,45] (online supplementary *Figure S1*). With the exception of hypertensive pulmonary oedema, routine use of isolated vasodilators in the acute HFpEF setting (especially when SV is low or preserved) should generally be avoided, and when used, heterogeneous haemodynamic response is to be expected.

In a large contemporary cohort of AHF patients, stratified by signs of congestion/hypoperfusion in the emergency department (ED), use of IV nitroglycerine in the ED was not associated with improved 30-day mortality, even after propensity matching analysis. In the subgroup analysis, only patients with HFrEF derived an apparent benefit with the use of IV nitroglycerine.[63]

## Neurosignalling in heart failure

Sympathetic nervous activation that drives peripheral vasoconstriction and fluid redistribution highlights the need for newer modalities to detect, prevent, and treat shifts in volume that cause or contribute to the development of AHF.[64] Autonomic nervous system modulation with suppression of sympathetic over-activity or augmentation of parasympathetic activity may improve symptoms and cardiac function in HF.[65–67] Different neuromodulation methods have been tested, including baroreflex activation, carotid body resection, renal sympathetic denervation, spinal cord stimulation, vagal nerve stimulation, and cardiac sympathetic denervation.[65,66,68–70] Despite the promising results in preclinical and preliminary clinical trials in terms of efficacy and safety, clinical data remain limited and controversial.[65,71,72]

# Classification and mechanism of action of vasodilators

Vasodilators can be classified depending on their end-mechanism of action: either acting solely on the vessel wall at different levels (isolated arterial dilators, venous dilators, balanced vasodilators influencing the entire vascular bed), or having another concomitant myocardial effects (these are the inodilators – i.e. levosimendan, milrinone) (*Table 2*). SNP acts as a nitric oxide (NO) donor, while cimlanod is nitroxyl (HNO) donor. NO and HNO donors increase the efficiency of calcium cycling and improve myocardial excitation–contraction coupling, thus having a positive inotropic effect[73,74] (*Figure 3*). The potent vasodilatory effects of HNO are partially attributable to soluble guanylate cyclase activation, but also relate to activation of vascular smooth muscle potassium channels.[52] Compared to nitrates, there is less chance for development of tolerance or tachyphylaxis.[52] Clevidipine is an ultra-fast-acting, dihydropyridine calcium channel blocker with a direct action on arteriolar resistance vessels and limited effects on venous capacitance vessels.[52] There are no signals that tolerance develops to prolonged infusions of clevidipine, although there is some evidence of rebound hypertension.[75]

## Vasodilating interventions

### Splanchnic nerve modulation

Preclinical and clinical investigations support the critical role of the sympathetic nervous system in modulating the capacitance and compliance of the splanchnic vascular bed via modulation of the greater splanchnic nerve (GSN). The GSN activation by stressors causes excessive splanchnic vasoconstriction, which may contribute to the decompensation of chronic HF via volume redistribution from the splanchnic vascular bed to the central compartment. GSN ablation for volume management has been proposed as a potential therapeutic intervention to increase unstressed blood volume.[76] Splanchnic nerve modulation (SNM) blocks the neural activity of the GSN and it is generally well-tolerated, with few side effects such as transient diarrhoea, abdominal colic and transient hypotension.[76] The pathogenetic importance of fluid redistribution

**Table 2 Mechanism of action for the main vasodilators used in acute heart failure**

| Class/drug | Mechanism of action | Relevant ancillary properties | Vascular bed target |
|---|---|---|---|
| Sodium nitroprusside | NO donor | + inotropism<br>+ lusitropy | All vascular territories |
| Isosorbide dinitrate, nitroglycerine | NO donor | Nitrate tolerance and tachyphylaxis<br>Tachycardia | Veins + large arteries |
| Cimlanod | HNO donor | + inotropism<br>+ lusitropy<br>No tachyphylaxis | Veins + arteries |
| Inorganic nitrates | Stimulates NO through the nitrate–nitrite–NO pathway and NO donor<br>Improves Ca handling | Modest + lusiptropic<br>No tachyphylaxis | Veins + arteries |
| Hydralazine | Inhibition of $Ca^{2+}$ release from the sarcoplasmic reticulum | Antioxidant effect; prevents nitrate tolerance when associated | Small arteries |
| Dihydropyridine-type calcium channel blockers (nifedipine, nicardipine, clevidipine) | Calcium channel blockers independent of NO pathway | Possibly – inotropism | Arteries |
| ACEI/ARNI | Blocking angiotensin I receptor and inhibit IP3 and decrease Ca influx in the smooth muscle cells | Neuroendocrine modulation | Arterial bed |
| Natriuretic peptide derivatives (nesiritide, ularitide) | Act on NP-R and activates guanylate cyclase and increases cGMP; independent of NO pathway | Diuretic effect | Veins + arteries (predominance on arterial bed) |
| Serelaxin | G-protein coupling to eNOS and stimulates eNOs<br>Stimulates an increase in VEGF<br>Inhibitory effect on angiotensin II and endothelin | Diuretic effect, increased renal blood flow and an increased glomerular filtration rate | Arterial bed |
| Levosimendan | Inhibition of PDE3, and an opening of ATP-dependent $K^+$ channels | + inotropism<br>Diuretic effect | Arterial bed |
| Milrinone | Inhibition of PDE3 which prevents the breakdown of cAMP in vascular muscle cells | + inotropism | Arterial bed |
| sGC activators (vericiguat, cinaciguat) | NO independent enhancement of sGC activity<br>Increased sensitivity of sGC to endogenous NO | Anti-inflammatory and anti-fibrotic effects | Arterial bed |

ACEI, angiotensin converting enzyme inhibitor; AT1-R, angiotensin 1 receptor; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; GTP, guanosine triphosphate IP3, inositol 3-phosphate; NO, nitric oxide; eNOs, endothelial nitric oxide synthase; HNO, nitroxyl; NP-R, natriuretic peptide receptor; PDE3, phosphodiesterase-3; sGC, soluble guanylate cyclase; VEGF, vascular endothelial growth factor.

from the splanchnic compartment in AHF and the safety of SNM provides the grounds for its evaluation in HF. Preliminary clinical evidence shows promising results of SNM in terms of haemodynamics (decrease in pulmonary artery pressure and PCWP, decrease in stressed blood volume, improved CI and exercise capacity).[77,78]

## Vasodilatory effect of effort and rehabilitation

Exercise training may lead to vasodilatation by improving endothelial function and increasing NO bioavailability, partly through upregulation of endothelial NO synthase expression.[79] This process can promote endothelial repair mechanisms in HF patients by mobilization of bone marrow-derived endothelial progenitor cells[80] and elicits a marked increase of maximal exercise hyperaemia,[81] decreases sympathetic nervous system activity[82] improves baroreflex sensitivity[83] and maximal cardiac output and oxygen extraction capacity.[84] Data are scarce for AHF, as these patients have been excluded from trials.[85] One proof-of-concept study showed that in patients >60 years of age hospitalized for AHF, initiating an in-hospital physical rehabilitation intervention is both feasible and safe and may improve physical function over 3 months and reduce all-cause rehospitalizations over 6 months.[86]

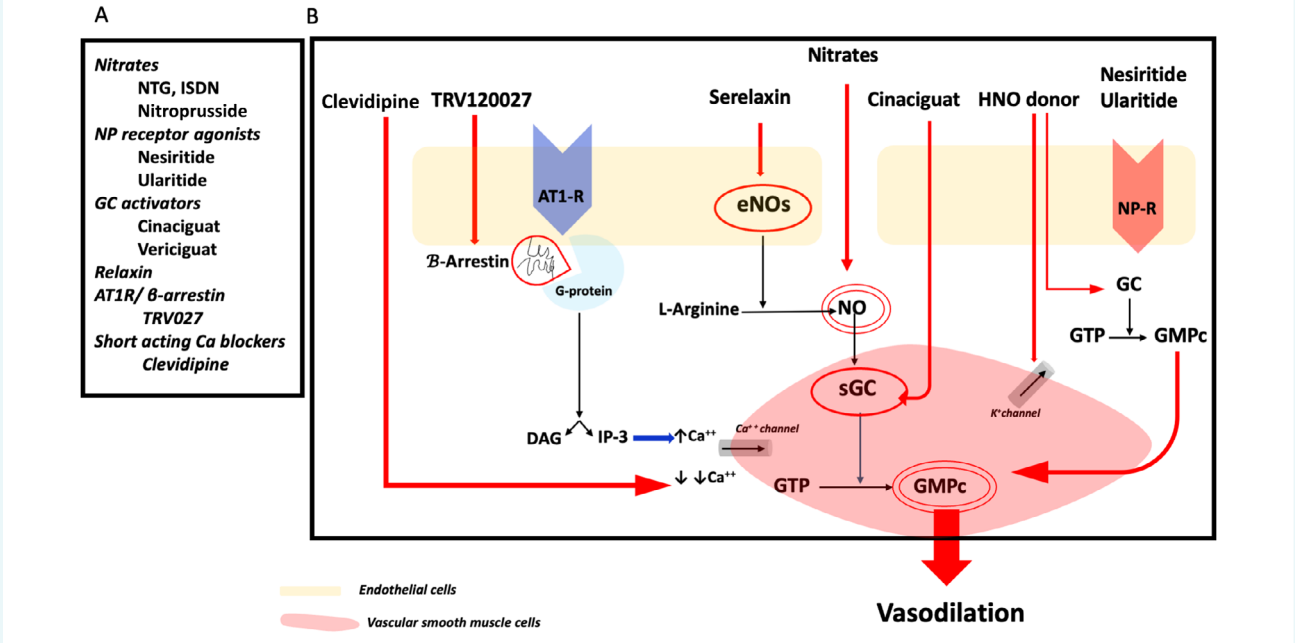



**Figure 3** The vasodilatory agents tested in clinical trials (*A*) and their mechanism of action (*B*). Nitric oxide (NO) is a major regulator of vascular homeostasis and its biosynthesis of NO occurs via the catalytic activity of NO synthase. Limited substrate availability, degradation by reactive oxygen species, and lower rates of production or higher rates of degradation may contribute to functional NO insufficiency. NO plays a key role in the regulation of vascular tone. An important signalling molecule downstream of NO is the second messenger 3′,5′-cyclic guanosine monophosphate (GMPc). GMPc is generated by NO-sensitive (soluble) guanylate cyclase (sGC). GMPc is involved in the main pathways regulating vascular functions and acts as second messenger for sympathetic and parasympathetic systems. cGMP controls endothelial cell permeability and ability to release vasoactive agents, such as NO or natriuretic peptide. Cinaciguat and nitroxyl (HNO) donors act independent of NO and endothelial NO synthase (eNOs). The novel vasodilatory agent, TRV120027, is also independent of NO signalling and acts via β-arrestin mediated patway. β-arrestins are a family of intracellular proteins that play a key role by inhibiting the activity of G protein coupled to angiotensin 1 receptors (AT1-R). Clevidipine is a short-acting calcium channel blocker that inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes. DAG, diacylglycerol; GTP, guanosine triphosphate; IP-3, inositol 3-phosphate; ISDN, isosorbide dinitrate; NP-R, natriuretic peptide receptor; NTG, nitroglycerine.

## Impact on biomarkers and organ protection

More than 70% of AHF patients have at least one organ dysfunction feature or injury that mainly relates to congestion.[87,88] Organ injury is directly associated with worse long-term outcomes (increased mortality and HF worsening).[88] There is evidence that earlier decongestion is associated with enhanced organ protection as indicated by biomarker trajectories and clinical outcomes.[87] Reducing central venous pressure, which is the main driver for renal and hepatic injury,[89–91] and improving distribution of stressed versus unstressed volume, using a drug with venous dilatory properties (i.e. organic nitrates) has pathophysiological rationale, as this should correlate to rapid improvement of organ failure or may prevent further deterioration. Nonetheless, in the largest meta-analysis, no benefit in renal function was found for neither vasodilators or inotropes.[62] Among vasodilators, serelaxin has a microcirculatory rationale for organ protection. In the Pre-RELAX-AHF and RELAX-AHF trials, serelaxin improved markers of cardiac, renal and hepatic injury, in parallel with faster decongestion.[87] In a post-hoc analysis, these changes were associated with better survival.[87]

## Adverse effects

Hypotension, when symptomatic or severe enough to compromise organ perfusion, is a significant adverse effect that strongly limits the use of vasodilators. A hypotensive event is a central safety criterion in studies of AHF, but its definition is arbitrary, leading to large variations in clinical interpretation and incidence. In the serelaxin trials, including AHF patients with normal or high SBP, the definition was prespecified, closely monitored, and consisted both of an absolute low SBP value <100 mmHg or a reduction from baseline of more than 40 mmHg.[92] These studies found an incidence of 23% of in-hospital hypotensive episodes and a SBP drop below 100 mmHg was associated with higher 14-day and 180-day mortality.[92] Also, early and larger SBP decrease was associated with worsening renal function in clinical trials.[93] In a retrospective analysis including AHF patients treated with

SNP, severe hypotension defined as mean arterial pressure (MAP) <65 mmHg was observed in only 5% patients and had no adverse clinical consequence.[94] This is probably due to the short acting life of NO that makes SNP easy to titrate.

Headache is reported with an incidence of 10–12%[62,95] and dizziness may also occur in 15–30% of AHF patients.[95] The reflex tachycardia encountered with nitroglycerine is common and may be deleterious, particularly in acute coronary syndrome (ACS) settings or acute valvular heart diseases.[96]

Organic nitrates can cause tolerance when used continuously.[96] Continuous nitrate exposure leads to a depletion of sulfhydryl groups (allows nitrates to activate guanylate cyclase-mediated smooth muscle relaxation), limiting persistence of vasodilatory capabilities.[96] This combination of decreased functionality and increased inactivity leads to reversal of the physiologic benefits of nitrate and to the development of tolerance. Discontinuation of nitrate administration produces restoration of the sulfhydryl groups and reestablishment of haemodynamic benefit.[96]

Distinct from tolerance, there is a phenomenon that has been referred as pseudo-tolerance. Continuous administration of nitrates leads to compensatory neurohormonal activation with increase in plasma renin activity, angiotensin II, norepinephrine, and arginine vasopressin, which may lead to adverse vascular and volume effects, increasing intravascular volume and leading to reversal of nitroglycerine haemodynamic benefits.[96]

One significant side effect specific to SNP is cyanide/thiocyanate toxicity, with an incidence of 12–16%.[97–99] Risk factors include hypoalbuminaemia, infusion rates above 2 μg/kg/min, and higher cumulative doses.[97–99]

## Review of randomized clinical trials with vasodilatation in acute heart failure

There are a multitude of RCTs with vasodilator agents in AHF (*Table 3*).[100–121] The main rationale behind these trials was the assumption that early short-term interventions that attenuate cardiac wall stress may reduce myocardial injury during a critical period and have favourable long-term effects by decreasing fibrosis and remodelling. However, the results of these RCTs demonstrated that no IV vasodilator agent has translated its use from pathophysiological evidence and acute haemodynamic improvement to clinical and prognostic benefit (*Graphical Abstract*). These trials include IV vasodilator therapies during hospitalization for AHF (such as in nesiritide in ASCEND-HF, ularitide in TRUE-AHF, serelaxin in RELAX-AHF-2), early IV nitrate boluses in the ELISABETH trial and comprehensive vasodilator regimen in the GALACTIC trial. Also, in the PRONTO trial[113] enrolling AHF patients with SBP >160 mmHg, although clevidipine significantly improved dyspnoea compared to standard of care, the effects on 30-day hospitalizations were non-significant.

There may be several explanation for the lack of clinical benefit of vasodilators: (i) indiscriminate use of vasodilators in AHF, including agents such as organic nitrates/hydralazine in HFpEF patients, for which fundamental research suggests unlikely benefit even in terms of haemodynamics; (ii) using vasodilators as an isolated strategy; while it is likely that vasodilators could promote better volume decongestion, even efficient volume redistribution may not be sufficient after the initial treatment phase[57,122]; (iii) individual variability of vasodilatory response with larger SBP drop; (iv) expecting improvement in long-term cardiovascular outcomes following a short-term therapy that does not alter the underlying cardiovascular substrate may not be possible.[123,124]

Compounds belonging to the natriuretic peptide family, such as nesiritide and ularitide, showed the expected beneficial improvement in short-term haemodynamics but without conclusive evidence in improving long-term cardiovascular outcomes.[105,111,115,125–130]

A 'biased' ligand of the angiotensin II type 1 receptor, that selectively antagonizes the vasoconstrictor effects of angiotensin II, while preserving the potential pro-contractility effects of $AT_1$ receptor stimulation, did not confer any symptomatic or survival benefit over placebo.[116]

In RELAX-AHF-2, 48-h infusion of serelaxin neither reduced 180-day cardiovascular deaths, nor reduced the incidence of short-term worsening HF.[119]

The systematic, wide and unselected use of nitrates, in the ED, was investigated in the ELISABETH trial. A care bundle was utilized in AHF patients older than 75 years (echocardiography was not required for inclusion).[120] In the usual care arm, only a quarter of the patients received IV nitrates as compared to 96% in the intervention arm. There were no differences found on short-term outcomes (number of days alive and out of the hospital at 30 days).[120]

## Randomized clinical trials with oral/sublingual therapies

Acute beneficial haemodynamic effects have been demonstrated with the administration of oral vasodilators. H-ISDN combination was the first therapy to show prognostic benefit in chronic HF in the landmark study V-HeFT I.[131] The next V-HeFT II trial comparing H-ISDN with enalapril showed a trend towards decreased all-cause mortality with enalapril (38.2% vs. 32.8%; $p = 0.08$).[132] Other trials demonstrated unequivocal benefit for ACEI and, subsequently for angiotensin receptor–neprilysin inhibitor (ARNI) too.[133–135]

In the CONSENSUS trial, oral enalapril was initiated in the AHF setting (hospitalized New York Heart Association class IV patients requiring treatment with diuretics).[133] In the PIONEER-HF trial, the in-hospital initiation of the oral ARNI, after patient stabilization, was safe and led to a better natriuretic peptide response along with a trend to lower rates of mortality and rehospitalization compared to enalapril.[134,135] Also, the drug's full titration within 10 weeks was possible in half of the patients in the TRANSITION trial.[136] The early and sustained benefit of ACEI/ARNI initiation in the pre-discharge or early post-discharge phase of AHF is very important given the increased mortality and readmission rates that characterize the vulnerable post-discharge period.[1,137–139] Subsequent to initiation, early and rapid up-titration of ACEI or ARNI was associated with more successful decongestion and better outcomes.[140,141]

**Table 3 Randomized controlled rials using medications with vasodilator properties**

| Trial | Study characteristics | Patient population | Key I/E criteria | Strategy | Primary outcome | Results |
|---|---|---|---|---|---|---|
| Annane *et al.*,[100] 1996 | Placebo-controlled, randomized, double-blind study | Acute pulmonary oedema ($n=20$) | SBP >80 mmHg; rales; PCWP >25 mmHg and no recent MI | IV enalapril 1 mg over 2 h vs. placebo | PCWP and renal blood flow | Significant decrease in PCWP (−37% vs. −10%, $p=0.001$) |
| Hirota *et al.*,[101] 1997 | Double-blind, placebo-controlled, dose-ranging, randomized clinical study | AHF in ED ($n=57$ in 3 groups) | Cardiac index <2.5 L/min/m$^2$; PCWP >15 mmHg; SBP >100 mmHg | IV nicardipine 0.5 μg/kg/min and 1 μg/kg/min vs. placebo | Optimal dose of IV nicardipine | Optimal dose: 1 μg/kg/min<br>Increase CI ($p<0.01$); decrease diastolic PAP ($p<0.01$) |
| Cotter *et al.*,[102] 1998 | Randomized, open-label study | Prehospital with acute pulmonary oedema ($n=110$) | SBP >110/70 mmHg; $SaO_2$ <90% on room atmosphere | IV ISDN bolus: 3 mg at 5 min vs. IV furosemide 80 mg at 15 min | Death, MI, IMV during hospitalization | Difference for mechanical ventilation 13% vs. 40% ($p=0.0041$); difference for MI 17% vs. 37% ($p=0.047$) |
| Sharon *et al.*,[103] 2000 | Randomized, open-label study | Acute pulmonary oedema at hospital admission ($n=40$) | SBP >110/70 mmHg; $SaO_2$ <90% on room atmosphere | ISDN bolus: 4 mg IV at every 4 min vs. BiPAP | Combined endpoint of death, AMI, IMV in the first 24 h of hospitalization | ISDN is safer and better than BiPAP ventilation; incidence of combined endpoint: 85% in BiPAP vs. 25% in ISDN ($p=0.0003$) |
| RITZ-1,[104] 2001 | Double-blind, parallel-group, multicentre, placebo-controlled study | Inpatients with AHF ($n=669$) | Without ACS or hypotension or need for invasive haemodynamics | Tezosentan 50 mg/h vs. standard treatment | Dyspnoea at 24 h | No significant improvement of dyspnoea and higher incidence hypotension, dizziness, and renal failure |
| VMAC,[105] 2002 | Double-blind, double-dummy design in which each patient received simultaneous infusions of NTG/placebo and nesiritide/placebo | Inpatients with rest dyspnoea from decompensated AHF ($n=489$) | Exclusion: CS or SBP <90 mmHg, any contraindication to IV vasodilator, need for IMV and anticipated survival <30 to 35 days | NTG vs. nesiritide vs. placebo | Change in PCWP and dyspnoea at 3 h | Nesiritide decreased PCWP and self-reported symptoms more effectively than IV NTG or placebo.<br>Mean (SD) decrease in PCWP from baseline to 3 h: −5.8 (6.5) mmHg for nesiritide (vs. placebo, $p<0.001$; vs. NTG, $p=0.03$) |
| RITZ-4,[106] 2003 | Multicentre, randomized, double-blinded, placebo-controlled study | Inpatients with AHF and ACS ($n=193$) | Exclusion: SBP <105 mmHg; rapid rate AF or AFl; evidence of digoxin toxicity; acute haemodialysis or ultrafiltration | Tezosentan (25 mg/h for 1 h, then 50 mg/h for 23 to 47 h) vs. placebo | Composite of death, worsening HF, recurrent ischaemia or MI within 72 h | No difference in primary endpoint tezosentan vs. placebo: 24.2% vs. 28.9% ($p=0.51$) |
| RITZ-5,[107] 2003 | Prospective, double-blind, placebo-controlled, multicentre, parallel (1:1), phase III randomized study | Acute pulmonary oedema ($n=84$) | $SaO_2$ <90% already receiving standard treatment Exclusion: SBP <110 mmHg; haemodynamically significant arrhythmias; STEMI | Placebo vs. tezosentan (50 or 100 mg/h) for up to 24 h | Change in $SaO_2$ at 1 h | The study failed to show an improvement of $SaO_2$ after 1 h of tezosentan infusion; change in $SaO_2$ from baseline to 1 h: 9.1 ± 6.3% in the placebo arm vs. 7.6 ± 10% in the tezosentan group ($p=0.29$) |
| VERITAS,[108] 2007 | Randomized, double-blind, placebo-controlled, parallel-group study | Inpatients with AHF already on IV furosemide and randomized within 24 h with persistent dyspnoea ($n=1435$) | Dyspnoea at rest (RR >24 breaths/min); SBP >100 mmHg if not on vasodilators or SBP >120 mmHg if on vasodilators Exclusion: CS, hypotension, STEMI, anaemia, creatinine >2.5 mg/dl | Tezosentan (5 mg/h for 30 min, followed by 1 mg/h for 24 to 72 h) vs. placebo | Change in dyspnoea at 24 h (assessed by VAS) and incidence of death/WHF at 7 days | Tezosentan did not improve symptoms or clinical outcomes in patients with AHF. The incidence of death/WHF at 7 days was 26% in each group (OR 0.99; 95% CI 0.82–1.21; $p=0.95$) |
| Pre-RELAX-AHF,[109] 2009 | Double-blind, placebo-controlled, parallel-group, dose-ranging, randomized clinical study | Inpatients with AHF ($n=234$) | Within 16 h of presentation and SBP >125 mmHg and eGFR 30–75 ml/min/1.73 m$^2$. Already received ≥40 mg IV furosemide or equivalent<br>Exclusion: treated with inotropes, ACS in the last 45 days, significant VHD, severe pulmonary disease | IV serelaxin (10 or 30 μg/kg or 100 or 250 μg/kg) 48 h vs. IV placebo | Dyspnoea relief and combined endpoint: CV death or readmission due to HF or renal failure at day 60 | Favourable relief of dyspnoea; combined incidence of CV deaths or readmission due to HF or renal failure at day 60 was 17.2% in the group receiving placebo and 6.1% in all relaxin groups combined ($p=0.13$).<br>A relaxin dose of 30 μg/kg has been selected for a phase III study (RELAX-AHF-1) |

**Table 3 (Continued)**

| Trial | Study characteristics | Patient population | Key I/E criteria | Strategy | Primary outcome | Results |
|---|---|---|---|---|---|---|
| VELOCITY trial analysis (post-hoc subgroup),[110] 2010 | Open-label, single-arm study | Inpatients with AHF in ED and SBP >180 mmHg ($n=19$) | | Clevidipine continuous infusion up-titrated every 3 min, for 18 to 96 h | Percentage ITR after 30 min (%) and proportion of patients with SBP below ITR within 3 min | ITR was reached in most patients (94%) within 30 min; no hypotension below ITR |
| ASCEND-AHF,[111] 2011 | Randomized, double-blind, placebo-controlled trial of nesiritide in addition to standard care | Inpatient with AHF ($n=7141$) | Dyspnoea at rest (RR ≥20 breaths/min) SBP >100 mmHg, randomized within 24 h, BNP ≥400 pg/ml or NT-proBNP ≥1000 pg/ml.<br>Exclusion: SBP <100 mmHg or 110 mmHg with the use of IV vasodilators, other contraindications for vasodilators, treatment with IV inotropes within the previous 30 days, persistent uncontrolled hypertension, ACS | IV nesiritide up to 7 days vs. placebo | Two coprimary endpoints: change in self-reported dyspnoea 6 and 24 h and the composite endpoint of HF rehospitalization and death from any cause to day 30 | Nesiritide had a small, non-significant effect on dyspnoea at 6 and 24 h<br>No difference in 30-day death/HF (9.4% vs. 10.1%; $p=0.31$) |
| RELAX-AHF,[112] 2013 | Prospective, randomized, double-blind, placebo-controlled, parallel-group trial | AHF patients within 16 h of presentation ($n=1161$) | SBP >125 mmHg and BNP >350 ng/L or NT-proBNP >1400 ng/L and eGFR 30–75 ml/min/1.73 $m^2$. Already received ≥40 mg IV furosemide or equivalent<br>Exclusion: treated with inotropes, MCS in the previous 2 h, ACS in the last 45 days, significant VHD, significant arrhythmias, active infection, severe pulmonary disease | IV serelaxin (30 μg/kg per day) 48 h vs. IV placebo | Primary endpoints: dyspnoea improvement by change from baseline in VAS to day 5 and the proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale during the first 24 h | Serelaxin was associated with dyspnoea relief but had no effect on readmission to hospital and did not significantly increase the days alive out of hospital at day 60. Serelaxin treatment was well tolerated and safe, supported by the reduced 180-day mortality.<br>Dyspnoea reliefon VAS scale (95% CI 120–775; $p=0.007$) |
| PRONTO,[113] 2014 | International 13-centre, prospective randomized, open-label, active control, safety and efficacy trial | AHF patients in ED ($n=104$) | SBP >160 mmHg and dysponea score >50 mm on VAS<br>Exclusion: endotracheal intubation, had contraindications to clevidipine, received any antihypertensive agent within the previous 2 h, or had chest pain or ischaemic ECG changes, suspected aortic dissection, AMI within 14 days, pregnancy, known liver or renal failure, or pancreatitis | IV clevidipine titrated at 3 min (from 2.0 to 32.0 mg/h) vs. usual care | Co-primary endpoints were median time to, and percent attaining, a SBP within a prespecified target BP range at 30 min. Dyspnoea reduction was the main secondary endpoint | Significant greater BP target met (71% vs. 37%; $p=0.002$) |
| RELAX-AHF-Japan,[114] 2015 | Multicentre, randomized, double-blind, placebo-controlled phase II clinical trial | Inpatients with AHF ($n=46$) | Same as Pre-RELAX-AHF | IV serelaxin (10 and 30 μg/kg) 48 h vs. placebo | AEs through day 5, serious AEs through day 14 and pharmacokinetics of serelaxin | No AEs of concern<br>Favourable beneficial trends on efficacy |
| BLAST-AHF,[116] 2017 | Multicentre, international, randomized, double-blind, placebo-controlled, parallel group, phase IIb dose-ranging study | Inpatient with AHF ($n=621$) | AHF with elevated natriuretic peptides (BNP >400 pg/ml or NT-proBNP >1600 pg/ml), SBP 120–200 mmHg, prior HF decompensation, eGFR 20–75 m/min/1.73 $m^2$<br>Exclusion: use of ARBs within 7 days prior, IV inotropes or vasopressors within 2 h prior, or IV nitrates within 1 h prior to randomization | TRV027 (1, 5, or 25 mg/h) for 48–96 h vs. placebo | Composite endpoint including: time from baseline to death through day 30, time from baseline to HF hospitalization through day 30, the first assessment time point following WHF through day 5, change in dyspnoea by VAS score from baseline through day 5, and length of initial hospital stay from baseline | TRV027 did not confer any benefit over placebo at any dose with regard to the primary composite endpoint or any of the individual components |

**Table 3 (Continued)**

| Trial | Study characteristics | Patient population | Key I/E criteria | Strategy | Primary outcome | Results |
|---|---|---|---|---|---|---|
| TRUE-AHF,[115] 2017 | Randomized, double-blind, parallel-group, placebo-controlled, event-driven trial | Inpatients with AHF randomized in the first 12 h from initial clinical evaluation ($n = 2157$) | Unplanned ED visit or hospitalization for AHF, dyspnoea at rest, BNP level >500 pg/ml or NT-proBNP >2000 pg/ml, and SBP 116–180 mmHg<br>Exclusion: ACS or any mechanical cause of AHF, myocarditis, IV inotropes, need for MCS, active infections, severe hepatic or renal dysfunction, pregnancy | Ularitide 15 ng/kg/min for 48 h vs. placebo | Two primary endpoints: CV death over the entire duration of the trial and the clinical course of patients during the first 48 h | Ularitide did not affect a clinical composite endpoint nor reduce long-term CV mortality (CV mortality: 21.7% vs. 21.0%; HR 1.03; 96% CI 0.85–1.25; $p = 0.75$) |
| GALACTIC,[117] 2019 | Randomized, open-label blinded-endpoint trial | Inpatients with AHF ($n = 788$) | AHF admission, BNP >500 ng/L or NT-proBNP >2000 ng/L, and SBP >100 mmHg. Exclusion: immediate ICU/ICCU admission or SBP <100 mmHg or creatinine >2.8 mg/dl | Combo of topical/SL/PO nitrates/hydralazine for 48 h (with rapid up-titration of ACEI/ARB/ARNI) vs. usual care | Composite of all-cause mortality or rehospitalization for AHF at 180 days | Early intensive and sustained vasodilatation, compared with usual care did not significantly improve a composite outcome of all-cause mortality and AHF rehospitalization at 180 days (adjusted HR 1.07, 95% CI 0.83–1.39; $p = 0.59$) |
| RELAX-AHF-EU,[118] 2019 | Multicentre, prospective, randomized, open-label, blinded-endpoint validation study | Inpatients with AHF ($n = 2666$) | Presented within 16 h prior to randomization for AHF with dyspnoea, pulmonary congestion on chest-X ray, BNP ≥500 pg/ml or NT-proBNP ≥2000 pg/ml, SBP ≥125 mmHg, and eGFR 25–75 ml/min/1.73 $m^2$, and received at least 40 mg furosemide | IV serelaxin (30 μg/kg/day) 48 h vs. placebo | Adjudicated in-hospital WHF or all-cause death through day 5 | Serelaxin reduced adjudicated in-hospital WHF or all-cause mortality through day 5 when added to standard care.<br>Reduced WHF or all-cause death through day 5 (5.0% vs. 6.9%; HR 0.71; 95% CI 0.51–0.98; $p = 0.0172$) |
| RELAX-AHF-2,[119] 2019 | Multicentre, double-blind, placebo-controlled, event-driven trial | Inpatients with AHF randomized in the first 16 h ($n = 6545$) | The same as Pre-RELAX-AHF and RELAX-AHF-EU | Serelaxin (30 μg/kg/min) for 48 h vs. placebo | Two primary efficacy endpoints: CV death at 180 days and WHF at 5 days | Serelaxin did not result in a lower incidence of 180-day CV deaths (OR 0.98; 95% CI 0.83–1.15; $p = 0.77$) or WHF at 5 days (OR 0.89; 95% CI 0.75–1.07; $p = 0.19$) |
| ELISABETH*,[120] 2020 | Multicentre, unblinded, open-label, superiority, stepped-wedge, cluster randomized clinical trial | AHF patients in 15 EDs in France ($n = 502$) | Patients with AHF and age >75 years, SBP >100 mmHg.<br>Exclusion: sepsis, STEMI, contraindication to nitrates, SBP <100 mmHg, time from entrance in ED to inclusion >6 h | Guideline-recommended care bundle for the early management of AHF (stepped wedge: 4-h care package-diuretics/nitrate boluses) + management of precipitating factors (ACS, AF) vs. usual care | The primary endpoint was the number of days alive and out of hospital during the 30-day period after the ED visit | A guideline-based comprehensive care bundle in the ED compared with usual care did not result in a significant difference in the number of days alive and out of the hospital at 30 days (adjusted OR 0.88, 95% CI 0.64–1.21) |
| STAND-UP AHF (phase IIb),[121] 2021<br>controlled ascending dose clinical trial | International, multicentre, randomized, double-blind, placebo- | Inpatients with AHF ($n = 322$)<br>phase I, randomized in the first 18 h; 97 patients<br>phase II, randomized in the first 48 h; 214 patients | Hospitalized for AHF, BNP >400 pg/ml or NT-proBNP >1600 pg/ml requiring treatment with IV loop diuretics. Patients were required to have a history of chronic HF with LVEF <40% within the previous 18 months and SBP 105–160 mmHg.<br>Exclusion: receiving IV vasodilators or IV inotropic agents at the time of randomization, SBP <105 mmHg or >160 mmHg | IV cimlanod (3–12 mg/kg/min) 48 h vs. placebo | Incidence of clinically relevant hypotension (SBP <90 mmHg or symptoms of hypotension) up to 6 h after end of cimlanod infusion | Cimlanod (6 mg/kg/min) in patients with AHF and LVEF <40% improved congestion at the cost of a modest increase in hypotension rates.<br>Clinically relevant hypotension: phase I, 20% vs. 8% (relative risk 2.45; 95% CI 0.83–14.53); phase II, 18% for placebo, 21% for cimlanod 6 μg/kg/min (relative risk 1.15; 95% CI 0.58–2.43), and 35% for cimlanod 12 μg/kg/min (relative risk 1.9; 95% CI 1.04–3.59) |

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AE, adverse event; AF, atrial fibrillation; AFl, atrial flutter; AHF, acute heart failure; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BiPAP, bilevel positive airway pressure; BNP, B-type natriuretic peptide; BP, blood pressure; CI, confidence interval; CS, cardiogenic shock; CV, cardiovascular; ECG, electrocardiogram; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; ICCU, intensive coronary care unit; ICU, intensive care unit; I/E, inclusion/exclusion; IMV, invasive mechanical ventilation; ISDN, isosorbide dinitrate; ITR, initial target range; IV, intravenous; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MI, myocardial infarction; NTG, nitroglycerine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PO, per os; RR, respiratory rate; SAE, serious adverse event; $SaO_2$, arterial oxygen saturation; SBP, systolic blood pressure; SD, standard deviation; SL, sublingual; STEMI, ST-elevation myocardial infarction; VAS, visual analogue scale; VHD, valvular heart disease; WHF, worsening heart failure.

The GALACTIC trial investigated the use of H-ISDN in AHF and elevated natriuretic peptides, irrespective of LVEF.[117] The intervention arm received sublingual nitrates followed by high and maximally tolerated blood pressure-adjusted doses of transdermal nitrates and oral hydralazine, while in the usual care group, only low transdermal nitrate doses. Starting at day 2, patients had ACEI/angiotensin receptor blocker/ARNI initiated/up-titrated, reaching maximum daily recommended doses through days 4–7. There were no significant differences in the primary endpoint of 180-day all-cause death or HF rehospitalization. The GALACTIC trial enrolled patients in the ED and had a shorter time from ED presentation to randomization (median 5 h) than other AHF studies. The trial was not designed to assess the individual effect of the H-ISDN strategy versus fast renin–angiotensin–aldosterone system inhibitor (RAASI) up-titration.[117] A strategy of RAASI up-titration after AHF discharge was recently proven to have efficacy in the STRONG-HF trial.[142]

In the most recent meta-analysis, including 46 RCTs that enrolled 28 374 patients, vasodilators did not reduce all-cause mortality or length of stay in patients with AHF.[143] Despite extensive subgroup analyses and analytical adjustments made to accommodate the type of vasodilator agent and patient groups (acute decompensated HF or APO), the result of this meta-analysis supports the conclusion that vasodilators do not significantly affect all-cause mortality, regardless of clinical settings and type of vasodilator. However, vasodilators were associated with reduced invasive mechanical ventilation rates.[143]

# Clinical settings

## Acute coronary syndrome-related acute heart failure

The combination of AHF and ACS is common[18] and associated with a higher risk of short-term mortality.[144]

In patients with ACS, intravenous nitrates are guideline-recommended in patients with uncontrolled hypertension or signs of HF in both ST-elevation myocardial infarction (STEMI) or non-STEMI settings, when SBP >90 mmHg in order to improve symptoms and reduce congestion, provided there is no right ventricular infarction, or use of phosphodiesterase type 5 inhibitors in the previous 48 h.[145,146] In addition, the 2017 STEMI guidelines suggest that nitrates should come as a second-line therapy, as hypertension should be initially treated with ACEI.[145] IV SNP should be considered for the severely hypertensive patients, to control blood pressure and improve HF symptoms.[145,146] The safety of SNP in ACS relies on two seminal studies, performed in the pre-revascularization era. In one study, SNP infusion during the first 24 h after anterior acute myocardial infarction, was associated with less complications (cardiogenic shock, worsening HF, worsening renal function).[147] In the second trial, 812 patients with acute myocardial infarction and elevated LV filling pressures received a 48-h infusion of SNP. Despite no significant overall mortality benefit, a secondary analysis suggested a beneficial effect in those whose infusions were begun later than 9 h.[148]

## Left-sided valvular regurgitation and acute heart failure

Early surgery is the most important therapy in patients with severe aortic/mitral organic regurgitation; the objective of medical therapy is only short-term improvement of cardiovascular performance. Vasodilators may have a role in optimizing short-term haemodynamics until establishing cardiopulmonary bypass.[149,150] The proof of haemodynamic benefit comes from studies performed in patients with severe chronic regurgitant valvular lesions that evolved to severe symptomatic HF. In both acute mitral (MR) and aortic regurgitation (AR), nitrates can be used to reduce filling pressures and SNP also reduces afterload and regurgitant fraction.[149,151]

There is a profound lack of data for medical therapy using vasodilators in the AR and AHF setting. In severe chronic AR and HF, SNP will effectively improve preload and afterload. In addition, titrating SNP administration to a 15% decrease in SBP was rapidly followed by a consistent increase in CI, LVEF, and by a reduced regurgitant fraction.[54,149,152,153] The administration of other vasodilators such as IV hydralazine and sublingual nifedipine has been associated with decreased SVR, but with inconsistent effects on cardiac performance (SV, CI), distinct from those described with SNP.[154–156]

In patients with severe MR, the administration of SNP, titrated to a MAP of 70–75 mmHg, significantly reduced pulmonary artery pressure and PCWP in parallel with improving LVEF and SV.[157] Results are consistent with those reported in other haemodynamic studies.[153,158]

There is a perceived increased risk of hypotension when using vasodilators in aortic stenosis (AS), as patients commonly have small ventricles and are preload-sensitive.[159] As low CI or low LVEF in AS represents the consequences of afterload mismatch, reducing afterload may actually improve LV performance at least in some patients.[160] Among vasodilators, SNP has been studied in the most vulnerable AS clinical settings. In an invasive haemodynamic study, SNP improved cardiovascular performance in low-gradient severe AS with preserved LVEF, both when SV is reduced or normal.[161] The increase of effective aortic valve area was reported in 25% of patients and SV increased in patients who had initially lower flow. Khot *et al.*[56] investigated the administration of SNP in 25 critically ill patients with severe AS with severely reduced LVEF and low flow (including preserved/low gradient) and having a baseline MAP >60 mmHg. CI and transaortic pressure gradients significantly increased, while SVR decreased at 6 and 24 h, irrespective of baseline gradient.[56]

## Pulmonary hypertension

Several pulmonary vasodilators have been tested in patients with pulmonary hypertension (PH) in the context of left-sided heart disease with diverse results (group 2 PH). Trials are mostly single-centre, with heterogeneous inclusion criteria and no evaluation of long-term clinical outcomes.[162] Two trials with the endothelin receptor antagonist bosentan, and the MELODY-1 with macitentan[163] showed increased risk of HF, owing to fluid retention.

The FIRST study with the prostaglandin epoprostenol in HFrEF was interrupted prematurely due to a trend towards increased mortality.[164] Due to these results, current guidelines do not support the use of pulmonary rterial hypertension-specific therapy in patients with group 2 PH.[165]

Patients with PH may present with acute right ventricular failure. In this context, there is a need to reduce right ventricular afterload, and usually parenteral prostacyclin analogues are used, often with other drugs indicated for arterial PH.[165]

In patients with right HF due to a variety of heart and lung diseases, levosimendan was well tolerated and improved right ventricular function and reduced systolic pulmonary artery pressure and pulmonary vascular resistance, with no significant changes in mean pulmonary pressure.[166] In patients with left ventricular assist device and resistant PH, NO, inhaled prostacyclin or oral phosphodiesterase type 5 inhibitors may be beneficial.[167]

## Acute pulmonary oedema

The only convincing evidence for the use of IV vasodilators is for ISDN when compared to the alternate therapy with diuretics and non-invasive ventilation, in the setting of hypertensive pulmonary oedema, where disproportionate elevation of filling pressures is related to high blood pressure. ISDN boluses improved the composite endpoint of death, need for mechanical ventilation and myocardial infarction.[103,104] In a contemporary, large-scale, real-world database of AHF patients presenting with APO, vasodilator use was not universally associated with improved in-hospital outcomes.[168] However, its effect might be highly dependent on individual clinical presentation, and in the subgroup analysis, AHF patients with high SBP and those without atrial fibrillation had better outcomes with vasodilator use.[168]

## Advanced heart failure

Patients with advanced HF have severe cardiac dysfunction, and optimization of the haemodynamic alterations provides the rationale for the use of vasodilators.[169] In patients with advanced HF and low-output SNP produced a more significant reduction in intracardiac pressures and increase in CI compared to control, and facilitated transition to an oral vasodilator regimen over standard therapy at the time of discharge.[170] SNP infusions were also safer and more effective than dobutamine in relieving severe HF symptoms.[171] Levosimendan use in ambulatory intermittent infusions may be another strategy but supported by conflicting evidence. In the LevoRep study, pulsed infusions in outpatients failed to show an improvement of functional capacity or quality of life as compared with placebo,[172] while in the LION-HEART study, levosimendan achieved reduced NT-proBNP levels and less worsening of health-related quality of life and HF hospitalization.[173]

## Specific patient populations

The retrospective analysis of several HF clinical trials suggested racial differences for the clinical benefit of the vasodilatory agents. Pooled analyses according to race in the SOLVD studies have shown significant differences between blacks and whites in the response to vasodilator agents, and enalapril was associated with a significant reduction in the risk of HF hospitalization among white patients, but not among black patients.[174] Similarly, in V-HeFT II, enalapril was more efficacious than H-ISDN in whites in reducing mortality, but not in blacks.[132,175] On the other hand, secondary analysis of the V-HeFT trials[131,132,176] suggested that there might be a race-dependent response to H-ISDN therapy, that produced a greater clinical benefit in black patients than in white patients. The hypothesis drawn from these observations was explored in the A-HeFT trial where H-ISDN added to HF standard therapy increased survival among black patients.[177]

The race-dependent response to H-ISDN may be due to biological differences, such as variations in NO homeostasis and the cardiovascular response to NO. Experimental data revealed that blacks have differences in NO homeostasis and impairments in NO-mediated cardiovascular effects compared with whites.[178,179] Since ISDN acts as an NO donor and hydralazine prevents NO degradation through its antioxidant properties, it is possible that the NO-mediated effects of H-ISDN could be responsible for the preferential treatment benefit in blacks.

No racial differences have been reported for ARNI, and in a pooled analysis of two global HF trials[180] and the benefits of ARNI were consistent across races.

# Guideline perspective and practical recommendations

## 2021 European Society of Cardiology recommendation and the change from 2016 to 2021

The use of IV vasodilators was downgraded in the 2021 ESC HF guidelines due to the neutral results of the GALACTIC and ELISABETH studies.[117,120] Thus, IV vasodilators are only currently indicated as an initial treatment in patients with AHF and SBP >110 mmHg, preferably in presence of APO.[1] The 2021 HF guidelines recommend that IV vasodilators may be given if SBP is high, with a goal to reduce LV afterload.[1] However, the numerical threshold of SBP, considered as 'high', is not mentioned. In one recent study, the survival benefit of IV vasodilator was seen only in APO patients with SBP >180 mmHg.[168]

Nitroglycerine, ISDN and SNP are the agents mentioned by the 2021 ESC HF guidelines (online supplementary *Table S21* of the original publication).[1] Both the 2021 ESC[1] and 2022 American Heart Association/American College of Cardiology (AHA/ACC) guidelines[181] gave the same class of recommendation.

### Monitoring vasodilator use

When using vasodilators, the 2021 ESC HF guidelines recommend to monitor their effects by checking evolution of clinical signs and symptoms and blood pressure, with the main goal of promptly modifying or discontinuing vasodilators if patients develop hypotension.[1] The 2017 ACC/AHA guidelines on management of high

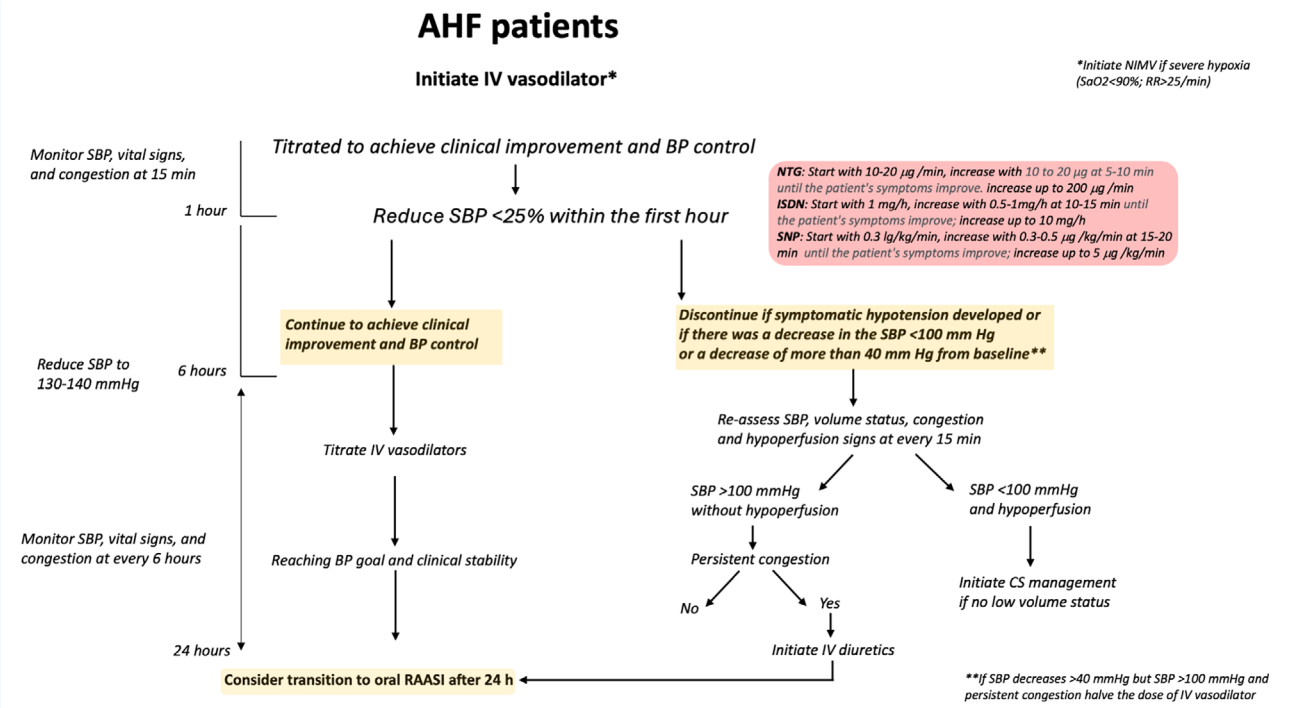



**Figure 4** Flowchart for use of intravenous (IV) vasodilators in acute heart failure (AHF). *If AHF clinical presentation is with SaO2<90% and RR>25/min, NIMV should be initiated before IV vasodilators. BP, blood pressure; CS, cardiogenic shock; ISDN, isosorbide dinitrate; NIMV, non-invasive mechanical ventilation; NTG, nitroglycerine; RAASI, renin–angiotensin–aldosterone system inhibitor; RR, respiratory rate; $SaO_2$, arterial oxygen saturation; SBP, systolic blood pressure; SNP, sodium nitroprusside.

blood pressure recommend reducing SBP to a maximum of 25% within the first hour; then, if the patient is clinically stable, lower blood pressure to 160/100 mmHg over the next 2–6 h, and then cautiously to normal values over the following 24–48 h.[182] For patients with APO, a similar recommendation has been provided by a recent document,[183] and SBP should be decreased initially by approximately 25% (first hour) and cautiously thereafter. There is very few RCT evidence to suggest how rapidly or how much blood pressure should be lowered in AHF patients with high SBP. In Cotter's study,[102] treatment was continued until oxygen saturation increased to at least 96% or mean arterial blood pressure decreased by at least 30%. In the PRONTO trial,[113] a minimum of 15% SBP reduction from baseline with a range of 20–40 mmHg has been considered as treatment target in the first 30 min. In AHF clinical trials,[112,115,119] the study drug was reduced or discontinued if symptomatic hypotension developed or if there was a decrease in SBP to a value of <100 mmHg or a decrease of more than 40 mmHg from baseline. In addition, time intervals to monitor SBP varied across RCTs and are not specified in HF guidelines. However, a consensus document suggested that measurements of vital signs, including SBP, should be repeated at intervals based on the changing clinical status of the patient.[184] For patients severely ill or with a very dynamic clinical profile, this may be every 15 min. In those patients whose clinical profile changes gradually and who are less severely ill, this could be as infrequent as three to four times daily.[184] A flowchart for the monitoring of vasodilator use is proposed in *Figure 4*.

Whether there is an optimal SBP or MAP target in AHF is a matter of debate. In a retrospective analysis of four serelaxin RCTs, a 6-h SBP of 130 to 140 mmHg was associated with the best short- and long-term prognosis.[92] For IV SNP, a SBP target of >90 mmHg was safe, effectively guiding reduction of left-sided filling pressures without requiring invasive pulmonary artery monitoring.[185] The GALACTIC trial used the same SBP interval target of 90–100 mmHg, which was proved to be safe.[117] MAP may be more representative for SVR and thus to a more adequate perfusion target potentially preventing organ damage. MAP target between 65 and 70 mmHg was also used for administering SNP therapy in advanced HF patients.[170] In the studies including patients with severe AS, patients were excluded from the use of SNP only when MAP <60 mmHg.[56,161]

## Future perspectives and unmet needs

Loop diuretics have remained the mainstay of AHF treatment even when guideline recommendations were stronger for vasodilators. Retrospective data from observational studies provided controversial evidence for the improvement of outcomes with the use of IV vasodilators. Data from the ALARM-HF registry showed mortality was lowest in patients where vasodilators were added to diuretics for in-hospital treatment (mortality for patients receiving diuretics + vasodilators vs. patients receiving diuretics alone: 7.6% vs.

14.2%; $p < 0.0001$).[186] In contrast, a large US retrospective analysis showed that the addition of IV nitrates/nesiritide to IV diuretics for the treatment of 82 808 patients with AHF did not improve cardiovascular mortality and actually generated significant costs.[187] RCT data showed no survival benefit with vasodilators in AHF. Also, the most recent meta-analysis showed that vasodilators do not significantly affect all-cause mortality, regardless of clinical settings and type of vasodilator.[143]

In the contemporary RCTs, there is a wide timespan from patient admission to AHF intervention (1–28 h), which may lead to an underestimation of the potential effect of vasodilators. Because vasodilators are often administered during emergency treatment at hospital admission, trials enrolling patients several hours later may risk only including patients who have been stabilized, which is not reflective of typical clinical practice and may restrict the applicability of the results. To avoid bias due to stabilization of patients before the intervention, future research should prioritize early intervention that aligns with real-life clinical practice and consider comparison of strategies of usual care, potentially using waiver of informed consent. In addition, a more precise phenotyping of AHF patients (lower EF, higher SBP, hypoxia, APO settings), as well as a protocolized administration to avoid hypotension events, may contribute to a potential benefit of vasodilators in future RCTs.

Alternative mechanisms of action to the classical pathway of direct vasodilatation are being explored. This is the case of adrecizumab, which stabilizes the vasoactive peptide hormone adrenomedullin and its redistribution from tissue into blood plasma without blocking adrenomedullin receptor signalling.[188]

Acute HF trials have investigated promising drugs, but generally have yielded negative/neutral results. Although survival and readmissions are the standard endpoints for RCTs, these standards may be too high to achieve because of the inability of a relatively short-term intervention to impact longer-term outcomes. Rapid in-hospital improvement of haemodynamics, symptoms and quality of life without altering safety outcomes could be more appropriate clinical objectives.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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