Current Heart Failure Reports (2019) 16:32–37
https://doi.org/10.1007/s11897-019-0421-4

EMERGENCY MEDICINE (F PEACOCK, SECTION EDITOR)

# Vasodilator Therapies in the Treatment of Acute Heart Failure

Daniel B. Holt Jr[1] · Peter S. Pang[1]

Published online: 14 February 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

## Abstract

**Purpose of Review** Vasodilators are commonly recommended to treat acute heart failure (AHF), yet they are infrequently used. This review aims to evaluate the clinical utility of traditional, historical, and novel vasodilators in the treatment of AHF.

**Recent Findings** No traditional vasodilator (i.e., nitroglycerin) therapy definitely improves short- or long-term outcomes. Despite repeated efforts to develop new pharmacologic treatments, no novel therapy outperforms traditional management. At the present time, we continue to recommend traditional vasodilators, such as nitroglycerin.

**Summary** The use of select vasodilators in the treatment of AHF improves hemodynamics and provides short-term relief; however, data regarding long-term benefits is lacking.

**Keywords** Acute heart failure · Vasodilator(s)

## Introduction

Heart failure (HF) continues to increase in prevalence. It is estimated that 6.5 million Americans have HF [1]. By 2030, > 8 million American adults will have HF [2]. While overall mortality from HF has improved, rates remain high, with 30-day, 1-year, and 5-year post-hospitalization fatality rates of 10.4%, 22%, and 42.3% [3]. As the prevalence of HF increases, presentations for AHF may also increase. AHF represents an even worse prognosis than chronic HF. Annually, > 900,000 American patients with acute heart failure (AHF) will be evaluated in emergency departments (ED). Of these, 80% will be admitted to the hospital [4].

As most patients initially present to the ER, prompt diagnosis and management are imperative. Historically, diuretics have been a mainstay in AHF therapy. Nearly 80% of cases receive IV loop diuretics, according to The Acute Decompensated Heart Failure National Registry (ADHERE). In contrast, only 19% of these patients receive IV vasodilators [5]. This data, although from 2003, is in line with the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology guidelines which emphasize escalating doses of diuretics for the treatment of AHF [6, 7]. As diuretics are covered elsewhere in the Journal, we will focus on vasodilators.

The use of vasodilators has a class IIb level of evidence A recommendation from the ACC/AHA (Table 1). This level of evidence largely stems from studies of nesiritide, the only new FDA-approved AHF therapy in the last 2 decades. Multiple smaller studies and previous reviews demonstrate nitrovasodilators in the emergency setting as safe and do provide acute symptomatic relief [9]. In fact, the use of nitrovasodilators in the treatment of AHF, particularly hypertensive AHF, is recommended in guidelines and supported by emergency medicine literature [10].

As persistently elevated left ventricular (LV) filling pressures predict mortality, the expectation then is that the physiologic mechanisms of vasodilators, such as nitrates, might improve mortality in AHF [11]. Unfortunately, definitive studies focusing on the effects of vasodilators on long-term outcomes and mortality rates have been lacking. Furthermore, with the exception of nesiritide, there is limited data on the longer term safety and efficacy of non-nitrate vasodilators in AHF management [9]. Being knowledgeable about advances in AHF therapies is imperative for the emergency physician, given the increasing prevalence of AHF, along with its high morbidity and mortality. The

This article is part of the Topical Collection on *Emergency Medicine*

✉ Daniel B. Holt, Jr
holt@iu.edu

[1] Department of Emergency Medicine, Indiana University, 720 Eskenazi Ave., Fifth Third Bank Building 3rd Floor, Indianapolis, IN 46202, USA

**Table 1** Recommendations for use of vasodilators in treatment of acute heart failure

| Name of vasodilator | ACC/AHA guideline recommendation [6] | ESC guideline recommendation [7] | ACEP clinical policy recommendation [8] |
|---|---|---|---|
| Nitroglycerin | Class IIb/LOE A | Class IIa/LOE B | LOE B |
| Nesiritide | Class IIb/LOE A | Class IIa/LOE B | LOE C* |
| IV ACEI or SL ACEI | Not mentioned | Not mentioned | LOE C |

*Should not be first-line therapy

following is a brief, focused review of the use of vasodilators in AHF, with a focus on studies from the past 5 years, in addition to classic vasodilator therapies.

## Nitrates

The use of nitrovasodilators (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate) in the treatment of AHF has become widely accepted. At high doses, nitrates lower left ventricular filling pressures as well as reduced systemic resistance through venous and arterial dilation. In principle, these physiologic affects target known derangements in AHF, which might improve outcomes. However, there are no definitive, sufficiently powered randomized controlled trials that have tested the safety and efficacy of nitrovasodilators on outcomes.

A 2013 Cochrane review [12] identified four randomized controlled trials [13–16] comparing nitrovasodilators with other AHF therapies. The inclusion criteria of these studies (634 total patients) varied, with two studies focusing on AHF following myocardial infarction (MI) [13, 14], one excluding patients with MI [15] and one studying AHF regardless of acute coronary syndrome [16]. Two of the studies utilized isosorbide dinitrate [13, 14] and the others nitroglycerin [15, 16]. This review found no significant difference between nitrovasodilators and other therapies in the treatment of AHF.

A broader 2014 systematic review included nine studies utilizing nitrovasodilators (6 nitroglycerin, 2 isosorbide dinitrate, 1 isosorbide mononitrate) in the management of AHF [9]. These studies included a range of 24 to 489 patients and included observational, retrospective, and prospective studies. The authors of this study concluded that nitrovasodilators are safe in the treatment of AHF and may provide a short-term clinical benefit, namely symptom relief. In particular, a 1998 prospective trial randomized 104 patients with AHF to receive either high-dose isosorbide dinitrate (ISDN) with low-dose furosemide versus low-dose ISDN with high-dose furosemide. Patients receiving high-dose ISDN less frequently required intubation and had lower rates of myocardial infarction [17]. Another 2007 non-randomized single-arm study of 29 patients, comparing high-dose bolus nitroglycerin to low-dose nitroglycerin infusion showed improvements in rates of intubation, non-invasive ventilation, intensive care unit admission and hospital length of stay [18]. No inference regarding long-term benefits or mortality reduction was able to be made.

An older nitrovasodilator, sodium nitroprusside, is used in < 1% of cases of AHF [19]. It provides both preload and afterload reduction, as well as dilation of pulmonary vasculature. Due to its risks of producing hypotension and thiocyanate toxicity, its use is typically relegated to the critical care setting [6]. Similar to nitroglycerin, the evidence to support SNP is largely based on smaller studies or retrospective analyses.

With the physiologic mechanism of nitrovasodilators, they are uniquely positioned as first-line agents in the treatment of AHF. While studies do seem to support the use of nitrates in the short-term treatment of AHF, there is no indication at this time of long-term benefits.

## Angiotensin-Converting Enzyme Inhibitors

By disturbing the renin-angiotensin system, ACE inhibitors lead to reductions in preload and afterload. Due to these physiologic benefits and proven mortality benefits, ACE inhibitors are widely used in the treatment of chronic HF with reduced ejection fraction. The use of ACE inhibitors in the treatment of AHF has been less widely observed. In fact, the American College of Emergency Physicians provide only a level C recommendation for the use of ACE inhibitors in the treatment of AHF and it is not mentioned in the ACC/AHA guidelines [20, 21]. While ACEI have appealing theoretical benefits, there are also risks, such as hypotension, kidney injury, and electrolyte disturbances.

Importantly, extrapolating benefits of ACEI from chronic HF to AHF is dubious at best [22, 23]. Furthermore, the benefits of ACEI in chronic HF are relegated only to those with reduced ejection fraction. These studies do not reflect treatment of AHF in the emergency setting, with only 1.2% of patients receiving enalapril in the hospital setting in one study and allowance of up to 14 days before administering enalapril in the other.

A randomized, double-blind, placebo-controlled trial tested the effect of enalaprilat in acute pulmonary edema [24]. In this

study, enalaprilat was administered to 11 patients (20 total patients) with acute pulmonary edema 12–18 h after the acute episode. Many physiologic benefits were observed in patients in the treatment arm, including decreased pulmonary capillary wedge pressures and systemic blood pressures, with an increase in renal blood flow. While mechanistically appealing, larger studies are needed.

## Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide (BNP), a known, beneficial, counter-regulatory hormone. Nesiritide has been used in the treatment of AHF due to its vasodilatory and natriuretic effects. The use of nesiritide in the treatment of AHF has been widely studied and its hemodynamic benefits have been demonstrated repeatedly. Nesiritide has been assigned a class IIb level of recommendation from the ACC/AHA. However, it should be used with caution, similar to other vasodilators, due to risks of symptomatic hypotension with limited demonstrable clinical benefit [6, 25].

Early studies such as the randomized controlled vasodilation in the Management of Acute CHF (VMAC) trial demonstrated significant improvement in dyspnea in patients treated with nesiritide. The VMAC trial included 489 patients and compared those receiving nesiritide to nitroglycerin or placebo [16]. In this study, patients treated with nesiritide had a statistically significant improvement in dyspnea at 3 h. These results were used in the approval of nesiritide by the US Food and Drug Administration [9].

After approval, however, several meta-analyses raised concerns about the safety of nesiritide [26]. As a result, a large outcome trial was designed and reported in 2011. The Acute Study of Clinical Effectiveness of Nesiritide in Heart Failure (ASCEND-HF) included 7141 patients with AHF and showed no statistically significant improvement in self-reported dyspnea or rehospitalization according to their pre-specified endpoints. This study, which randomized patients to either nesiritide or placebo, both in addition to usual therapy, did demonstrate a significant risk of both symptomatic and asymptomatic hypotension in those treated with nesiritide, though there were no differences in serious adverse events [25]. Due to these results, the routine use of nesiritide in the treatment of AHF is not recommended.

## Clevidipine

Clevidipine is a short-acting intravenous dihydropyridine calcium channel blocker. A 2014 prospective, randomized, open-label trial of 104 ED patients compared clevidipine with standard vasodilator therapies. Patients with AHF and systolic blood pressures > 160 were eligible. Those treated with clevidipine demonstrated a more rapid reduction in systolic blood pressure and improvement in dyspnea. This improvement in dyspnea remained significant for up to 3 h. No significant difference in serious adverse events or mortality was observed in the study [27].

Despite these observed short-term improvements, it is unclear whether clevidipine has any sustained benefit. Furthermore, the open-label nature of the study leads to risk of bias.

## BLAST-AHF—TRV027 [28•]

The biased ligand of the angiotensin II type I receptor in patients with acute heart failure (BLAST-AHF) was an international multi-center, randomized, double-blinded, parallel-grouped, placebo-controlled dose-finding trial. The trial evaluated the safety and efficacy of three different doses of TRV027 in the treatment of AHF. TRV027 is a "biased" ligand specific to the angiotensin II type 1 receptor (A1TR). Unlike complete angiotensin receptor blockers, TRV027 "biased" mechanism mitigates the vasoconstrictive effects while maintaining potential cardiac augmentation that would otherwise be blunted by full receptor blockade. While the blockade of angiotensin receptors in the treatment of chronic systolic heart failure improves morbidity and mortality, the effects in AHF were less clear [29].

BLAST-AHF included 621 patients presenting in AHF, with systolic blood pressures between 120 and 200 mmHg. These patients were randomized in parallel to receive placebo versus three different doses of TRV027 (1.0, 5.0, 25.0 mg/h). Pre-clinical and early human data for the ligand had been promising and BLAST-AHF was designed to determine the dose to carry forward into further studies. The primary outcome was a composite (1) time to death through day 30, (2) time to HF rehospitalization through day 30, (3) worsening heart failure through day 5, (4) change in dyspnea, and (5) length of stay.

Final analysis showed no significant difference in the composite primary endpoint, regardless of the dose of TRV027 compared to placebo. No significant differences were seen in adverse events between placebo and TRV027 doses. Despite one purported mechanistic effect of vasodilation, no significant decreases in systolic blood pressures were seen nor differences in natriuretic peptides. A 180-day follow-up of 540 patients (86.9%) was undertaken to evaluate the safety of the ligand. Rates of 180-day mortality between placebo and each dose of TRV027 (1.0, 5.0, 25.0 mg/h) were not significantly different (13.1, 11.0, 12.6, 13.6%). Despite promising pre-clinical data, BLAST-AHF concluded the TRV027 ligand to have no benefit over placebo in the treatment of AHF.

## TRUE-AHF—ULARITIDE [30•]

The Trial of Ularitide Efficacy and Safety in acute heart failure (TRUE-AHF) was a randomized, double-blinded, parallel-grouped, and placebo-controlled study of ularitide in treatment of AHF. Ularitide is a chemical analogue of urodilatin, a natural vasodilator which had previously shown benefits in patients with decompensated heart failure [31,32]. In TRUE-AHF, 2157 patients in AHF with systolic blood pressures between 116 and 180 were randomized to receive either intravenous ularitide (15 ng/kg/min) or placebo for 48 h, if they remained dyspneic after receiving intravenous furosemide. The primary outcomes for TRUE-AHF were 1) cardiovascular death over the course of the study and 2) a hierarchical clinical composite which utilized a patient global assessment to determine if a patient's course was "worse," "improved," or "unchanged."

Ularitide was found to significantly decrease systolic blood pressure compared to placebo (6.8 mmHg at 6 h, 3.9 mmHg at 48 h, $p < 0.001$), and to lower NT-proBNP levels ($p < 0.001$) over 48 h. A post-hoc analysis also showed a decrease in in-hospital "heart failure events" in patients treated with ularitide ($p = 0.005$). However, no difference was identified between ularitide and placebo with respect to cardiovascular death (21.7% versus 21.0%, $p = 0.75$) or to the clinical composite outcome ($p = 0.82$). More patients receiving ularitide required either dose discontinuation or decrease due to hypotension ($p < 0.001$). TRUE-AHF concluded that the decrease in NT-proBNP levels in the ularitide arm indicate a reduction in cardiac wall stress. Unfortunately, ularitide did not exhibit any benefits in clinical progression or cardiac mortality.

## RELAX-AHF—SERELAXIN [33•]

RELAXin in acute heart failure (RELAX-AHF) was a prospective, randomized, double-blinded, placebo-controlled trial. Serelaxin is recombinant human relaxin-2, which itself is a natural occurring peptide. Human relaxin-2 is responsible for many hemodynamic changes in pregnancy [34], including increases to cardiac output, vasodilation and renal blood flow [35]. Such benefits were hypothesized to benefit patients with AHF. Pre-RELAX-AHF, a phase 2, dose-finding study of 234 patients, showed improvements in dyspnea as well as signals for clinical outcomes including: hospital stay, cardiovascular death/rehospitalization risk, and all-cause death/rehospitalization [36].

Utilizing dose data from this study, RELAX-AHF randomized 1161 patients to receive either placebo or serelaxin 30μg/kg/day for up to 48 h. To be eligible, patients had mild to moderate renal dysfunction, systolic blood pressures greater than 125 mmHg, received intravenous furosemide, and enrolled within 16 h of presentation. Primary outcomes for this trial centered on improvement in dyspnea over 5 days, measured utilizing a visual analogue scale (VAS) and improvements in dyspnea during the first 24 h of treatment, measured by Likert scale.

Serelaxin was found to significantly improve dyspnea compared to placebo, as measured by the area under the curve (AUC) of the visual analog scale ($p < 0.007$). No significant improvement in dyspnea was measured utilizing the Likert scale ($p = 0.70$). Although dose adjustments for patients receiving serelaxin compared to placebo were more frequent due to hypotension, the number of adverse events related to hypotension were not significant (placebo = 4%, serelaxin = 5%, $p = 0.78$). Patients receiving placebo were found to have more events related to renal impairment (placebo = 9%, serelaxin = 6%, $p = 0.03$). Outside of this, no significant safety concerns were identified.

A number of secondary outcomes were analyzed in RELAX-AHF. Many of these clinical outcomes favored serelaxin, including decreased hospital stay (0.9 days, $p = 0.04$), reduction in cardiovascular death at 180 days (placebo = 55 deaths, serelaxin = 35 deaths, HR = 0.63, $p = 0.028$), and reduction in all-cause mortality at 180 days (placebo = 65 deaths, serelaxin = 42 deaths, HR = 0.63, $p = 0.02$). Greater end organ injury was observed in the placebo group, supporting the hypothesis that less organ injury might lead to improved longer term outcomes. However, the study was not adequately powered to formally assess mortality. RELAX-AHF-2 was undertaken to validate these findings. Although yet to be published, top line data did not replicate the mortality findings from RELAX-AHF [37].

## Conclusions

Traditionally, nitrates are the most common vasodilator used in the treatment of AHF [38]. Nitrates improve hemodynamics, provide symptom relief, have a long track record of use, and are safe to use. The use of ACE inhibitors in the treatment of AHF is intriguing given their demonstrable benefits in the treatment of chronic HF with reduced ejection fraction. Unfortunately, study findings to date should not be extrapolated to the emergency setting in the treatment of AHF.

In the past 5 years, three randomized controlled trials have studied the effects of three different vasodilators in the treatment of AHF. The use of each drug, TRV027, ularitide, and serelaxin, had appealing mechanisms of action. TRV027 in phase II and ularitide in phase III did not demonstrate any significant benefits with regard to improved long-term outcomes for patients with AHF. In the case of serelaxin, there appeared to be some benefit in mortality at 180 days. However, the larger RELAX-AHF-2 trial failed to confirm the initial trial results [37, 39].

At the present time, we continue to recommend nitrovasodilators as first line for patients with AHF in need of vasodilation. Similar to all drugs in this category, the risk of hypotension is real. Both careful monitoring and avoidance of hypotension are key-management pearls when using vasodilators.

## Compliance with Ethical Standards

**Conflict of Interest** Daniel B. Holt Jr. declares no conflicts of interest.

Peter S. Pang reports grants from AHA, NHLBI, and AHRQ during the conduct of the study; grants from Roche; personal fees, non-financial support, and other from Novartis, BMS, and Trevena; personal fees and non-financial support from Baxter; and other from Orthodiagnostics and Edwards outside the submitted work, and associate editor for JACC Heart failure, and Editorial board for the *Journal of Cardiac Failure*.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## References

Papers of particular interest, published recently, have been highlighted as:

- Of importance


1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. American Heart Association Council on epidemiology and prevention statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67–e492. https://doi.org/10.1161/CIR.0000000000000558.
2. Heidenreich PA, Albert NM, Allen LA, American Heart Association Advocacy Coordinating Committee, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Radiology and Intervention, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606–19. https://doi.org/10.1161/HHF.0b013e318291329a.
3. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the atherosclerosis risk in communities study). Am J Cardiol. 2008;101(7):1016–22. https://doi.org/10.1016/j.amjcard.2007.11.061.
4. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, et al. The burden of acute heart failure on U.S. emergency departments. JACC Heart Fail. 2014;2(3):269–77. https://doi.org/10.1016/j.jchf.2014.01.006.
5. Wong YW, Fonarow GC, Mi X, Peacock WF IV, Mills RM, Curtis LH, et al. Early intravenous heart failure therapy and outcomes among older patients hospitalized for acute decompensated heart failure: findings from the acute decompensated heart failure registry emergency module (ADHERE-EM). Am Heart J. 2013;166(2):349–56. https://doi.org/10.1016/j.ahj.2013.05.014.
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey de Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2013;62(16):e147–239. https://doi.org/10.1016/j.jacc.2013.05.019.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200. https://doi.org/10.1093/eurheartj/ehw128.
8. Acute Heart Failure Syndromes. Critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. American College of Emergency Medicine, May, 2007. https://www.acep.org/patient-care/clinical-policies/acute-heart-failure-syndromes/#sm.00000ixjak0swgfqwwnufn8dak1b0.
9. Alexander P, Alkhawam L, Curry J, Levy P, Pang PS, Storrow AB, et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: a systematic review. Am J Emerg Med. 2015;33(2):133–41. https://doi.org/10.1016/j.ajem.2014.09.009.
10. Collins SP, Storrow AB. Acute heart failure. In: Tintinalli JE, Stapczynski JS, Ma OJ, et al., editors. Tintinalli's emergency medicine: a comprehensive study guide. New York: McGraw-Hill Education; 2016.
11. Fonarow GC. The treatment targets in acute decompensated heart failure. Rev Cardiovasc Med. 2001;2(Suppl 2):S7–S12.
12. Wakai A, McCabe A, Kidney R, Brooks SC, Seupaul RA, Diercks DB, et al. Nitrates for acute heart failure syndromes. Cochrane Database Syst Rev. 2013;8:CD005151. https://doi.org/10.1002/14651858.CD005151.pub2.
13. Nelson GI, Silke B, Ahuja RC, Hussain M, Taylor SH. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart-failure following myocardial infarction. Lancet. 1983;1(8327):730–3.
14. Verma SP, Silke B, Hussain M, Nelson GIC, Reynolds GW, Richmond A, et al. First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function. J Cardiovasc Pharmacol. 1987;10(1):38–46.
15. Beltrame JF, Zeitz CJ, Unger SA, Brennan RJ, Hunt A, Moran JL, et al. Nitrate therapy is an alternative to furosemide/morphine therapy in the management of acute cardiogenic pulmonary edema. J Card Fail. 1998;4(4):271–9.
16. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287(12):1531–40 Erratum in: JAMA 2002 Aug 7;288(5):577.
17. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998;351(9100):389–93.
18. Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med. 2007;50(2):144–52.
19. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 2008;52(3):200–7. https://doi.org/10.1016/j.jacc.2008.02.083.

20. Silvers SM, Howell JM, Kosowsky JM, Rokos IC, Jagoda AS, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. Ann Emerg Med. 2007;49(5):627–69.
21. Long B, Koyfman A, Gottlieb M. Management of heart failure in the emergency department setting: an evidence-based review of the literature. J Emerg Med. 2018. https://doi.org/10.1016/j.jemermed.2018.08.002.
22. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429–35.
23. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293–302.
24. Annane D, Bellissant E, Pussard E, Asmar R, Lacombe F, Lanata E, et al. Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. Circulation. 1996;94(6):1316–24.
25. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32–43. https://doi.org/10.1056/NEJMoa1100171.
26. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293(15):1900–5.
27. Peacock WF, Chandra A, Char D, Collins S, der Sahakian G, Ding L, et al. Clevidipine in acute heart failure: results of the a study of blood pressure control in acute heart failure-a pilot study (PRONTO). Am Heart J. 2014;167(4):529–36. https://doi.org/10.1016/j.ahj.2013.12.023.
28.• Pang PS, Butler J, Collins SP, et al. Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF). Eur Heart J. 2017;38(30):2364–73. https://doi.org/10.1093/eurheartj/ehx196. **This randomized controlled trial investigated the safety and efficacy of an angiotensin II type I receptor ligand, for use in the treatment of acute heart failure**.
29. Felker GM, Butler J, Collins SP, Cotter G, Davison BA, Ezekowitz JA, et al. Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor. Rationale and design of the BLAST-AHF study (biased ligand of the angiotensin receptor study in acute heart failure). JACC Heart Fail. 2015;3(3):193–201. https://doi.org/10.1016/j.jchf.2014.09.008.
30.• Packer M, O'Connor C, McMurray JJV, et al. TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376(20):1956–64. https://doi.org/10.1056/NEJMoa1601895. **This randomized controlled trial investigated ularitide, an analogue of the natural vasodilator urodilantin, in the treatment of acute heart failure**.
31. Mitrovic V, Lüss H, Nitsche K, et al. Effects of the renal natriuretic peptide uro- dilatin (ularitide) in patients with decom- pensated chronic heart failure: a double- blind, placebo-controlled, ascending-dose trial. Am Heart J. 2005;150:1239.
32. Mitrovic V, Seferovic PM, Simeunovic D, Ristic AD, Miric M, Moiseyev VS, et al. Haemodynamic and clinical effects of ularitide in decompensated heart failure. Eur Heart J. 2006;27:2823–32.
33.• Teerlink JR, Cotter G, Davison BA, et al. RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381(9860):29–39. https://doi.org/10.1016/S0140-6736(12)61855-8. **This randomized controlled trial investigated the effects of serelaxin, a recombinant of human relaxin-2, responsible for hemodynamic changes in pregnancy, in the treatment of acute heart failure**.
34. Conrad KP. Maternal vasodilation in pregnancy: the emerging role of relaxin. Am J Physiol Regul Integr Comp Physiol. 2011;301(2):R267–75. https://doi.org/10.1152/ajpregu.00156.2011.
35. Teichman SL, Unemori E, Teerlink JR, Cotter G, Metra M. Relaxin: review of biology and potential role in treating heart failure. Curr Heart Fail Rep. 2010;7(2):75–82. https://doi.org/10.1007/s11897-010-0010-z.
36. Ponikowski P, Metra M, Teerlink JR, et al. Design of the RELAXin in acute heart failure study. Am Heart J. 2012;163(2):149–55.e1. https://doi.org/10.1016/j.ahj.2011.10.009.
37. RELAXin in acute heart failure-2 - RELAX-AHF-2. American College of Cardiology, May 8, 2017. https://www.acc.org/latest-in-cardiology/clinical-trials/2017/05/07/16/09/relax-ahf-2.
38. Collins SP, Pang PS, Lindsell CJ, Kyriacou DN, Storrow AB, Hollander JE, et al. International variations in the clinical, diagnostic, and treatment characteristics of emergency department patients with acute heart failure syndromes. Eur J Heart Fail. 2010;12(11):1253–60. https://doi.org/10.1093/eurjhf/hfq133.
39. Novartis heart drug portfolio hit by failed serelaxin study. Reuters, March 22, 2017 http://www.reuters.com/article/ us-novartis-heart-idUSKBN16T0QG.