

Consensus Statement

Clinical and Research Considerations for Patients With Hypertensive Acute Heart Failure: A Consensus Statement from the Society of Academic Emergency Medicine and the Heart Failure Society of America Acute Heart Failure Working Group

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ABSTRACT

Management approaches for patients in the emergency department (ED) who present with acute heart failure (AHF) have largely focused on intravenous diuretics. Yet, the primary pathophysiologic derangement underlying AHF in many patients is not solely volume overload. Patients with hypertensive AHF (H-AHF) represent a clinical phenotype with distinct pathophysiologic mechanisms that result in elevated ventricular filling pressures. To optimize treatment response and minimize adverse events in this subgroup, we propose that clinical management be tailored to a conceptual model of disease based on these mechanisms. This consensus statement reviews the relevant pathophysiology, clinical characteristics, approach to therapy, and considerations for clinical trials in ED patients with H-AHF. (*J Cardiac Fail* 2016;22:618–627)

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Pathophysiology of Hypertension in Acute Heart Failure

Hypertensive acute heart failure (H-AHF) is defined as the rapid onset of pulmonary congestion in the setting of a systolic blood pressure >140 mm Hg, and often >160 mm Hg.¹ Many patients with H-AHF have a history of poorly controlled hypertension.² The consequences of longstanding hypertension include changes to both the vasculature as well as the left ventricle (LV), resulting in increased stiffness and reduced compliance across the cardiovascular system.^{3,4} Such stiffening increases systolic load on the LV myocardium, triggering intra- and extracellular adaptations that tend to normalize systolic and diastolic sarcomere stress.¹ Many of these changes occur at the expense of LV compliance and ultimately lead to clinically significant diastolic dysfunction.^{5,6} As the functional ventricular-vascular relationship becomes uncoupled, the LV has insufficient cardiac reserve to compensate for the increases in afterload and preload that accompany hypertensive episodes and physical exertion.⁷ As a result, the poorly compliant cardiovascular system with chronic hypertension responds with larger changes in LV filling pressure for a given change in preload or afterload.⁸ Therefore, it is important that therapy for H-AHF includes interventions to both improve vascular compliance and reduce intravascular filling pressure.

Vascular Dysfunction and Its Role in Acute Heart Failure

Normal cardiovascular function requires close integration between the heart and vasculature to provide adequate blood flow to the vital organs and periphery.⁹ A compliant aorta acts as a capacitor, reducing the peak pressure generated during ventricular systole and promoting continuous forward flow throughout the cardiac cycle. When the force of this flow reaches the junction of medium and small resistance arterioles, vessel expansion and recoil occurs, generating both forward and backward waveforms. While the forward component provides perfusion to target organs through the microcirculation, the reflected wave propagates back up the vascular tree, augmenting central aortic pressure. The net effect is a dynamic process of ventricular-arteriolar coupling that serves as a major determinant of cardiac output, providing a mechanism for adaptive changes in response to metabolic needs.⁹

In patients with chronic hypertension the aorta and large arteries stiffen, enhancing the amplitude and velocity of the reflected pulse wave generated by resistance arterioles.¹⁰ Arterioles also adapt to chronic increases in systemic blood pressure through smooth muscle hypertrophy, a process that normalizes end-arteriolar pressure at the expense of a further increase in large-artery pressure and increased pulse wave velocity. The reflected wave, which normally reaches the central aorta after aortic valve closure, can increase velocity enough to return to the proximal aorta in late systole. This results in

increased load for ventricular contraction and may trigger early aortic valve closure. An immediate consequence of shortened LV systole due to premature aortic valve closure is compromised coronary artery perfusion, as well as increased diastolic volume and pressure, resulting in increased pulmonary venous pressures, predisposing to development of pulmonary congestion.^{11,12} In the setting of compromised ventricular function, the effect of vasoconstriction, especially when abrupt, is harder to overcome, contributing to the onset of H-AHF.

Blood Pressure and Its Relationship to Acute Heart Failure

Large registries have shown that 50% of patients with AHF have elevated blood pressure at presentation to the ED.^{13,14} Moreover, the initial systolic blood pressure is a strong predictor of outcomes, with higher blood pressures associated with lower rates of in-hospital mortality and 30-day myocardial infarction, death, or rehospitalization, as well as a greater likelihood of discharge within 24 hours.^{15,16} These associations may have corresponding anatomic implications as a result of contractile reserve, because higher systolic blood pressure¹⁵ is more often seen in the setting of preserved ejection fraction, with the likelihood of an ejection fraction >40% increasing 3% for every 1 mm Hg presenting systolic blood pressure >120 mm Hg (Table 1).¹⁷ However, presenting blood pressure depends on multiple factors, including medication adherence, making it difficult to reliably predict underlying ejection fraction based on blood pressure alone.

Ultimately, blood pressure summarizes cardiac contractile force relative to the vascular resistance it encounters.^{18,19} Maintenance of blood pressure is tightly regulated by baroreceptors, primarily in the aorta and carotid arteries although renal mechanisms are also involved. Changes in cardiac output and systemic vascular resistance are triggered by sympathetic nervous system and neurohormonal activation in response to baroreceptor-mediated detection of alterations in vascular pressure. Thus, when confronted with increased arterial resistance, a heart with normal contractile reserve is able to maintain cardiac output with a net increase in systolic blood

Table 1. Heart Failure With Preserved Ejection Fraction According to Presenting Blood Pressure

Systolic Blood Pressure (mm Hg)	Proportion With Heart Failure With Preserved Ejection Fraction (%)
110	43.5
120	46.6
130	47.8
140	48.0
160	58.7
180	63.6
200	73.3

From Styron et al.¹⁷

pressure.^{20,21} However, in the setting of chronic hypertension and heart failure (HF), baroreceptor responses shift to be more tolerant to greater tonic pressure and expected responses to acute perturbations may be altered.^{22–24} As a result, cardiac output is not able to rise in response to elevated systemic vascular resistance, making elevated blood pressure a de facto impediment to forward flow.

Intravascular Volume and Its Role in Acute Heart Failure

Elevated cardiac filling pressures are a hallmark of patients presenting with AHF. Although total body sodium and water retention has traditionally been implicated as the main driver for elevated filling pressures, recent studies have shown that many patients do not gain weight before AHF onset.^{25,26} This suggests that both fluid accumulation and redistribution, likely driven by alterations in the autonomic nervous system,²⁷ contribute to AHF. This finding is supported by studies showing changes in heart rate variability and cardiac filling pressure occurring weeks before presentation for AHF, in the absence of a change in weight and before the development of symptoms.²⁸ Although human data are limited, neurohormonal activation of renal sodium and water retention appear to contribute to and may be accompanied by abrupt redistribution of blood volume from vasoconstriction, especially from the splanchnic vascular bed. Mobilization of fluid into the central and pulmonary circulation leads to a dramatic rise in intravascular volume and triggers an acute surge in sympathetic tone.²⁷ Such increases in filling volume also trigger the Frank-Starling mechanism in the right ventricle (RV), which combines a catecholamine-mediated increase in RV contractile force to drive up pulmonary artery and capillary wedge pressures.²⁹

Although volume accumulation and redistribution are responsible for many of the cardinal signs and symptoms of AHF, the history and physical exam findings of dyspnea, elevated jugular venous pressure, S3 gallop, hepatojugular reflux, and peripheral edema have low sensitivity for estimating volume status.³⁰ Bioelectrical impedance vector analysis (BIVA) and inferior vena cava size and collapsibility have been shown to facilitate identification of volume overload in patients with AHF and may be a useful adjunct to clinical assessment.^{31–33} In patients with reduced ejection fraction, direct measurement of blood volume with the use of a radionuclide-dilution technique during AHF has shown a wide range of fluid distribution patterns,³⁴ with most, but not all, showing elevated total body volume. In canine and human models of HF where the arterial sodium and water content were pathologically elevated over control subjects, elevated tissue sodium and water content, specifically in the vasculature, was found to be the likely mechanism for increased arteriolar stiffness and decreased capacitance in HF.^{35,36} In this way, it is not just the accumulation of intravascular volume itself, but where that volume is located that may be particularly important in the setting of H-AHF.

Other Considerations

Age

Heart failure is predominantly a condition of the older population in developed countries where the prevalence increases markedly with age, rising sharply at 75.^{37,38} Older adults, particularly women, are more likely than younger adults to develop HF with preserved ejection fraction, elevated systemic vascular resistance, and impaired ventricular-arteriolar coupling.³⁹ Pulmonary edema in the setting of severe systolic hypertension is a common presentation of AHF in patients with advanced age. With the exception of a small retrospective study suggesting clinical benefit with acute nitrate therapy,⁴⁰ evidence supporting treatment options targeted for elderly patients is limited by their exclusion from and underrepresentation in randomized trials in the acute care setting.

Renal Function

Approximately 30% of patients with chronic HF have moderate to severe renal impairment.⁴¹ Detrimental effects of renin-angiotensin-aldosterone system (RAAS) activation extend to the myocardium and the vasculature, contributing to the pathophysiology in both chronic HF and H-AHF. Maladaptive mechanisms that contribute to progressive renal disease in this setting are also important therapeutic targets in the management of H-AHF. The cardiorenal syndrome is also often present in ED patients with AHF and can be due to both underfilling and venous congestion. Treatment may include vasodilators and diuretics to reduce venous congestion or inotropic agents to improve cardiac output. For those patients with significant venous congestion (enlarged noncollapsible inferior vena cava, jugular venous distention), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers are recommended for patients with renal insufficiency and AHF unless renal dysfunction is severe.⁴² However, patients with HF with reduced ejection fraction and stage 4–5 chronic kidney disease treated in-hospital with an RAAS antagonist appear to have better 1-year survival.⁴³ Despite this, ACE inhibitors and angiotensin receptor blockers are administered less frequently to patients with AHF and severe kidney dysfunction,^{44,45} and more data are needed if current recommendations and clinical practice are to be altered. Worsening renal function (WRF) during AHF is of particular concern in those with baseline renal insufficiency. Diuretics and vasodilators are used to achieve pulmonary decongestion but may be associated with WRF.⁴⁶ RAAS activation has been suggested as a possible underlying mechanism. This may be of greater importance in patients with H-AHF, where volume redistribution may be more prominent than volume overload.

Treatment

Expert opinion, supplemented by small cohort and randomized studies, suggests that initial therapy might best be informed by clinical parameters rather than a typical diuretic-only approach.^{47–49} Although there is no randomized trial

Table 2. Suggested Management of Hypertensive Acute Heart Failure*

Stepwise Approach	Comments
1. Administer oxygen as needed to keep saturation $\geq 95\%$, give sublingual nitroglycerin.	Sublingual nitroglycerin may be repeated up to 1 per minute.
2. If severe dyspnea, consider NIV or intubation.	
3. If blood pressure $>150/100$ mm Hg, add IV nitroglycerin or nitroprusside; if blood pressure falls to <100 mm Hg, stop nitrates or nitroprusside, monitor for persistent hypotension or symptoms. If blood pressure $<150/100$ after sublingual administration and if clinically improved, consider transdermal nitroglycerin.	See text for discussion of these agents.
4. Start IV loop diuretic (furosemide or bumetanide or torsemide) in the setting of volume overload.	Initiate nitrates before diuretics.
5. Assess for severity of illness/high risk: altered mental status persistent, hypoxia despite NIV, hypotension, troponin elevation, ischemic ECG changes, blood urea nitrogen >43 mg/dL, creatinine over 2.75 mg/dL, tachycardia, tachypnea, or inadequate urine output.	
6. Admit to ICU if high severity of illness or risk of decompensation.	
7. Choose discharge or ED observation unit admission if good response to therapy and no need for ongoing intravenous vasodilators, no high-risk features, and good social support. Admit the rest to ICU if any ongoing cardiorespiratory compromise or acute ischemia.	Scoring systems may not reliably identify all patients at risk.

Adapted from Collins and Storrow.⁵⁶ NIV, noninvasive ventilation; IV, intravenous; ECG, electrocardiography; ICU, intensive care unit; ED, emergency department.

*Inclusion: systolic blood pressure >140 mm Hg.

evidence evaluating initial treatment strategies for patients with AHF based on hemodynamics, systolic blood pressure plays a central role in AHF as a predictor of morbidity and mortality.⁵⁰ Accordingly, we suggest that initial treatment may be more effective if it is based on presenting systolic blood pressure.^{47,49,51–55}

Stabilization with noninvasive positive pressure ventilation (NIPPV) is useful in patients with H-AHF who have significant work of breathing (Table 2).⁵⁶ Meta-analyses suggest that it decreases the need for intubation in both ED and hospitalized patients with AHF.^{57–59} A randomized trial of NIPPV in the prehospital setting suggests that it may not affect 7-day mortality or the need for intubation, but it decreases work of breathing.⁶⁰ However, the study was powered for 7-day mortality, not immediate mortality, and whether it has additive value to aggressive use of intravenous vasodilators in H-AHF patients is unclear.⁶¹

The OPTIMIZE-HF investigators reported $\sim 50\%$ of patients with AHF had a systolic blood pressure of >140 mm Hg at presentation; in-hospital mortality was lowest among those with the highest values (189–300 mm Hg).⁵⁰ Intravenous diuretics are the cornerstones of AHF therapy⁶² and a small study suggests that, in patients with AHF, a beneficial vasodilatory effect does occur with diuresis and may be present for up to 24 hours.⁶³ However, the failing heart is sensitive to afterload and some patients may develop pulmonary edema with a systolic blood pressure as low as 150 mm Hg. Prompt recognition and afterload reduction with vasodilators may avoid the need for intubation.⁶⁴ Until recently, evidence regarding the safety and efficacy of vasodilator therapy in AHF was limited.^{65,66} However, data from contemporary studies suggest specific phenotypes of AHF patients, such as those with H-AHF, benefit from intravenous vasodilators.^{53,54,67}

Nitrovasodilators

Nitroglycerin is a short-acting rapid-onset venous and arterial dilator. It decreases mean arterial pressure by preload

reduction and at higher doses by afterload reduction as well. Nitroglycerin has coronary vasodilatory effects and is associated with decreased ischemia, but it should be avoided in patients on phosphodiesterase inhibitors. The choice between intravenous, sublingual, or transdermal routes is often based on symptoms. Sublingual is easily administered, rapidly bioavailable, and can be given as needed. A 10%–20% reduction in blood pressure, leading to reduction in filling pressures, is usually sufficient to improve symptoms of dyspnea. Transdermal nitroglycerin has been demonstrated to reduce filling pressures in patients with HF who had pulmonary artery catheters in place.^{68,69} Owing to slow onset of action, transdermal nitroglycerin should be used after initial therapy has improved clinical status or in patients with less severe symptoms.

When using intravenous nitroglycerin, a starting dose of 35–50 $\mu\text{g}/\text{min}$ is common and titrated upward every few minutes, up to 200–400 $\mu\text{g}/\text{min}$, based on blood pressure (avoiding large drops) and symptoms (Tables 2 and 3). High doses (2 mg by means of repeated intravenous bolus) may be beneficial acutely, and adverse events are uncommon.⁵⁴ Transient hypotension may occur with the intravenous and sublingual forms, and usually resolves after cessation of the drug. If hypotension is persistent, consideration should be given to volume depletion, RV infarct, or an etiology other than AHF causing the current symptoms, and a saline fluid bolus may be administered. Headache is frequent and usually responds to acetaminophen. Despite its common use and pathophysiologic rationale, nitroglycerin has little published efficacy data beyond its effects on symptom resolution.^{70,71}

Nitroprusside is a potent arterial and venous dilator that produces a decrease in blood pressure and LV filling pressure leading to increases in cardiac output. Nitroprusside is generally considered to be more effective than nitroglycerin, despite a small study showing similar hemodynamic responses.⁷² The initial dose is 0.3 $\mu\text{g kg}^{-1} \text{min}^{-1}$, titrated upward every 5–10 minutes based on blood pressure and clinical response (maximum 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$). The major complication is hypotension; rarely cyanide toxicity may occur with high doses, prolonged use, and hepatic or renal impair-

Table 3. Currently Used Medications for Acute Heart Failure

Vasodilators			
Medication	Dose	Onset and duration of effect	Complications
Sublingual NTG	0.4 mg every 1–5 min	Onset: 1–3 min; peak effect: 5 min; duration: 20–30 min	Hypotension
Transdermal NTG	1–2 mg every 6 h	Onset: 15–30 min; peak effect: 2 h; duration: 10–12 h	Delayed transdermal absorption; possible prolonged hypotension
Intravenous NTG	35–50 µg/min (starting dose)	Onset: 2–5 min; peak effect: time of onset; duration: 5–10 min	Headache, hypotension, rarely tachyphylaxis
Sodium nitroprusside	0.3 µg kg ⁻¹ min ⁻¹ (starting dose)	Onset: immediate; peak effect: time of onset; duration: 1–2 min	Hypotension, cyanide/thiocyanate toxicity, coronary steal
Enalaprilat	0.625–1.25 mg IVP every 15 min (max 5 mg)	Onset: within 15 min; peak effect: 2–4 h; duration: 6–12 h	May produce delayed and prolonged hypotension; avoid in pregnancy
Clevidipine	2–32 µg/h	Onset: 1–2 min; peak effect: time of onset; duration: 1–5 min	Lipid formulation; reflex tachycardia
Nicardipine	5–15 mg/h	Onset: 1–2 min; peak effect: by 3 min; duration: up to 1 h	Reflex tachycardia
Diuretics			
Medication	Dose (IV)	Onset and Duration of Effect	Complications
Furosemide	No previous use: 20–40 mg IVP. If prior use: total daily IV dose 1–2.5 times the patient's previous total daily oral dose, divided in half and given IV bolus every 12 hours. If no effect by 20–30 min, increase subsequent dose.	Onset: 15–20 min; peak effect: 1–2 h; duration: 4–6 h	↓ K ⁺ , ↓ Mg ²⁺ , hyperuricemia, hypovolemia; ototoxicity, prerenal azotemia, sulfa allergy
Bumetanide	1–3 mg IV	Onset: within 10 min; peak effect: by 1 h; duration: 2–4 h	Same as above
Torsemide	10–20 mg IV	Onset: within 10 min; peak effect: 1–2 h; duration: 2–4 h	Same as above

Used with permission from Collins and Storrow.⁵⁶ IVP, intravenous push; NTG, nitroglycerin; ↓, decreased.

ment. Though uncommonly used in the acute setting, a historical goal of nitroprusside therapy is rapid reduction of systemic vascular resistance and pulmonary capillary wedge pressure in an effort to prevent the need for endotracheal intubation. Logistical considerations related to the need for close monitoring, often with an arterial line in an intensive care unit, make it less convenient to use.

Loop Diuretics

As previously discussed, not all patients with H-AHF are volume overloaded, so routine diuretic administration may not be necessary when treating this phenotypic variant. Despite vasodilator therapy and blood pressure control, patients with H-AHF may still require diuretics (Table 3) for continued symptoms or evidence of excess fluid accumulation. Successful management of blood pressure and filling pressure often results in marked improvement in respiratory status before any diuresis. Furosemide has been used most commonly, but

alternatives include bumetanide (1 mg equivalent to 40 mg furosemide) and torsemide (20 mg equivalent to 40 mg furosemide). All trigger rapid diuresis after an intravenous dose, often within 10–15 minutes.

Calcium Channel Blockers

Clevidipine and nicardipine (Table 3) are rapidly acting intravenous calcium channel blockers that lower blood pressure by selective arteriolar vasodilation and secondarily increase cardiac output as peripheral vascular resistance declines. Because these agents have no negative inotropic or chronotropic effects, they may be beneficial in H-AHF. In an open-label trial in patients with H-AHF, clevidipine was more effective than nitroglycerin or nicardipine in rapid control of blood pressure and dyspnea relief.⁵⁵ However, concerns for reflex tachycardia do exist, and this was a small study (n = 104), suggesting further safety and efficacy data on clevidipine and nicardipine are needed.⁷³

ACE Inhibitors and Angiotensin Receptor Blockers

The use of ACE inhibitors and angiotensin receptor blockers has been widely adopted for hypertension and chronic HF, but the utility of intravenous formulations (enalaprilat) for AHF has received very little study.^{74–77} The only significantly large investigation evaluated a subset of patients with AHF after acute myocardial infarction in the medical intensive care unit,⁷⁸ and this cohort is not representative of typical ED patients with H-AHF. Although other studies suggest that enalaprilat is safe, is well tolerated, and may be effective in patients with AHF, the studies suffer from small sample sizes and designs lacking contemporary treatment reflective of standard ED treatment.^{70,79–83} Such observations make it difficult to translate these findings to the ED setting.

Contraindications and Alternatives to Vasodilation

Because all vasodilators lower blood pressure, they are not recommended if there are signs of hypoperfusion or existing hypotension. Flow-limiting preload-dependent cardiovascular states, such as RV infarction, aortic stenosis, and hypertrophic obstructive cardiomyopathy, increase the risk of hypotension associated with vasodilator use.⁵⁶ Combined with acute pulmonary edema, these conditions can be extremely difficult to manage. Patients with AHF and mental status changes in whom an acute neurologic event cannot be readily excluded may also be poor candidates for vasodilation and its associated risk of hypotension.

Considerations for Clinical Trial Design

Similar to other biomarkers, use of systolic blood pressure alone as eligibility criteria inefficiently discriminates AHF patients. Therefore, trials use blood pressure in conjunction with other criteria to identify patients that will likely derive the most net benefit from novel therapy. Another consideration is whether H-AHF is the primary reason for decompensation or secondary to other issues, eg, worsening renal function or acute coronary syndrome. Recent trials report precipitous drops in blood pressure may lead to worse outcomes, and therefore subsequent studies have used higher blood pressure inclusion criteria.^{67,84} The upper limit of systolic blood pressure for eligibility has been debated. Patients with very high systolic blood pressure may improve quickly with appropriately therapy, making symptom improvement a difficult target for new therapies. Focusing enrollment on such patients would therefore make conduct of clinical trials especially challenging because prompt dyspnea resolution may preclude eligibility unless patients were identified early in their course. Also, a rapid response to usual therapy may make it difficult to achieve a clinically significant effect size. This highlights a paradox in AHF that the sickest-appearing patient, such as those with flash pulmonary edema, may have the best outcome.

In contrast, patients with advanced chronic HF may have a low blood pressure and present with milder symptoms, such as fatigue and dyspnea on exertion, yet are at the greatest risk for adverse events. Despite their infrequent use in practice, the absence of “head-to-head” comparisons of novel agents versus traditional vasodilators in patients with elevated blood pressure is a frequent criticism, raising questions as to whether the novel agent is truly going against usual standard therapy. Regardless, the ideal systolic blood pressure range for both current and novel therapies has yet to be determined. The Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) study⁸⁵ targeted patients with systolic blood pressures >125 mm Hg and showed both clinical and biomarker evidence of benefit with serelaxin, suggesting that there may be effect modification within phenotypic subgroups. [Table 4](#) presents the more recent AHF trials and their systolic blood pressure entry criteria at enrollment.^{67,84,86–91}

Conclusion and Future Directions

The hallmark of patients presenting to the ED with H-AHF is an altered relationship between ventricular and vascular function, leading to reduced cardiovascular reserve and an inability to adequately accommodate increases in venous return. Arterioles adapt to chronic increases in arterial pressure associated with hypertension, resulting in increased afterload triggering early aortic valve closure. An immediate consequence is increased diastolic volume and pressure. Subsequent increases in pulmonary venous pressures may result in pulmonary congestion. Many of these patients are older with concomitant renal disease. Preliminary data raise the possibility that future treatment might be better focused on preload and afterload reduction with the use of vasodilators rather than volume removal with the use of diuretics. Clinical trial design has begun to account for patients with H-AHF by raising the minimum enrollment blood pressure, thus limiting the proportion of patients who are likely to develop symptomatic hypotension. Results from several ongoing clinical trials will provide insight into safety and efficacy in this cohort. In addition, it is still unclear whether an upper blood pressure limit is necessary, but reasons to exclude may be more a function of logistics than clinical concern. Future investigations should consider a diuretic-sparing approach, because the pathophysiology of H-AHF strongly supports volume redistribution rather than volume overload. The lower limit of blood pressure for clinical trial enrollment should be investigated to determine the optimal response to investigational agents in this cohort of patients. Similarly, further data are needed to assess the similarities and differences in the pathophysiology and management of H-AHF with reduced versus preserved ejection fraction.⁸

Disclosures

None.

Table 4. Selected Acute Heart Failure Vasodilator Clinical Trials

Trial and Intervention	Year	n*	Systolic Blood Pressure Criteria	Timing of Enrolment	Dyspnea as End Point
VERITAS ^{86,87} Tezosentan vs placebo	2007	1448 (1453) [†]	EXCL: <100 mm Hg or <120 mm Hg in patients receiving a vasodilator	After admission (within 24 hours)	Yes (Primary)
VMAC ⁸⁸ Nesiritide vs nitrates vs placebo	2002	489	EXCL: <90 mm Hg	After admission (no specific time window except need for hospitalization and IV therapy)	Yes (coprimary with PCWP)
Pre-RELAX-AHF ⁸⁹ Serelaxin (4 doses) vs placebo	2009	234	INCL: >125 mm Hg	Within 16 h of presentation, including time spent in the ED	Yes (Part of primary treatment targets)
ASCEND-HF ⁹⁰ Nesiritide vs placebo	2011	7141	EXCL: <100 mm Hg or <110 mm Hg if on IV nitrates	Within 24 h of first IV AHF therapy	Yes (primary)
COMPOSE-EARLY ⁹¹ Cinaciguat (3 doses) vs placebo	2012	160 planned (halted early)	INCL: ≥120 mm Hg	Within 12 h of admission	Yes (primary)
RELAX-AHF 1 ⁶⁷ Relaxin vs placebo	2012	1161	INCL: >125 mm Hg	<16 h from presentation	Yes (primary)
PRONTO ⁵⁵ Clevidipine vs standard-therapy vasodilators [‡]	2012	104	INCL: ≥160 mm Hg		Yes (secondary)
Trials below are either currently enrolling or their results have yet to be reported					
TRUE AHF Ularitide vs placebo	Enrollment completed June 2015	2152	INCL: ≥116 and <180 mm Hg	Within 12 h of presentation	No
BLAST-AHF ⁸⁴ TRV 027 vs placebo	Enrolling	620 (increased from 500)	INCL: ≥120 and ≤200 mm Hg	Within 16 h of presentation	Yes (composite)
RELAX-AHF 2 Relaxin vs placebo	Enrolling	6800 planned (event driven)	INCL: ≥125 mm Hg	Within 16 h of presentation or first IV loop diuretic dose	Yes (composite secondary)

EXCL, exclusion; IV, intravenous; PCWP, pulmonary capillary wedge pressure; INCL, inclusion; ED, emergency department; AHF, acute heart failure.

*Planned enrollment.

[†]VERITAS was discontinued before full enrolment due to improbability of achieving significant treatment effect.

[‡]PRONTO is the only study to enroll H-AHF patients.

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