Review Articles

Review of Vasodilators in Acute Decompensated Heart Failure: The Old and the New

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ABSTRACT

Despite substantial improvements in treatment for chronic heart failure, morbidity and mortality for acute decompensated heart failure (ADHF) remain high. Treatment of ADHF is focused on controlling symptoms rather than improving long-term outcomes. The vasodilators nitroglycerin (NTG) and sodium nitroprusside (SNP) have been used in ADHF for decades, but, since the development of nesiritide 10 years ago, interest in new vasodilators has grown. Therapies that improve not only hemodynamics and symptoms but also long-term outcomes are in high demand, and numerous new vasodilatory agents have been investigated, including various natriuretic peptides, soluble guanylyl cyclase agents, renin-angiotensin-aldosterone system−modifying agents, and others. A review of the literature shows that few of them rise to the challenge set by NTG and SNP. (*J Cardiac Fail 2013;19:478−493*)
Key Words: Nitroglycerin, sodium nitroprusside, natriuretic peptide.

Almost 1 million patients yearly receive a primary diagnosis of acute decompensated heart failure (ADHF) at hospital discharge in the United States (US),[1] with the direct cost of these hospitalizations reaching $209 billion in 2010.[2] In-hospital mortality varies among recent registries from ∼3% to 5%,[3,4] a decrease from the 8% rate found in a Medicare beneficiary registry from 1991 to 1994,[5] but long-term statistics remain bleak, with rehospitalization rates of 25%−40% and post-hospitalization mortality rates of 10%−20% 2−3 months after discharge.[3,6,7]

ADHF results in poor outcomes for many reasons, including the natural course of the disease and the age and comorbidities of those most affected,[1,8] with a paucity of treatment shown to decrease morbidity and mortality.[3] Management of ADHF focuses on improving symptoms by relieving congestion rather than improving long-term outcomes, which may be appropriate to a certain extent:

> [B]oth patients and physicians desire therapies that improve signs, symptoms, and/or quality of life, assuming an acceptable safety profile. Expecting therapies used for 48 hours to improve outcomes at 2 to 6 months in a complex, heterogeneous substrate […] may set the bar too high.[9]

ADHF is a complex syndrome rather than a single pathologic entity, aising from a variety of etiologies manifesting as diverse clinical presentations in patients with systolic dysfunction as well as in those with preserved ejection fraction (EF).[8,10,11] Various forces are involved in the pathophysiology of ADHF, ranging from molecular and immunologic disturbances to ischemic and mechanical dysfunction.[12] Many of these derangements are driven by neurohormones, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, antidiuretic hormone (ADH), natriuretic peptides (NPs), and endothelins.[12,13] As shown in Figure 1, neurohormones can affect cardiac function either directly or by modulating preload, afterload, natriuresis, and diuresis. In ADHF, many neurohormones are elevated, resulting in increased afterload and preload, decreased natriuresis and diuresis, and decreased ventricular contractility.[12−14]

First-line management for ADHF consists of intravenous diuretic therapy, which improves ventricular contraction and decreases heart failure (HF) symptoms via natriuresis and diuresis. Heart Failure Society of America (HFSA)

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See page 490 for disclosure information.

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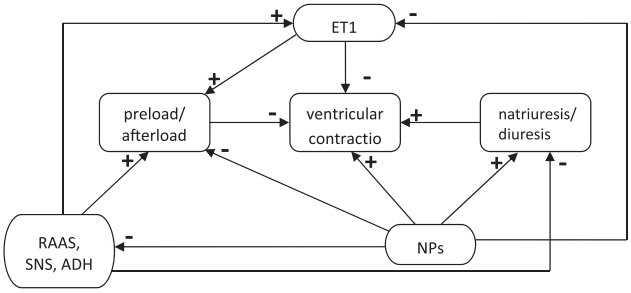

Fig. 1. Neurohormonal effects on cardiac function.[12–14,16] In acute decompensated heart failure, the RAAS, the SNS, ADH, and ET1 act to increase preload and afterload and decrease natriuresis and diuresis, thereby decreasing ventricular contraction. NPs counteract these effects, improving ventricular contractions via vasodilatation. ADH, antidiuretic hormone; ET1, endothelin-1; NPs, natriuretic peptides; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

guidelines suggest considering a vasodilator for symptoms of congestion, particularly in the setting of acute pulmonary edema or severe hypertension.[15] As illustrated in Figure 2, most vasodilators act via cyclic guanosine monophosphate (cGMP) to increase intracellular calcium, thereby causing smooth muscle relaxation and vasodilation.[16] This results in decreased preload and afterload, thereby causing improved contractility.[12] A combination of diuretic and vasodilator therapy has also been shown to rapidly decrease neurohormonal activation, including NPs, endothelin, and norepinephrine.[14]

Clinical society practice guidelines specifically mention the vasodilators nitroglycerin (NTG) and sodium nitroprusside (SNP), which have been used in ADHF for 30 years, and nesiritide, which has been in use for a decade.[10,15] Numerous new vasodilatory agents have been developed and investigated in the past 10 years in the search for therapies that might improve not only hemodynamics and symptoms but long-term outcomes as well. We reviewed published randomized controlled trials (RCTs) and selected observational trials of vasodilators used in the management of ADHF, including nitric oxide (NO) donators, NPs, soluble guanylyl cyclase (sGC) agents, RAAS-modifying agents, endothelin antagonists, relaxin, and hydralazine. Appraisal of the literature shows that few agents rise to the challenge set by NTG and SNP.

Methods

Pubmed was searched from 1982 to the present for experimental clinical trials in humans with ADHF reporting relevant clinical outcomes with the use of the phrase (“heart failure” NOT chronic) AND “drug name.” The following drug names were used: “aliskiren,” “BAY 58-2667,” “carperitide,” “CD-NP,” “cinaciguat,” “enalapril,” “hydralazine,” “nesiritide,” “nitroglycerin,” “nitroprusside,” “tezosentan,” “relaxin,” “ularitide,” and “urodilatin.” The search was limited to articles in the English language. References from potentially relevant articles and from review articles were searched to identify additional studies. Clinicaltrials.gov was searched for ongoing trials, and manufacturers of the various drugs were contacted directly to request information regarding current and ongoing trials. ADHF was defined as worsening of HF signs or symptoms requiring hospitalization and intravenous therapy (the signs and symptoms reported varied among trials). Relevant clinical outcomes included hemodynamic effects, change in dyspnea or clinical status, change in creatinine (Cr), worsening HF, total or cardiovascular (CV) mortality, and readmission. Trials that focused solely on pharmacodynamics, pharmacokinetics, and safety were excluded. The quality of each trial was assessed based on randomization, blinding, and handling of patient attrition in analysis with the use of the Jadad scale.[17] A trial with a Jadad score of ≥3 was considered to be of reasonable

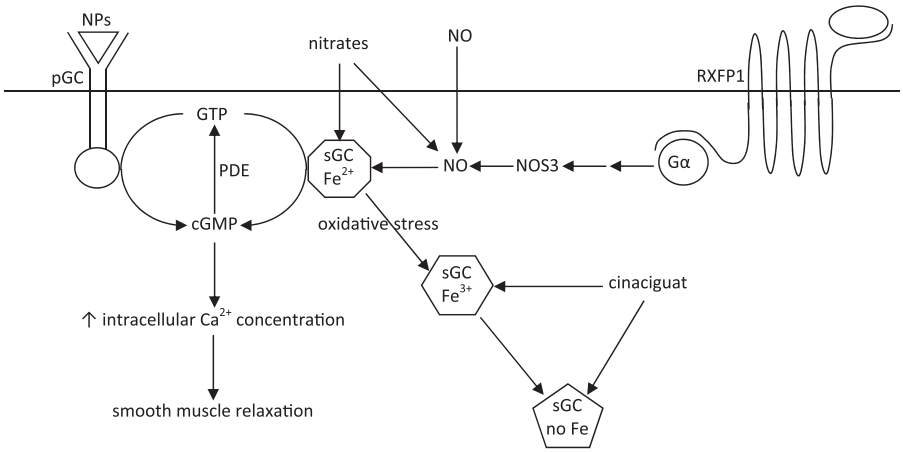

Fig. 2. Mechanisms of action of selected vasodilators.[13,16,20,21,29,56,78] NO and nitrates diffuse across the cell membrane and convert GTP to cGMP via sGC bound to a reduced heme moiety. cGMP increases intracellular calcium, thereby resulting in smooth muscle relaxation and vasodilatation. Cinaciguat acts via sGC bound to an oxidized heme moiety or with no heme moiety, while NPs act via membrane-bound pGC. Relaxin binds RXFP1, a G-coupled protein receptor, to activate NOS3 and increase intracellular NO. cGMP, cyclic guanosine monophosphate; Gα, guanine nucleotide-binding protein; GTP, guanosine triphosphate; NPs, natriuretic peptides; NO, nitric oxide; NOS3, endothelial nitric oxide synthase; PDE, phosphodiesterase; pGC, particular guanylyl cyclase; RXFP1, relaxin/insulin-like family pepide receptor 1; sGC, soluble guanylyl cyclase.

quality. Table 1 provides a summary of pertinent clinical trials, and Table 2 presents drug dosing. Forest plots were constructed for the relative risks of selected clinical outcomes, including improvement in dyspnea in Figure 3 and mortality, readmission, intubation, and/or myocardial infarction (MI) in Figure 4.[18]

Results

Description of Studies

Twenty-three completed RCTs and 5 RCTs in process met the inclusion criteria. Three observational trials of interest were also selected. See Table 1 for characteristics of the included studies.

Nitric Oxide Donators

Intravenous Nitroglycerin. Originally used for the treatment of angina and acute coronary syndrome (ACS), NTG was first investigated in ADHF in the early 1980s.[19] It is an NO prodrug that activates sGC when it is bound to a reduced heme moiety.[20] The hemodynamic effects of NTG have been well characterized, including decreased preload at any dose, decreased afterload at high doses, decreased myocardial oxygen consumption, and improved coronary blood flow, making it particularly appealing in ACS.[20,21] Adverse effects include neurohormonal activation, headache, and hypotension, and the duration of infusion is limited by tachyphylaxis. The American College of Cardiology (ACC), American Heart Association (AHA), HFSA, and European Society of Cardiology (ESC) all recommend NTG for patients with symptomatic fluid overload without hypotension or for normotensive patients not responding appropriately to intravenous diuretics and standard oral therapies.[10,15,22] It may be optimal for use in patients with hypertension, ischemia, or significant mitral regurgitation.[10] Despite longstanding and widespread use in ADHF, a search of the literature revealed only 1 RCT.[23]

An open-label RCT in patients with ADHF presenting to the emergency department (ED) randomized participants to high-dose isosorbide dinitrate (ISDN) plus low-dose furosemide or to high-dose furosemide plus low-dose ISDN until oxygen saturation (SpO_2) increased to 86% or mean arterial pressure (MAP) decreased by 30% or to <90 mm Hg.[23] The high-dose ISDN group received doses that were presumed to be large enough to decrease preload and afterload, whereas the high-dose furosemide group received ISDN doses that were intended to be sufficient to decrease preload alone.[24] In general, participants were quite hypoxic and hypertensive at presentation (mean SpO_2 79%, mean MAP 128 mm Hg). The primary outcome, a composite of in-hospital all-cause mortality, intubation within 12 hours, or MI within 24 hours, occurred in 25% of the high-dose ISDN and 46% of the high-dose furosemide group ($P = .041$).

An observational trial of early ED-initiated NTG therapy observed a 14% rate of intubation within 6 hours in the intervention group compared with 27% in the control group receiving standard therapy for ADHF (no P value reported).[25] In secondary outcomes, only 38% of NTG-treated patients required intensive care unit (ICU) admission compared with 80% of control patients. Although patients were quite hypertensive at presentation (mean MAP 154 mm Hg), the rate of baseline hypoxia was lower than in the Cotter study (mean SpO_2 94%).

Aziz et al retrospectively reviewed patients with chronic kidney disease admitted with ADHF and divided them into those treated with NTG and diuretics, those treated with diuretics alone, and those who received neither therapy in the ED.[26] There was no significant difference among the groups for the primary composite end point (combined 30-day readmission and 24-month all-cause mortality) or for the secondary end point of 30-day readmission. In safety end points, 24-month survival was significantly greater in the NTG group (87% vs 82% in the diuretic group and 79% in the group receiving no therapy; $P = .0001$). These data are clouded by the significantly higher blood pressure (BP) in the NTG group, because lower BP on presentation is a well known marker for poor outcomes in ADHF[27] (mean $\pm$SD systolic blood pressure [SBP] 150 $\pm$ 21 mm Hg in the NTG group, 125 $\pm$ 19 mm Hg in the group receiving only diuretics, and 125 $\pm$ 18 mm Hg in the group receiving no diuretics; $P = .001$).

Despite evidence of improved clinical outcomes with NTG therapy in hypertensive patients with ADHF, no large randomized double-blinded placebo-controlled trial has been performed. Because NTG has become accepted as a standard of care, sufficient equipoise may not exist for a placebo-controlled trial, and absence of patent protection and low cost are likely to ensure that other targets will receive higher priority for funding. On the other hand, recent attention to comparative effectiveness research and interest in cost containment for HF treatment at a federal level may provide options for support of such a trial. No current studies of intravenous NTG in ADHF are listed at Clinicaltrials.gov (accessed February 19, 2013).

Sodium Nitroprusside. SNP was originally used for post-MI left ventricular (LV) failure in the mid-1970s.[28] It has the same mechanism of action as NTG, but hemodynamically it produces an equivalent decrease in preload and afterload, decreases myocardial oxygen demand, and increases stroke volume and cardiac output (CO).[28–30] Adverse effects include hypotension, possible coronary steal, and ventilation-perfusion mismatching, likely due to pulmonary arteriolar dilatation in nonventilated areas.[21] SNP is light sensitive and should be hung in a protective cover. Low infusion rates can actually result in inactivation within intravenous tubing. Tachyphylaxis is not a consideration, but cyanide toxicity can occur with prolonged infusions (usually >72 hours) or in the presence of renal dysfunction. This can be avoided with concomitant sodium thiosulfate infusion, of which there is unfortunately a national shortage.[31] According to clinical guidelines, SNP can be used in situations similar to NTG, and ACC/AHA guidelines specifically suggest its use in patients with

Table 1. Characteristics and Limitations of Selected Trials of Vasodilator Therapy in Acute Decompensated Heart Failure

Trial	Intervention (n) Control (n)	Primary End Point	Results	Comments (Jadad Score)
Nitroglycerin				
Cotter[23]	HD ISDN/LD furosemide (52); LD ISDN/HD furosemide (52)	Composite of mechanical ventilation at 12 h, MI at 24 h, and death in hospital	↓ with HD ISDN	Small size, open-label, HD ISDN group received higher doses of furosemide than specified (3)
Levy[25]	HD NTG (29); Standard therapy (45)	Intubation at 6 h	↓ with HD HTN	Small size, observational, designed as feasibility study with no subsequent RCT (NA)
Aziz[26]	NTG/diuretics (46); Diuretics (127); Neither therapy (257)	Composite of readmission at 30 d and all-cause mortality at 24 mo	NS	Observational, patients in the NTG group were more likely to have a history of HF and to be hypertensive at presentation (NA)
Sodium nitroprusside				
Hockings[32]	SNP (25); Furosemide (25)	Δ in hemodynamics at 1 h*	↓ PCWP, ↓ SVR, ↑ CI with SNP	Small size, open-label, limited to patients with MI (2)
Cohn[33]	SNP (407); Placebo (405)	All-cause mortality at 48 h, 21 d, and 13 wk*	NS for any time point	Slightly underpowered to detect a mortality difference, limited to patients with MI (5)
Mullens[34]	SNP (78); No SNP (97)	All-cause mortality; cardiac transplant; all-cause mortality/cardiac transplant; readmission for HF	↓ with SNP, NS; ↓ with SNP, NS	Observational, hemodynamics significantly different at baseline, both groups received various inotropes, medication doses not reported (NA)
Nesiritide				
NSG efficacy trial[37]	LD nesiritide (43); HD nesiritide (42); Placebo (42)	Δ in PCWP at 6 h	Dose-dependent ↓ with nesiritide	Patients and clinicians scoring symptoms and global clinical status may have been aware of hemodynamic effects (5)
NSG comparative trial[37]	LD nesiritide (103); HD nesiritide (100); Standard therapy (102)	Global clinical status, dyspnea, and fatigue evaluated at 6 h, 24 h, and the end of therapy*	NS for any outcome	Open-label (3)
VMAC[44]	Nesiritide (204); NTG (143); Placebo (142)	Coprimary end points: Δ in PCWP at 3 h (patients with PAC); Δ in dyspnea at 3 h (all patients)	↓ with nesiritide; ↓ with nesiritide and NTG	Nesiritide group more likely to receive concomitant inotrope therapy, NTG dose was lower than that indicated for ADHF (5)
ASCEND-HF[53]	Nesiritide (3,496); Placebo (3,511)	Coprimary end points: Δ in dyspnea at 6 h; Δ in dyspnea at 24 h; all-cause mortality/HF readmission at 30 d	NS; NS; NS	Statistical analysis by European group found a significant difference in dyspnea (5)
ROSE-HF[54]	LD nesiritide; LD dopamine; Placebo	Efficacy: cumulative urine volume at 72 h; Safety: Δ in cystatin C at 72 h	—	Recruiting participants, goal 360
Carperitide				
Kitashiro[61]	Carperitide (18); Placebo (18)	Δ in hemodynamics at 48 h*	↓ PCWP, ↑ CI, ↑ urine volume with carperitide	Small, unclear blinding (2)
Kasama[62]	Carperitide (29); Standard therapy (29)	Δ in hemodynamics at 48 h; NYHA functional class and echo parameters at 4 wk*	↓ PCWP with carperitide; ↓ NHYA functional class with carperitide	Small, open-label, excluded patients with a history of CAD (2)
PROTECT[63]	Carperitide (26); Standard therapy (23)	CV death or readmission*	↓ with carperitide	Small, open-label, control group more likely to have NYHA functional class IV at baseline, not powered to detect a mortality difference (2)
Urodilatin				
SIRIUS II[68]	LD ularitide (60); MD ularitide (53); HD ularitide (55); Placebo (53)	Coprimary end points: Δ in PCWP at 6 h; Δ in dyspnea at 6 h	↓ with MD and HD ularitide; ↓ with all ularitide doses	No follow-up of adverse events after hospitalization in this safety trial (5)

(*continued on next page*)

Table 1. (*Continued*)

Trial	Intervention (n) Control (n)	Primary End Point	Results	Comments (Jadad Score)
TRUE-AHF[69]	Ularitide; Placebo	Moderate or marked improvement in global assessment at 6, 24, and 48 h	—	Recruiting participants, goal 2,116
Cinaciguat				
Erdmann[81]	Cinaciguat (97); Placebo (51)	Δ in PCWP at 8 h	↓ with cinaciguat	Terminated early owing to high incidence of hypotension in the cinaciguat group (3)
COMPOSE-1[82]	MD cinaciguat (9); Placebo (3)	Δ in PCWP at 8 h	Descriptive ↓ PCWP with cinaciguat	Terminated early owing to high incidence of hypotension in the cinaciguat group (3)
COMPOSE-2[82]	LD cinaciguat (3); Placebo (1)	Δ in PCWP at 8 h	No statistical analysis performed	Terminated early owing to difficulty with recruitment, concern for timely completion (3)
COMPOSE-EARLY[82]	MD cinaciguat (9); Placebo (3)	Δ in dyspnea at 8 h	Descriptive analysis showed NS	Terminated early owing to high incidence of hypotension in the cinaciguat group (3)
Enalaprilat				
Annane[88]	Enaprilat (11); Placebo (9)	Hemodynamic changes at various time points*	↓ PCWP, ↓ MAP, ↓ MPAP, ↑ RBF with enalaprilat	Small, no safety end points reported (3)
Podbregar[89]	Enalaprilat bolus (10); Enalaprilat infusion (10)	Decrease in PCWP by 20% at 30 min	NS	Small, open-label, no placebo, no safety end points reported (1)
Aliskiren				
ASTRONAUT[93]	Aliskiren (808); Placebo (807)	CV mortality or HF readmission at 6 mo	NS	Recruitment stopped early owing to results of ALTITUDE, required power was calculated to have been reached (3)
Tezosentan				
RITZ-1[100]	Tezosentan (331); Placebo (338)	Δ in dyspnea at 24 h	NS	(insufficient data to calculate Jadad score)
RITZ-2[99]	Tezosentan (191); Placebo (94)	Δ in CI at 6 h	↓ CI with tezosentan	(5)
RITZ-4[101]	Tezosentan (97); Placebo (95)	Composite of all-cause mortality, worsening HF, recurrent ischemia, and recurrent MI at 72 h	NS	All patients had ACS at presentation in addition to ADHF (3)
RITZ-5[102]	Tezosentan (97); Placebo (95)	Δ in SpO_2 at 1 h	NS	(2)
VERITAS-1,2[103]	LD tezosentan (730); Placebo (718)	Coprimary end points: Δ in dyspnea over 24 h; all-cause mortality or worsening HF at 7 d	NS; NS	Terminated early owing to lack of efficacy (4)
Relaxin				
Pre-RELAX-AHF[107]	Relaxin, various doses (173); Placebo (61)	Δ in dyspnea at 6, 12, and 24 h*	↓ with 30 μg kg^{-1} d^{-1} relaxin	Exploratory dose-finding study (5)
RELAX-AHF-1[108]	Relaxin; Placebo	Coprimary end points: Δ in dyspnea at 6, 12, and 24 h; Δ in dyspnea over 5 d	—	Completed, results not published, goal 1,160
Hydralazine				
GALACTIC[112]	NTG, hydralazine, ACE-I/ARB; Standard therapy	HF death and readmission	—	Recruiting, goal 700

ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; CI, cardiac index; CV, cardiovascular; HD, high-dose; HF, heart failure; ISDN, isosorbide dinitrate; LD, low-dose; MD, moderate-dose; MI, myocardial infarction; NA, not applicable; NS, no significant difference; NSG, nesiritide study group; NTG, nitroglycerin; NYHA, New York Heart Association; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; RCT, randomized controlled trial; SNP, sodium nitroprusside.

*Primary end point not specified.

Table 2. Dosing Regimens in Selected Trials of Vasodilator Therapy in Acute Decompensated Heart Failure

Study	Intervention	Control
Nitroglycerin		
Cotter[23]	Mean ISDN 11.4 mg IV bolus; Mean furosemide 56 mg IV bolus	Mean ISDN 1.4 mg IV bolus; Mean furosemide 200 mg IV bolus
Levy[25]	Mean NTG 6.5 mg IV bolus, then 23.6−50.2 μg/min IV infusion; Mean furosemide 85.5 mg IV bolus	Mean initial NTG 31.7 μg/min to unknown max IV infusion; Mean furosemide 82.1 mg IV bolus
Aziz[26]	NTG 5−15 μg/min IV infusion; Mean furosemide 75 mg IV bolus in ED, 50 mg IV bolus in hospital	Mean furosemide 59 mg IV bolus in ED, 53 mg IV bolus in hospital / Mean furosemide dose 52 mg IV bolus in hospital
Sodium nitroprusside		
Hockings[32]	Peak SNP 235 μg/min IV infusion	Mean furosemide 440 mg IV bolus
Cohn[33]	Mean SNP 92.3 μg/min IV infusion at 24 h, 94.4 μg/min IV infusion at 48 h	Placebo
Mullens[34]	SNP 10−400 μg/min IV infusion; mean dose not reported	Standard therapy without SNP
Nesiritide		
NSG efficacy trial[37]	Nesiritide 0.3 μg IV bolus, then 0.015 μg kg^{-1} min^{-1} IV infusion or 0.6 μg IV bolus, then 0.03 μg kg^{-1} min^{-1} IV infusion	Placebo
NSG comparative trial[37]	Nesiritide 0.3 μg/kg IV bolus, then 0.015 μg kg^{-1} min^{-1} IV infusion or 0.6 μg IV bolus, then 0.03 μg kg^{-1} min^{-1} IV infusion	Standard therapy
VMAC[44]	Nesiritide 2 μg/kg IV bolus, then 0.01 μg kg^{-1} min^{-1} IV infusion; after 3 h, 23 patients with PAC had dose titrated to 0.03 μg kg^{-1} min^{-1}	Mean NTG 39 μg/min IV infusion at 3 h without PAC; 42 μg/min IV infusion at 3 h with PAC / Placebo; at 3 h patients crossed over to nesiritide or NTG
ASCEND-HF[53]	Nesiritide 2 μg/kg IV optional bolus then 0.01 μg kg^{-1} min^{-1} IV infusion	Placebo
ROSE-HF[54]	Low-dose nesiritide IV infusion / Low-dose dopamine IV infusion	Placebo
Carperitide		
Kitashiro[61]	Carperitide 0.05−0.2 μg kg^{-1} min^{-1} IV infusion; mean dose not reported	Placebo
Kasama[62]	Carperitide 25 ng kg^{-1} min^{-1} IV infusion	Standard therapy
PROTECT[63]	Carperitide 0.01−0.05 μg kg^{-1} min^{-1} IV infusion; mean 0.024 μg kg^{-1} min^{-1}	Standard therapy
Ularitide		
SIRIUS II[68]	Ularitide 7.5, 15, or 30 ng kg^{-1} min^{-1} IV infusion	Placebo
TRUE-AHF[69]	Ularitide 15 ng kg^{-1} min^{-1} IV infusion	Placebo
Cinaciguat		
Erdmann[81]	Cinaciguat 100 μg/h IV infusion initially, titrated from 50 to 600 μg/h; mean dose not reported	Placebo
COMPOSE-1[82]	Cinaciguat 50, 100, or 150 μg/h IV infusion	Placebo
COMPOSE-2[82]	Cinaciguat 10 or 25 μg/h IV infusion	Placebo
COMPOSE-EARLY[82]	Cinaciguat 50, 100, or 150 μg/h IV infusion	Placebo
Enalaprilat		
Annane[88]	Enalaprilat 1 mg IV infusion over 2 h	Placebo
Podbregar[89]	Enalaprilat 0.004 mg IV bolus or infusion over 1 h	NA
Aliskiren		
ASTRONAUT[93]	Aliskiren 150 mg PO daily, could be increased to 300 mg daily after 2 wk	Placebo
Tezosentan		
RITZ-1[100]	Tezosentan 50 mg/h IV infusion	Placebo
RITZ-2[99]	Tezosentan 50 or 100 mg/h IV infusion	Placebo
RITZ-4[101]	Tezosentan 50 mg/h IV infusion	Placebo
RITZ-5[102]	Tezosentan 50 or 100 mg/h IV infusion	Placebo
VERITAS-1,2[103]	Tezosentan 5 mg/h IV loading dose over 1 h, then 1 mg/h IV infusion	Placebo
Relaxin		
Pre-RELAX-AHF[107]	Relaxin 10, 30, 100, or 200 μg/kg/d IV infusion	Placebo
RELAX-AHF-1[108]	Relaxin 30 μg/kg/d IV infusion	Placebo
Hydralazine		
GALACTIC[112]	Sublingual and transdermal nitrates and oral hydralazine followed by rapid up-titration of ACE-I or ARB	Standard therapy

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ED, emergency department; ISDN, isosorbide dinitrate; NA, not applicable; NTG, nitroglycerin; PAC, pulmonary artery catheter; SNP, sodium nitroprusside.

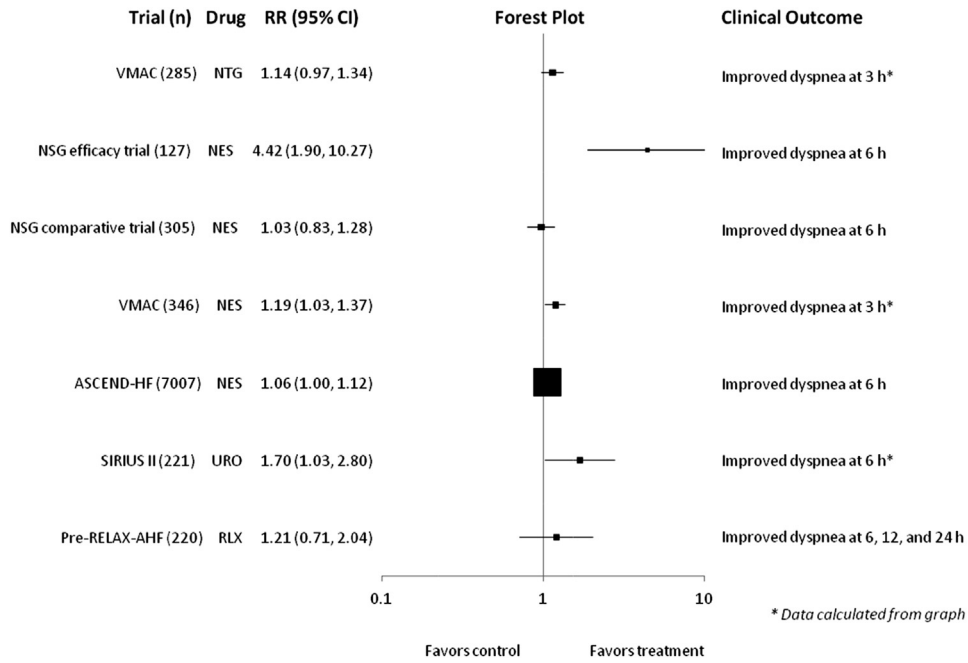

Fig. 3. Relative risk of improvement in dyspnea in selected trials of vasodilator therapy in acute decompensated heart failure. NES, nesiritide; NTG, nitroglycerin; RLX, relaxin; SNP, sodium nitroprusside; URO, urodilatin. References: ASCEND-HF,[53] NSG efficacy trial and comparative trial,[37] Pre-RELAX-AHF,[107] SIRIUS II,[68] VMAC.[44]

severe volume overload and hypertension or mitral regurgitation.[10,15,22]

In an open-label RCT evaluating hemodynamic effects in patients with LV failure after MI, SNP was associated with a greater decrease in pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), and increase in cardiac index (CI) at 1 hour compared with furosemide (-9 vs -4 mm Hg, -21% vs $+10\%$, and $+16\%$ vs -7%, respectively; $P < .001$ for all).[32] Hemodynamic differences, except for PCWP, were maintained at 48 hours. No significant difference in the safety end point of all-cause mortality at 48 hours or 12 months was noted.

A large multicenter double-blinded randomized trial by Cohn et al evaluated all-cause mortality for SNP compared with placebo in patients with LV failure after MI.[33] There was no significant difference in all-cause mortality at 48 hours, 21 days, or 13 weeks, either between treatment groups or by prespecified subgroups (including age, SBP,

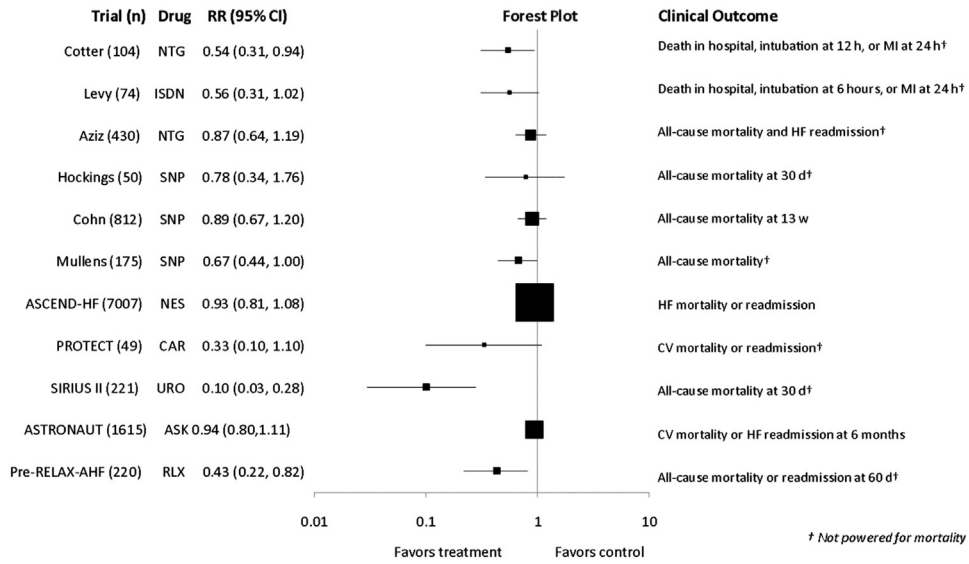

Fig. 4. Relative risk of mortality, readmission, intubation, or MI in selected trials of vasodilator therapy in acute decompensated heart failure. ASK, aliskiren; CAR, carperitide; HF, heart failure; ISDN, isosorbide dinitrate; MI, myocardial infarction; NES, nesiritide; NTG, nitroglycerin; RLX, relaxin; SNP, sodium nitroprusside; URO, urodilatin. References: ASCEND-HF,[53] ASTRONAUT,[93] Aziz,[26] Cohn,[33] Cotter,[23] Hockings,[32] Levy,[25] Mullens,[34] Pre-RELAX-AHF,[107] PROTECT,[63] SIRIUS II.[68]

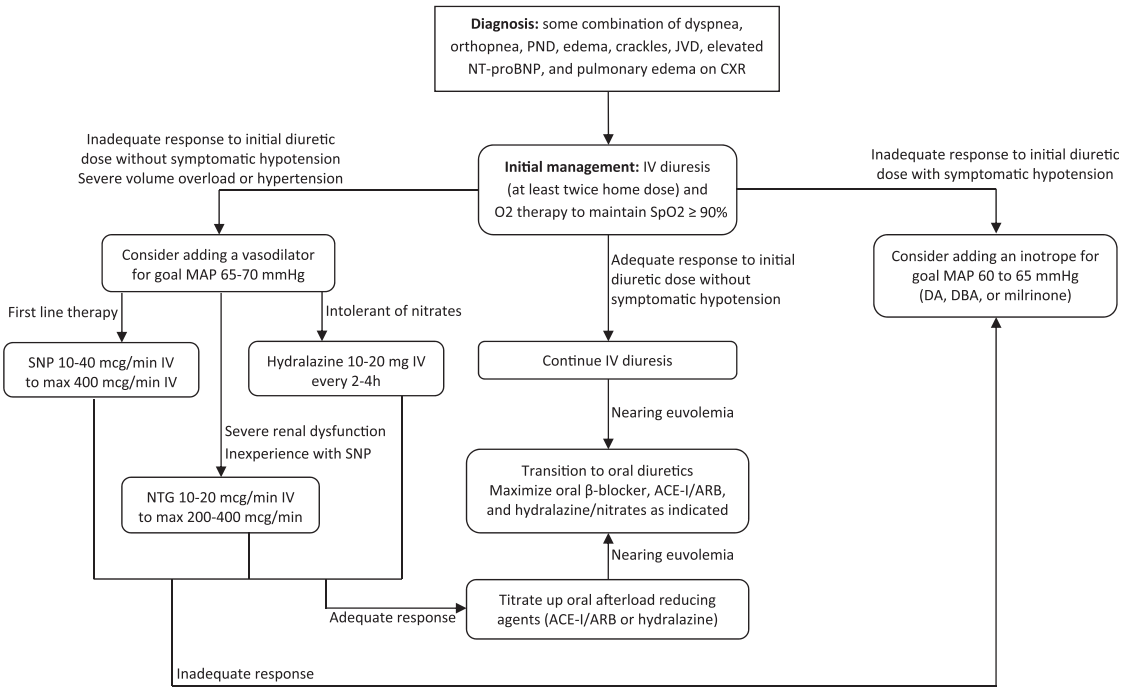

Fig. 5. Algorithm for management of acute decompensated heart failure.[10,11,15,34,112] CXR, chest X-ray; DA, dopamine; DBA, dobutamine; IV, intravenous; JVD, jugular venous distention; MAP, mean arterial pressure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NTG, nitroglycerin; PND, paroxysmal nocturnal dyspnea; SpO_2, oxygen saturation; SNP, sodium nitroprusside.

and LV filling pressure). The use of diuretics was 45% in the placebo group versus 11% in the SNP group ($P < .001$). As in the study by Hocking et al,[32] it is unclear if results in patients with LV failure after MI would generalize to all patients with acute HF.

An observational study by Mullens et al reviewed patients with ADHF admitted to a specialized HF ICU and compared those treated with SNP to an MAP goal of 65−70 mm Hg with those who did not receive SNP.[34] At baseline, those who received SNP had significantly higher central venous pressure (CVP), PCWP, and MAP, and significantly lower CI ($P < .05$ for all). Primary end points included all-cause mortality, heart transplant, a combination of the two, and readmission for HF. There were no significant differences between the 2 groups for heart transplant or readmission, but those treated with SNP had a lower all-cause mortality of 29% compared with 44% in those who did not receive SNP ($P = .005$), with an early and persistent separation of survival curves. SNP remained an independent predictor of survival on multivariate analysis. Of note, in subgroup analysis of those patients with MAP ≤85 mm Hg, SNP was still associated with lower all-cause mortality ($P = .0001$). There was a nonsignificant trend toward less inotrope use in the SNP group, raising the possibility that patients who did not receive SNP were "sicker." However, this is not supported by the baseline characteristics, which showed no significant difference between the 2 groups in serum sodium, renal function, or hemoglobin, all markers of HF severity.[35] Alternatively, treatment with SNP may have resulted in clinical improvement and decreased the need for inotropes.

Given this mixed data, a large randomized double-blinded placebo-controlled trial of SNP for the treatment of ADHF not due to MI would be of interest. However, as with NTG, SNP has become a standard of care and is off patent, making such a trial unlikely. No current studies of intravenous SNP in ADHF are listed at Clinicaltrials.gov (accessed February 20, 2013), and the manufacturer of SNP (Nitropress; Hospira) was not aware of any current or upcoming clinical trials (personal communication, February 25, 2013).

Natriuretic Peptides

Nesiritide. Nesiritide, recombinant human B-type natriuretic peptide (BNP), acts at the natriuretic peptide A receptor (NPR-A) to decrease preload, afterload, and PCWP, increase CO,[21,36−38] increase urine output,[37] and improve diastolic function.[39] Adverse effects include headache and hypotension.[37,39] ACC/AHA and HFSA guidelines recommend nesiritide as an alternative therapy to NTG and SNP that decreases LV filling pressure and improves dyspnea more rapidly than diuretic therapy alone.[10,15]

The Nesiritide Study Group performed 2 RCTs examining the use of nesiritide in patients with ADHF admitted for vasoactive therapy.[37] The double-blinded placebo-controlledefficacy trial showed a significant, dose-dependent decrease in PCWP with nesiritide therapy (+2.0 mm Hg with placebo, −6.0 mm Hg with low-dose nesiritide, and −0.6 mm Hg with high-dose nesiritide; $P < .001$), and secondary outcomes of hemodynamics, symptoms, and global clinical status were significantly

improved in a higher percentage of patients in the nesiritide groups. The open-label comparative RCT demonstrated no significant difference in global clinical status, dyspnea, and fatigue at 6 hours, 24 hours, or the end of treatment for low-dose and high-dose nesiritide infusions versus standard therapy.

The Vasodilatation in the Management of Acute CHF (VMAC) study, a large double-blinded RCT, compared the change in PCWP and subjective evaluation of dyspnea at 3 hours in patients treated with nesiritide, NTG, or placebo.[39] PWCP at 3 hours was significantly decreased with nesiritide versus NTG and placebo (−5.8 mm Hg, −3.8 mm Hg, and −2 mm Hg, respectively; $P < .05$), but by 24 hours there was no difference in PCWP between the nesiritide and NTG groups. Although dyspnea at 3 hours was significantly decreased in the nesiritide group versus placebo ($P = .03$), there was no significant difference between nesiritide and NTG-treated participants. At 3 hours, placebo patients crossed over to nesiritide or NTG, and clinical end points were evaluated over the next 6 months. Although the trial was not powered to detect a reduction in mortality, there was no significant difference between groups in MI at 30 days, readmission at 30 days, or mortality at 7 days or 6 months. The study was limited by the fact that the mean dose of NTG used (39−42 μg/min intravenously [IV]) was far below the optimal NTG dose in the treatment of ADHF, which is in the range of 120−200 μg/min IV.[40] When patients did receive adequate doses of NTG, as in the subgroup analysis reported by Elkayam et al (where those treated with NTG received an average dose of 160 μg/min IV), nesiritide resulted in only a transient significant decrease in PCWP compared with NTG that disappeared by 30 minutes.[41]

Approved and widely used on the basis of symptomatic improvement in the VMAC study, nesiritide appeared to be safe and effective for use in patients with coronary artery disease,[42] those on β-blockers,[43] and those with chronic kidney disease.[44,45] The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) trial showed that nesiritide did not carry the proarrhythmic risks of dobutamine,[46] and a subgroup analysis of the Nesiritide Study Group comparative trial found that it resulted in significantly fewer HF readmissions and lower 6-month all-cause mortality than dobutamine.[47] In 2005, however, 2 meta-analyses by Sackner-Bernstein et al called into question its safety, showing that nesiritide significantly increased the risk of worsening renal function compared with other therapies for ADHF (21% vs 15%; $P = .001$)[48] and tended to increase 30-day all-cause mortality (7.2% vs 4.0%; $P = .059$).[49] Two subsequent meta-analyses of RCTs did not show an increase in 30-day or 180-day all-cause mortality with nesiritide,[50,51] but doubts regarding its safety remained.

To respond to these concerns, an independent panel was convened and recommended a large clinical trial to evaluate the safety and efficacy of nesiritide.[52] Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), a multicenter randomized double-blinded placebo-controlled trial, was designed to compare nesiritide with placebo in patients admitted with ADHF.[53] Coprimary outcomes were change in dyspnea at 6 hours and 24 hours and a composite of 30-day HF rehospitalization and all-cause mortality. Although more nesiritide patients experienced a decrease in dyspnea, the difference did not reach statistical significance, nor was there a significant difference between the groups in the combined end point of rehospitalization for HF and 30-day all-cause mortality or in the safety end point of renal dysfunction. These results were consistent across prespecified subgroups.

Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF), sponsored by the National Heart, Lung, and Blood Institute, is the only active clinical trial of nesiritide registered at Clinicaltrials.gov (accessed February 21, 2013). The study is recruiting patients with ADHF and renal dysfunction and randomizing them to low-dose dopamine, low-dose nesiritide, or placebo in addition to optimal diuretic dosing as a renal-protective therapy.[54] The manufacturer of nesiritide (Natrecor; Scios, a subsidiary of Johnson & Johnson) did not communicate regarding any additional current or upcoming clinical trials. Finally, despite its lack of efficacy in other situations, nesiritide benefits patients with profound renal failure and diuretic resistance following ventriculectomy and placement of a total artificial heart, because these patients no longer produce endogenous BNP.[55]

Carperitide. Carperitide, or A-type natriuretic peptide (ANP), acts as a stronger agonist than BNP at NPR-A.[56] Its hemodynamic effects are similar to those of nesiritide, although it has more robust natriuretic and diuretic effects that are more pronounced in healthy subjects than in patients with HF.[57,58] It increases and decreases MAP and PCWP,[57,58] and its most common adverse effect is hypotension.[59,60] It has been investigated and used extensively in Japan, where it was approved in 1995,[59] whereas American and European societal clinical guidelines do not address its use.[10,15,22]

A small RCT in patients with ADHF resistant to other therapies showed a decrease in PCWP, an increase in CI, and an increase in urine volume at 48 hours with carperitide compared with placebo (−10 vs 0 mm Hg, +0.77 vs +0.01 L min^{-1} m^{-2}, and +868 vs −63 mL/d, respectively; $P <$ .005 for all).[61] These effects persisted without evidence of tachyphylaxis after 7 days of infusion.

Kasama et al evaluated patients with new-onset acute HF who were treated with dopamine and furosemide, and then randomized to ANP or placebo.[62] At 48 hours, CVP and PCWP decreased and CI increased significantly from baseline in the carperitide group (−3.5 mm Hg, −6.9 mm Hg, and +0.5 L min^{-1} m^{-2}, respectively; $P < .05$ for all), but only PCWP was significantly lower than in the placebo group (15 vs 19 mm Hg; $P < .05$). Small statistically significant decreases in LV end-diastolic volume, LV end-systolic volume, EF, and New York Heart Association (NYHA) functional class in the ANP group were noted at

4 weeks, but only NHYA functional class was significantly lower than in the placebo group ($P < .05$).

Prospective Trial of Cardioprotective Effect of Carperitide Treatment (PROTECT), a multicenter open-label RCT, evaluated patients with ADHF treated with standard therapy with or without carperitide.[63] The combined end point of CV mortality and rehospitalization occurred in 12% of the carperitide group vs 35% of the standard therapy group ($P = .036$), but the study was underpowered to detect a difference in mortality.

Two large cohort studies examined the safety and efficacy of carperitide and found that it improved subjective symptoms and hemodynamics in just over 80% of patients.[59,60] It was less likely to be effective in patients with MI, more severe HF, or renal dysfunction. The randomized trials accomplished to date are unconvincing regarding the noninferiority of carperitide compared with standard therapy. Replication of the ASCEND-HF trial using ANP rather than BNP could demonstrate the benefit-risk ratio of carperitide but would be very costly. No active carperitide trials are currently registered at Clinicaltrials.gov (accessed February 22, 2013), because the US company affiliated with the Japanese manufacturer terminated their license agreement in January 2007, ending carperitide development in the US.[64] The manufacturer of carperitide (Daiichi Sankyo) did not communicate regarding any current or upcoming clinical trials in other countries.

Urodilatin. Ularitide, the product of differential processing of the pro-ANP precursor in the kidney, acts on NPR-A in the collecting duct, thereby increasing excretion of water and sodium.[13] Intravenous urodilatin, its synthetic form, increased diuresis and natriuresis in compensated patients with HF to an extent similar to that of ANP, but caused a greater and more sustained increase in cGMP.[65] Compared with placebo, it decreased PCWP, decreased MAP, and increased CI,[66,67] while down-regulating the RAAS and improving renal sodium excretion in healthy volunteers.[13] The most common adverse effect is dose-dependent hypotension.[67,68]

The second Safety and Efficacy of an Intravenous Placebo-Controlled Randomized Infusion of Ularitide in a Prospective Double-blind Study in Patients with Symptomatic, Decompensated Chronic Heart Failure (SIRIUS II), a double-blinded RCT of patients hospitalized with ADHF, compared urodilatin at various doses with placebo, evaluating the coprimary end points of change in PCWP and self-assessed dyspnea at 6 hours.[68] PCWP was significantly decreased in the 15 ng kg^{-1} min^{-1} and 30 ng kg^{-1} min^{-1} intravenous urodilatin groups compared with placebo ($P < .001$ for both comparisons), and patient-assessed dyspnea was significantly decreased in all 3 urodilatin groups compared with placebo ($P < .01$ for all).

Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure (TRUE-AHF) is an active trial of urodilatin registered at Clinicaltrials.gov that will compare the effects of ularitide and placebo in ADHF.[69] The primary end point is moderate or marked improvement in global assessment at 6, 24, and 48 hours. The manufacturer of ularitide (Cardiorentis) did not communicate regarding any additional current or upcoming clinical trials.

CD-NP. CD-NP (or "cenderitide") is a chimeric NP synthesized from C-type natriuretic peptide (CNP) and *Dendroaspis* natriuretic peptide (DNP).[56] CNP originates from endothelial cells and activates NPR-B, resulting predominately in venodilation, and DNP was isolated from the green mamba snake and activates NPR-A, with effects similar to those of ANP and BNP. By fusing the DNP tail to CNP, an NP is created that acts as a partial agonist of NPR-A and an agonist of NPR-B.[70] CD-NP decreases PCWP and causes natriuresis and diuresis without a significant decrease in MAP in animal models,[71] and in healthy humans it increases urine output and urine sodium excretion and decreases serum aldosterone.[72] It significantly decreases Cr compared with furosemide in patients with stable HF.[73] CD-NP is still in the early stages of investigation but has been demonstrated to cause a dose-dependent decrease in SBP (with some symptomatic hypotension) without evidence of worsening renal function compared with placebo in patients with ADHF and renal dysfunction.[74]

The safety and pharmacokinetics of CD-NP are currently being evaluated in patients with chronic HF.[75–77] It may prove to be beneficial for long-term therapy of HF, given its antifibrotic and antihypertrophic effects.[56] There are no active trials of CD-NP in ADHF registered at Clinicaltrials.gov (accessed February 25, 2013), nor did the manufacturer of cenderitide (Nile Therapeutics) communicate regarding any additional current or upcoming clinical trials.

Soluble Guanylyl Cyclase Agents

Cinaciguat. Cinaciguat (or BAY 58-2667) is an NO-independent sGC activator that is effective even in oxidative conditions, unlike NTG and SNP (Fig. 2).[13,16] The oxidative stress of many disease states, including hypertension, coronary artery disease, and HF, renders sGC unresponsive to NO, decreasing the efficacy of NTG and SNP. In comparison, cinaciguat activates sGC bound to oxidized Fe^{3+} or without a bound heme moiety, thereby targeting diseased vessels for vasodilatation.[78] In healthy humans, cinaciguat decreases diastolic blood pressure compared with placebo without significantly decreasing SBP,[79] and in patients with ADHF it decreases PCWP and MAP and increases CO without significantly changing Cr.[79] Dose-dependent hypotension is the most common adverse effect.[80–82]

Erdmann et al performed a double-blinded RCT examining the safety and efficacy of cinaciguat versus placebo in 139 patients hospitalized with ADHF.[81] The primary end point, PWCP at 8 hours, was significantly decreased in the treatment group compared with placebo (−7.7 mm Hg vs −3.7 mm Hg; $P < .0001$). Other significant hemodynamic effects at 8 hours included increased CI and decreased MAP. There were no significant differences

in dyspnea, renal function, or 30-day all-cause mortality between the 2 groups, but a significant increase in hypotension occurred in patients treated with cinaciguat (73% vs 26% with placebo), particularly at doses ≥200 μg/h, necessitating early termination of the trial.

The COMPOSE (A Placebo Controlled, Randomized, Double-blind, Fixed-dose, Multicenter, Phase IIb Study to Investigate the Efficacy and Tolerability of Cinaciguat Given Intravenously to Subjects with ADHF) program, a series of randomized, double-blinded, placebo-controlled trials, evaluated the safety and efficacy of varying doses of cinaciguat in patients with ADHF.[82] COMPOSE 1 examined the hemodynamic effects of higher doses of cinaciguat in patients with pulmonary artery catheterization (PAC), and COMPOSE EARLY examined the effect on dyspnea of the same doses of cinaciguat in patients without PAC. Both trials were terminated early owing to higher rates of hypotension in the treatment groups. COMPOSE 2, which evaluated low-dose cinaciguat in patients with PAC, was terminated owing to concerns that the study could not be completed in a reasonable period. Statistical analysis was not performed, but descriptive analysis of COMPOSE 1 showed a decrease in PCWP and RAP with cinaciguat, and COMPOSE EARLY did not demonstrate any difference in dyspnea between the treatment arms. There was difficulty recruiting patients who required PAC for hemodynamic monitoring, perhaps owing to the results of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[83] It was also problematic to use dyspnea as a primary end point, because it is often improved with initial therapy for ADHF before randomization to a treatment arm.[82]

Cinaciguat may be of value in long-term therapy of chronic HF,[81] but there are no active trials registered at Clinicaltrials.gov (accessed February 25, 2013). The manufacturer of cinaciguat (Bayer Healthcare) did not communicate regarding any current or upcoming clinical trials.

RAAS-Modifying Agents

Enalaprilat. Enalaprilat, the intravenous form of enalapril, is an angiotensin-converting enzyme inhibitor (ACE-I) that decreases circulating angiotensin II and increases bradykinin, which acts as a vasodilator.[84] In observational studies of patients with acute LV failure after MI, intravenous ACE-Is decreased PCWP, MAP, and SVR.[85,86] Adverse effects include hypotension, renal dysfunction, and angioedema.[87]

In a small double-blinded RCT of patients hospitalized with acute cardiogenic pulmonary edema and stabilized with furosemide, ISDN, and dobutamine, a small dose of enalaprilat significantly decreased PCWP, MAP, and mean pulmonary artery pressure (MPAP) at 8 hours and increased renal blood flow at 4 hours compared with placebo ($P < .05$ for all comparisons).[88] No significant effect on CI was apparent, and no adverse effects, including hypotension, occurred.

A similar nonblinded RCT in patients with refractory ADHF not currently on an ACE-I evaluated the hemodynamic effects of enalaprilat bolus versus infusion and found that the 2 treatments caused a similar decrease in PCWP, MAP, and MPAP, although these effects were achieved more rapidly and were more transient with the bolus dose.[89] Both groups met the primary hemodynamic end point of a 20% decrease in PCWP by 30 minutes. Asymptomatic hypotension occurred, and change in Cr and potassium were not reported.

There are no current trials of enalaprilat in ADHF registered at Clinicaltrials.gov (accessed February 25, 2013), nor was the manufacturer of enalaprilat (Vasotec IV; Valeant Pharmaceuticals Internationa) aware of any current or upcoming clinical trials (personal communication, March 12, 2013). In general, enalaprilat is not indicated for early management of ADHF, given its high risk for hypotension,[87] though it can be considered in ACS with acute LV dysfunction.[90]

Aliskiren. Aliskiren is an oral direct renin inhibitor that blocks formation of angiotensin I and II without affecting kinin metabolism.[16] Hemodynamically, it has been shown to decrease SVR and PCWP in patients with decompensated HF,[91] and its neurohormonal effects include decreased N-terminal prohormone of BNP (NT-proBNP), plasma renin activity, and urinary aldosterone.[92] Hyperkalemia, hypotension, and decreased renal function have been reported as adverse effects.[93]

Results from Six Months Efficacy and Safety of Aliskiren Therapy on Top of Standard Therapy, on Morbidity and Mortality in Patients With Acute Decompensated Heart Failure (ASTRONAUT), a multicenter double-blinded RCT comparing aliskiren with placebo in addition to standard therapy (including ACE-I or angiotensin receptor blocker) in patients hospitalized for ADHF were recently reported.[94] Therapy began during hospitalization once the patient was stabilized and continued for 12 months after discharge.[93] There was no significant difference between the 2 groups in the primary end point of time to CV death or HF rehospitalization within 6 months. Post hoc subgroup analysis showed that patients with diabetes tended to be less likely to benefit from aliskiren than those without diabetes ($P = .08$ for interaction), consistent with the results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial.[95] It might be reasonable to consider a second ASTRONAUT trial that excludes patients with diabetes.

There are no other active trials of aliskiren in ADHF registered at Clinicaltrials.gov (accessed February 26, 2013), and the manufacturer of aliskiren (Novartis) did not communicate regarding any current or upcoming clinical trials.

Other Vasodilators

Tezosentan. Tezosentan is an intravenous dual endothelin A- and B-receptor antagonist that preferentially antagonizes the endothelin A-receptor, resulting in

vasodilation.[87] Its development was prompted by the discovery that elevated plasma levels of endothelin-1 in patients with HF correlated with ventricular arrhythmias and mortality.[96] Early hemodynamic studies demonstrated a dose-dependent increase in CI and decrease in PCWP.[96–98] Adverse effects include hypotension, worsening renal function, and headache.[99–103]

The Randomized Intravenous Tezosentan (RITZ) trials compared the effect of relatively high-dose tezosentan and placebo on various hemodynamic and clinical outcomes in patients with ADHF, including ADHF associated with MI. RITZ-2 demonstrated a significant increase in CI with tezosentan compared with placebo,[99] but there was no significant difference between the two arms in clinical end points evaluated by the other RITZ trials.[100–102]

The Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS) compared the effect of a lower dose of tezosentan with placebo on change in dyspnea, all-cause mortality, and worsening HF in patients with ADHF, but they showed no clinical benefit and were discontinued early for futility.[103] No further trials of tezosentan in ADHF are registered at Clinicaltrials.gov (accessed February 26, 2013), and the manufacturer of tezosentan (Actelion) is not aware of any current or upcoming trials of the agent (personal communication, February 19, 2013).

Relaxin. Relaxin, the hormone responsible for many of the maternal hemodynamic changes in pregnancy, acts as a systemic, renal, and coronary vasodilator in animal models, thereby decreasing afterload, increasing CO, and decreasing the risk of infarction during periods of myocardial ischemia.[16,104] In humans with HF, relaxin levels were increased and correlated with disease severity,[105] and in patients with compensated HF it increased CI and decreased PCWP, NT-proBNP, and Cr.[106] No adverse effects have been reported.[106,107]

Relaxin for the Treatment of Patients With Acute Heart Failure (Pre-RELAX-AHF), an exploratory dose-finding study, examined various clinical outcomes in patients with acute HF and renal dysfunction treated with intravenous relaxin or placebo.[107] Dyspnea at 6, 12, and 24 hours was moderately or markedly better in 40% of patients treated with 30 $\mu g\ kg^{-1}\ d^{-1}$ relaxin compared with 23% treated with placebo ($P = .044$). This dose of relaxin was thought to be sufficiently effective and safe to warrant further study in ADHF. Relaxin appeared to be less effective at higher doses, perhaps owing to down-regulation of relaxin receptors at higher plasma concentrations or other counterregulary effects.

RELAX-AHF-1 is a multicenter randomized double-blinded placebo-controlled trial assessing symptom relief and clinical outcomes in patients with acute HF and renal dysfunction treated with relaxin or placebo for 48 hours.[108] Coprimary end points are moderately or markedly improved dyspnea at 6, 12, and 24 hours and change in dyspnea through day 5. Safety end points include days alive and out of hospital at day 60 and CV death or rehospitalization for HF or renal failure through day 60 (the trial is powered only to detect moderately large effects on long-term outcomes). RELAX-AHF-1 has been completed, but results have not yet been published.[109] There are no other active trials of relaxin in ADHF registered at Clinicaltrials.gov (accessed February 26, 2013), and the manufacturer of the agent (Novartis) did not communicate regarding any current or upcoming clinical trials.

Hydralazine. Hydralazine is a direct vasodilator with an unknown mechanism of action that decreases afterload and improves stroke volume, increases renal blood flow, and has a moderate direct inotropic effect.[29] Adverse effects include hypotension, nausea, headache, and tachycardia.[20] It is used in combination with long-term nitrate therapy to prevent nitrate tolerance.[110] In ADHF, it is most often used as an oral vasodilator agent in combination with nitrates during down-titration of SNP or inotropes.[111]

Given its hemodynamic effects, it may be efficacious as an initial agent in ADHF, particularly in those with renal dysfunction. The Goal-Directed Afterload Reduction in Acute Congestive Cardiac Decompensation (GALACTIC) trial will evaluate early goal-directed preload and afterload reduction in patients hospitalized with acute HF and is currently recruiting participants.[112] The open-label protocol involves initial therapy with sublingual and transdermal NTG and oral hydralazine followed by titration of ACE-Is or angiotensin receptor blockers to an SBP target of 90–110 mm Hg. The primary outcome is HF death or rehospitalization, and all-cause mortality or rehospitalization will be evaluated as a secondary outcome. No other trial involving hydralazine in ADHF is currently registered at Clinicaltrials.gov (accessed February 28, 2013).

Discussion

Therapy of ADHF continues to focus on symptom management. Along with diuretics and oxygen therapy, vasodilators are first-line agents for patients who are persistently hypertensive, severely volume overloaded, or in acute pulmonary edema (see Fig. 5 for treatment algorithm).[10,11,15] Vasodilators should also be used in those who do not respond adequately to intravenous diuretic therapy, whereas inotropes are reserved for those with an inadequate response to diuretics and symptomatic hypotension. Those who do not respond to vasodilator therapy may benefit from an inotrope.

Of those vasodilators currently approved for use in ADHF in the US, NTG may decrease intubation rates, occurrence of MI, and all-cause mortality in hypertensive hypoxic patients.[23,25] SNP did not improve all-cause mortality when originally studied in patients with LV dysfunction after MI[33] but was associated with improved survival in a more recent retrospective study of patients with ADHF not due to MI, including normotensive patients.[34] Nesiritide, despite initially promising data and inclusion in earlier guidelines,[10,15] was not superior to placebo in the ASCEND-HF trial,[53] so it is not included in the treatment algorithm in Figure 5. Minimal clinical data exist to

support the use of carperitide, and it is not available for use in the US.[64] Among older agents not specifically approved for use in ADHF, enalaprilat, though a potent vasodilator, is not indicated in most patients owing to the high risk for hypotension,[87] and hydralazine is generally used for transitioning to oral vasodilators rather than in the acute phase.[111]

Of the newer investigational agents, tezosentan and cinaciguat are no longer being investigated in ADHF owing to hypotension and a lack of efficacy, respectively.[82,103] CD-NP is not registered for any further clinical trials in patients with ADHF but is being investigated in chronic HF.[73–75] The oral agent aliskiren has not been shown to be effective, although there is some suggestion that it may benefit patients without diabetes.[93] The oral agent hydralazine and the IV agents relaxin and urodilatin are currently undergoing large multicenter double-blinded placebo-controlled randomized trials examining clinical end points in patients with ADHF.[69,109,112] RELAX-AHF-1 (relaxin) has already been completed, so data from this trial may be available soon.[109]

In conclusion, of all the new vasodilatory agents developed in the past decade, none have been shown to be as effective as SNP or NTG. In VMAC, the only head-to-head trial of old and new vasodilators, nesiritide was compared with less-than-optimal doses of NTG and no significant difference in dyspnea was found.[39,41] Because NO donators are generally accepted as the standard of care, it would be reasonable for new vasodilators to be tested against optimal doses of NTG and SNP. If aliskiren, hydralazine, relaxin, or urodilatin is shown to be effective in clinical trials against placebo, a comparative effectiveness trial against SNP or NTG would be ideal, with dyspnea, all-cause mortality, and HF readmission as coprimary end points and worsening HF and change in Cr as safety end points. Until then, SNP and NTG continue to be first-line vasodilators for use in ADHF.

Disclosures

None.

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