

Acute Decompensated Heart Failure: Pathophysiology and Treatment

Anekwe Onwuanyi, MD,^{a,*} and Malcolm Taylor, MD^b

Acute decompensated heart failure (ADHF) is an important milestone in the clinical course of heart failure (HF). It is an event associated with a significant deterioration in the prognosis of HF. Despite the progress that has been made in the development of new pharmacologic and nonpharmacologic therapy for HF, there is surprisingly limited advancement in the treatment of acute HF. There are currently no guidelines for the treatment of ADHF. This is a review of the current diagnostic evaluation and treatment of patients with ADHF. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:25D–30D)

Heart failure (HF) is a chronic progressive disease that affects a large segment of the population, particularly the elderly. About 5 million (2.2% of the population) people in the United States currently have HF, with 550,000 new cases annually.¹ It is the leading cause of hospitalization for those aged ≥ 65 years, in whom the incidence is 10 per 1,000. In addition to the increased prevalence of risk factors for HF, the aging of the US population has contributed to the emergence of HF as the leading cardiovascular disease. This trend is, in part, a reflection of the important successes in the treatment of diseases that have occurred in the past decades and, more specifically, the improved survival rate after myocardial infarction (MI). HF is associated with increased morbidity and mortality.¹ The annual mortality rate for HF, despite advances in treatment, is high. Approximately 50% of patients diagnosed with HF are dead within 5 years of the diagnosis. HF is a chronic condition characterized by recurrent hospitalization for decompensation. The financial cost resulting from such hospitalizations accounts for a significant portion of the total healthcare cost of patients with HF. The direct cost for patients with HF in 2004 was estimated at \$28.8 billion.¹ This is a significant economic burden, and all indications are that the cost of care will increase. The estimated rate of hospital readmission after an index admission for HF is approximately 50% by 6 months and is greatest among the elderly.^{2,3} Reduction of hospitalizations and the length of stay are critical variables for healthcare cost reduction in the treatment of chronic HF.

Pathophysiology: Neurohormones in Heart Failure

In the past 2 decades, there has been considerable progress in elucidating the pathophysiology and treatment of HF. Based on the neurohormonal model, HF is associated with an index event such as an MI, valvular heart disease, uncontrolled hypertension, and others. The common pathway to HF of all these causative factors occurs through the activation of the neurohormonal pathway, specifically the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, leading to the production of several neurohormones. These neurohormones have both hemodynamic and biologic effects on the left ventricular (LV) myocardium and systemic vascular bed. These effects contribute to the development and progression of LV dysfunction and ultimately result in the clinical syndrome of HF. As part of this process, counterregulatory vasodilatory neurohormones are also released to counter the effects of the vasoconstrictive RAAS and sympathetic nervous system. The RAAS is activated by a reduction in renal artery perfusion that may result from a decrease in cardiac output, such as may occur from an MI or vasoconstrictive changes as seen in hypertension. Renin is released from the kidneys as a result and acts on circulating angiotensinogen to form angiotensin I. Circulating angiotensin-converting enzymes are released from the vascular endothelium, converting angiotensin I to angiotensin II, which is a potent vasoconstrictor^{4,5} that promotes sodium and water reabsorption in the kidneys as well as the release of a complex series of proinflammatory cytokines, critical in the pathogenesis and progression of HF. A separate and independent RAAS is also present in several local tissues, such as the myocardium, kidneys, and blood vessels. Angiotensin II and aldosterone cause an increase in myocardial hypertrophy, fibrosis, and a reduction in endothelial nitric oxide release, resulting in deleterious changes in vascular compliance and the induction and progression of ventricular dysfunction.^{5,6} Sympathetic adrenergic system activation by similar causative factors as in the RAAS results in the release of norepinephrine.

From the ^aDivision of Cardiology, Morehouse School of Medicine, Atlanta, Georgia, USA; and ^bJackson Cardiology Associates, PA, Jackson, Mississippi, USA.

This work was supported, in part, by Grant No. 5P20RR11104 from the National Center for Research Resources (NCCR), a component of the National Institutes of Health.

*Address for reprints: Anekwe Onwuanyi, MD, Division of Cardiology, Department of Medicine, Morehouse School of Medicine, 720 Westview Drive SW, Atlanta, Georgia 30310.

E-mail address: aonwuanyi@msm.edu.

The effects of norepinephrine include peripheral vasoconstriction, direct myocardial toxicity, induction of apoptosis, and arrhythmias and RAAS activation. Other neurohormonal systems involved with the initiation and progression of HF include endothelin, vasopressin, and cytokines, such as the tumor necrosis factor. It is the overactivation of the neurohormonal systems, primarily the RAAS and sympathetic nervous system at the expense of the counterregulatory systems that is responsible for the causation and progression of HF.

The natriuretic peptides are a major counterregulatory system consisting of the atrial natriuretic peptide and B-type natriuretic peptide (BNP), which are produced in the myocardium, and the C-type peptide, which is produced mainly by the vascular endothelium.⁵ Both atrial natriuretic peptide and BNP are released in response to increased myocardial wall stress, but BNP is more specific for ventricular wall stress. BNP levels have been shown to be significantly increased in patients with HF.^{5,7} These peptides promote natriuresis and diuresis. They also inhibit the RAAS and reduce sympathetic vascular tone, thus augmenting vascular endothelial function and blood pressure reduction.⁸ In acute decompensated HF (ADHF), the counterregulatory vasodilators are overwhelmed by the RAAS-related fluid retention. A vicious circle thus exists in ADHF, where in conjunction with acute HF, several factors perpetuate and lead to progressive LV dysfunction, resulting in reduced cardiac output and renal hypoperfusion, despite an increase in blood volume and filling pressure of the left ventricle. Concurrently, alteration in the balance of fluid between the vascular and interstitial spaces occurs. As LV filling pressure increases, the hydrostatic pressure increases, causing transudation of fluid from the vascular compartment. Normally, fluid accumulation in the interstitial space is cleared by the lymphatic system. However, in ADHF, accumulation of fluid in the interstitial space overwhelms the lymphatic drainage system, resulting in pulmonary edema. Decompensation may also occur without a fundamental worsening of ventricular function but from factors, such as poor adherence to medications and dietary indiscretion or the clinical deterioration of comorbid conditions.⁹

Diagnosis

The clinical presentation of ADHF is, to a large extent, related to the degree of fluid overload. This is reflected by elevation of the filling pressures and dyspnea, a cardinal symptom of ADHF. The initial evaluation of a patient with symptoms suggestive of ADHF includes a history and physical examination. Chest radiography and electrocardiography are routine investigations in the emergency department. However, arriving at an accurate diagnosis in the emergency department only on this basis can be challenging because there are multiple clinical conditions in which dyspnea is the chief complaint.⁷ Symptoms, such as orthopnea and

paroxysmal nocturnal dyspnea (the result of elevated filling pressure), are specific for HF but have low sensitivity. The findings on physical examination that are helpful in the diagnosis of ADHF include a distended internal jugular vein,^{10,11} which represents elevated filling pressures. Its presence has a specificity of 96% for HF and is believed to be the best predictor of ADHF of all the physical signs. Other important signs in support of the diagnosis of ADHF include S₃ or S₄ gallop, pulmonary rales, resting tachycardia, peripheral edema, and displaced apical impulse. None of the findings from the history or physical examination is a good predictor of LV function or LV ejection fraction.^{10,11} However, this fact may not be crucial because ADHF occurs as frequently in patients with preserved systolic function. Electrocardiography is helpful in identifying underlying cardiac diseases, such as coronary artery disease (CAD) or cardiac dysrhythmia, which may be implicated in the decompensation of HF. Chest radiography¹² may help confirm the findings from the physical examination; however, the radiographic findings are not good predictors of ADHF.

Therefore, it is quite often the case that clinical assessment may not provide a definitive diagnosis of ADHF, and thus, the potential for the misdiagnosis of ADHF exists, leading to wrong triage of patients and incorrect treatment. The recent validation of the natriuretic peptides, namely BNP and N-terminal pro-BNP, as a diagnostic aid for the differentiation of HF and non-HF causes of dyspnea in the emergency department has helped to reduce diagnostic errors and associated mismanagement. The multicenter Breathing Not Properly study⁷ enrolled 1,586 patients presenting with acute dyspnea to the emergency department. A plasma BNP cutoff value >29.0 pmol/L (100 pg/mL) was found to be superior to clinical assessment for the diagnosis of HF. The diagnostic utility of BNP was seen in patients with HF with either preserved or reduced systolic function. But, in the elderly population, especially women with HF, the cutoff value of 29.0 pmol/L did not offer the same predictive accuracy for HF.¹³ N-terminal pro-BNP is another peptide whose usefulness in aiding the diagnosis of congestive HF (CHF) has been studied. The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study¹⁴ enrolled 600 patients presenting with dyspnea. In this study, the plasma N-terminal pro-BNP was found to correlate with acute CHF with cut points of >53.1 pmol/L (450 pg/mL) for patients <50 years of age and >106.2 pmol/L (900 pg/mL) for patients ≥50 years of age, with high sensitivity and specificity. The clinical utility of these biomarkers as diagnostic aides for HF was best observed in patients presenting with dyspnea where the diagnosis of HF is uncertain. In patients at the extremes of the diagnostic spectrum for HF, the BNP and N-terminal pro-BNP levels rarely alter the diagnosis. These biomarkers are diagnostic aids, and their measured values should always be interpreted in the context of all of the available clinical data.¹⁵ This recommendation is important for several reasons, including the fact that considerable overlap of

Table 1
Treatment goals for patients admitted for acute decompensated heart failure

-
- Improve symptoms, especially congestion and low-output symptoms
 - Optimize volume status
 - Identify etiology
 - Identify precipitation factors
 - Optimize chronic oral therapy
 - Minimize side effects
 - Identify patients who might benefit from revascularization
 - Educate patients about medications and self-assessment of HF
 - Consider and, where possible, initiate a disease management program
-

HF = heart failure.

Reprinted from *J Card Fail*.¹⁵

BNP ranges occur for patients with and without HF.⁷ Also, BNP and N-terminal pro-BNP levels may be elevated in pulmonary diseases, such as pulmonary embolism and cor pulmonale, making the interpretation of values difficult.^{7,14}

Some patients with HF may have low BNP levels, demonstrating that BNP determination does not always help identify HF and should not be interpreted in isolation.

Treatment

Acute pulmonary edema can be life threatening. This is a period in the natural history of HF when there is a considerable increase in the risk of death and a significant change in prognosis. In an analysis of 38,702 consecutive patients hospitalized for the first time with HF, the 30-day and 1-year mortality ranged from 2.3% and 7.6%, respectively, in the younger subgroup with minimal comorbidities to 23.8% and 60.7% in the oldest subgroup with significant comorbidities.¹⁶ Krumholz and colleagues¹⁷ observed that almost half of the elderly Medicare patients discharged after an episode of CHF were readmitted within 6 months, and HF accounted for 18% of these readmissions. Several randomized controlled clinical trials on HF in the last 2 decades have identified effective pharmacologic therapy in HF; however, these studies have focused on stable chronic ambulatory HF. There are surprisingly limited data from controlled clinical trials on the treatment of acute HF.

The few trials available have several important limitations, such as the inclusion mainly of patients with reduced systolic function and a primary focus on symptomatic end points rather than mortality. In the Acute Decompensated Heart Failure National Registry (ADHERE) of patients hospitalized with a primary diagnosis of ADHF,^{18,19} about half of the patients presenting with ADHF had preserved systolic function. These observations pose a critical challenge in the treatment of patients with ADHF. First, extrapolating the results from studies in stable chronic ambulatory patients with HF to ADHF will be wrong because these are 2 unique phases of the disease process. Second, the data on chronic HF studies were derived from patients with abnormal systolic function, whereas about 50% of patients with ADHF

have preserved systolic function, as reported from the ADHERE registry. Consequently, the data from these studies should be interpreted with caution. This concern is reflected in the recently published comprehensive review of the evaluation and management of patients with ADHF by the Heart Failure Society of America (HFSA) in 2006.¹⁵

The immediate treatment goals for patients admitted with ADHF are to relieve congestive symptoms and to begin to optimize cardiac function (Table 1).¹⁵ Further treatment objectives are to achieve a euvolemic status and to identify the underlying etiology or precipitating factor for the acute decompensation. It is also an opportunity to review and recalibrate the overall care of the patient with HF and to develop a comprehensive care plan. The choice of initial therapy in patients with ADHF can be derived from physical examination findings using the hemodynamic algorithm shown in Figure 1. In the patients who are either wet and cold or wet and warm, the treatment is with intravenous vasodilators and diuretics. There may be need for the addition of an inotropic agent for the wet and cold patient, in the event that hypotension occurs despite adequate filling pressure, a situation that indicates inadequate cardiac output. The wet and warm patients account for the larger proportion of patients with ADHF, whereas the dry and cold patients are in the minority, and their prognosis is poor. Initial therapy can occur in the emergency department observation unit, and the decision to admit can be based on clinical response. Table 2 lists the clinical indications for hospitalization in ADHF. This list can be modified to meet the needs of the local practice environment.

Accumulating data from recent clinical trials indicate that initial therapy used for ADHF either in the emergency department or the intensive care unit has important short-term and long-term clinical consequence. Intravenous inotropic agents typically used on a short-term basis to improve hemodynamics and relieve symptoms in ADHF may have deleterious effects. Dobutamine causes neurohormonal activation, increased myocardial oxygen utilization, and ventricular ectopia, and it may lead to troponin release.²⁰ Troponin release may also occur in ADHF because of increased susceptibility of myocytes to necrosis and apoptosis. The use of milrinone, a phosphodiesterase inhibitor, raises sim-

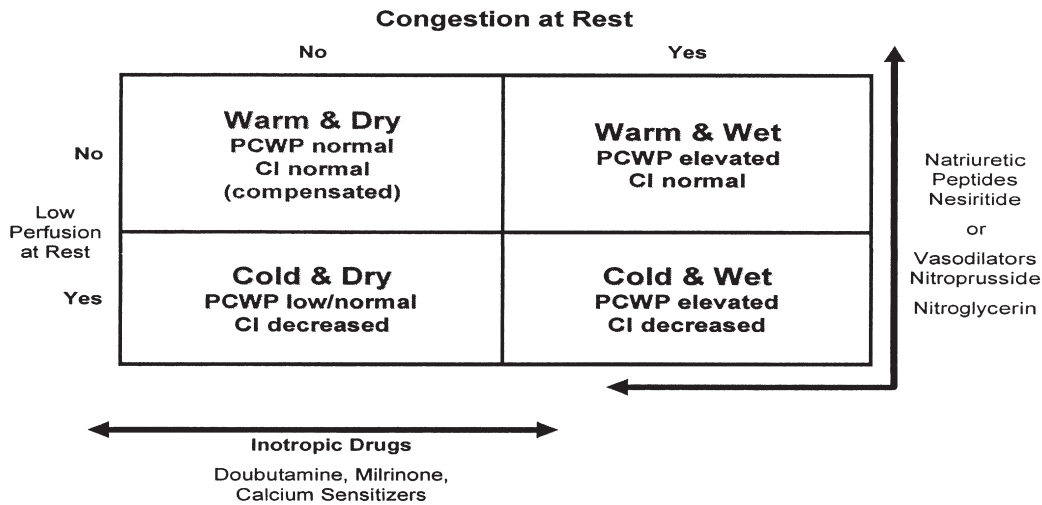


Figure 1. Clinical stratification and treatment. CI = cardiac index; PCWP = pulmonary capillary wedge pressure.

Table 2
 Recommendations for hospitalizing patients presenting with acute decompensated heart failure

Recommendation	Clinical Circumstances
Hospitalization	<ul style="list-style-type: none"> ● Evidence of severely decompensated HF, including: <ul style="list-style-type: none"> —Hypotension —Worsening renal function —Altered mentation ● Dyspnea at rest <ul style="list-style-type: none"> —Typically reflected by resting tachypnea —Less commonly reflected by oxygen saturation <90% ● Hemodynamically significant arrhythmia <ul style="list-style-type: none"> —Including new onset of rapid atrial fibrillation ● Acute coronary syndromes
Hospitalization should be considered	<ul style="list-style-type: none"> ● Worsened congestion <ul style="list-style-type: none"> —Even without dyspnea —Typically reflected by a weight gain of >5 kg ● Signs and symptoms of pulmonary or systemic congestion <ul style="list-style-type: none"> —Even in the absence of weight gain ● Major electrolyte disturbance ● Associated comorbid conditions <ul style="list-style-type: none"> —Pneumonia —Pulmonary embolus —Diabetic ketoacidosis —Symptoms suggestive of TIA or stroke ● Repeated ICD firings ● Previously undiagnosed HF with signs/symptoms of systemic or pulmonary congestion

HF = heart failure; ICD = implantable cardioverter defibrillator; TIA = transient ischemic attack.

ilar concerns as with dobutamine. It causes increased myocardial contractility and systemic and pulmonary vasodilation. However, the increase in heart rate is less than the increase seen with dobutamine. Unlike dobutamine, whose effects are mediated through stimulation of β -receptors, the action of milrinone is not deterred to the same extent by concomitant use of β -blocking drugs. Milrinone was found to be associated with increased adverse events compared with standard therapy in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-HF) trial.²¹

Vasodilators used in treatment of ADHF include nitroglycerin, nitroprusside, and nesiritide. These agents reduce preload, afterload, and pulmonary congestion. Adverse effects of intravenous nitroglycerin use include hypotension, activation of the neurohormonal system, and development of tachyphylaxis. Hypotension can occur with any of these agents and can be corrected by a dose adjustment or temporary discontinuation of drug. The risk for hypotension is greater in the setting of volume depletion, and the duration is longer for nesiritide compared with nitroglycerin because of a longer half-life. Sodium nitroprusside is a potent vaso-

dilator. However, despite the favorable hemodynamic profile, it is not widely used in patients with ADHF. In the first place, the setup for administration of this drug is cumbersome. Not only is continuous invasive hemodynamic monitoring required, but also the preparation of the intravenous infusion is time consuming. Moreover, there is considerable concern with its use in patients with underlying CAD because of the potential for increasing mortality. Side effects include thiocyanate poisoning, which is relatively uncommon.

The efficacy of nesiritide in ADHF was demonstrated in the Vasodilator in the Management of Acute Heart Failure (VMAC) study,²² a multicenter, randomized, double-blind, controlled trial of 489 patients admitted for worsening HF. The combination of nesiritide and standard therapy significantly decreased pulmonary capillary wedge pressure ($p = 0.001$) and dyspnea score ($p = 0.03$) at 3 hours compared with standard therapy alone. Nesiritide also lowered pulmonary capillary wedge pressure significantly ($p = 0.03$) more than nitroglycerin, but it did not improve the dyspnea score compared with nitroglycerin. Similar results in favor of nesiritide were observed at 24 hours. Since completion of the initial nesiritide studies, emerging data from meta-analyses have shown that nesiritide use is associated with a significant increase in serum creatinine, a known marker of poor outcome in acute HF.^{23,24} There are also data suggesting a trend toward increased 30-day mortality in nesiritide-treated patients in pooled data analyzed from 3 randomized, controlled, nesiritide trials.²⁵ These findings indicate the need for additional large-scale studies to evaluate both the short- and long-term risks, if any, associated with nesiritide use. Meanwhile, the consensus is that nesiritide is indicated in patients with ADHF who have congestion but not hypotension.¹⁵ The occurrence of hypotension with nesiritide use appears to be dose dependent, especially if coadministered with diuretics.

Another vasoactive agent that is currently being evaluated for treatment of ADHF is levosimendan, a calcium-sensitizing agent that increases myocardial contractility by enhancing the sensitivity of myofilaments to calcium. Levosimendan also has coronary and systemic vasodilatory effects, producing favorable hemodynamic effects without increasing myocardial oxygen demand or causing arrhythmia. The Levosimendan Infusion versus Dobutamine (LIDO)²⁶ study compared 24-hour infusion of levosimendan with dobutamine in patients with severe low-output HF. The hemodynamic performance of levosimendan was superior to dobutamine, and the 6-month mortality was lower.

Intravenous diuretics are a standard component of treatment in ADHF, and even in the so-called dry patient, there is still considerable volume expansion and fluid retention. Diuretics, especially when used in high doses, could activate the neurohormonal systems, with a potentially deleterious outcome in patients with ADHF.²⁷ Moreover, clinical studies have shown high-dose diuretic use to be a marker for increased in-hospital mortality for HF.²⁸ The exact mecha-

nism for this adverse outcome has not been fully elucidated, but the severity of the underlying HF may partly account for the negative outcomes. Loop diuretics alone or in combination with non-loop diuretics are typically given as first-line therapy. The dose of diuretic and frequency of administration depend on the severity of the clinical presentation and therapeutic response. In general, the use of intravenous loop diuretics results in prompt relief of congestive symptoms, but treatment should be continued for several days to attain a euvolemic state. These patients require serial determination of electrolytes and renal function to prevent electrolyte abnormalities, as well as monitoring for any deterioration in renal function. A decrease in renal function in association with diuretic therapy during the treatment of acute HF may occur while symptoms and signs of congestion persist. There are no treatment guidelines for this clinical scenario; still, a substantial number of physicians will continue diuretics as long as the increase in serum creatinine is moderate, and considerable fluid overload still exists. The patient's medications should be reviewed and changes made, if needed, to optimize renal perfusion and function, such as the temporary discontinuation of the diuretic agent or addition of inotropic therapy. In rare cases, dialysis may be required for the extreme case of fluid overload, notwithstanding aggressive diuretic use. Traditional dialysis or hemofiltration can be used. Clinical trial data indicate the safety and superiority of venovenous ultrafiltration compared with aggressive intravenous diuresis in reaching a euvolemic state.²⁹

Conclusion

ADHF marks a significant turning point in the clinical course of patients with HF. There is an urgent need for well-conducted clinical trials with adequate sample size to answer key questions, including questions regarding short- and long-term treatment outcomes. These studies will help provide the basis for the sorely needed ADHF treatment guidelines.

1. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, TX: American Heart Association, 2004.
2. Philbin EF, Dec GW, Jenkins PL, DiSalvo TG. Socioeconomic status as an independent risk factor for hospital readmission for heart failure. *Am J Cardiol* 2001;87:1367–1371.
3. Vinson JM, Rich MW, Sperry JC, Shah AS, McNamara T. Early readmission of elderly patients with congestive heart failure. *J Am Geriatr Soc* 1990;38:1290–1295.
4. Lage SG, Kopel L, Medeiros CC, Carvalho RT, Creager MA. Angiotensin II contributes to arterial compliance in congestive heart failure. *Am J Physiol Heart Circ Physiol* 2002;283:H1424–H1429.
5. Baig MK, Mahon N, McKenna WJ, Caforio ALP, Bonow RO, Francis GS, Gheorghiade M. The pathophysiology of advanced heart failure. *Am Heart J* 1998;135:S216–S230.
6. Weber KT. Aldosterone in congestive heart failure [review]. *N Engl J Med* 2001;345:1689–1697.
7. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu HA, et al. Rapid

- measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–167.
8. Oelkers W, Kleiner S, Bahr V. Effects of incremental infusions of atrial natriuretic factor on aldosterone, renin, and blood pressure in humans. *Hypertension* 1988;12:462–467.
 9. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart* 1998;80:437–441.
 10. Badgett RG, Lucey CR, Mulrow CD. Can the clinical examination diagnose left sided heart failure in adults? *JAMA* 1997;277:1712–1719.
 11. Gillespie ND, McNeill G, Pringle T, Ogston S, Struthers AD, Pringle SD. Cross sectional study of contribution of clinical assessment and simple cardiac investigations to diagnosis of left ventricular systolic dysfunction in patients admitted with acute dyspnea. *BMJ* 1997;314:936–940.
 12. Badgett RG, Mulrow CD, Otto PM, Ramirez G. How well can the chest radiograph diagnose left ventricular dysfunction? *J Gen Intern Med* 1996;11:625–634.
 13. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, et al. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J* 2004;147:1078–1084.
 14. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurny JT, Chae CU, et al. The N-Terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95:948–954.
 15. Heart Failure Society of America. Executive Summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2006;12:10–38.
 16. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure. *Arch Intern Med* 2002;162:1689–1694.
 17. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997;157:99–104.
 18. Fonarow GC, Corday E, for the ADHERE Scientific Advisory Committee. Overview of acutely decompensated congestive heart failure (ADHF): a report from the ADHERE registry. *Heart Fail Rev* 2004;9:179–185.
 19. Yancy CW, Lopatin M, Stevenson LW, DeMarco T, Fonarow GC, for the ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. *J Am Coll Cardiol* 2006;47:76–84.
 20. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73(suppl III):111–168.
 21. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiu M, O'Connor CM, for the OPTIME-CHF investigators. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41:997–1003.
 22. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure. *JAMA* 2002;287:1531–1540.
 23. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005;111:1487–1491.
 24. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure. *JAMA* 2005;293:572–580.
 25. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson KD. Short-term risk of death after treatment with nesiritide for decompensated heart failure. *JAMA* 2005;293:1900–1905.
 26. Follath F, Cleland JG, Just H, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) study. Efficacy and safety of the IV levosimendan compared to dobutamine in severe low output heart failure. *Lancet* 2002;360:196–202.
 27. 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: activation of the neurohormonal axis. *Ann Intern Med* 1985;103:1–6.
 28. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M, for the PRAISE investigators. Diuretic resistance predicts mortality in patients with advanced heart failure: Prospective Randomized Amlodipine Survival Evaluation. *Am Heart J* 2002;144:31–38.
 29. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, Mackedanz S, Sobotka PA, Schollmeyer M, Goldsmith SR. 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;46:2043–2046.