

Contemporary Drug Development in Heart Failure Call for Hemodynamically Neutral Therapies

Muthiah Vaduganathan, MD, MPH; Javed Butler, MD, MPH; Bertram Pitt, MD; Mihai Gheorghiadu, MD

Until now, successful drug development in chronic heart failure (HF) with reduced ejection (HFrEF) has followed a conceptual model of targeting the secondary consequences of HF and its associated peripheral maladaptive processes leading to cardiovascular adverse remodeling. Step-wise modulation of angiotensin-II, the adrenergic system, and aldosterone have contributed to reductions in mortality in chronic HFrEF. Moreover, other vasodilators, such as hydralazine and nitrates, have improved outcomes in African American patients with HFrEF. Similarly, the combination of a neprilysin inhibitor and an angiotensin-II receptor blocker (ARB) provided incremental improvement in cardiovascular outcomes albeit at the cost of a higher risk of hypotension. The introduction of many other novel HFrEF agents beyond these therapies has largely failed, and the outcomes for these patients, especially after hospital discharge, have remained relatively stagnant and exceedingly high.¹

To date, almost all disease-modifying therapies in HFrEF cause blood pressure lowering as an intended or unintended consequence. Low systolic blood pressure (SBP), which may reflect the extent of myocardial reserve, is one of the strongest determinants of clinical course in ambulatory and hospitalized patients with HFrEF.²⁻⁴ Hypotension, especially in high-risk or susceptible patients, presents a major hurdle to the contemporary HFrEF drug development paradigm and will likely pose an even greater obstacle once sacubitril/valsartan achieves widespread clinical application. The continued addition of hemodynamically active novel agents does not seem to be a practical or sustainable approach to further optimize HFrEF outcomes. Herein, we critically explore recent trends in the HFrEF drug development pipeline and discuss the importance of shifting to a strategy of developing therapies that directly target primary cardiac abnormalities without significantly influencing blood pressure or heart rates.

Risks of Hypotension

Optimal blood pressure is critical for maintaining adequate coronary and renal perfusion pressures, especially in patients with overt or subclinical vascular disease. Patients with elevated left ventricular end diastolic pressures with

hemodynamic congestion,⁵ those with pre-existing coronary artery disease,⁶ and collateral dependent areas of myocardial perfusion are at particular risk of jeopardizing coronary perfusion pressure with systemic hypotension. Milrinone was shown to have bidirectional effects in acute HF with an excess risk of the primary clinical end point in patients with ischemic HF and similar or decreased risk in patients with nonischemic cardiomyopathy compared with placebo.⁷ In a recent analysis from the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine (SHIFT) trial, every 10-mmHg reduction in SBP was associated with an increased risk of all-cause mortality by 12% in patients with chronic HFrEF on background contemporary medical therapies.³ Patients hospitalized for worsening HFrEF even with low-normal SBP face a higher risk for adverse events. In the Organized Program to Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, patients with SBP <120 mmHg at the time of hospital presentation experienced in-hospital and postdischarge mortality rates of 6.2% and 14.9%, respectively, compared with 1.4% and 4.7% in patients with SBP >160 mmHg.⁴ In addition, symptomatic hypotensive episodes on therapy may contribute to nonadherence by patients and unwillingness by providers to optimize doses, leading to treatment failures.^{8,9}

Blood Pressure as a Target for Drug Development

Despite afterload reduction, blood pressure lowering represents a poor target for novel HFrEF drug development. First, most patients on optimal doses of contemporary HF therapy are already facing relatively low blood pressure in the chronic setting. Second, although neurohormonal blockers are often titrated based on in-clinic vital sign assessment, 24-hour ambulatory blood pressures in these patients show substantial diurnal variation. In a small prospective study, the step-wise addition of neurohormonal agents contributed to significant daytime and especially nocturnal hypotensive episodes, which were associated with an increase in cardiovascular events, despite stable pre- and post-treatment in-clinic blood pressure measurements.¹⁰ Patients on angiotensin-converting

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From the Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston (M.V.); Division of Cardiology, Stony Brook University, NY (J.B.); University of Michigan School of Medicine, Ann Arbor (B.P.); and Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL (M.G.).

Correspondence to Mihai Gheorghiadu, MD, Center for Cardiovascular Innovation, Northwestern University, Feinberg School of Medicine, 201 E Huron, Galter 3-150, Chicago, IL 60601. E-mail m-gheorghiadu@northwestern.edu

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enzyme inhibitors (ACEi) or ARBs are at increased risk of nocturnal hypotension because angiotensin-II is an important factor in maintaining systemic blood pressure. Recent data from Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) revealed that visit-to-visit variability in blood pressure measurements were common in ambulatory patients with HFrEF and were associated with increased death or HF hospitalization.¹¹ Third, even in well-monitored clinical trials, there is a disconnect between symptoms of reduced cerebral perfusion and measured blood pressures. Indeed, blood pressures in contemporary HFrEF trials have been largely unchanged despite the step-wise addition of hemodynamically active agents and variable rates of hypotension (Table 1). This may reflect variability and lack

of standardization in the definitions used for adverse events related to hypotension and inconsistencies in blood pressure monitoring in clinical trials. For instance, in the Beta-Blocker Evaluation of Survival Trial (BEST) trial, rates of dizziness were 39%, hypotension 20%, syncope 10%, and postural hypotension 9%.¹² Finally, although maximally tolerated doses of hemodynamically active agents are often desired in practice, the efficacy of these agents is not consistently linked to reductions in SBP. For instance, in the Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, SBP trajectory as a time-varying covariate was not a determinant of benefit of sacubitril/valsartan compared with enalapril.¹³

Table 1. Hemodynamically Active Background Therapy and Rates of Hypotension in Select Successful Phase III Randomized Controlled Clinical Trial Programs of Oral Therapies in Chronic Heart Failure With Reduced Ejection Fraction

Trial	Study Recruitment Start Date	Study Drug	n	NYHA	Mean Systolic BP at Enrollment	Hemodynamic Exclusion Criteria	ACEi/ARB†	β-Blockers	MRA‡	Nitrates§	Postrandomization Hypotension	Definition of Hypotension
ACEi												
CONSENSUS	April, 1985	Enalapril	253	IV	121/76	*	*	1.6	43.7	35.7	0	Withdrawal from the study
SOLVD treatment	June, 1986	Enalapril	2569	II and III	124.5/76.4	*	*	7	9.1	43.8	*	*
SOLVD prevention	July, 1986	Enalapril	4228	I and II	125.6/78	*	*	23.7	4	29.9	*	*
β-Blockers												
CIBIS I	March, 1989	Bisoprolol	641	III and IV	125.6/77.9	SBP<100 mm Hg	91	*	*	40	0.9	*
BEST	May, 1995	Bucindolol	2708	III and IV	117/71	SBP<80 mm Hg	91/7	*	4	48	20	*
MERIT-HF	February, 1997	Metoprolol CR/XL	3991	II–IV	129.5/78.1	SBP<100 mm Hg	96	*	*	*	*	*
COPERNICUS	October, 1997	Carvedilol	2289	II and III	123/76	SBP<85 mm Hg	97	*	20	*	*	*
CIBIS II	*	Bisoprolol	2647	III and IV	130.2/80	SBP<100 mm Hg	96	*	*	58	0.8	Requiring hospitalization
Mineralocorticoid receptor antagonists												
RALES	March, 1995	Spirinolactone	1663	III and IV	122/75	*	94	10	*	*	*	*
EMPHASIS-HF	March, 2006	Eplerenone	2737	II	124/75	*	92.9	86.9	*	*	2.7	*
Novel agents												
SHIFT	October, 2006	Ivabradine	6558	II–IV	121.4/75.6	Symptomatic hypotension	78/14	90	59	*	*	*
PARADIGM-HF	December, 2009	Sacubitril/valsartan	8442	II–IV	121/*	Symptomatic hypotension or SBP<100 mm Hg	*	92.9	57	*	9.2	Symptomatic

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BEST, Beta-Blocker Evaluation of Survival Trial; BP, blood pressure; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS, Carvedilol prospective randomized cumulative survival; CR, controlled release; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; PARADIGM-HF, Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SBP, systolic blood pressure; SHIFT, Systolic Heart Failure Treatment with the If Inhibitor Ivabradine; SOLVD, Studies of Left Ventricular Dysfunction; and XL, extended release.

Trials within each drug development program are ordered by study recruitment start date.

*Data not available on query of the primary results publication.

†ACEi/ARB use; if available, ACEi and ARB rates are stated separately if available.

‡Includes early trial reports of potassium-sparing diuretics, if MRA use specifically was not detailed.

§Includes nitrates and other vasodilators.

Hypotension—A Major Clinical Trial Roadblock

Several converging lines of evidence support reassessment of our current model of neurohormonal modulation. First, there are variable incremental benefits seen with more complete renin–angiotensin–aldosterone system blockade with higher dose ACEi (compared with lower dose)^{8,14} or the addition of ARBs^{15,16} and direct renin inhibitors (to ACEi, β -blockers, and mineralocorticoid receptor antagonists).^{17,18} Second, there has not been net clinical benefit of adjunctive blockade of alternative neurohormonal or cytokine pathways.^{19–21} Failures of these drug development programs may be driven by diminishing marginal efficacy because of saturation of available neurohormonal targets.

However, risk of hypotension with increasing neurohormonal blockade represents a major concern and was commonly observed in many of these chronic HFrEF trials. Indeed, multiple HFrEF drug development programs have failed or experienced significant setbacks due to adverse therapy-related hemodynamic effects. Hypotension may manifest by 2 potential mechanisms: (1) direct therapy-related vasodilatation or (2) volume depletion with improvement in myocardial function and reduction in diuretic requirement over time. Mak et al¹⁰ have demonstrated that patients who experience hypotensive episodes after addition of ACEi, ARB, or β -blockers are at higher risk for subsequent HF readmissions and composite all-cause mortality and readmissions. Thus, therapy-related hemodynamic perturbations may have contributed to the inverse-J relationship between intensity of neurohormonal modulation and event rates (Figure).^{22,23} Moreover, it is well known that intolerance to these medications in patients with advanced HFrEF is a marker of poor prognosis, and hence, the patients most in need of therapy are often the ones who cannot tolerate these hemodynamically active agents.

The deleterious effects of hypotension are perhaps best highlighted in acute HF trials (Table 2). Low baseline and post-treatment blood pressures have significantly limited the development of intravenous, hemodynamically active agents in early²⁴ and late^{25–30} phases of evaluation. In this setting, hypotension is commonly observed, well-documented, and

may lead to adverse outcomes, even if occurring transiently during drug administration. Patients admitted or evaluated for worsening chronic HF may be particularly susceptible to hypotension and its attendant adverse effects as a result of rapidly changing clinical status, elevated left ventricular filling pressures, and concurrent administration of vasoactive agents. In the Randomized Evaluation of Intravenous Levosimendan Efficacy (REVIVE) program, any occurrence of hypotension was the most frequent adverse event observed (50.2% in levosimendan group; 36.4% in placebo group), occurred primarily during the first 24-hours of infusion, and represented the most common reason for drug withdrawal.²⁸ Levosimendan-related risk of death (compared with placebo) after 14 days varied by baseline SBP; the relative risk of death was 1.9 in patients with SBP <100 mm Hg and 1.1 in patients with SBP \geq 100 mm Hg.²⁸ Hypotension related to intravenously dosed agents occurs despite careful in-hospital titration.²⁵ More recent trials in acute HF, including Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), have excluded patients with normal or low baseline blood pressure and those concomitantly being administered vasoactive agents.²⁷ Relaxin in Acute Heart Failure (RELAX-AHF) used strict hemodynamic enrollment criteria that enriched the trial population with primarily normal or hypertensive patients with an average blood pressure at enrollment of 142/82 mm Hg. Despite this, significant transient reductions in blood pressure were observed during infusion requiring in-hospital dosing adjustments in 29% of patients and withdrawal from the study protocol in 19% of patients randomized to serelaxin.³⁰

Success of Established Therapies

Hypotension is an attendant risk of drug therapy even in successful trial programs of oral therapies in chronic HFrEF (Table 1). Although overt and persistent hypotensive episodes requiring drug discontinuation are infrequently observed in trials, rates of clinical or subclinical hypotension approach 10%.¹³ Contemporary clinical trials use various strategies that limit the incidence of hypotensive episodes compared with real-world clinical practice. First, exclusion criteria at enrollment restrict patients with baseline lower SBP. Second, early trials initiated and titrated hemodynamically active oral agents in the in-hospital setting to allow for close monitoring.³¹ This period of intensive observation and stabilization is rarely mirrored in clinical practice. Third, the use of run-in periods confounds the real-world risks of hypotension. In Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), early detection of symptomatic hypotension led to revision of the trial protocol and 12% of patients ultimately required withdrawal before receiving the full dose study drug.³¹ Similarly, 2.2% of patients were excluded from entering the Studies of Left Ventricular Dysfunction (SOLVD) program because of symptomatic hypotension.^{32,33} Even more recent trials, such as PARADIGM-HF, have used run-in periods to diminish the risk of hemodynamic perturbations on drug therapy. Patients ultimately randomized had to demonstrate stability and tolerance of both enalapril and sacubitril/valsartan.¹³ Finally, there has been a recent trend toward trials with larger numbers of enrolled patients with earlier stage

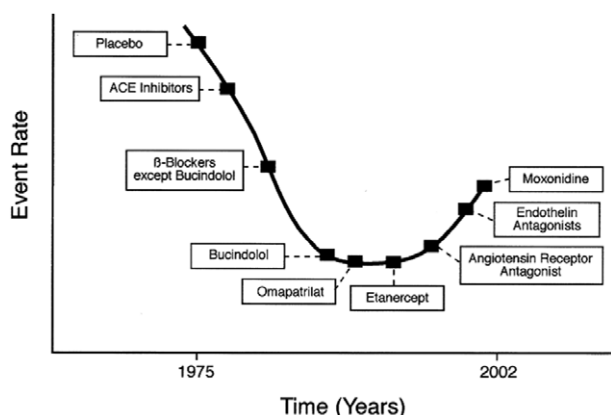


Figure. Saturation of benefits with incremental neurohormonal blockade in chronic heart failure (1975–2003). ACE indicates angiotensin-converting enzyme. Reprinted from Gheorghiade et al²² with permission of the publisher. Copyright © 2015, Elsevier.

Table 2. Rates of Hypotension and Short-Term Mortality in Select Phase III Randomized Controlled Clinical Trials of Intravenous Therapies in Acute Heart Failure

Trial	Study Recruitment Start Date	Study Drug	n	Systolic BP at Enrollment	Hemodynamic Exclusion Criteria	Postrandomization Hypotension	Definition of Hypotension	All-Cause Mortality†	Mortality Assessment
FIRST	*	Epoprostenol	471	105/70	SBP<80 mm Hg	*	*	30% vs 24%	90-d
OPTIME-CHF	July, 1997	Milrinone	951	120/71	SBP<80 mm Hg; requiring inotropes	10.7% vs 3.2%	SBP<80 mm Hg for more than 30 min, requiring intervention	10.3% vs 8.9%	60-d
REVIVE	December, 2001	Levosimendan	600	116/69	SBP<90 mm Hg	8.1% vs 2.3%	Requiring withdrawal	15.1% vs 11.6%	90-d
PROTECT	May, 2007	Rolofylline	2033	124/74	SBP<95 mm Hg; SBP<90 mm Hg if outpatient blood pressures are consistent	7.3% vs 6.0%	*	17.9% vs 17.4%	180-d
ASCEND-HF	May, 2007	Nesiritide	7141	124/*	SBP<100 mm Hg; SBP<110 mm Hg with use of intravenous nitroglycerin; recent use of dobutamine, milrinone, or levosimendan	7.2% vs 4.0%	Symptomatic	3.6% vs 4.0%	30-d
RELAX-AHF	October, 2009	Serelaxin	1161	142/82	SBP<125 mm Hg; SBP>150 mm Hg	19% vs 12%	Requiring withdrawal	2.1% vs 3.3%	30-d

All comparators were placebo or standard care. ASCEND-HF indicates Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure; FIRST, Flolan International Randomized Survival Trial; OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; PROTECT, Prophylaxis of Thromboembolism in Critical Care; RELAX-AHF, Relaxin in Acute Heart Failure; REVIVE, Randomized Evaluation of Intravenous Levosimendan Efficacy; and SBP, systolic blood pressure.

*Data not available on query of the primary results publication.

†Mortality expressed as event rates in study drug vs placebo (or standard therapy).

disease,³⁴ and certain high-risk groups for adverse events, are not well represented, limiting the trials' ability to ensure drug safety in the sickest patients. For example, in PARADIGM-HF, which is the largest chronic HFrEF trial conducted to date, elderly patients and those with functional class III or IV were relatively under-represented.¹³

Despite their potential hemodynamic effects, certain successful drugs actually improve blood pressure profile over time secondary to improving cardiac mechanics and function.³⁵ Many successful HFrEF vasoactive agents may exert heterogeneous blood pressure-lowering effects, such that deleterious hypotensive effects may be limited to select clinical subgroups including patients, for example, those with advanced age, coronary artery disease, renal dysfunction, and poor functional status. Although omapatrilat did not reduce mortality or hospitalization risk compared with enalapril in the overall Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, post hoc analysis supported clinical benefit of omapatrilat in the subgroup with higher blood pressure.³⁶ Consistently, despite the robust net clinical benefits of sacubitril/valsartan in PARADIGM-HF, interaction analyses suggested reduced drug efficacy in patients with New York Heart Association class III and IV (albeit enrolled in small numbers to draw definitive conclusions).¹³ Similarly, underlying comorbid disease burden and

etiology of cardiomyopathy may modify the risk of treatment-related outcomes in HF trials.⁷ In sum, select clinical benefits observed with add-on neurohormonal blockade may be balanced or even neutralized by adverse risks of hypotension.

Future of HF Drug Development

Neurohormonal blockade and hemodynamically active agents have historically been successful in reducing morbidity and mortality in HFrEF. Saturation of available peripheral neurohormonal targets and adverse hemodynamic risks with such agents, however, have hindered the progress of contemporary drug development in HFrEF. Treatment-related hypotension is a real risk observed in both clinical and research settings, limiting optimization of disease-modifying HF therapies in patients who most need them. Unfortunately, clinical trials may underestimate the real-world risk of hypotension because currently used tools are relatively insensitive to therapy-related hemodynamic disturbances, and high-risk patients with low baseline blood pressures are categorically excluded from many studies.

So, what can be done to improve the detection and avoidance of therapy-related hypotension? First, future HF clinical trials should use standardized definitions of hypotension, preferably leveraging the use of ambulatory blood pressure monitoring to capture diurnal variation. This seems to be feasible

as recent chronic HFREF trials have successfully used 24-hour ambulatory heart-rate monitoring.³⁷ Second, robust phase II programs are required to ensure hemodynamic safety across a range of selected doses. Third, more definitive studies should routinely include vulnerable populations that may experience adverse hemodynamic events at increased frequency. The risk of untoward drug-related hypotension may be diminished with more careful titration of vasoactive therapies in these high-risk subgroups to more lenient blood pressure targets. Trial protocols should specify and tailor dosing changes of hemodynamically active agents based on age, baseline blood pressure, and presence of obstructive coronary artery disease or chronic kidney disease. Fourth, clinicians and care teams should be trained in frequent and close monitoring of patients with HF to approximate practice in contemporary clinical trials, which may facilitate early adjustment of HF therapies in response to hemodynamic perturbations. The routine measurement of orthostatic vital signs may increase the detection therapy-related hypotension.

Finally, new paradigms of drug development need to be forged to refocus treatment of HF with reduced and preserved ejection fraction on the heart as a primary target for therapy. In order to achieve this, therapeutic strategies should directly aim to attenuate adverse cardiac remodeling by targeting abnormalities in the non- or hypo-contractile myocyte (eg mitochondria), microcirculation, interstitium, or metabolic pathways. The safe amelioration of these components may result in improvement in clinical outcomes in HF without undue hemodynamic consequences. Newer agents under development such as mitochondria-targeting peptides, partial adenosine A1 receptor agonists, and chimase inhibitors appear to be hemodynamically neutral (limited effects on systemic blood pressure and heart rate), and possess attributes that improve various aspects of cardiac remodeling. The development of novel therapies intended to exclusively attenuate peripheral, neurohormonal systems, in the background of already available therapies, is unlikely to produce incremental benefit and may cause excess risk related to hypotension.

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