Journal of Intensive Care Medicine
1-11

DOI: 10.1177/0885066616669494
jic.sagepub.com
SAGE

Acute Decompensated Heart Failure

Drayton A. Hammond, PharmD, MBA, BCPS, BCCCP[1], Melanie N. Smith, PharmD[2], Kristen C. Lee, PharmD, BCPS[3], Danielle Honein, PharmD[4], and April Miller Quidley, PharmD, BCPS, FCCM[5]

Abstract

Heart failure (HF) is a societal burden due to its high prevalence, frequent admissions for acute decompensated heart failure (ADHF), and the economic impact of direct and indirect costs associated with HF and ADHF. Common etiologies of ADHF include medication and diet noncompliance, arrhythmias, deterioration in renal function, poorly controlled hypertension, myocardial infarction, and infections. Appropriate medical management of ADHF in patients is guided by the identification of signs and symptoms of fluid overload or low cardiac output and utilization of evidence-based practices. In patients with fluid overload, various strategies for diuresis or ultrafiltration may be considered. Depending on hemodynamics and patient characteristics, vasodilator, inotropic, or vasopressor therapies may be of benefit. Upon ADHF resolution, patients should be medically optimized, have lifestyle modifications discussed and implemented, and medication concierge service considered. After discharge, a multidisciplinary HF team should follow up with the patient to ensure a safe transition of care. This review article evaluates the management options and considerations when treating a patient with ADHF.

Keywords

acute decompensated heart failure, heart failure, diuretic, vasodilator, inotrope

Introduction

There are approximately 5.1 million American adults with a diagnosis of heart failure (HF), with an estimated 1 million hospitalizations annually for HF exacerbations.[1,2] The rate of hospitalization has not changed significantly since 2000,[3] with up to 50% of patients readmitted within 6 months.[4,5] More than 274 000 deaths were related to HF in 2009, totaling 1 in 9 mortalities in the United States.[1] A 2008 study found that in patients with stage D HF who were discharged from the hospital for acute decompensated heart failure (ADHF), only 32.9% were alive and had not been rehospitalized after 1 year.[5] The estimated cost of a hospital admission for a HF exacerbation is greater than US$12 000.[6] The total direct and indirect costs associated with HF approach US$32 billion (in US 2008 dollars), with more than 70% of these expenses associated with the provision of health-care services including hospitalizations.[1,7] This number is expected to reach US$70 billion by 2030.[1] Because of the high prevalence of HF, frequent readmissions for ADHF, and economic burden associated with the spectrum of HF, utilization of evidence-based practices can have significant patient and societal benefits.

Pathophysiology

The heart is classically described as a pump that functions almost exclusively on pressure gradients established by physiological changes. The heart provides cardiac output to the systemic vasculature, which may be adjusted to meet physiologic needs by changes in stroke volume, heart rate, or both.[8] The HF can occur with a reduced ejection fraction (HFrEF), a preserved ejection fraction, or both. When ventricular preload increases, short-term benefits are seen as stroke volume increases as a function of ventricular contractility. However, chronically, the contractile force of a failing heart is reduced due to its inability to overcome excessive pressure and volume. This hemodynamic mismatch is accommodated through ventricular remodeling. In the long term, the extent of ventricular

[1] Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy, Little Rock, AR, USA
[2] Department of Pharmacy, Medical University of South Carolina, Charleston, SC, USA
[3] Department of Pharmacy, Orlando Regional Medical Center, Orlando, FL, USA
[4] Department of Pharmacy, Sarasota Memorial Hospital, Sarasota, FL, USA
[5] Department of Pharmacy, Vidant Medical Center, Greenville, NC, USA

Received May 28, 2016. Received revised August 25, 2016. Accepted August 25, 2016.

Corresponding Author:
Drayton A. Hammond, Department of Pharmacy Practice, University of Arkansas for Medical Sciences College of Pharmacy, 4301 West Markham Street, Slot 522, Little Rock, AR 72205, USA.
Email: dahammond@uams.edu

remodeling leads to a significant reduction in the left ventricular ejection fraction (LVEF), which subsequently leads to a cardiac output that is insufficient for systemic demands.[9]

In this state of HFrEF, neurohumoral hyperactivity develops in an attempt to preserve cardiac output. Increased secretion of specific hormones, most notably those in the renin–angiotensin–aldosterone system (RAAS), represents the humoral limb of this preservation response, whereas the sympathetic nervous system (SNS) represents the neuronal limb.[10]

The RAAS, which affects cardiac pathophysiology through systemic vasoconstriction and sodium retention leading to intravascular fluid retention, was the first humoral system studied in HF.[11] Renin is converted from prorenin and then cleaves angiotensinogen to form angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is the most potent systemic vasoconstrictor in humans and responds to relative volume depletion and hypotension via vasoconstriction and increasing aldosterone levels to maintain homeostasis. Aldosterone is produced in the adrenal glands in response to perceived systemic volume depletion and leads to the retention of sodium by the kidneys. The increase in systemic vasoconstriction increases afterload, which leads to RAAS upregulation in order to overcome these elevated pressures. In patients with HF, this RAAS upregulation predisposes a failing heart to development of ADHF.[9] Aldosterone and angiotensin II produced in the brain affect SNS activation and progression of HFrEF.[12,13] It is postulated that angiotensin II initiates a positive feedback mechanism, including upregulation of the angiotensin II type 1 receptor, increased production of superoxide anions, and nitric oxide inhibition.[14]

Additionally, the SNS is hyperactive in HF. Although it is difficult to clinically evaluate the SNS, particularly in ADHF, changes in SNS activity have been observed.[15] In HFrEF, increased concentrations of plasma norepinephrine result from a combination of decreased clearance and increased central nervous system sympathetic outflow.[16] The SNS hyperactivity may exacerbate HF by stimulating the RAAS and contributing to the development of left ventricular dysfunction.[17,18]

Several factors increase the likelihood that a patient will develop HF. Coronary artery disease and myocardial ischemia, the leading causes of HF in the United States, cause decreased perfusion and thus increased hypertension. Primary myopathy and myocardial infarction affect contractility that leads to volume and pressure overload. Hypertension and stenotic valves can lead to increased myocardial stiffness, hypertrophy of the affected ventricle, and restricted stroke volume. Valvular regurgitation may result in the development of elevated end-diastolic pressure, ventricular dilation, and reduced systolic function. Each of these causes and many more lead to ventricular remodeling, reductions in cardiac output, and elevated filling pressures.[9] Common etiologies of ADHF include medication and diet noncompliance, arrhythmias, deterioration in renal function, poorly controlled hypertension, myocardial infarction, viral, fungal, and bacterial infections, congenital cardiomyopathies, and amyloidosis.[19] Additionally, many medications may precipitate or exacerbate HF, including those with negative inotropic effects (eg, nondihydropyridine calcium channel blockers, itraconazole, and terbinafine), drugs that promote sodium and water retention (eg, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and thiazolidinediones), and those that are directly cardiotoxic (eg, doxorubicin, cocaine, and amphetamines).[20,21]

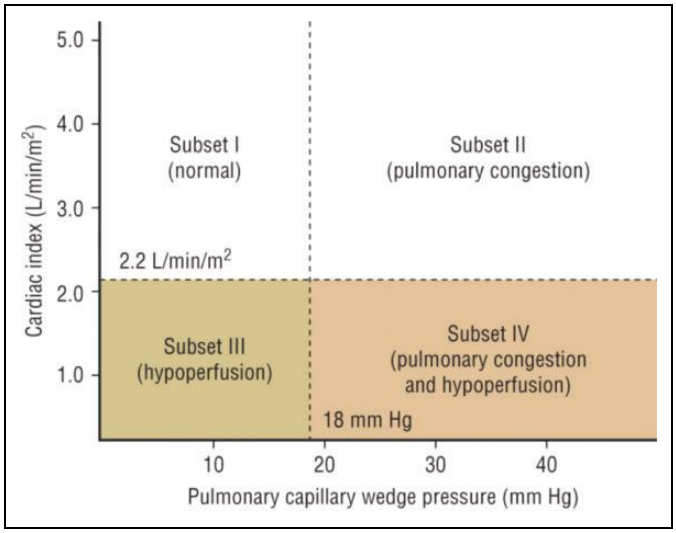

Figure 1. Forrester classification of acute decompensated heart failure.[22]

Clinical Features

The presentation of a patient with ADHF varies depending on fluid status and cardiac output. Therapy for ADHF is selected based on this clinical presentation.[19] Patients may be congested (wet) or not congested (dry) and exhibit poor perfusion (cold) or adequate perfusion (warm). These clinical presentations are described in the Forrester classification system (Figure 1). Hemodynamic parameters may be included in this assessment; however, the utilization of a pulmonary artery catheter has decreased in recent years because its addition to clinical assessment has not been shown to affect length of stay and overall mortality[23-25]. A careful clinical assessment includes a thorough patient history, physical examination, and evaluation of hemodynamic parameters, which may change as interventions are initiated and titrated to effect. Patients with clinical features representing congestion often will have the cardinal symptoms of ADHF, including dyspnea, fatigue, and fluid retention that manifest with an S3 gallop and jugular venous distention.[19] Of note, the presence of an S3 gallop upon cardiac auscultation is highly specific for ADHF. Patients with pulmonary edema may present with respiratory acidosis, hypoxemia, and greatly increased work of breathing.[9] Patients who present with poor perfusion (cold), and especially those who are dry, are more difficult to distinguish than those with fluid overload. They present with signs of low cardiac output including extreme fatigue, cool extremities, and often but not always with gastrointestinal symptoms of poor appetite, nausea, and early satiety. Additionally, they typically present with worsening renal function and low serum sodium.[26]

Biomarkers

The diagnosis of ADHF primarily should be based on signs and symptoms, with biomarkers playing a supporting diagnostic role.[27] The role of B-type natriuretic peptide (BNP) in the diagnosis, management, and prognosis of ADHF has evolved over time.[28] It is secreted from cardiac myocytes in response to atrial or ventricular wall stretch, as seen in HF. Its physiological roles include diuresis, natriuresis, and inhibition of neurohormonal activity. Increased levels of BNP correlate well with findings of impaired left ventricular function. A finding of BNP >100 pg/mL in a patient with dyspnea improves diagnostic accuracy, especially in patients with an intermediate likelihood of HF exacerbation.[29] In fact, BNP values less than 100 pg/mL have a 96% negative predictive value for HF as the source of dyspnea.[26] A relative increase of greater than 123% of the baseline BNP value likely represents a clinically meaningful elevation in cardiac filling pressures and supports the diagnosis of ADHF.[30] However, in patients taking sacubitril–valsartan, neprilysin inhibition leads to increased BNP unassociated with a HF exacerbation.[31] Beyond initial diagnosis of exacerbation, frequent BNP measurements have not been shown to provide additional benefit in guiding diuretic therapy during a hospitalization.[32]

The Acute Decompensated Heart Failure National Registry (ADHERE) study provides specific data on the prognostic value of a variety of physiologic markers in ADHF. A quartile division of BNP (<430 pg/mL, 430-839 pg/mL, 840-1729 pg/mL, and >1730 pg/mL) accurately predicted the risk of inpatient death (1.9%, 2.8%, 3.8%, and 6.0%, respectively).[33,34]

In addition to BNP, other parameters described in the ADHERE study were blood urea nitrogen (BUN), systolic blood pressure (SBP), and serum creatinine. A BUN ≥43 mg/dL served as the best predictor of in-hospital mortality, followed by SBP <115 mm Hg and serum creatinine >2.75 mg/dL. Patients meeting all 3 parameters had an in-hospital mortality of 20%.[34] Other negative prognostic factors include poor functional capacity, ischemic etiology, elevations in troponin I, and hyponatremia. In patients with ADHF, 30% to 70% have detectable plasma levels of troponin I, which is associated with an increase in both postdischarge mortality and rehospitalization. Approximately 25% of patients with ADHF have mild hyponatremia, which is associated with a 2- to 3-fold increase in in-hospital and postdischarge mortality.[35]

General Management Principles

An appropriate medical management of ADHF is guided by the identification of signs and symptoms of fluid overload or low cardiac output. Assessment of the patient using the Forrester classification system is useful in tailoring care to a specific patient. Regardless of ADHF subset, strict fluid intake and output, weight monitoring, recognition of changes in HF signs and symptoms, and appropriate electrolyte management are essential. Supplemental oxygen, positive pressure ventilation, and mechanical support are other medical strategies for the management of ADHF. This review will focus on pharmacological treatment, including the optimization of both in-hospital and oral, evidence-based medications prior to discharge. Specific monitoring recommendations for patients hospitalized with ADHF should be followed to provide safe care while determining efficacy of therapies (Table 1). Accurate monitoring of pulse oximetry, blood pressure, and electrocardiography are needed to provide safe and effective care. Patients should be admitted to an intensive care unit (ICU) if there is persistent hemodynamic instability that necessitates frequent, invasive monitoring and titration of intravenous (IV) medications, such as diuretic and vasoactive agents.[19] Treatment teams should strive to meet specific goals for patients admitted for ADHF (Table 2).[27]

In order to optimize therapy for discharge, physicians should only temporarily discontinue or reduce the dose of oral medications under certain circumstances. The ACE inhibitor, angiotensin receptor blocker (ARB), neprilysin inhibitor, and aldosterone antagonist therapies should be continued when possible. Hyperkalemia or oliguria may necessitate dose reduction or discontinuation. After the improvement of renal function, these agents may be added back cautiously, with monitoring of potassium and urine output. Patients experiencing symptomatic hypotension or cardiogenic shock may require a dose reduction or discontinuation of an ACE inhibitor

Table 1. Monitoring for Hospitalized Patients With Acute Decompensated Heart Failure.[27]

Characteristics	Monitoring Frequency	Specifics
Electrolytes	At least daily	Potassium
		Sodium
Fluid status		Fluid intake and output
Heart failure signs		Ascites
		Edema
		Hepatojugular reflex
		Hepatomegaly
		Increased jugular venous Distention
		Liver tenderness
		Pulmonary rales
Heart failure symptoms		Dyspnea
		Fatigue
		Lightheadedness
		Nocturnal cough
		Orthopnea
		Paroxysmal nocturnal dyspnea
Renal function		Blood urea nitrogen
		Serum creatinine
Weight		Determine after voiding in the morning
		Take possible food intake due to improved appetite into account
Vital signs	More than daily	Orthostatic blood pressure if indicated
		Oxygen saturation daily until stable

Adapted with permission from Lindenfeld et al. J Card Fail. 2010;16(6):e1-e194.

Table 2. Treatment Goals for Patients Admitted for Acute Decompensated Heart Failure.[27]

Consider and, where possible, initiate a disease management program
Educate patients concerning medications and self-management of heart failure
Identify and address precipitating factors
Identify etiology
Identify patients who might benefit from device therapy
Identify patients who might benefit from revascularization
Identify risk of thromboembolism and need for anticoagulant therapy
Improve symptoms, especially congestion and low-output symptoms
Minimize side effects
Optimize chronic oral therapy
Optimize volume status
Restore normal oxygenation

Adapted with permission from Lindenfeld et al. J Card Fail. 2010;16(6):e1-e194.

and β-blocker in order to prevent further hemodynamic compromise.[27,36] However, discontinuation of β-blocker therapy should be done with caution in patients with fluid overload who maintain adequate end-organ perfusion (ie, ADHF subset II) due to the substantially higher adjusted risk for rehospitalization and mortality with cessation.[37-40] Patients taking digoxin should be continued on therapy with serum concentration monitoring to ensure a target concentration of 0.5 to 1 ng/mL because digoxin withdrawal frequently leads to worsening of HF.[22,41] Table 3 contains complete management of oral pharmacotherapy in ADHF.[42]

Subset I

Patients in subset I have adequate perfusion and are not fluid overloaded; their cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) are within clinically acceptable ranges (CI > 2.2 L/min/m^2, PCWP < 18 mm Hg). If these patients present to the hospital, it often is because their normal compensatory mechanisms are only able to partially correct their worsening hemodynamic profiles. The key interventions for these patients are to maximize their evidence-based, oral medications and continue appropriate monitoring. These patients have the lowest mortality rate among the 4 subsets of ADHF.[27]

Subset II

Patients in subset II have adequate perfusion but are fluid overloaded; their CI is acceptable but their PCWP is elevated, often leading to a clinical picture of pulmonary edema. The specific treatment goal is to reduce congestion by lowering PCWP without reducing CI, significantly increasing HR, or further activating neurohormonal pathways more than is essential to restore appropriate hemodynamics. Preload reduction using IV loop diuretic therapy is the mainstay of therapy in patients with ADHF subset II. The IV vasodilator therapy may be added for acute symptomatic relief in patients not adequately responding to diuresis or ultrafiltration (UF). The mortality rate in subset II is twice that of subset I.[27]

Management of fluid balance with IV diuretics is a balancing act and preload, represented by PCWP, should not be excessively decreased because it may compromise cardiac output. Target PCWP values are 15 to 18 mm Hg, rather than the normal values of 5 to 12 mm Hg, to optimize cardiac output.[27] Because the Frank–Starling curve has a shallower slope over the 15 to 18 mm Hg range, patients routinely maintain cardiac output upon reaching this goal PCWP.[9] Various strategies exist for providing diuresis to accomplish this goal effectively. Because of observational experiences with IV loop diuretics and the variable oral absorption with oral furosemide, IV therapy is preferred in ADHF.[27] The IV bolus dosing of loop diuretics can reduce ventricular filling pressures within 15 minutes, which can help alleviate patient symptoms of ADHF before diuresis even begins.[43] Because electrolyte disturbances and worsening renal function may occur with aggressive diuresis, a basic metabolic panel should be obtained routinely while diuresis is provided. Strict sodium limitation (less than 2 g daily) and fluid restriction (less than 1.5-2 L daily) help accomplish diuresis more effectively while protecting against moderate and severe hyponatremia.[27]

Although there is no universally accepted methodology for dosing, monitoring, and evaluating end points with diuretic therapy, there are benefits and risks associated with the various strategies studied and used in clinical practice, including high versus low dose and intermittent versus continuous infusion dosing.[27,44-46] Studies that compared intermittent bolus versus continuous infusion dosing of IV loop diuretics have predominately had smaller sample sizes and shown conflicting results.[44,45,47] In the largest, randomized trial of IV loop diuretic use in ADHF, a 4-way comparison between high- and low-dose intermittent bolus and continuous dosing revealed differences in the strategies. There were no significant differences in patient-reported global assessment of symptoms between the low-dose (defined as the daily outpatient oral loop diuretic dose given IV) and high-dose (defined as 2.5× the daily outpatient oral loop diuretic dose given IV) groups or between the intermittent (defined as twice daily IV loop diuretic) and continuous infusion groups. The low-dose group experienced less transient acute kidney injury compared to the high-dose group (14% vs 23%; $P = .04$). However, the high-dose group had greater net volume loss and change in weight. Additionally, patients who received continuous infusions were not provided an initial bolus dose before beginning the infusion, which may have reduced the effectiveness of the continuous infusion and does not represent current practice.[46] Clinicians should balance the benefit of greater diuresis from a high-dose strategy with the risk of transient renal dysfunction. In patients with ADHF subset II, it is reasonable to use a more aggressive, high-dose IV loop diuretic dosing strategy because these patients are far less likely to experience symptomatic hypotension or significantly worsened renal function upon presentation.

The goal diuresis in ADHF patients is 1 to 2 L/d, with 2 L/d being more appropriate in patients presenting in subset II. If this diuresis goal is not being met, and the patient still exhibits signs and symptoms of congestion, several strategies may be attempted to achieve adequate diuresis. Further sodium and

Table 3. Management of Oral Pharmacotherapy in Acute Decompensated Heart Failure.[a,42]

	ACEi/ARB/NI	β-Blocker	Digoxin	Diuretic	MRA
Subset I	Maintain or increase while checking renal function	Maintain or increase	Maintain; often not needed	Maintain or reduce, if possible	Maintain or increase
Subset II	Maintain; defer uptitration	Maintain; defer uptitration	Maintain; verify plasma concentration	Increase dosage and/or add a second diuretic	Maintain; defer uptitration
Subset III	Reduce or withdraw	Reduce or withdraw; evaluate the need for inotropic support	Maintain; verify plasma concentration	Maintain/reduce with caution	Reduce or withdraw
Subset IV	Withdraw	Withdraw; evaluate the need for inotropic support	Maintain; verify plasma concentration	Individual cases must be evaluated	Withdraw

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NI, neprilysin inhibitor.

[a] Recommendations reflect expert opinions and relevant clinical trials data. Dose reductions may be up to one-half the patient's home dose. After resolution of the decompensation event, medication dosages should be uptitrated to the previous dose or best-tolerated dose as soon as safely possible.

Adapted with permission from Piepoli et al. Int J Cardiol. 2014;176(2):321-326.

fluid restriction may resolve the congestion. As mentioned previously, patients who were initiated on a low-dose IV loop diuretic strategy may be transitioned to a high-dose strategy.[27] Because the plasma concentration of the loop diuretic must exceed the threshold concentration to elicit diuresis, a high-dose strategy may benefit patients previously unresponsive to the low-dose strategy.[48] Other strategies include transitioning to a continuous infusion loop diuretic strategy, adding a thiazide diuretic due to its different mechanism of action or UF.[27]

If greater than 200 mg/d of IV furosemide or an equivalent dose of another IV loop diuretic does not provide adequate diuresis, the patient is considered to have failed IV loop diuretic monotherapy.[27] This may occur if the renal tubular epithelial cells distal to the loop of Henle are hypertrophied and have increased compensatory sodium reabsorption.[49,50] Thiazide and thiazide-like diuretics inhibit this sodium reabsorption and create a synergistic effect that improves signs and symptoms of congestion.[51,52] However, no improvement in long-term morbidity or mortality has been shown with this combination of diuretics.[53-55] Oral metolazone at doses of 2.5 to 5 mg provided once 30 minutes before an IV loop diuretic dose is the most studied and cost-effective regimen.[51] The IV chlorothiazide should not be used preferentially to metolazone because of its high cost without a proven superiority to metolazone.[50] Close monitoring is needed as patients who previously were not achieving diuresis goals may overshoot those goals with this synergistic strategy and develop renal dysfunction, electrolyte abnormalities, and symptomatic hypotension.[27,51]

Another option to relieve congestion is UF, which removes isotonic plasma by establishing a transmembrane pressure gradient that allows filtering across a semipermeable membrane. Although UF removes total body sodium better than diuresis, determining the appropriate rate of intravascular volume removal remains a challenge. Accepted common practice is serial monitoring of electrolytes and hematocrit values and maintaining them within normal limits.[56] Common removal rates are 200 to 500 mL/h in 8 to 12 hours of sessions, but fluid removal should be individualized to the patient.[56,57] When intravascular volumes are depleted too rapidly or too extensively, neurohormonal activation, renal dysfunction, and hypotension may occur. Preliminary trials that evaluated UF compared with IV diuresis for initial fluid removal strategies were small in size and showed no differences in dyspnea at 48=hours.[58,59] In patients with persistent congestion and worsening renal function, there was no difference in change in body weight at 96 hours, but there was a statistically significant increase in serum creatinine in the UF group.[60] One limitation of this trial is the lack of individual tailoring of UF rate to each patient, which may have precipitated the acute kidney injury in some patients and inadequate resolution of congestion in other patients.[61,62] If clinicians choose to use UF, diligent monitoring of end-organ function and intravascular volume is essential.

In patients who do not respond adequately to IV diuresis, addition of an IV vasodilator may be considered. Nitroglycerin is the preferred agent for preload reduction in patients with ADHF subset II. A continuous infusion is started at 5 to 10 μg/min and increased by 5 to 10 μg/min every 5 to 10 minutes as necessary and tolerated by the patient. Major dose-limiting side effects include hypotension and excessive decrease in PCWP. The IV nitroglycerin preferentially venodilates at lower doses, which leads to a reduction in the left ventricular filling pressure and pulmonary congestion. As the dose of nitroglycerin is increased, arterial dilation develops, leading to afterload reduction, increased stroke volume and increased cardiac output. It should not be used in patients with elevated intracranial pressure, restrictive cardiomyopathy, pericardial tamponade, or constrictive pericarditis.[27] The IV nitroglycerin was compared to nesiritide, milrinone, and dobutamine in 15 230 patients with predominant ADHF subset II. Nitroglycerin and nesiritide were associated with lower in-hospital mortality rates compared to dobutamine and milrinone.[33]

In patients with concomitant hypertension or in whom nitroglycerin is not providing an adequate effect, sodium nitroprusside may be considered because of its equal arterial and venous

vasodilatory effects and ease of titration.[27] Infusions are started at 0.1 to 0.2 μg/kg/min and increased by 0.1 to 0.2 μg/kg/min every 5 to 10 minutes as necessary and tolerated by the patient. Use requires an arterial line and ICU admission due to potential side effects and need for accurate blood pressure monitoring. The effective dose range is usually 0.5 to 3 μg/kg/min.[63,64] Nitroprusside use is contraindicated in patients with compensatory hypertension secondary to disease states such as aortic coarctation, ventricular septal defect, or elevated intracranial pressure. Patients with hepatic impairment are at increased risk of developing cyanide toxicity, and those with renal impairment are at increased risk of developing thiocyanate toxicity.[64] However, these complications occur very infrequently when used by an experienced care team at doses less than or equal to 3 μg/kg/min for up to 72 hours.[63-65] In the largest, retrospective trial of patients in ADHF who received nitroprusside, long-term benefits were seen in mortality and progression to heart transplant. However, patients who received nitroprusside were transitioned to isosorbide dinitrate, hydralazine, or a combination of these 2.[64] Because there is more substantial data in HF that suggest African Americans derive a mortality benefit with the combination of hydralazine and isosorbide dinitrate, these results may not be due exclusively to nitroprusside.[66]

The role of nesiritide, recombinant human BNP, has diminished in recent years.[27,67] After nesiritide was originally approved for ADHF subset II based on the improvements in PCWP, suggested dosing and monitoring strategies were still evolving.[68] Subsequent meta-analyses found that nesiritide use was associated with increased 30-day mortality and worsening renal function.[69-71] Some of this effect may be attributed to the use of higher doses and more frequent dose titrations than are now recommended. Subsequent studies have compared nesiritide to placebo and to fixed-dose dopamine at 2.5 μg/kg/min. In both instances, there were no significantly different effects on mortality, rehospitalization, or resolution of congestion.[72,73] Additionally, patients in the nesiritide group developed more asymptomatic and symptomatic hypotension.[72] In light of the possible risk for renal failure, hypotension, and increased mortality, nesiritide should be considered only for the normotensive patient needing emergent resolution of pulmonary congestion who has a contraindication to nitroglycerin or nitroprusside.

Inotropic agents, such as milrinone and dobutamine, are not recommended in ADHF subset II except as a last resort after failure of all other therapies.[27] When milrinone was compared with placebo, there were no differences in in-hospital mortality or cumulative days of hospitalization. More patients in the milrinone group developed sustained hypotension requiring intervention as well as new atrial arrhythmias.[74] Both milrinone and dobutamine increased mortality in these patients.[34] Dopamine has not demonstrated a role in ADHF subset II.[27,73]

Subset III

Patients in subset III have inadequate perfusion, often due to a decreased intravascular volume; their CI is insufficient, and their PCWP may or may not be adequate to support end-organ perfusion. The specific treatment goal is to restore adequate end-organ perfusion, which is accomplished by providing isotonic IV fluids if the PCWP is below 15 mm Hg. If the PCWP is 15 to 18 mm Hg, the mean arterial pressure (MAP) and SBP dictate treatment. These patients have a greater mortality than those in subset I but less than those in subsets II and IV.[27]

In patients who initially are dehydrated (PCWP <15 mm Hg), provision of IV fluids may or may not result in adequate perfusion. Among patients with mild reduction in LVEF, IV fluids alone are likely to restore adequate perfusion; whereas patients with depressed LVEF often require fluids and inotrope therapy. Additionally, if hemodynamics permits (MAP >50 mm Hg and SBP >90 mm Hg), a trial of IV vasodilator therapy is reasonable if there are no signs of acute kidney injury or symptomatic hypotension.[27]

The IV vasodilator of choice for patients in subset III is nitroprusside due to its mixed arterial and venous vasodilation seen at safe doses.[27,63,64] The same precautions exist in these patients as are present in subset II patients who receive IV nitroprusside; however, these patients are at greater risk for hypotension and end-organ dysfunction. Because the ongoing processes of increasing intravascular volume and mobilization of volume through arterial and venodilation are intertwined, an imbalance in the pharmacotherapies prevents a sufficient upward, leftward shift in the Frank–Starling curve and may predispose patients to symptomatic hypotension and end-organ dysfunction. In patients who do not tolerate or have a contraindication to nitroprusside, IV nitroglycerin is the preferred vasodilator and IV nesiritide may be considered as a last-line therapy. Every attempt should be made to avoid using IV inotrope therapy due to the poor outcomes associated with the use of these agents.[27,67,74] The IV inotrope therapy should only be added to the treatment regimen in patients who do not qualify for initial therapy with an IV vasodilator or have resistance to vasodilator therapy.[27]

Dopamine should only be started before previously discussed IV vasodilator and IV inotrope therapies in patients who initially have a MAP <50 mm Hg.[27] Dopamine demonstrates dose-dependent hemodynamic effects. Lower doses of dopamine (2.5-10 μg/kg/min) should be used, with a focus on the β-1 adrenergic receptor activity. Vasoconstriction and arrhythmias due to dopamine occur frequently with doses >10 μg/kg/min; however, the individual effects on target receptors differ between individual patients.[75,76] This vasoconstriction may complicate treatment and necessitate the use of an IV inotrope instead of dopamine.[27,75]

Subset IV

Patients in subset IV have inadequate perfusion despite being overloaded with fluid; their CI is decreased in the face of an elevated PCWP. These patients are in cardiogenic shock. In many patients, dopamine or IV inotrope therapy should be considered initially. However, in patients with an adequate SBP and stable renal function, treatment should be directed

at reducing afterload with an IV vasodilator and supporting compensatory hemodynamic changes. At two-and-a-half times that of subset I patients, these patients have the greatest mortality of any ADHF subset.[27]

Diuresis in patients with cardiogenic shock and fluid overload is a delicate balance of relieving fluid overload, while avoiding worsening of hypotension and shock. Additionally, due to hypotension, patients may also have some degree of acute kidney injury. Careful assessment of the patient's hemodynamic parameters is necessary to determine whether diuretic therapy is indicated and whether such therapy is having the intended effects. Although the role of invasive devices is not well defined, this subset of patients often benefits most from short-term monitoring. If hemodynamics is supported with other modalities, including medications and devices, a reasonable approach is to use initial diuretic doses as seen for other subsets of ADHF. This includes IV therapy at doses equivalent or larger than home diuretic doses.[27,77] Based on responses in both urine output and hypotension, dose adjustments may be made including escalating doses, addition of continuous infusion loop diuretics, or adjunctive therapy to loop diuretics. Of note, while not studied in ADHF, doses of loop diuretics have been shown to induce an acute vasoconstrictor response in chronic HF.[78] Depending on the patient's underlying systemic vascular resistance in the setting of shock, this may be beneficial or harmful.

Vasodilator therapy should be avoided in subset IV patients who are volume overloaded with hypotension due to their propensity for worsening hypotension.[19,27] The direct vasodilatory effects of nitroglycerin and nitroprusside lower SVR and decrease blood pressure, further complicating the management of shock.[79] Although nesiritide works via different neurohormonal mechanisms, hypotension is a recognized adverse effect, and its longer half-life further complicates its use in these patients.[80] Additionally, the renal dysfunction associated with its use is likely to be worsened in the setting of shock.[69]

Despite the risks, patients in subset IV have the greatest potential benefit from inotropic therapy. In patients with cardiogenic shock, inotropes can treat acute hypotension by increasing cardiac output with less reduction in filling pressures.[27] They must still be used with caution since inotropic agents can increase heart rate, promote myocardial ischemia, and increase myocardial oxygen consumption. However, there is little direct evidence for or against their use in cardiogenic shock. Of note, the major trials refuting the use of inotropic therapy in ADHF including Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure, with milrinone, excluded patients with cardiogenic shock.[74] Likewise, the ADHERE registry which evaluated patients receiving milrinone, dobutamine, or nesiritide demonstrated increased mortality with these agents, but the vast majority of included patients did not have hypotension, making these results less applicable to this subset.[67] Although direct evidence is lacking, patients with cardiogenic shock are at high risk of imminent death, and therefore, augmenting cardiac function and blood pressure with these agents is usually justified. In particular, levosimendan offers another option that requires more evaluation in ADHF but proposes potential benefits.[81] In these cases, they either provide additional time for patient decision-making or act as a ''bridge'' to more definitive therapy including mechanical device support or transplant.

Mechanical support in the setting of ADHF including intra-aortic balloon pumps, ventricular assist devices, or extracorporeal membrane oxygenation can be useful for patients with cardiogenic shock. These modalities are useful for both bridge to transplant and destination therapy, and a full discussion on the indications and use of these treatments is available elsewhere.[82]

Keys for Discharge

Medications

The transition of care from hospital to discharge originates at the time of admission. As mentioned previously, chronic maintenance therapy should be continued during a hospitalization unless contraindications exist.[19] Continuing β-blocker and ACE inhibitor therapies during ADHF has been shown to be beneficial.[37-39] Results from the Carvedilol or Metoprolol European Trial (COMET) and OPTIMIZE-HF studies demonstrated that the risk of death was greater in patients with ADHF whose β-blocker dose was reduced or discontinued altogether.[37,39] Conversely, initiation of a low dose of a β-blocker is recommended only after euvolemia is achieved, and diuretics, vasodilators, and inotropes are discontinued.[19] Loop diuretic therapy should be transitioned from an IV to oral dosage form after volume status is restored.[83] Patients may be placed back on their chronic maintenance dose and should be instructed to adjust that dose according to increases in weight gain and presence of congestive symptoms.[27] Initiating an aldosterone antagonist during hospitalization allows for careful monitoring of potassium, serum creatinine, and medication dosing, reducing the risk of development of hyperkalemia and renal insufficiency.[77,83] After the acute decompensation is resolved, chronic maintenance medications should be uptitrated to their recommended target doses. Depending on length of stay, patients may continue uptitration in the outpatient setting.[84]

Lifestyle Modifications

Patients should be counseled prior to discharge on essential lifestyle modifications. Dietary education points that should emphasized include restricting sodium intake to less than 2 g/d and fluid intake to less than 2 L/d or 1 to 1.5 L/d in patients with hyponatremia. Patients are encouraged to perform moderate exercise for 30 minutes at least 5 d/wk, if deemed safe. In addition, patients should be advised to quit smoking and limit alcohol consumption to 2 or less drinks per day for men and 1 or less drink per day for women. All patients with HF are at high risk for influenza and pneumococcal disease and should receive vaccinations according to recommended schedules. Also, patients should be counseled to avoid certain over-the-counter medications that may exacerbate HF symptoms and affect disease progression including NSAIDs and

sympathomimetic (eg, pseudoephedrine, amphetamines, and methylphenidate) medications.[27,85]

Pharmacy Concierge Services

As the rate of hospital readmission for HF continues to rise, the need for identifying and resolving potential causes for these readmissions remains a paramount concern for health systems.[86,87] Since the establishment of the Hospital Readmissions Reduction Program in 2012, the Centers for Medicare and Medicaid Services can reduce reimbursement to hospitals with excess readmissions due to HF.[88] Nonadherence to medications and lifestyle modifications is a major contributor for readmissions, and pharmacist involvement in patient care has demonstrated a reduction in HF hospitalization and mortality.[89-91] A study conducted in Spain by Lopez-Cabezas et al showed that the implementation of a pharmacist in discharge counseling and telephone follow-ups reduced readmission rates up to 12 months, decreased total days of hospital stay, and improved treatment compliance.[92] More recently, a study by Warden et al evaluated the impact of a pharmacy-driven discharge program and revealed a reduction in 30-day all-cause mortality and HF-related readmissions after the involvement of pharmacists in medication reconciliation, discharge counseling, and follow-up telephone calls after discharge.[93]

Specialized HF Clinics

Management of patients with HF through specialized clinics has been shown to reduce hospitalization, increase medication adherence, and increase titration efficacy of evidence-based HF medications.[94,95] Recently, Jackevicius et al found that increasing early follow-up within 1 to 2 weeks with a multidisciplinary HF clinic team consisting of a physician assistant, pharmacist, case manager, and cardiologist led to decreased 90-day readmission rates. Additionally, clinic patients had lower 90-day all-cause mortality.[96]

Conclusion

The management of ADHF is quite complex and requires a systematic and multidisciplinary approach. Accurate patient assessment to determine fluid status and hemodynamics is a key to determining optimal treatment for a particular patient. Therapies commonly used in management include diuretics, vasodilators, and, in selected patients, inotropes. Additionally, patient education and management of concomitant disease states can optimize therapy and successfully reduce readmissions and minimize morbidity and mortality.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Heidenreich PA, Trogdon JG, Khavjou OA, et al; on behalf of the American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933-944.
2. Hall MJ, Levant S, DeFrances CJ. *Hospitalization for Congestive Heart Failure: United States, 2000–2010*. NCHS data brief, no 108. Hyattsville, MD: National Center for Health Statistics; 2012.
3. Hall MJ, DeFrances CJ, Williams SN. *National Hospital Discharge Survey: 2007 Summary*. National health statistics reports, no 29. Hyattsville, MD: National Center for Health Statistics; 2010. http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf. Accessed August 25, 2016.
4. Unroe KT, Greiner MA, Hernandez AF, et al. Resource use in the last 6 months of life among Medicare beneficiaries with heart failure, 2000–2007. *Arch Intern Med*. 2011;171(3):196-203.
5. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008;156(4):662-673.
6. Lee WC, Chavez YE, Baker T, Luce BR. Economic burden of heart failure: a summary of recent literature. *Heart Lung*. 2004; 33(6):362-371.
7. Biermann J, Neumann T, Angermann CE, et al; German Competence Network Heart Failure. Economic burden of patients with various etiologies of chronic systolic heart failure analyzed by resource use and costs. *Int J Cardiol*. 2012;156(3):323-325.
8. Holubarsch C, Ruf T, Goldstein DJ. Existence of the Frank–Starling mechanism in the failing human heart: investigations on the organ, tissue, and sarcomere levels. *Circulation*. 1996;94(4): 683-689.
9. Francis GS, Tang W, Walsh RA. Pathophysiology of heart failure. In: Fuster V, Walsh RA, Harrington RA. eds. *Hurst's The Heart*, 13th ed. New York, NY: McGraw-Hill; 2011:Chap 26.
10. Dzau VJ, Colucci WS, Hollenberg NK, Williams GH. Relation of the renin–angiotensin–aldosterone system to clinical state in congestive heart failure. *Circulation*. 1981;63(3):645-651.
11. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273(18):1450-1456.
12. Lal A, Veinot JP, Leenen FH. Critical role of CNS effects of aldosterone in cardiac remodeling post-myocardial infarction in rats. *Cardiovasc Res*. 2004;64(3):437-447.
13. Wang H, Huang BS, Ganten B, Leenen LH. Prevention of sympathetic and cardiac dysfunction after myocardial infarction in

transgenic rats deficient in brain angiotensinogen. *Circ Res*. 2004; 94(6):843-849.
14. Li YF, Wang W, Mayhan WG, Patel KP. Angiotensin-mediated increase in renal sympathetic nerve discharge within the PVN: role of nitric oxide. *Am J Physiol Regul Integr Comp Physiol*. 2006;290(4):R1035-R1043.
15. Triposkiadis F, Karayannis G, Giamouzis G. The sympathetic nervous system in heart failure: physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009;54(19):1747-1762.
16. Pepper GS, Lee RW. Sympathetic activation in heart failure and its treatment with beta-blockade. *Arch Intern Med*. 1999;159(3): 225-234.
17. Grassi G, Seravalle G, Quarti-Trevano F, et al. Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. *Hypertension*. 2009;53(2):205-209.
18. Goldsmith SR. Interactions between the sympathetic nervous system and the RAAS in heart failure. *Curr Heart Fail Rep*. 2004; 1(2):45-50.
19. Yancy CW, Jessup M, Bozkurt B; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 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-e239.
20. Rich MW. Pharmacotherapy of heart failure in the elderly: adverse events. *Heart Fail Rev*. 2012;17(4-5):589-595.
21. Amabile CM, Spencer AP. Keeping your patient with heart failure safe: a review of potentially dangerous medications. *Arch Intern Med*. 2004;164(7):709-720.
22. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med*. 1993;329(1):1-7.
23. Binanay C, Califf RM, Hasselblad V, et al; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294(13):1625-1633.
24. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA*. 2005;294(13):1664-1670.
25. Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev*. 2013;(2):CD003408.
26. Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. *Am J Cardiol*. 2005;96(6A):32G-40G
27. Lindenfeld J, Albert NM, Boehmer JP. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010;16(6): e1-e194.
28. Green SM, Green JA, Januzzi JL Jr. Natriuretic peptide testing for the heart failure therapy guidance in the inpatient and outpatient setting. *Am J Ther*. 2009;16(2):171-177.
29. McCullough PA, Duc P, Omland T. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;41(3):571-579.
30. O'Hanlon R, O'Shea P, Ledwidge M, et al. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *J Card Fail*. 2007;13(1):50-55.
31. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail*. 2014;2(6):663-670.
32. Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. *Am Heart J*. 2006;152(5): 828-834.
33. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;48(19):1943-1950.
34. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293(5):572-580.
35. Gheorghiade M, Zannad F, Sopko G. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112(25):3958-3968.
36. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2016;pii:S0735-S1097(16):33024-33028.
37. Fonarow GC, Abraham WT, Albert NM, et al; OPTIMIZE-HF Investigators and Coordinators. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol*. 2008;52(3):190-199.
38. Butler J, Young JB, Abraham WT, et al; ESCAPE Investigators. Beta-blocker use and outcomes among hospitalized heart failure patients. *J Am Coll Cardiol*. 2006;47(12):2462-2469.
39. Metra M, Torp-Pedersen C, Cleland JGF. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail*. 2007;9(9):901-909.
40. Jondeau G, Neuder Y, Eicher JC, et al; B-CONVINCED Investigators. B-CONVINCED: beta-blocker continuation vs. interruption in patients with congestive heart failure hospitalized for a decompensation episode. *Eur Heart J*. 2009;30(18):2186-2192.
41. Uretsky B, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. *J Am Coll Cardiol*. 1993; 22(4):955-962.
42. Piepoli M, Binno S, Villani GQ, Cabassi A. Management of oral chronic pharmacotherapy in patients hospitalized for acute decompensated heart failure. *Int J Cardiol*. 2014;176(2):321-326.
43. Verma SP, Silke B, Hussain M, 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.
44. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail*. 2010;16(3): 188-893.
45. Allen LA, Turer AT, Dewald T, Stough WG, Cotter G, O'Connor CM. Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. *Am J Cardiol*. 2010;105(12): 1794-1797.
46. Felker GM, Lee KL, Bull DA, et al; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9): 797-805.
47. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol*. 1996;28(2):376-382.
48. De Bruyne LK. Mechanisms and management of diuretic resistance in congestive heart failure. *Postgrad Med J*. 2003;79(931): 268-271.
49. Kim GH. Long-term adaptation of renal ion transporters to chronic diuretic treatment. *Am J Nephrol*. 2004;24(6):595-605.
50. Loon N, Wilcox C, Unwin R. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kidney Int*. 1989;36(4):682-689.
51. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol*. 2010;56(19):1527-1534.
52. Ellison D. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. *Ann Intern Med*. 1991;114(10): 886-894.
53. McMurray JJV, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787-1847.
54. Jessup M, Abraham WT. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the international society for Heart and Lung Transplantation. *Circulation*. 2009; 119(14):1977-2016.
55. Hunt SA, Abraham WT, Chin MH, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112(12):e154-e235.
56. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol*. 2001;38(4):963-968.
57. Bart BA, Insel J, Goldstein MM, et al. The improved outcomes following ultrafiltration versus intravenous diuretics in UNLOAD are not solely due to increased weight loss in the ultrafiltration group. *J Card Fail*. 2007;13(suppl 2):S188.
58. Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol*. 2005; 46(11):2043-2046.
59. Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR, Sobotka PA; Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) Investigators. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. *J Card Fail*. 2010;16(4): 277-284.
60. Bart BA, Goldsmith SR, Lee KL, et al; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367(24): 2296-2304.
61. Tang WHW. Reconsidering ultrafiltration in the acute cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2351-2352.
62. Bart BA, Hernandez AF. Ultrafiltration in heart failure with cardiorenal syndrome. *N Engl J Med*. 2013;368(12):1159-1160.
63. Elkayam U, Janmohamed M, Habib M, Hatamizadeh P. Vasodilators in the management of acute heart failure. *Crit Care Med*. 2008;36(suppl 1):S95-S105.
64. Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. *J Am Coll Cardiol*. 2008; 52(3):200-207.
65. Opasich C, Cioffi G, Gualco A. Nitroprusside in decompensated heart failure: what should a clinician really know? *Curr Heart Fail Rep*. 2009;6(3):182-190.
66. Taylor AL, Ziesche S, Yancy C, et al; African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351(20):2049-2057.
67. Abraham WT, Adams KF, Fonarow GC, et al; ADHERE Scientific Advisory Committee and Investigators; ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol*. 2005;46(1):57-64.
68. VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1531-1540.
69. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely

decompensated heart failure. *Circulation*. 2005;111(12): 1487-1491.
70. 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):1900-1905.
71. Aaronson KD, Sackner-Bernstein J. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA*. 2006;296(12):1465-1466.
72. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365(1):32-43.
73. Chen HH, Anstrom KJ, Givertz MM, et al; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013;310(23): 2533-2543.
74. Cuffe MS, Califf RM, Adams KF Jr, et al; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287(12): 1541-1547.
75. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med*. 2011;183(7):847-855.
76. De Backer D, Biston P, Devriendt J, et al; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779-789.
77. Yancey CW, Jessup M, Bozkurt B. 2013 ACC/AHA Guideline for the management of heart failure. *Circulation*. 2013;128(16): e240-e327.
78. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Int Med*. 1985;103(1):1-6.
79. Mills RM, Cunningham MS. Long-term hemodynamic responses to vasodilator therapy in patients with severe left ventricular dysfunction. *Am J Cardiol*. 1999;84(8):939-941.
80. Mills RM, LeJemtel TH, Horton DP. Sustained hemodynamic effects of an infusion of nesiritide (human B-type natriuretic peptide) in hear failure: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 1999;24(1):155-162.
81. Tasal A, Demir M, Kanadasi M, et al. Comparison of single-dose and repeated levosimendan infusion in patients with acute exacerbation of advanced heart failure. *Med Sci Monit*. 2014; 20:276-82.
82. Peura JL, Colvin-Adams M, Francis GS, et al; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Recommendations for the use of mechanical circulatory support: device strategies and patient selection. *Circulation*. 2012;126(22): 2648-2667.
83. Patel SR, Pina IL. From acute decompensated to chronic heart failure. *Am J Cardiol*. 2014;114(12):1923-1929.
84. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. *JAMA*. 2010;303(21):2141-2147.
85. Wiggins BS, Rodgers JE, DiDomenico RJ, Cook AM, Page RL 2nd. Discharge counseling for patients with heart failure or myocardial infarction: a best practices model developed by members of the American College of Clinical Pharmacy's Cardiology Practice and Research Network based on the Hospital to Home (H2H) Initiative. *Pharmacotherapy*. 2013;33(5):558-580.
86. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med*. 1997;157(1):99-104.
87. Curtis LH, Greiner MA, Hammill BG, et al. Early and long-term outcomes of heart failure in elderly persons, 2001-2005. *Arch Intern Med*. 2008;168(22):2481-2488.
88. Centers for Medicare and Medicaid Services. Readmissions reduction program. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html. Published April 18, 2016. Accessed April 24, 2016.
89. Annema C, Luttik ML, Jaarsma T. Reasons for readmission in heart failure: perspectives of patients, caregivers, cardiologists, and heart failure nurses. *Heart Lung*. 2009;38(5):427-434.
90. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. *Arch Intern Med*. 2008;168(7): 687-694.
91. Milfred-LaForest SK, Chow SL, DiDomenico RJ, et al. Clinical pharmacy services in heart failure: an opinion paper from the Heart Failure Society of America and American College of Clinical Pharmacy Cardiology Practice and Research Network. *Pharmacotherapy*. 2013;33(5):529-548.
92. Lopez-Cabezas C, Salvador CF, Quadrada DC, et al. Randomized clinical trial of a postdischarge pharmaceutical care program vs regular follow-up in patients with heart failure [In English, Spanish]. *Farm Hosp*. 2006;30(6):328-342.
93. Warden BA, Freels JP, Furuno JP, Mackay J. Pharmacy-managed program for providing education and discharge instructions for patients with heart failure. *Am J Health-Syst Pharm*. 2014;71(2): 134-139.
94. Howlett JG, McKelvie RS, Arnold JM, et al; Canadian Cardiovascular Society. Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials. *Can J Cardiol*. 2009; 25(2):85-105.
95. Martineau P, Frenette M, Blais L, Sauvé C. Multidisciplinary outpatient congestive heart failure clinic: impact on hospital admissions and emergency room visits. *Can J Cardiol*. 2004; 20(12):1205-1211.
96. Jackevicius CA, de Leon NK, Lu L, Chang DS, Warner AL, Mody FV. Impact of a multidisciplinary heart failure post-hospitalization program on heart failure readmission rates. *Ann Pharmacother*. 2015;49(11):1189-1196.