Management of Acute Decompensated Heart Failure

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Abstract: Acute decompensated heart failure is the most common cause for hospitalization among patients over 65 years of age. It may result from new onset of ventricular dysfunction or, more typically, exacerbation of chronic heart failure symptoms. In-hospital mortality remains high for both systolic and diastolic forms of the disease. Therapy is largely empirical as few randomized, controlled trials have focused on this population and consensus practice guidelines are just beginning to be formulated. Treatment should be focused upon correction of volume overload, identifying potential precipitating causes, and optimizing vasodilator and beta-adrenergic blocker therapy. The majority of patients (>90%) will improve without the use of positive inotropic agents, which should be reserved for patients with refractory hypotension, cardiogenic shock, end-organ dysfunction, or failure to respond to conventional oral and/or intravenous diuretics and vasodilators. The role of aldosterone antagonists, biventricular pacing, and novel pharmacological agents including vasopressin antagonists, endothelin blockers, and calcium-sensitizing agents is also reviewed. (Curr Probl Cardiol 2007;32: 321-366.)

Heart failure is the only common cardiovascular disease in the United States that has a rising prevalence (Fig 1).[1-3] The latest statistics from the American Heart Association estimate that approximately five million Americans have this disorder.[1] The current incidence of disease exceeds 400,000 new symptomatic cases per year and it directly accounts for 250,000 deaths annually.[1,4] Between 1.5 and

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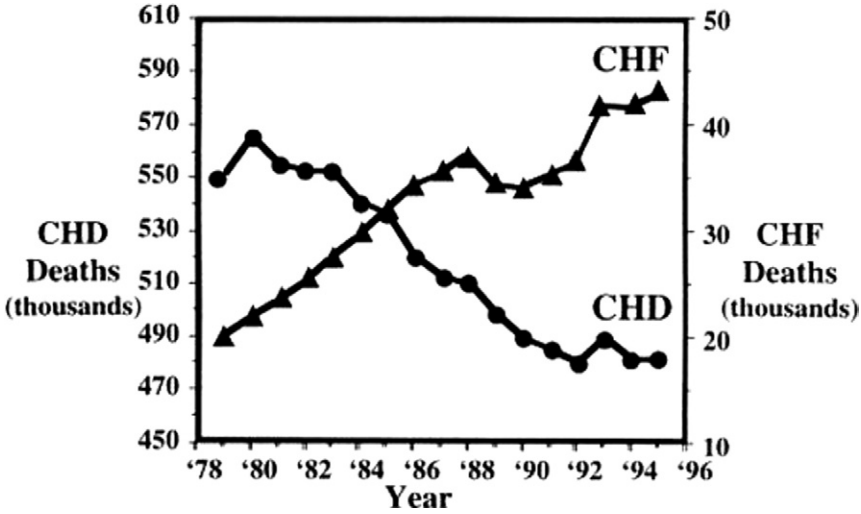


FIG 1. Evolving profile of deaths resulting from coronary artery disease (CHD) and chronic heart failure (CHF) in the United States from 1978 to 1996. [Used with permission; Adams KF. Am J Med 2001;110(supp 7A):6S-13S (Fig 1).]

2% of the U.S. population have symptomatic heart failure and its prevalence is estimated to range from 6 to 10% for individuals over the age of 65 years.[1] The burden of heart failure and its public health implications are greatest in the elderly, where its prevalence exceeds 10% for individuals over 80 years of age.[1] Among patients hospitalized with acute decompensated heart failure (ADHF), 80% are over 65 years of age.[4,5] In the Acute Decompensated Heart Failure Registry (ADHERE), the median age of 27,000 patients hospitalized for heart failure was 75 years.[5]

ADHF is the most common indication for hospitalization in the United States and results in nearly one million hospitalizations annually.[1] Heart failure admissions have grown steadily during the past two decades; since 1979, there has been an increase of 164% in heart failure hospitalizations.[1] Patients hospitalized with ADHF are at high short-term risk of death or rehospitalization; short-term readmission rates range from 15 to 50%.[6,7] Additionally, repeat hospitalizations for heart failure are a major component of health care costs with about 75% of the more than 10 billion dollars spent annually on heart failure care directed to the cost of hospitalization.[7] In-hospital mortality for all participants in the ADHERE registry averaged 4% but was substantially higher in the cohort over 75 years of age.[5] The mortality rate attributable to heart failure hospitaliza-

tion is highest in the elderly and approximates that of acute myocardial infarction.[5] Potential explanations for the high prevalence of heart failure in the elderly include the high rate of hypertension, ventricular remodeling from prior myocardial infarction, age-related loss of functional myocytes (which averages 5%/year among patients >65 years of age), and increased extracellular matrix that contributes to alterations in left ventricular compliance. Several of these features combine to create a ventricular phenotype of "heart failure with a preserved systolic function." Thus, 40 to 50% of heart failure admissions in the elderly occur in the setting of preserved systolic function; however, these episodes carry the same in-hospital rate of mortality.[5] Further, Smith et al have shown that all-cause readmission rates (hazard ratio [HR], 0.77; 95% confidence intervals [CI], 0.38 to 1.56) did not differ between systolic and diastolic heart failure.[8] Further, the likelihood of developing worsening of functional capacity was nearly identical between systolic and diastolic heart failure patients during the next year.

R. Mills and J. Narula: Although the cellular and physiologic details of heart failure are critically important, clinicians must also consider the important psychosocial and psychological issues of the HF population. Many of these HF patients are alone, deprived of the social support, and depressed. Some of the "noncompliance" issues in this population may reflect deteriorating cognitive function, limited coping skills, and inability to deal with expensive polypharmaceutical medical regimens.

Most (>70%) acute heart failure admissions are the result of worsening of chronic heart failure.[9] The differentiation of new-onset decompensated heart failure from subacute or acute worsening of chronic heart failure is important as their pathophysiologies differ.[10,11] Patients with new-onset heart failure have intense sympathetic activation and enhanced microvascular permeability.[11] Consequently, jugular venous distension may be more difficult to assess in these patients because of venous vasoconstriction and redistribution of fluids. Over 60% of patients hospitalized with ADHF have a history of coronary artery disease (53 to 70%), hypertension (>30%), chronic or paroxysmal atrial fibrillation (>45%), diabetes mellitus (>20%), or renal dysfunction (>20%).[12] Approximately 80% of acute heart failure admissions occur via the emergency room and strategies to target patients at high risk for readmission such as disease management programs attempt to avoid this avenue for treatment whenever possible. While dramatic, only 10% of patients with acute decom-

pensation present with "sudden onset" pulmonary edema.[13] The majority of patients typically demonstrate progressive heart failure symptoms that, if identified early enough, may be amenable to intensification of outpatient pharmacologic therapy.

Establishing the Diagnosis of Heart Failure

Symptoms remain the most sensitive method for diagnosing overt heart failure.[14] Orthopnea and paroxysmal nocturnal dyspnea are the most specific symptoms. Sensitivity of common symptoms ranges from 23 to 66% and their specificity ranges from 52 to 81%.[14] Pulmonary rales are absent in up to 80% of patients with chronic heart failure due to enhancing pulmonary lymphatic drainage but often appear during periods of acute decompensation.[9] Likewise, peripheral edema is evident in only 25% of patients under the age of 70 years with chronic heart failure but it is more prevalent during periods of hospitalization.[15] In advanced heart failure, a positive hepatojugular reflux and Valsalva square-wave signs may provide ancillary evidence of elevated filling pressures during periods of decompensation.[15] Unfortunately, accurate definition of heart failure due to systolic versus diastolic dysfunction is not possible based on physical examination, electrocardiographic findings, or chest x-ray findings.[16] This is not entirely surprising as heart failure is a syndrome and has a variety of potential etiologies. Given the important differences in treatment and prognosis, echocardiographic evaluation should be undertaken in all patients with suspected new diagnosis of heart failure to differentiate its pathophysiology.

R. Mills and J. Narula: The advent of widely available laboratory measures of BNP (Biosite Triage assay) or NT-proBNP (Roche) represents a significant advance in the clinical diagnosis of HF. The Breathing Not Properly (BNP) (Maisel AS: New Engl J Med 2002;347:161-7) and BASEL (Mueller C: New Engl J Med 2004;350:647-4) studies have demonstrated that addition of BNP or NT-proBNP levels to clinical assessment significantly enhances the accuracy of diagnosis and effectiveness of acute management. We have a lot to learn about these assays, and exactly what molecular species they measure. With increased use, we have learned that HF patients with significant obesity often have relatively low natriuretic hormone levels. Nonetheless, ADHF risk assessment using biomarkers, including both measurement of natriuretic hormones and troponin and troponin determinations, clearly adds important new data highly relevant to clinical care.

Reversible Causes for Acute Decompensation

A careful search should be undertaken for reversible or precipitating factors causing exacerbation of chronic heart failure symptoms (Table 1).

TABLE 1. Potentially reversible causes of decompensated heart failure

Dietary or pharmacological noncompliance
Systemic infection
Myocardial ischemia
Acute or worsening valvular insufficiency
Supraventricular tachycardias
Uncontrolled hypertension
Alcohol consumption
Cocaine, amphetamines, excessive bronchodilator use
Sleep disordered breathing
Hyperthryoidism and hypothyroidism
Anemia
Pulmonary embolism
Peripartum cardiomyopathy

Acute decompensation is often precipitated by a new disturbance that places additional hemodynamic load on the failing ventricle such as an infection or tachyarrhythmia. The most frequent cause of reversible cardiac decompensation is noncompliance with a complex dietary and pharmacological treatment regimen. An increase in dietary sodium intake, fluid intake, or inappropriate decrease in medications can precipitate heart failure in this population. The possibility of reversible myocardial ischemia causing transient ventricular noncompliance, myocardial hibernation, or myocardial infarction should always be considered.[4] Revascularization is often quite useful if active angina accompanies acute heart failure or substantial areas of viable myocardium with impaired coronary blood flow at rest or during low level exercise are documented.[4] The benefit of revascularization is most evident when left ventricular dysfunction is accompanied by three-vessel coronary artery disease or significant left main coronary disease, substantial viable myocardium is evident, and coronary anatomy is suitable for complete coronary revascularization.

Hypertension is now a less common cause of heart failure than in the past but may be an important contributor, particularly among African Americans.[17] Even modest elevations in arterial pressure (>130 mmHg) can further compromise a failing left ventricle and should be aggressively treated.

Tachyarrhythmias may cause a reversible form of dilated cardiomyopathy in previously normal hearts. More commonly, supraventricular tachyarrhythmias lead to further deterioration in ventricular function and heart failure symptoms. Atrial fibrillation is present in approximately 20% of patients with chronic heart failure. Restoration of

normal sinus rhythm or adequate control of a rapid ventricular response rate are frequently associated with marked clinical and echocardiographic improvement.

Heavy alcohol consumption is estimated to cause approximately 10% of cases of dilated cardiomyopathy in adults and often goes unrecognized. Two or more drinks daily may be sufficient to worsen heart failure among patients with underlying left ventricular dysfunction. Cocaine, amphetamines, and other drugs may also contribute to acute dilated cardiomyopathy.

Both hyper- and hypothyroidism may compromise cardiac function and these etiologies should be considered in the patient with unexplained worsening of heart failure symptoms. Anemia, both acute and chronic, may lead to decompensation in patients with previously stable ventricular dysfunction. Finally, a variety of drugs may exacerbate heart failure. First-generation calcium antagonists have been associated with clinical deterioration and decreased survival among patients with heart failure. Anti-arrhythmic agents that depress myocardial contractility (such as disopyramide and sotalol) may transiently aggravate heart failure symptoms. Beta-blockers, while beneficial for long-term therapy, may also acutely exacerbate heart failure symptoms when initiated rapidly or given in high doses to patients with advanced left ventricular systolic dysfunction. Nonsteroidal anti-inflammatory agents are a frequent cause of fluid retention and deterioration in renal function and can worsen symptoms and signs of heart failure.

Clinical Presentations

Indications for hospitalization for patients with ADHF have recently been summarized by the Heart Failure Society of America's updated practice guidelines (Table 2).[18] A minority of patients (10 to 20%) present with hypertension and marked interstitial/alveolar pulmonary edema. Increased sympathetic tone leads to redistribution of fluids from the systemic to the pulmonary circulation. These patients are often older and more likely to be female. Symptom onset is typically rapid; left ventricular systolic function is preserved, and marked elevations in pulmonary capillary wedge pressure are noted.[10,13] In contrast, the majority of patients typically present with gradual worsening of symptoms (over days), normal blood pressure, less pulmonary congestion but more weight gain, and peripheral edema. These patients are younger and often demonstrate little or no overt pulmonary congestion despite low ejection fractions and chronically elevated pulmonary capillary wedge pressures.[10] Finally, a small

TABLE 2. Recommendations for hospitalization of patients with acute decompensated heart failure symptoms

Hospitalization recommended	Evidence of severely decompensated heart failure: Hypotension Worsening renal function Altered mentation Dyspnea at rest: Resting tachypnea Oxygen saturation <90% Hemodynamically significant arrhythmias Acute myocardial ischemia
Hospitalization should be considered	
	Worsening congestion even without dyspnea Weight gain ≥5 kg Signs or symptoms of pulmonary or systemic congestion Major electrolyte disturbances Associated comorbidities: Pneumonia, pulmonary embolus Uncontrolled diabetes mellitus Symptoms suggestive of stroke or transient ischemic attack Repeated ICD firings Previously undiagnosed heart failure with sign or symptoms of systemic or venous congestion

[Reproduced with permission from Adams KF, Lindenfeld J, Arnold JM, et al. J Card Fail 2006;12:30 (Table 12.1).]

minority (<10%) will present with hypotension and markedly depressed cardiac index as manifested by cool, mottled extremities, end-organ hypoperfusion, overt pulmonary edema (3%), or cardiogenic shock (<1%).[12]

R. Mills and J. Narula: The ADHERE registry data (ADHERE® Q1 2006 National Benchmark Report: JAMA 2006;293:572-80) showed that half of all ADHF patients presented with systolic BP greater that 140 mmHg. Interestingly, many of these patients had impaired LVEF. Sweitzer and associates (JACC 2005;45:13A) had shown that increased pulse pressure, rather than increased systolic BP alone, correlated with HF and preserved systolic function. In ADHERE, patients with HF and preserved systolic function tended to be older women with hypertension, wide pulse pressure, and impaired renal function. These findings suggest that the syndrome of HF with preserved systolic function may be a primary vascular disorder, driven more by impaired vascular compliance than the classic neurohormonal pathways of HF with impaired LVEF.

Pathophysiologic Considerations

A variety of potential pathophysiologic mechanisms are at work during an ADHF episode. A key feature is volume overload with pulmonary and/or venous congestion. Hemodynamic measurements typically reveal increased right- and left-sided ventricular filling pressures; cardiac index is often but not always depressed. Congestion may be related to poor adherence to diet or medication or progression of left ventricular dysfunction with concomitant activation of vasoconstrictor neurohormones and worsening renal dysfunction. Other comorbidities, particularly poorly controlled hypertension, new-onset atrial fibrillation, or active myocardial ischemia may each contribute to acute decompensation.

The cardiorenal syndrome is increasingly recognized to play an important role in ADHF.[10] Angiotensin II actively induces secretion of endothelin-1 and vasopressin. Further elevation of these neurohormones leads to sodium and fluid retention, increased myocardial wall stress, and decreased renal perfusion. A deleterious positive-feedback loop is often established resulting in chronic elevation of vasoconstrictor neurohormones and worsening heart failure.[10]

R. Mills and J. Narula: No authoritative definition exists for the "cardio-renal syndrome." This term has been used to explain clinical resistance to oral diuretics, on one hand, to impending need for renal replacement therapy on the other. At least three processes may cause increased azotemia in HF patients, and two of the three processes are associated with poor outcomes: (1) Increased prerenal azotemia associated with excessive diuresis, intravascular volume depletion, or poor perfusion and (2) increasing azotemia on the basis of progressive (comorbid) parenchyma renal disease. Both processes do not bode well for the patient. On the other hand, within acceptable limits the increases in serum creatinine associated with RAAS-blocking pharmacotherapy may be associated with improved long-term outcomes (Bakris: Arch Intern Med 2000;160:685-93).

Myocardial injury is now recognized as an important element of the ADHF syndrome.[10] Myocyte loss is triggered by subendocardial myocardial ischemia, mechanical strain (consequent to elevated filling pressures), neurohormonal activation (eg, angiotensin II, endothelin, aldosterone), inflammation, and oxidative stress (Fig 2).[19] Myocyte loss occurs via both necrosis and apoptosis. Perna et al have convincingly demonstrated that over 50% of patients with cardiogenic pulmonary edema (but without evidence for myocardial infarction) have elevated troponin T

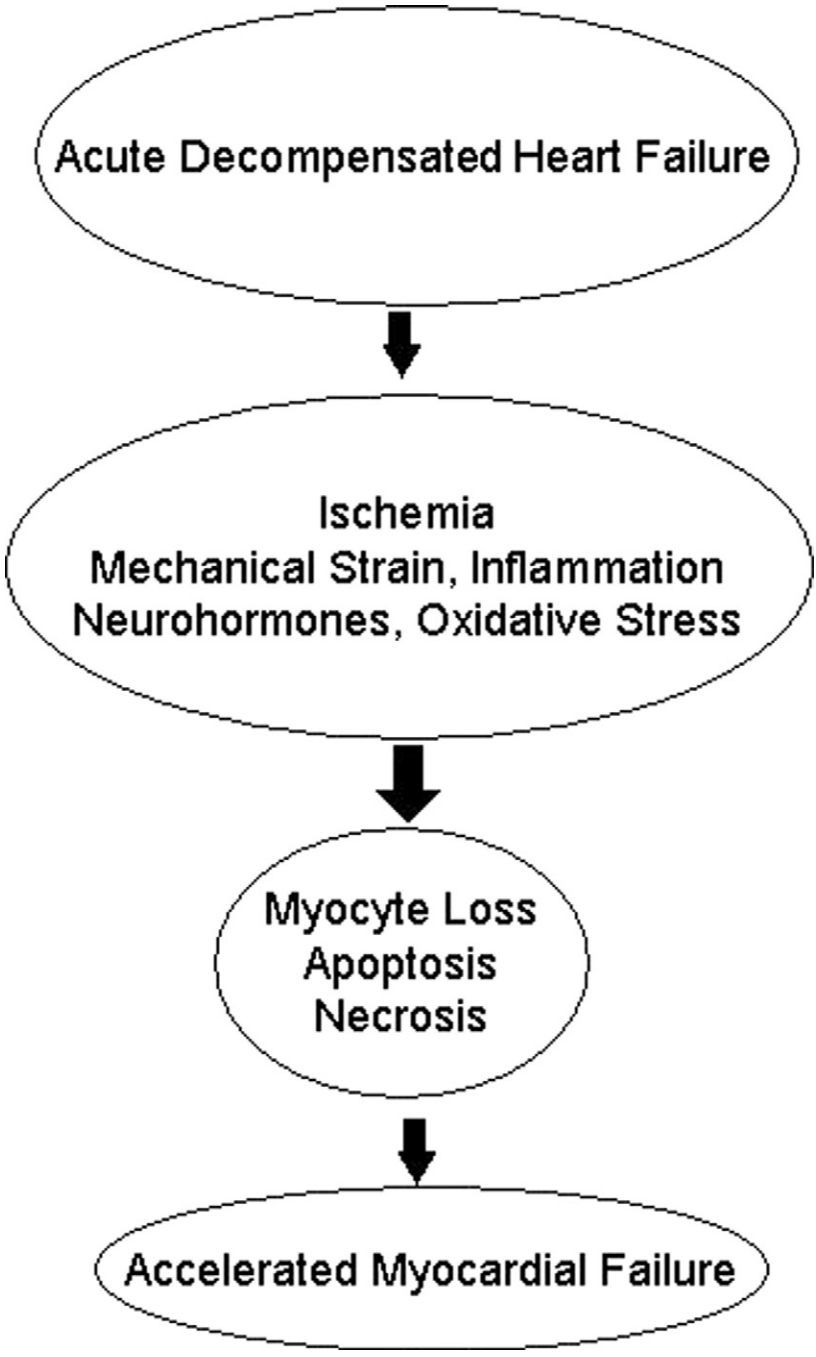


FIG 2. Potential pathogenesis of myocardial injury during periods of acute decompensated heart failure. [Used with permission; Maytin M, et al. Am J Cardiol 2005;96(suppl):29G.]

levels.[20] Strategies aimed at preventing or limiting acute myocardial injury should be considered a treatment goal during management of the acute episode of decompensation.

R. Mills and J. Narula: Peacock and colleagues have recently shown that the mortality risk for any given level of BNP elevation roughly doubles if troponin assays are also positive (Peacock: Circulation 2006:114:II-771).

Predictors of Prognosis

Chronic Heart Failure

During the past two decades, over 50 variables have been examined in univariate and multivariate models and shown to predict mortality in heart failure populations. Unfortunately, no single study has assessed all, or even most, of these predictors simultaneously in a multivariate fashion. Thus, it is impossible to rank prognostic factors strictly on their order of importance in an ambulatory population. Nonetheless, several factors appear repeatedly in the published literature. In his comprehensive review, Eichorn identified plasma norepinephrine level, B-type natriuretic peptide level, left ventricular ejection fraction, peak oxygen uptake during cardiopulmonary exercise testing, advanced age, and a history of symptomatic ventricular arrhythmias or sudden death as the most important predictors of outcome in chronic *compensated* heart failure populations.[21] Women typically had lower mortality rates than men, while African Americans appear to have less favorable outcomes than other racial groups.[22] Findings on physical examination, particularly the presence of a chronic third heart sound, elevation in jugular venous pressure, and the presence of moderate-to-severe mitral or tricuspid regurgitation predict increased morbidity and mortality.[23-25]

Hospitalized Patients

Patients hospitalized for ADHF have a 2.4-fold higher 4-year mortality rate than that observed for stable chronic heart failure patients (60% versus 15%).[11] Only a small number of studies are available that predict short-term outcomes in ADHF patients.[26,27] Risk stratification at the time of hospitalization is not specifically addressed in the most recent American Heart Association/American College of Cardiology Guidelines for Heart Failure Management.[4] Almost a decade ago, Chin and Goldman identified systolic blood pressure below 90 mmHg (adjusted OR, 5.5; 95% CI, 1.7 to 17.1), respiratory rate above 30 breaths/min (OR, 4.6; 95%

TABLE 3. Predictors of adverse outcome during hospitalization for acutedecompensated heart failure

Hypotension
Renal dysfunction
Older age
Male gender
Ischemic heart failure etiology
Previous heart failure hospitalizations
Respiratory rate on admission >30/min
Anemia, acute or chronic
Hyponatremia
Elevated troponin T or I
Elevated pre-discharge B-type natriuretic peptide level
Left ventricular ejection fraction <40%
Comorbid conditions:
Chronic obstructive pulmonary disease
Dementia
Cerebrovascular or peripheral vascular disease
Hepatic cirrhosis
Malignancy

CI, 2.4 to 8.8), serum sodium <135 mEq/L (OR, 2.2; 95% CI, 1.3 to 4.0), and ST T-wave abnormalities on admission electrocardiogram (OR, 5.1; 95% CI, 2.9 to 8.9) as independent predictors of major complications or death during the index hospitalization by multivariate analyses.[28] Hyponatremia has been convincingly shown to predict increased short-term mortality in hospitalized patients.[29] The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) evaluated the relationship between admission serum sodium and primary and secondary endpoints that included in-hospital mortality, 60-day mortality, and 60-day mortality plus rehospitalization rates. The number of days hospitalized for cardiovascular causes was highest among patients in the lowest quartile for serum sodium; 60-day mortality was also highest in this cohort, and a trend toward higher rehospitalization rates was also noted.[29] Table 3 lists independent parameters that had been correlated with clinical outcomes among hospitalized patients with heart failure. These include older age,[30] male sex,[31] heart failure etiology,[31,32] history of previous heart failure hospitalization,[33] respiratory rate,[26] anemia,[33] comorbid conditions,[26,31] and predischarge B-type natriuretic peptide level.[34,35]

The utility of biomarkers as prognostic indicators for ADHF outcomes has recently been validated. B-type natriuretic peptide (BNP) is released from the myocardium in response to increased wall stress and shows a modest relationship to left ventricular filling pressures. Increased BNP at

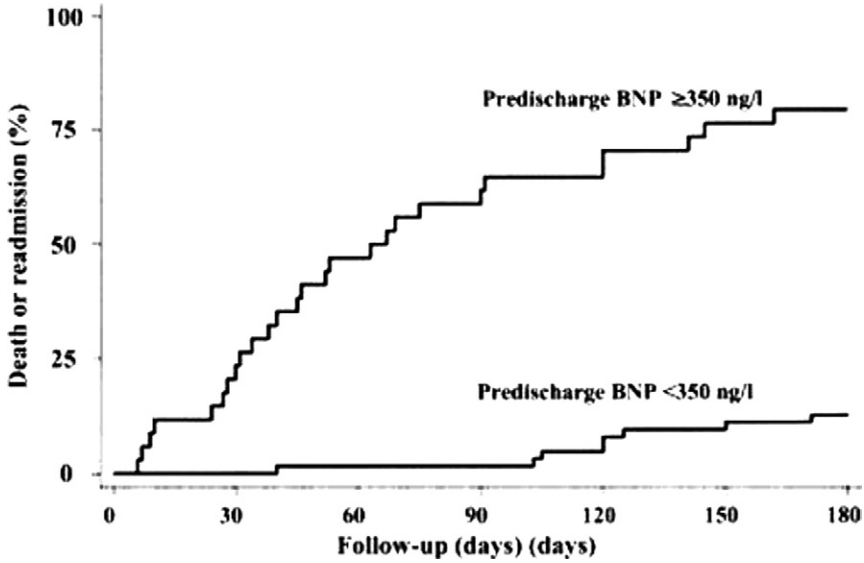


FIG 3. Kaplan–Meier curves showing the cumulative incidence of deaths or readmissions according to predischarge B-type natriuretic peptide (BNP) level cutoff value of 350 ng/L in a validation cohort. [Used with permission; Logeart D, et al. J Am Coll Cardiol 2004;43:635-41 (Fig 3).]

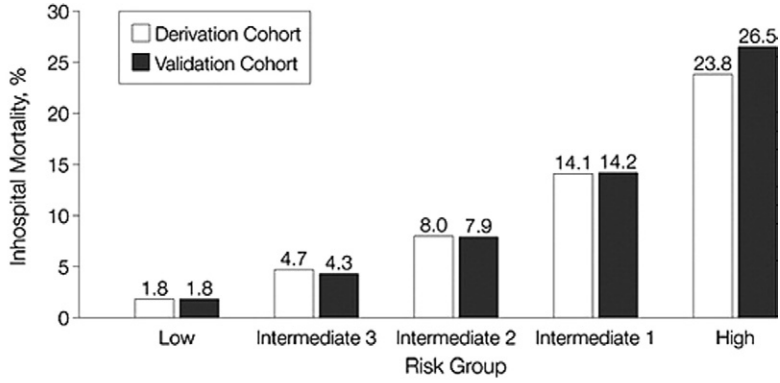
hospital discharge appears to identify patients at increased risk for readmission or death following treatment for ADHF (Fig 3).[34,35] Troponin I or T release occurs in 30 to 70% of ADHF patients.[36] Elevated troponin I or T is associated with a 2-fold increase in postdischarge mortality and a 3-fold increase in rehospitalization rates.[36] Further, the combination of elevated BNP and troponin has been associated with a 12-fold increased risk of mortality.[37] Ongoing trials are now evaluating the use of these biomarkers to guide management in ADHF patients.

Lee and colleagues, using data from an analysis of a large Canadian cohort of patients hospitalized for ADHF, identified older age, lower systolic blood pressure, higher blood urea nitrogen, and severity of hyponatremia as independent predictors of hospital mortality.[26] Felker and colleagues, using data from the OPTIME-CHF trial of 949 patients hospitalized with ADHF, identified increased age, lower systolic blood pressure, New York Heart Association (NYHA) class IV symptoms, elevated blood urea nitrogen, and decreased serum sodium as predictors of 30-day mortality.[38] Predictors of a composite endpoint of death or rehospitalization within 60 days included the number of heart failure hospitalizations during the preceding 12 months, elevated blood urea

nitrogen, lower systolic blood pressure, anemia, and a history of percutaneous coronary intervention.[38] Renal dysfunction has recently been recognized as an extremely important predictor of heart failure outcome. Deterioration in renal function may occur from diminished cardiac output and a corresponding reduction in glomerular filtration rate, alterations in the distribution of cardiac output, intrarenal vasoregulation, alterations in circulatory volume, more intense neurohormonal activation, and/or the nephrotoxic effects of medications administered during hospitalization.[39] Approximately 25% of hospitalized patients with heart failure will exhibit a deterioration in renal function despite appropriate medical therapy.[40] A rise in serum creatinine of only 0.1 to 0.5 mg/dL is associated with a longer hospital length of stay and increased in-hospital mortality.[41] This constellation of poorly understood pathophysiologic mechanisms has been termed the "cardiorenal syndrome" and its optimal management remains to be defined.

R. Mills and J. Narula: Alterations in SCr represent a final common manifestation of many inputs to the kidney: changes in perfusion pressure, changes in renal blood flow, and changes in the neurohormonal milieu. If an increase in SCr of 0.5 mg/dL occurs in association with high-dose diuretic management, the outcome is often longer hospitalization and increased risk for death. On the other hand, in a stabilized patient who is clinically euvolemic, with hypertension, diabetes, and a baseline SCr of 2.0, an increase in SCr of 0.5 mg/dL in association with the initiation of ACE-inhibitor therapy would be acceptable (Bakris: Arch Intern Med 2000;160:685-93).

Fonarow et al, using ADHERE registry data, performed the most detailed risk stratification of in-hospital mortality for ADHF.[42] The ADHERE registry tracks patients hospitalized with a primary diagnosis of ADHF in 263 hospitals in the United States. The initial 33,046 hospitalizations served as the derivative cohort (October 2001-February 2003) and facilitated the development of a predictive model for in-hospital mortality. The validity of the model was prospectively tested using data from 32,229 subsequent hospitalizations (validation cohort, March-July 2003). Patients had a mean age of 72.3 years and 52% were female. Recursive partitioning of the derivation cohort for 32 key variables indicated that the best single predictor for mortality was high admission level of blood urea nitrogen (>43 mg/dL), followed by an admission systolic blood pressure below 115 mmHg and a serum creatinine level >2.75 mg/dL. On the basis of these three variables, patients were readily stratified into groups at low, intermediate, and high risk for in-hospital mortality with mortality rates ranging from 2.1 to 21.9% (Fig 4). Once



No. of Patients					
Derivation Cohort	20764	4087	5087	1419	617
Validation Cohort	20518	4010	4919	1370	471

FIG 4. In-hospital mortality based upon regression modeling. Log-odds of mortality was calculated for all patients in a derivation cohort and risk group cut-points were established at percentile rankings equivalent to initial classification and regression tree models (65th, 78th, 95th, and 98th percentiles). [Used with permission; Fonarow GL, et al. JAMA 2005;293:572-80.]

again, the importance of indices of renal function in predicting in-hospital mortality risk was confirmed. The early identification of patients at increased risk may ultimately lead to better strategies designed to improve their outcome.

Goals of Therapy

Treatment goals differ between ambulatory heart failure patients with chronic symptoms and patients admitted with ADHF.[18] Principal goals for chronic heart failure include relief of symptoms (congestion and low output), improvement in submaximal exercise capacity, fewer hospitalizations and/or emergency room visits for heart failure management, amelioration of left ventricular remodeling, and improvement in survival. While all of these goals are important considerations during hospitalization, the specific goals of therapy are much more focused on immediate management. The first and foremost goal is rapid relief of symptoms. The vast majority of patients present with symptoms of congestion (ie, volume overload) due to elevated ventricular filling pressures. Every effort should also be made to improve end-organ perfusion. Arrhythmias, particularly those that could exacerbate heart failure such as rapid atrial fibrillation or flutter, should be controlled. Following immediate stabilization, each

patient's pharmacologic regimen should be reviewed in detail to ensure that it has been optimized (see below). This is also an opportunity for patient and family education regarding the signs, symptoms, and management of heart failure as well as specific information regarding medications and their role in treatment. Finally, hospitalization provides another opportunity to consider other treatment options, specifically, coronary revascularization for patients with underlying ischemic heart disease, cardiac resynchronization therapy for individuals who remain in normal sinus rhythm and demonstrate evidence for left ventricular dyssynchrony, or investigational agents for those with refractory symptoms (see below).

R. Mills and J. Narula: Treatment goals in ADHF should reflect a careful assessment of the balance of benefit and risk. Many emergency and primary care physicians who manage HF patients are unaware of the impact of early initiation of vocative therapy and tend to rely far too much on repeated doses of loop-blocking diuretics, further activating the RAAS in these patients (Peacock: Cardiology 2007;107:44-51). Reasonable goals include rapid relief of symptoms and improvement of hemodynamics without further exacerbation of the underlying neurohormonal disorder, followed by instruction of appropriate diet, activity, and oral drug therapy.

Hemodynamic Assessment and Monitoring

Nohria and colleagues have popularized a 2-minute bedside clinical assessment tool to ascertain the hemodynamic profiles for heart failure patients (Fig 5).[43,44] The two fundamental hemodynamic abnormalities relate to presence or absence of elevated filling pressures (so-called "wet" or "dry" profiles) and end-organ perfusion that is adequate or impaired ("warm" or "cold" profiles). Physical findings have been shown to correlate reasonably closely with acute hemodynamic measurements and to determine prognosis following hospital discharge.[44-46] Identification of elevated filling pressures in chronic heart failure patients relies heavily on the symptoms of orthopnea and paroxysmal nocturnal dyspnea and the finding of elevated jugular venous pressure. Rales are absent in more than 80% of patients with chronically elevated filling pressures but may be evident during periods of acute decompensation. Likewise, peripheral edema is relatively insensitive for detecting elevated right-sided filling pressures. The most accessible evidence for adequate perfusion is blood pressure. Pulse pressure is also important. Patients with evidence for pulsus alternans typically have severely reduced perfusion.[45] Cool forearms and legs may be more specific for low cardiac output than cool

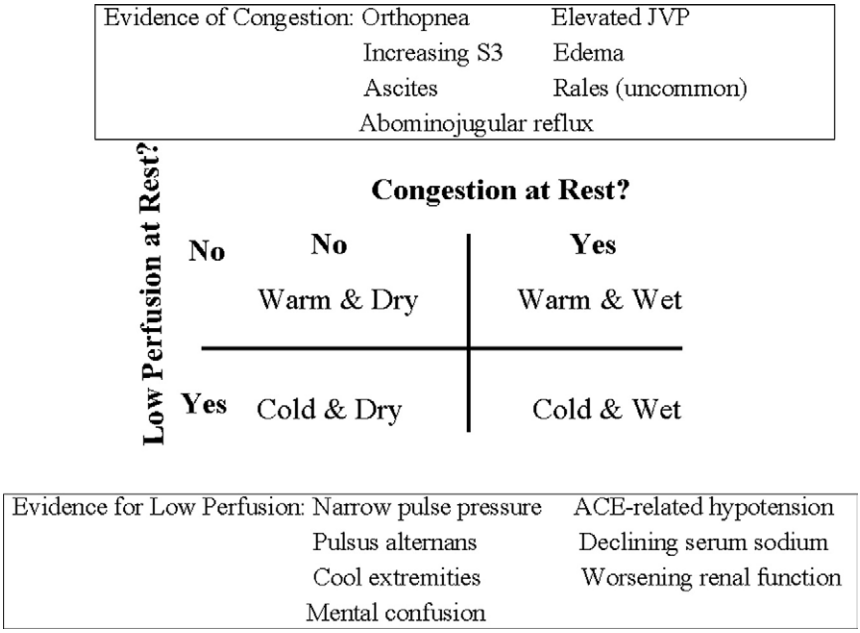


FIG 5. Diagram indicating 2 × 2 table of hemodynamic profiles for patients presenting with heart failure. Most patients can be classified in a 2-minute beside assessment according to their signs and symptoms. This classification system can help guide therapy and predict prognosis. [Used with permission; Nohria A, et al. JAMA 2002;287:628-40 (Fig 4).]

hands and feet.[45] Inadequate perfusion should be suspected when patients with obvious volume overload develop symptomatic hypotension, particularly during treatment with low-dose vasodilator therapy.[45]

"Warm and dry" patients have normal resting hemodynamics and are well compensated. Other potential etiologies for their acute dyspnea or worsening fatigue should be considered such as pulmonary embolism, obstructive lung disease, or infection. The majority (50 to 60%) of patients admitted with worsening heart failure symptoms fit into the "warm and wet profile."[44] These individuals are volume overloaded but demonstrate adequate end-organ perfusion. The primary treatment goal is relief of "congestive symptoms." Intravenous loop diuretics alone (or combined with the thiazide agent) should be initiated. The maintenance dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers should generally be continued. Likewise, patients who respond adequately to enhanced diuretic therapy need not have their outpatient beta-blocker dose decreased. For patients who are difficult to

diurese, beta-blocker dose should be decreased by at least 50% or the drug may be withheld for several days and then reinstituted at half of the usual outpatient dose.

R. Mills and J. Narula: In the ADHERE registry also, about 2% of patients presented with systolic BP less than 90 mmHg. Such patients can undergo very rapid assessment in the emergency department. If the BUN is over 43 mg/dL, and/or the SCr >2.7, the hypotensive patient is at high risk for death (>20%) on the index admission (Fonarow GC: JAMA 2005;293:572-80). After appropriate discussion among the treating physician, the patient, and the family, hemodynamic assessment and "tailored therapy" remain appropriate for this group of patients.

A very small minority of patients (<5%) will fall into the "cold and dry" profile. These individuals have impaired cardiac output but do not adequately utilize the Frank–Starling mechanism to increase their preload. Judicious hydration should be attempted. Patients who fail to demonstrate improvement in end-organ perfusion may require a positive inotropic agent such as dobutamine or milrinone (see below).

Approximately 20% of ADHF patients will demonstrate marked hemodynamic abnormalities on admission ("cold and wet" profile). These patients have impending cardiogenic shock. Potential causes for acute decompensation such as recent myocardial infarction, rhythm change, worsening valvular heart disease, or medication noncompliance should be sought. The recently completed ESCAPE trial randomized 433 patients at 26 sites to receive conventional medical therapy based on physical signs and symptoms alone versus tailored hemodynamic monitoring following insertion of a pulmonary artery catheter.[47] Therapy to reduce volume overload during hospitalization led to marked improvement in signs and symptoms of elevated filling pressures in both groups. Use of a pulmonary artery catheter to "guide therapy" did not significantly affect the primary endpoint of days alive and out of hospital during the first 6 months following treatment (HR, 1.00), mortality (10% versus 9%), or the number of days hospitalized (8.7 versus 8.3).[47] In-hospital adverse events, however, were more common among patients in the pulmonary artery catheter cohort (21.9% versus 11.5%, $P = 0.04$). No deaths related to pulmonary artery catheter use were noted.

Certain high-risk subgroups may, nonetheless, benefit from short-term hemodynamic monitoring for management of ADHF. Principal indications include evidence for worsening end-organ dysfunction, need for withholding vasoactive medications due to hypotension or renal failure,

TABLE 4. Indications for hemodynamic monitoring in decompensated heart failure

Ongoing congestive symptoms and suspected end-organ hypoperfusion	
Narrow pulse pressure	Cool extremities
Declining renal function	Hypotension on ACE or ARB
Mental confusion	Progressive hyponatremia
Heart failure and other medical comorbidities	
Cardiac: unstable angina pectoris; stenotic valvular lesions, hypertrophic cardiomyopathy	
Noncardiac: severe obstructive or restrictive pulmonary disease, advanced renal disease, sepsis	
Other situations	
Perioperative monitoring to optimize status for high-risk procedure	
Symptoms disproportionate to clinical assessment of degree of compensation	
Uncertain volume status	
Inability to wean inotropic support	

ACE, angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker.

TABLE 5. Principles of hemodynamic tailored heart failure therapy

Measure baseline resting hemodynamics (CVP, PAP, PCW, CI, SVR)
Administer intravenous diuretics, vasodilator (nitroprusside, nitroglycerin, or nesiritide), or inotropic agent (milrinone or dobutamine) dosed to achieve specific hemodynamic goals:
Pulmonary capillary wedge pressure $<$16 mmHg
Right atrial pressure $<$8 mmHg
Cardiac index $>$2.2 L/min/m^2
Systemic vascular resistance $<$1000-1200 dyn s cm^{-5}
Systolic blood pressure $>$80 mmHg
Maintain optimal hemodynamics for 24 to 48 h
Up-titration of oral vasodilators as intravenous vasodilators are weaned
Adjust oral diuretics to maintain optimal volume status

CVP, central venous pressure; *PAP,* pulmonary artery pressure; *PCW,* pulmonary capillary wedge pressure; *CI,* cardiac index; *SVR,* systemic vascular resistance.
[Adapted from Stevenson LW. Eur J Heart Fail 1999;1:251-7 (Table 3, p 254); Reproduced with permission.]

heart failure associated with other medical comorbidities (ie, unstable angina pectoris or valvular heart disease), or inability to wean positive inotropic support (Table 4).[18] The use of "tailored" hemodynamic treatment for refractory heart failure is outlined in Table 5.[43,45]

R. Mills and J. Narula: For many patients with ADHF, the reduction in RAAS activation associated with intravenous vasodilators offers an opportunity to initiate low-dose ACE inhibitors or ARB therapy without exacerbating renal dysfunction. Similarly, milrinone infusion can provide homodynamic support during initiation of beta-adrenergic blockade in tenuous patients.

The patients who cannot tolerate reduction of PCWP to less than 16 mmHg without developing signs and symptoms of poor perfusion have a poor outlook. In this setting, it may be prudent to consider LVAD support in appropriate patients. Excessive delay in referral for LVAD may contribute to vicious cycle of worsening risk.

Following initial assessment of baseline hemodynamics, intravenous agents such as diuretics, vasodilators, or positive inotropes should be administered to achieve desired hemodynamic goals, which generally include a pulmonary capillary wedge pressure below 15 mmHg and a cardiac index above 2.2 L/min/m^2. This intravenous vasoactive program should be maintained for at least 24 to 48 hours to affect desired diuresis and improve end-organ perfusion. Following this initial stage, oral vasodilators should be up-titrated as intravenous agents are weaned off. Further adjustments in diuretic dose and ambulation should be completed during the final 24 to 48 hours of hospitalization. This "tailored-approach" has been shown to produce sustained improvements in filling pressures, forward output, decreased mitral regurgitation, and decreased neurohormonal activation.[44,46,48] Oral vasodilator therapy and beta-blockers should be withheld during treatment with vasoactive agents. Considerable controversy continues to exist regarding the relative roles of intravenous vasodilator drugs (ie, nitroglycerin, nitroprusside, or nesiritide) and positive inotropic agents (ie, dobutamine, dopamine, or milrinone) in this population.[18,49] Previously, positive inotropic drugs were used for patients with moderate heart failure to promote rapid diuresis. These agents, however, have been shown to be associated with an increased risk of ischemic events and tachyarrhythmias.[32] A second major limitation of short-term inotropic support is the additional complexity needed to readjust oral regimens as the intravenous infusions are weaned.[44] Although positive inotropic agents should not be routinely used for "warm and wet" patients, these agents can be lifesaving for patients with progressive hemodynamic collapse.[44,49,50] Patients who present or develop obtundation, anuria, persistent hypotension, or lactic acidosis may only respond to inotropic support, which should be continued until the cause of acute cardiac deterioration is determined and definitive therapy (if any) can be implemented. Brief inotropic treatment may also be appropriate for some patients who develop the cardiorenal syndrome. Although improvement in systemic perfusion may sometimes require intravenous inotropic therapy, most patients with low cardiac output symptoms or hemodynamic abnormalities have high systemic vascular resistance that predictably improves with vasodilator treatment alone.[44]

Specific Pharmacologic Agents for Acute Heart Failure Management

Diuretics

Loop diuretics (ie, furosemide, torsemide, ethacrynic acid, and bumetanide) are the mainstays of treatment for ADHF. These drugs inhibit sodium and chloride reabsorption in the ascending limb of the loop of Henle. Up to 30% of the filtered load of sodium chloride is excreted in the urine after intravenous administration of furosemide. While these drugs are first-line therapy, randomized controlled clinical trials evaluating clinical outcomes or comparing agents have not been undertaken. In general, patients on chronic diuretic therapy should receive the same intravenous dose as their oral outpatient dose. Neurohormonal activation (renin-angiotensin, endothelin, and BNP) acutely decreases after short-term diuretic therapy designed to lower markedly elevated filling pressures.[51] However, over-diuresis can lead to enhanced neurohormonal activation and increased sensitivity to angiotensin-converting enzyme inhibitors and beta-blockers.[52] Thus, the lowest dose of diuretic that achieves the desired diuretic effect should be prescribed.

R. Mills and J. Narula: It is important to add that Domanski and coworkers (J Card Fail 2006;12:327-32) and Fonarow (JACC 2003) have shown increased risk associated with daily diuretic use and high-dose diuretics in the outpatient arena as well.

Retrospective data from registries and clinical trials suggest that diuretics may, at times, be harmful. Data from the ADHERE registry demonstrate that patients treated with intravenous diuretics have a higher in-hospital mortality, longer total length of stay, and longer length of stay in the intensive care unit compared to patients who did not receive intravenous diuretics, even after adjusting for other prognostic factors.[53]

Diuretic unresponsiveness is often encountered in patients with advanced heart failure during periods of acute decompensation. Lack of a diuretic response may be caused by excessive sodium or fluid intake, agents that antagonize their effects (particularly nonsteroidal anti-inflammatory drugs), worsening renal function, addition of potentially nephrotoxic agents during hospitalization, compromised renal blood flow due to worsening cardiac function or periods of hypotension due to overaggressive diuresis, or vasodilator therapy. Combined intravenous loop diuretic plus a thiazide may create a synergistic response and should be consid-

ered for patients who fail a loop diuretic alone. Likewise, metolazone exerts a markedly additive effect when administered with a loop diuretic. High-dose furosemide, when administered as a continuous infusion (1-10 mg/h), may be more effective than bolus administration for hospitalized patients.[54] For a minority of patients with refractory volume overload, venovenous ultrafiltration can provide rapid volume removal and improvement in symptoms.[55] Randomized trials are now evaluating the efficacy of ultrafiltration compared to intravenous diuretic therapy in this population.

A low sodium diet (2 grams daily) is recommended during hospitalization. Fluid restriction (<2 L/day) should be instituted for patients with moderate hyponatremia (Na^+ <130 mEq/L) and is generally also useful in the management of fluid overload in nonhyponatremic patients.[18] A stricter fluid restriction may be necessary for patients with severe (Na^+ <120 mEq/L) or worsening hyponatremia during attempted diuresis.

Aldosterone Antagonists

Circulating aldosterone levels are elevated in relationship to heart failure severity, affect long-term prognosis, and contribute to adverse left ventricular remodeling following acute myocardial infarction.[56] Potential deleterious effects include endothelial dysfunction, increased oxidative stress, enhanced platelet aggregation, activation of matrix metalloproteinases, and increased sympathetic neurohormonal activation.[56] The nonselective mineralocorticoid receptor antagonist, spironolactone, has been shown to reduce mortality in patients with advanced heart failure by 30%.[57] Further, results from the recently completed Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial in patients with heart failure following acute myocardial infarction confirm reductions in mortality and morbidity in post-myocardial infarction populations as well.[58] Aldosterone antagonists' beneficial effects occur independent of their actions as mild diuretics. Spironolactone should not be initiated during the initial treatment of ADHF. It can be added (25 mg QOD) to the patient's medical regimen prior to discharge following optimization of other heart failure therapies. Patients who have been receiving this agent as an outpatient should have it continued during hospitalization unless marked hemodynamic instability, electrolyte disturbances, or worsening renal function ensues.

R. Mills and J. Narula: Physiologically, the natriuretic peptides counter RAAS activation. Nesiritide reduces aldosterone levels in patients with ADHF.

In a small but very carefully conducted trial, Sica and colleagues showed that infusion of nesiritide prior to administration of a furosemide bolus blocked the aldosterone rise produced by diuretic alone (J Card Fail 2006;12:S85-6). Similarly, in the NAPA trial, perioperative administration of nesiritide to stable HF patients undergoing on-pump CABG surgery significantly attenuated postoperative increases in SCr (Mentzer: JACC 2007;49:716-26). These data suggest that, in addition to producing balanced vasodilation, nesiritide may have beneficial effects on aldosterone production in ADHF.

Digoxin

Digoxin has been a mainstay of therapy for chronic heart failure for several hundred years. Digoxin inhibits the sodium–potassium–ATPase pump, leading to increased intracellular sodium.[59] This action results in a decrease in calcium efflux via the sodium–calcium exchanger and increases cytoplasmic calcium, which leads to increased myocardial contractility. The drug has mild positive inotropic effects on cardiac muscle, reduces activation of the sympathetic and renin-angiotensin systems, and partially restores the favorable inhibitory effects of cardiac baroreceptor function.[60,61] Post-hoc analyses have shown that the patients most likely to respond to outpatient therapy have severe symptoms, marked left ventricular systolic dysfunction, and the presence of an audible third heart sound.[62] Gheorghiade and colleagues studied the acute effects of intravenous captopril and intravenous digoxin on hemodynamics in 16 patients with severe heart failure and sinus rhythm.[63] Captopril and digoxin independently decreased pulmonary capillary wedge pressure by 24 and 34%, respectively. Digoxin increased cardiac index by 23% and stroke work index by 52%. The combination of captopril and digoxin resulted in greater decreases in pulmonary capillary wedge pressure and increases in cardiac index then were observed for either drug alone. Although digoxin has been shown to produce favorable short-term hemodynamic effects, its efficacy on clinical outcomes in patients with ADHF is unknown. As renal function may fluctuate considerably during hospitalization, measurement of serum digoxin levels is important.[64] Retrospective subgroup analyses have suggested an increased all-cause mortality risk among both men and women who have digoxin levels >1.0 ng/dL.[65,66] Impaired renal function, small lean body mass, and older age are at greatest risk for developing digoxin toxicity. Further, a number of commonly utilized drugs, including verapamil, flecainide, spironolactone, and amiodarone significantly increase serum digoxin levels and their concomitant use requires dose reductions.

Beta-Adrenergic Blockers

Beta-blockers act principally by inhibiting the deleterious effects of excessive sympathetic neurohormonal activation in heart failure. Periods of acute decompensation lead to further increases in sympathetic neural activity that result in additional peripheral vasoconstriction, impaired renal sodium handling, and provocation of arrhythmias and can trigger apoptosis by stimulating cytokines and oxidative stressors.[67] Three distinct classes of beta-blockers are now clinically utilized. Propranolol and other "first-generation" compounds such as timolol are nonselective agents that have equal affinity for $beta_1$- and $beta_2$-receptors.[68] Metroprolol and bisoprolol are "cardioselective" second-generation compounds that block the $beta_1$-receptor to a greater extent than the $beta_2$-receptor. Metoprolol is approximately 75-fold more selective for $beta_1$- than $beta_2$-receptors, while bisoprolol is 120-fold more selective.[68] Labetalol, carvedilol, and bucindolol are third-generation compounds that block $beta_1$- and $beta_2$-receptors with almost equal affinity.[69] These agents also have ancillary properties that include $alpha_1$-blockade (labetalol, carvedilol), antioxidant properties (carvedilol), and intrinsic sympathomimetic activity (bucindolol).[68,69] A growing percentage of patients hospitalized for ADHF have been receiving oral beta-blocker therapy as part of their maintenance regimen. The dose of beta-blockers is often decreased by 50% during the initial phase of hospitalization for patients already receiving a stable dose of the drug. Patients with relatively mild symptoms and prompt response to diuretics may not require a dose decrease. Conversely, patients with marked symptoms and a hemodynamic profile indicating congestion and impaired perfusion (ie, "cold and wet" profile) should have their beta-blocker withheld until hemodynamic stabilization has been achieved. Beta-blockers should not be up-titrated when either acute volume overload or hemodynamic instability is present.

Initiation of beta-blocker therapy for drug-naïve patients in the inpatient setting after initial stabilization of hospitalized patients should be considered and has several potential advantages over outpatient initiation.[70] The structured setting can facilitate treatment initiation using physician prompts such as care guidelines, preprinted order sets, and discharge forms. Hospital-based initiation may help alleviate patient and physician concerns about beta-blocker tolerability and side effects. The Carvedilol Prospective Randomized Cumulative Survival trial studied the impact of beta-blocker initiation in patients with severe heart failure symptoms.[71] The trial enrolled 2289 patients with heart failure symptoms at rest or on minimal exertion and a left ventricular ejection fraction $< 25\%$. The drug

could be initiated while the patient was still hospitalized but patients could not have been in an intensive care unit setting or have received intravenous inotropic agents during the preceding 4 days. Treatment with carvedilol resulted in a significant 35% reduction in all-cause mortality and a significant reduction in the combined risk of death or hospitalization in this severely symptomatic heart failure population.[71] Further, beta-blocker-treated patients subsequently experienced 40% fewer hospital days for ADHF.[71] Benefits were seen across all subgroups of patients examined including patients with recent and/or recurrent decompensation.[71] Carvedilol was very well tolerated with more patients withdrawn from the placebo group because of adverse events than the carvedilol group.[71]

The Initiation Management Pre-Discharge: Process for Assessment of Carvedilol Therapy for Heart Failure trial was a multicenter, open-label study that enrolled 363 heart failure patients with an left ventricular ejection fraction ≤40% admitted for ADHF.[72] Patients were randomized to receive initiation of carvedilol before hospital discharge or to usual care (recommended initiation of any beta-blocker within 2 to 4 weeks after discharge). At 60-day follow-up, 91% of the predischarge initiation patients were receiving beta-blocker compared to only 73% of patients in the postdischarge group ($P < 0.001$). Further, the mean percentage of patients who were receiving the target dose was 36% in the predischarge group compared to 28% for the postdischarge group.

A minority (<10%) of patients with resistant heart failure are unable to tolerate even the lowest doses of beta-blocker. Some investigators are now combining a phosphodiesterase inhibitor (enoximone or milrinone) with low-dose beta-blockade.[73,74] Theoretically, beta-blockers should counteract the ischemic and arrhythmic properties associated with phosphodiesterase inhibition and provide synergistic effects. Small, uncontrolled, short-term studies suggest that this approach may be beneficial in at least a cohort of patients with refractory heart failure symptoms.[73,74] A randomized, controlled trial is now evaluating the safety and efficacy of this novel approach.

Oral Vasodilator Therapy

Vasodilators remain a cornerstone of acute heart failure management. Mechanisms of action vary and include direct effects on venous capacitance vessels (eg, nitrates), arterioles (eg, hydralazine), or balanced effects (sodium nitroprusside, nesiritide, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers [ARBs]). Primary venodilators reduce cardiac filling pressures and effectively improve pulmo-

nary congestion while having little effect on systemic blood pressure. Conversely, agents that primarily dilate arterioles (pure afterload reducing agents) reduce systemic vascular resistance and increase cardiac output while producing little change in ventricular filling pressures. While balanced vasodilators should generally be chosen as first-line therapy for outpatient management, this approach may not be optimal for patients in the acute decompensated state. The outpatient vasodilator regimen should generally be maintained during hospitalization. However, if there is evidence for significant end-organ dysfunction (eg, progressive renal dysfunction), persistent hypotension (eg, systolic blood pressure <85 mmHg), or hemodynamic instability, oral vasodilators should be withheld or the dose substantially decreased. The recently completed assessment of treatment with lisinopril and survival (ATLAS) trial confirmed that even low doses of an ACE inhibitor can effectively improve symptoms and mortality in chronic heart failure.[75] Intravenous ACE inhibitors are not routinely indicated for initial stabilization of ADHF patients.[18] Combination therapy with an ACE inhibitor plus an angiotensin II receptor blocker may be useful for patients who have experienced recurrent hospitalizations for ADHF.[4,18] Although no survival benefit is conveyed by combined treatment, repeat hospitalizations and overall morbidity can be decreased with this approach.

Alternative therapy with a combination of hydralazine and nitrates should be considered for patients with substantially impaired renal function (creatinine >2.5 to 3 mg/dL) and those with a documented intolerance to ACE inhibitors. Similar hemodynamic goals can be achieved with these agents among patients with NYHA class III or IV heart failure symptoms.[76] Important racial differences may also exist in pharmacological responsiveness to different vasodilator regimens. Two retrospective post-hoc analyses from large clinical trials confirmed ACE inhibitor therapy to be less effective in blacks than whites with heart failure symptoms of similar severity.[77] The recently completed African-American Heart Failure trial confirmed the benefit of hydralazine plus isosorbide dinitrate in this population. This combination should be considered when initiating therapy for hospitalized black patients.[78]

Vasodilators are the mainstay of therapy for ADHF in Europe; 32% of admitted patients receive nitrates during their hospitalization.[79] Recent Heart Failure Society guidelines recommend intravenous vasodilator therapy (nitroglycerin, nitroprusside, or nesiritide) for rapid symptom relief in patients with acute pulmonary edema, significant hypertension, or persistent severe heart failure symptoms despite aggressive treatment with diuretics and oral vasodilators.[18] There is little doubt that nitroglyc-

erin is a very effective medication for the treatment of acute symptoms due to its prompt preload reduction. Its limited use in the United States and its significant underdosing in clinical practice underscores widespread inexperience in prescribing nitrates in the context of heart failure as opposed to angina pectoris.

R. Mills and J. Narula: Only a few RCTs have investigated the efficacy of nitroglycerin for this indication. In the VMAC Trial, nitroglycerin was used as a safety comparator, not an efficacy comparator. In a substudy of the VMAC trial, Elkayem and colleagues (AJC 2004;93:237-40) reported their experience with nitroglycerin in patients with homodynamic monitoring and aggressive up-titration of nitroglycerin to meet homodynamic goals. Despite doses on the order of 160 μm/min, patients receiving nitroglycerin experienced a steady rise in PCWP after 4 to 6 hours of treatment, consistent with loss of vascular responsiveness to the drug. This phenomenon is consistent with the known pharmacology of nitroglycerin and suggests that the initial homodynamic improvement with nitroglycerin may not be sustained without nitrate-free periods or supplemental intervention.

Intravenous nitroprusside is another highly effective intravenous vasodilator. In an early uncontrolled study of 18 hospitalized patients, nitroprusside resulted in a decrease of 15 mmHg in pulmonary capillary wedge pressure, significant diuresis, and natriuresis.[80] Another study of 25 patients with heart failure, markedly impaired left ventricular function, and critical aortic stenosis surprisingly demonstrated that nitroprusside could decrease ventricular filling pressures, increase cardiac output by over 50%, and improve renal function.[81] In addition, there is now convincing evidence that short-term therapy with combined nitroprusside and diuretics markedly decreases neurohormonal activation as hemodynamics improve.[82] Nitroprusside is underutilized in acute heart failure management, largely because of concerns regarding hypotension and the need for hemodynamic monitoring.

R. Mills and J. Narula: Safe and effective use of nitroprusside in critically ill patients requires invasive homodynamic monitoring.

Nitroprusside administration has also been studied in the setting of acute myocardial infarction complicated by left heart failure. Cohn and colleagues demonstrated that nitroprusside decreased survival at 13 weeks when it was initiated within 9 hours of pain onset but improved survival when administered beyond the 9-hour time window.[83] In

addition to these concerns regarding timing during acute myocardial infarction, other concerns (particularly thiocyanate toxicity, precipitation of hypotension with potential exacerbation of ischemia, and the requirement in most centers for invasive blood pressure monitoring) combined with the absence of outcome data from larger controlled clinical trials will most likely continue to limit the widespread use of this potent vasoactive agent.[84]

Nesiritide (human B-type natriuretic peptide) acts by increasing cyclic guanosine monophosphate, thereby causing vasodilatation and a resultant decrease in ventricular filling pressures. Despite its nomenclature as a "natriuretic" peptide, nesiritide has not been associated with major diuresis in most heart failure studies, although it may potentiate the effect of concomitant diuretics and may slightly reduce the total dose required.[85] Multiple clinical trials of nesiritide demonstrate that it can be effective in decreasing pulmonary capillary wedge pressure and improving patient symptoms.[84,86]

The Vasodilation in the Management of Acute CHF (VMAC) trial was designed to evaluate the efficacy of nesiritide in the treatment of ADHF.[86] The trial enrolled 489 patients with dyspnea at rest requiring hospitalization. Patients were stratified according to the treating physicians' decision to use invasive pulmonary artery catheter monitoring management. Patients with hemodynamic data were eligible if their pulmonary capillary wedge was >20 mmHg; noncatheterized patients had to have two or more distinct signs and symptoms of volume overload. Patients were randomized to receive placebo, nesiritide (either fixed or adjustable dose in the hemodynamically monitored cohort), or nitroglycerin infusions for the first 3 hours.[86] The primary endpoints were both a change in pulmonary capillary wedge compared to placebo at 3 hours and the patient's self-evaluation of dyspnea compared with placebo at 3 hours.[86] Significant improvements in both endpoints were noted. Nesiritide significantly decreased pulmonary capillary wedge compared to both placebo and nitroglycerin (nesiritide, 5.8 mmHg; nitroglycerin, 3.8 mmHg; placebo, 2.0 mmHg). Nesiritide significantly improved dyspnea score compared to placebo but was identical to nitroglycerin. Since the VMAC publication, nesiritide has been increasingly utilized in the management of ADHF.

Silver et al evaluated the effects of nesiritide versus dobutamine on short-term outcomes in acute heart failure in an open-label, randomized, controlled trial.[87] Hemodynamically unstable patients who required immediate inotropic or vasodilator support or whose initial blood pressure fell below 90 mmHg were excluded. Although no difference in hospital

length of stay was noted, a trend towards fewer readmissions was observed for nesiritide-treated patients. Importantly, 6-month mortality was lower for patients treated with low-dose nesiritide (18%) compared with those treated with dobutamine (31%).[87]

Abraham et al have helped further clarify the role of intravenous vasoactive therapy for inpatient management of ADHF.[53] Data were obtained from the ADHERE registry, which included more than 65,000 admissions for heart failure. Cases in which patients received nitroglycerin, nesiritide, milrinone, or dobutamine were identified (approximately 20% of the total cohort). Risk factor and propensity score-adjusted odds ratios for in-hospital mortality were calculated. Unadjusted in-hospital mortality varied widely, ranging from 4.1% for the entire cohort to as much as 14% for patients who received intravenous inotropic support.[53] Patients treated with either nitroglycerin or nesiritide had intermediate mortality rates that ranged from 4.7 to 7.1%. Adjusted inpatient mortality odds ratios of 0.59 and 0.47 were observed for nesiritide versus milrinone or dobutamine, respectively. Similarly, adjusted inpatient mortality odds ratios of 0.69 and 0.46 were noted for nitroglycerin therapy versus milrinone or dobutamine, respectively. Mortality did not differ between nesiritide- or nitroglycerin-treated groups. This observational study strongly suggested that intravenous vasodilator therapy was associated with lower in-hospital mortality than positive inotropic therapy among patients hospitalized with ADHF. Concerns remain about the validity of this conclusion as these data were retrospective and may not have controlled for choice of agent. Physicians were allowed to choose whichever agent they felt would be most appropriate and it is possible that patients who received positive inotropes may have been more substantially compromised leading to initiation of that class of vasoactive support.

R. Mills and J. Narula: Wang et al (Circulation 2004;110:1620-5) studied a small group of patients selected for the protocol because of worsening renal function; they found no effect, either improvement or deterioration, associated with nesiritide intervention in this group. Sackner-Bernstein and coworkers did not actually perform a new study but performed "meta-analyses" of several Scios-sponsored clinical trials (Scios makes Nesiritide for clinical use and Dr. Mills works for Scios), which had been posted in the public domain on the FDA web site (Sackner-Bernstein et al, Circulation 2005; 111:1487-91; JAMA 2005;293:1900-5). Sackner-Bernstein and coworkers did not have access to the full clinical database and they acknowledge this limitation. Despite the strength of the observation that worsening renal function is associated with worse clinical outcomes, no data in these or other studies demonstrate that this relationship is true for nesiritide as it is for some other therapies. The physiology of antagonizing the renin–angiotensin system appears to be an exception in which the relationship does not hold between transient worsening renal function and adverse outcome (Sackner-Bernstein,

et al: Circulation 2005;111:1487-91). A careful, propensity-matched assessment of nesiritide and other agents used in the management of ADHF has been subsequently published (Abraham WT, et al: JACC 2005;46:57-64), which demonstrated no increased risk associated with this treatment. In fact, the available evidence indicates that the benefit–risk profile for nesiritide in the management of ADHF may be favorable.

Several recent studies have suggested that nesiritide may worsen renal function.[85,88] Further, Sackner-Bernstein et al have also reported increased short-term mortality after treatment with nesiritide for decompensated heart failure using a post-hoc pooled analysis of three randomized, controlled trials.[89] Given these recent reports, the verdict on the safety and efficacy of nesiritide for inpatient management of ADHF remains unknown and is the subject of ongoing randomized clinical trials.

Intravenous Positive Inotropic Agents

The majority of patients hospitalized with ADHF do not have clinical evidence for hypoperfusion but present with the "wet and warm" profile.[44] Inotropic infusions have often been initiated at the time of hospitalization to shorten hospital stay, improve ability to up-titrate ACE inhibitors, or decrease rehospitalizations. Few controlled clinical trials have actually evaluated the impact of intravenous inotropic therapy in this population. In the OPTIME-CHF study, 5.5% of patients with normal or elevated blood pressure (admission systolic blood pressure between 119 and 200 mmHg) and 18.5% of those with relative hypotension (admission systolic blood pressure <119 mmHg) received inotropic therapy.[90] Approximately 9% of all hospitalized patients in the ADHERE registry received inotropic support at some time during their index hospitalization.[53]

Dobutamine, a mixed $beta_1$- and $beta_2$-receptor agonist, is the most commonly prescribed positive inotropic agent. Through its actions on $beta_1$-receptors, dobutamine activates G-proteins, which leads to increased adenylate cyclase activity and increased intracellular cyclic AMP. Enhanced intracellular cyclic AMP causes release of calcium from the sarcoplasmic reticulum, which results in increased stroke volume.[91] The typical infusion rate for dobutamine ranges from 2.5 to 15 μm/kg/min. Onset of action is 1 to 2 minutes but it may take as long as 10 minutes to see a peak effect of a particular infusion rate. Patients taking a beta-blocker on admission will have an attenuated initial response to dobutamine administration until the beta-blocker has been metabolized. Milrinone, a phosphodiesterase-3 inhibitor, leads to increased intracellular cyclic AMP by inhibiting its intracellular breakdown. This results in an

increased intracellular calcium concentration and myocardial contractility as well as acceleration of myocardial relaxation. Treatment with milrinone may be initiated with or without a loading dose of 50 μg/kg over 10 minutes followed by a continuous infusion of between 0.375 and 0.75 μg/kg/min.[91] Most patients demonstrate improvement in hemodynamics within 15 minutes after initiation of therapy. The elimination half-life is generally 30 to 60 minutes but may be doubled in the presence of severe heart failure.[91] Hypotension is a major side effect of milrinone, which can be decreased by withholding the loading dose.

R. Mills and J. Narula: Although there are no published data to support it, it is an astute clinical recommendation to omit the loading dose of milrinone. In fact, this recommendation could be extended to nesiritide as well.

Liang and colleagues studied the effects of a 72-hour dobutamine infusion in 15 patients with NYHA class III-IV heart failure.[92] No deaths were observed during a 4-week period of follow-up. Maximum exercise time and left ventricular ejection fraction increased significantly in the dobutamine group. Functional class improved in six of eight patients in the treatment group compared to two of seven controls. More recently, the effect of dobutamine was compared to nesiritide on short-term outcomes in an acute heart failure trial by Silver et al.[87] No difference was noted in hospital length of stay. Significantly, patients treated during their index hospitalization with dobutamine had a higher 6-month mortality following discharge (31%) compared with patients treated with low-dose nesiritide (18%).[87]

The OPTIME-CHF trial represents the largest randomized, controlled trial of a positive inotropic agent.[90] A total of 951 patients with ADHF for whom inotropic therapy was "indicated but not required" were randomized to intravenous treatment with milrinone or a placebo infusion. The mean left ventricular ejection fraction was 23% and infusion duration ranged from 48 to72 hours. The primary endpoint was hospitalization for cardiovascular cause within 60 days of treatment. Milrinone was associated with a higher rate of early treatment failure, more sustained hypotension, new atrial arrhythmias, and a trend toward higher in-hospital mortality (3.8% versus 2.3%; $P = 0.19$). The OPTIME-CHF investigators subsequently performed a retrospective analysis to ascertain the interaction between heart failure etiology (ischemic versus nonischemic) and clinical outcome.[32] The composite endpoint of death or rehospitalization at 60 days was significantly lower in the treatment group compared with

placebo in the nonischemic group (28% versus 35%, $P = 0.01$). Mortality at 60 days was similar between milrinone treatment and placebo treatment in this cohort. In contrast, the composite endpoint of death or rehospitalization at 60 days was significantly greater in the ischemic cohort following milrinone treatment (42% versus 36%; $P = 0.01$). Whether this finding represents a post-hoc artifact or a true physiologic difference in drug response remains uncertain at this time. Thus, routine use of milrinone should be discouraged in this population. The increased mortality associated with inotropic therapy has been attributed to its pro-arrhythmic effects and to direct myocardial injury leading to accelerated disease progression. Several investigators have suggested that the addition of a beta-blocker to a phosphodiesterase inhibitor may partially ameliorate these detrimental effects while facilitating beneficial effects.[73,74] This approach remains investigational at this time.

Two controlled trials have directly compared milrinone to dobutamine for ADHF management.[93,94] Both studies demonstrated similar hemodynamic effects with increases in stroke volume and decreases in pulmonary capillary wedge pressure. Milrinone-treated patients also had a significant reduction in pulmonary artery pressures.[93] Both agents appear to provide adequate hemodynamic support.

R. Mills and J. Narula: In the same issue of *Journal of the American Medical Association* in which VMAC (Publication Committee for the VMAC Investigators: JAMA 2002) and OPTIME (Cuffe MS, et al: JAMA 2002;287:1541-7) were published, an editorial from Poole-Wilson (JAMA 2002;287:1587-80) summarized many of the salient issues about ADHF management. He made the point that essentially all drugs that act by increasing intracellular cyclic AMP in the myocyte have been associated with increased mortality.

It is important to point out that, while the routine use of dobutamine or milrinone is not warranted, these agents can be lifesaving for patients with rapidly progressive hemodynamic collapse.[43,95] Patients who present with obtundation, anuria, or lactic acidosis may *only* respond to inotropic therapy (or mechanical circulatory support), which should be continued until the cause of shock is determined and definitive therapy is implemented.[95] It is important to note that this critically ill population represents only a minority of patients admitted with ADHF.

Current practice guidelines from the American College of Cardiology and the American Heart Association accept the use of intravenous inotropic support for stage D patients (ie, refractory symptoms) as palliative treatment or as a bridge to cardiac transplantation, but only after

all alternative therapies to achieve stability have failed (Class IIB indication).[4] Long-term ambulatory use of intermittent or continuous infusions of positive inotropic agents is considered a Class III recommendation. However, the recent European Society of Cardiology guidelines do support the use of inotropic agents in the presence of peripheral hypoperfusion with or without congestion that is refractory to diuretics and vasodilators at optimum doses (Class IIA recommendation).[79] It is likely that their use will continue to decrease as newer agents (see below) become available.

R. Mills and J. Narula: Inotropes may be "lifesaving" in the short-term management of patients with hemodynamic collapse, but cannot be viewed as anything other than a last salvage effort that may buy sufficient time for an adequate evaluation.

Management of Arrhythmias

Atrial fibrillation commonly occurs as a precipitant for ADHF or may occur during hospitalization due to enhanced sympathetic adrenergic stimulation. Initial therapy should focus on adequate rate control. Digoxin and beta-adrenergic blockers are generally ineffective in restoring sinus rhythm but are first-line agents for controlling ventricular response rate. Uncontrolled, sustained, rapid (>120 beats/min) atrial fibrillation can result in a reversible dilated cardiomyopathy or, more typically, can worsen preexisting left ventricular systolic dysfunction.[96] Amiodarone is highly effective for rate control when other agents have proven unsuccessful or cannot be used because of the severity of the heart failure.[97] Amiodarone, dofetilide, and sotalol remain the most useful drugs for chemical cardioversion or in preparation for electrical cardioversion.[98] For patients with advanced heart failure symptoms or recent decompensation, the loading dose of amiodarone should be kept below 1000 mg/day to prevent further heart failure exacerbation. Dofetilide, a Class III anti-arrhythmic drug that blocks the repolarizing potassium current, is highly effective in restoring sinus rhythm but is associated with torsades de pointes in up to 3% of patients; continuous electrocardiographic monitoring during the first 24 hours after its initiation is essential.[98] Patients who experience active angina pectoris or hemodynamic instability during rapid atrial fibrillation should undergo urgent synchronized cardioversion and initiation of an atrial stabilizing agent to prevent recurrence. Systemic anticoagulation using unfractionated heparin should be instituted if the duration of atrial fibrillation exceeds 48 hours.

Frequent ventricular premature beats or short runs of nonsustained ventricular tachycardia are often noted during hospitalization in patients with marked ventricular dysfunction. Precipitating causes such as electrolyte disturbances (hypokalemia or hypomagnesemia), enhanced sympathetic tone, withholding of beta-blocker doses, or withholding of prior anti-arrhythmic therapy should be considered. The majority of patients remain asymptomatic and do not require pharmacologic suppression. Symptomatic runs of ventricular tachycardia or sustained monomorphic ventricular tachycardia require anti-arrhythmic treatment. Amiodarone (0.5 to1.0 mg/min intravenously) or lidocaine (0.5 to2 mg/min) are most effective for acute management. Beta-blockers, sotalol, or oral amiodarone are effective long-term treatment options.

Cardiac resynchronization therapy is increasingly employed for ambulatory patients with resistant heart failure symptoms. It has not been examined for management of ADHF or for patients who have received recent intravenous vasodilator or inotropic therapy. Anecdotal reports have suggested that it does not provide sufficient benefit in the acute setting to warrant consideration for patients who are hemodynamically unstable or inotrope dependent.[99] On the basis of randomized clinical trials, cardiac resynchronization therapy should be considered for patients who have either ischemic or nonischemic cardiomyopathy, who have a left ventricular ejection fraction ≤35%, persistent NYHA class III or IV symptoms despite optimized medical therapy, who have a QRS duration >120 milliseconds, and who remain in normal sinus rhythm.[99,100] Device placement prior to hospital discharge may complement pharmacologic adjustments that have been made during the hospitalization and may decrease the likelihood of subsequent heart failure readmissions.[99,100]

R. Mills and J. Narula: The decision to treat symptomatic nonsustained ventricular tachycardia represents an extraordinarily complex balance. Should the patient have an ICD in place? Would a biventricular pacing ICD be the most appropriate choice? How will drug treatment alter the effectiveness of the device? Should we ever consider anti-arrhythmic drug therapy for symptoms without a backup device?

Investigational Pharmacological Therapies

Endothelin Antagonists

Endothelin-1 is the major endothelin isopeptide produced by the cardiovascular system and plays a major role in the pathophysiology of acute heart failure as it is a potent vasoconstrictor, pro-arrhythmic

potentiator, and mediator of increased vascular permeability.[84,101] Endothelin-1 levels are among the strongest predictors of death in chronic heart failure populations.[102] Thus, endothelin receptor antagonism might be beneficial by reducing neurohormone-mediated end-organ damage. Tezosentan is a dual endothelin A/B antagonist that was specifically developed for intravenous treatment of ADHF.[101] The Randomized Intravenous TeZosentan (RITZ) program was designed with two pivotal trials in this population: (1) RITZ-1, that assessed symptom improvement, and (2) RITZ-2, that evaluated hemodynamic changes during tezosentan treatment.[103]

The RITZ-1 trial randomized 669 patients with acute heart failure and dyspnea at rest or with minimal exertion to ≥24 hours of tezosentan infusion (25 mg/h) or placebo in addition to standard therapy.[104] There was no statistical significance between treatment groups in the primary endpoint, change in dyspnea score at 24 hours, nor any difference in the main secondary endpoint of time to worsening heart failure or death. The RITZ-2 trial enrolled 292 ADHF patients who had low cardiac output and high ventricular filling pressures (NYHA functional class III or IV symptoms, cardiac index <2.5 L/min/m^2, pulmonary capillary wedge pressure >15 mmHg).[102] Patients were randomized to receive tezosentan in one of two doses (50 or 100 mg/h) or placebo in addition to standard therapy.[103] Both doses of tezosentan significantly decreased pulmonary capillary wedge pressure and improved cardiac index; most of the hemodynamic benefit was achieved at the initial 50 mg/h dose.[103]

The safety of tezosentan was evaluated in the RITZ-4 study of patients with ADHF and acute coronary syndromes.[105] The composite endpoint of death, worsening heart failure, recurrent ischemia, or recurrent/new myocardial infarction within 72 hours was not significantly different between tezosentan and placebo-treated groups.[105] The efficacy and safety data from the RITZ program and a recent dose finding study have suggested that the optimal dose of tezosentan may be lower than the 50 mg/h utilized in most earlier trials.[106] Most recently, the Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure study randomized over 1400 patients with acute heart failure to test the efficacy of a 1 mg/h dosing regimen of tezosentan versus placebo.[107] The trial was stopped prematurely for lack of efficacy.

The nonselective endothelin receptor antagonist, bosentan, has also been studied in chronic heart failure.[101] The Research on Endothelin Antagonism in Chronic Heart Failure trial evaluated 370 patients with NYHA class IIIB or IV heart failure symptoms despite diuretics and angiotensin-converting enzyme inhibitor therapy (Acelion Pharmaceuti-

cals, personal communication). No improvement in clinical status at 6 months of treatment was observed. Further, the study was stopped prematurely by the Data Safety Monitoring Board due to a high incidence (>15%) of asymptomatic liver enzyme elevation in the bosentan group.

The Endothelin Antagonism Bosentan for Lowering Cardiac Events trials randomized 1613 patients with NYHA class IIIB or IV symptoms to receive either bosentan (target dose 125 mg twice daily) or placebo.[108] The primary endpoint was clinical status at the end of 9 months of treatment in addition to all-cause mortality and heart failure-related hospitalizations. No difference was noted between treatment groups in clinical status. However, higher hospitalization rates were observed in the bosentan group during the first 4 to 8 weeks of treatment. Mortality rates did not differ at any point during the trial. Again, a high incidence (9.5%) of asymptomatic elevation in transaminases was noted during bosentan treatment.[101]

The selective AT_A receptor antagonist, darusentan, was studied in the Heart Failure ET Receptor Blockade trial.[109] A total of 157 patients with NYHA class III symptoms were randomized to placebo or one of three doses of darusentan. Hemodynamic changes were evaluated over 3 weeks. Only cardiac index significantly improved; higher doses were associated with a trend toward more adverse events.[109] Overall, the results of endothelin blockade in both acute and chronic heart failure have been disappointing and it remains uncertain whether this class of drugs will ever have a major role in the treatment of ADHF.

Calcium Sensitizer Agents

"Calcium sensitizers" are a class of drugs designed to directly influence the way that intracellular Ca^{2+} is transduced into myocardial contractility. Mechanisms of action vary widely and include the following: direct activators of motor proteins such as myosin (eg, EMD-57033), enhancers of force generation by cross-bridging, and agents that augment Ca^{2+}-troponin C binding (levosimendan).[110] Many experimental agents have additional effects, such as phosphodiesterase 3a inhibition (pimobendan), calcium-dependent increases in heart rate, and inhibition of ATP-sensitive K^+ channels (levosimendan).[110]

Levosimendan has undergone a number of clinical trials and produces increased contractility principally by increasing cardiac troponin C sensitivity to intracellular ionized calcium.[84,110] The agent also produces peripheral vasodilatation via its effects on vascular ATP-dependent potassium channels.[84] Clinical studies have demonstrated that levosimendan significantly increases myocardial contraction and results in sustained

hemodynamic benefits.[111,112] The drug is approved in many countries in Europe but remains investigational in the United States.

An early study of levosimendan included 146 ADHF patients who had evidence of abnormal hemodynamics at randomization (pulmonary capillary wedge pressure >15 mmHg and cardiac index <2.5 L/min/m^2).[112] In this acute dosing study, levosimendan produced dose-dependent improvements in stroke volume and cardiac index, moderate increases in heart rate, and decreases in ventricular filling pressures.[110] Patients treated with levosimendan also had a significantly higher likelihood of reporting symptomatic improvement (29% versus 15%). Limitations of this study included withholding concomitant medications during active treatment and potential unblinding bias introduced by invasive hemodynamic monitoring.[84]

In the Levosimendan Infusion Versus Dobutamine trial, 203 patients were randomized to receive intravenous dobutamine or levosimendan.[113] Levosimendan treatment improved hemodynamic performance more effectively than dobutamine with 28% of the levosimendan-treated patients achieving a primary hemodynamic endpoint compared to only 15% of dobutamine-treated patients. Symptomatic improvement did not differ between groups. However, the levosimendan group had significantly lower 6-month mortality than the dobutamine cohort (26% versus 38%, $P = 0.029$). While encouraging, the improved survival in the Levosimendan Infusion Versus Dobutamine trial could have been driven more by the adverse event rates of dobutamine therapy than a true beneficial effect of levosimendan.[84]

Preliminary data from four additional trials of levosimendan, CASINO (Calcium Sensitizer or Inotrope or None in Low Output Heart Failure),[114] REVIVE-1 (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-term Treatment of Decompensated Heart Failure),[115] REVIVE-2,[116] and SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support)[117] trials have recently been reported. CASINO randomized patients with NYHA class IV symptoms hospitalized for ADHF with a primary composite endpoint of death or rehospitalization at 6 months. The study was terminated prematurely because a survival advantage was observed at 6 months in the levosimendan group (mortality: 15.3, 24.7, and 39.6% for the levosimendan, placebo, and dobutamine cohorts, respectively).[114] In the REVIVE-2 trial, 600 patients were randomized to levosimendan or placebo. By day 5, 33% more levosimedan-treated patients had improved and 30% fewer had worsened compared with the placebo group ($P = 0.01$).[116] However, all-cause mortality was not

improved (15.1% versus 11.6%). The SURVIVE trial evaluated 1327 patients with ADHF who were felt to require inotropic support after failing to respond to conventional diuretic and vasodilator therapy. Patients were randomized to dobutamine or levosimendan infusion, with the primary endpoint of all-cause mortality at 180 days.[117] There was no significant difference in mortality between groups (26% for levosimendan versus 28% for dobutamine). In aggregate, these trial data suggest that levosimendan can provide symptomatic improvement in ADHF patients but no consistent beneficial effect on intermediate-term mortality. Additional trials may further define the population of patients most likely to benefit from this novel therapeutic agent.

R. Mills and J. Narula: The spotlight of media attention directed to benefit–risk questions in the evaluation of heart failure drugs has focused on assessment of intermediate-term mortality after short-term treatment. The long-term effect of this new scrutiny will be to further raise the bar for entry of new drugs in the field.

Vasopressin Antagonists

Arginine vasopressin is a neurohormone produced by the central nervous system in response to changes in serum osmolality, hypovolemia, or hypotension. Two types of vasopressin receptors are present—V_1 and V_2; the V_{1A} receptor mediates vasopressin-induced vasoconstriction, while the V_2 receptor mediates water resorption in the kidneys.[84,118] Vasopressin release results in vasoconstriction, fluid retention, and hyponatremia, effects that are exaggerated during bouts of decompensated heart failure.[118,119] Conivaptan is a combined V_{1A}- and V_2-receptor antagonist and has been administered acutely to 142 patients with stable NYHA class III or IV heart failure.[120] The conivaptan-treated patients had significant decreases in right- and left-sided filling pressures, increased urinary output, but no change in cardiac index.[121]

Selective blockade of the V_2-receptor results in aquaresis without electrolyte disturbance or neurohormonal stimulation. Lixivapatan and tolvaptan are selected V_2-receptor antagonists. Tolvaptan has been shown to produce sustained decreases in body weight and edema during 25 days of oral administration in a trial of 50 patients with mild chronic heart failure.[121] The Acute and Chronic Therapeutic Impact of Vasopressin Antagonism in Congestive Heart Failure trial evaluated the efficacy of three doses of tolvaptan compared with placebo among 319 patients with systolic dysfunction who were hospitalized for ADHF associated with

volume overload.[122] Oral study medication was initiated during the hospitalization and maintained for 60 days. The primary in-hospital endpoint was reduction in body weight at 24 hours, whereas the outpatient outcome was worsening heart failure (defined as death, hospitalization, or unscheduled visit for heart failure) at 60-day follow-up. All three tolvaptan doses resulted in significant weight reduction at 24 hours (2.0 kg versus 0.9 kg for placebo). No differences were noted for in-hospital mortality or worsening heart failure at 60 days.[122] Patients admitted with hyponatremia (serum sodium <135 mEq/L) had improvement in serum sodium to 137 mEq/L at hospital discharge, which was maintained at 60-day follow-up. This improvement was not observed in the placebo-treated group. The effect of tolvaptan on mortality in patients hospitalized for ADHF is now being evaluated in the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study of Tolvaptan trial.[123] This pivotal trial will provide significantly more information about the potential role of this class of agents for acute heart failure management.

Conclusion

The treatment of ADHF remains largely empirical. Few controlled trials have evaluated therapeutic options and a limited number of practice guidelines from the Heart Failure Society exist at this time. Initial treatment should generally be aimed at relief of congestive symptoms with intravenous diuretics. Ultrafiltration may occasionally be necessary. New agents such as adenosine and vasopressin antagonists that enhance diuresis without compromising renal blood flow are undergoing evaluation and may decrease the frequency of the cardiorenal syndrome in this population. Intravenous vasoactive therapy with vasodilators (nitroglycerine, nitroprusside, nesiritide) or positive inotropic agents (milrinone or dobutamine) should be reserved for patients with severe hemodynamic compromise associated with end-organ hypoperfusion (ie, the "wet and cold" profile). It is increasingly recognized that agents that stimulate myocardial contractility during acute periods of decompensation may subsequently lead to adverse outcomes following hospital discharge. Thus, inotropic agents should be limited to the most critically ill individuals (<15% of hospital admissions). Investigational agents including endothelin antagonists and calcium sensitizers have yielded disappointing results to date in controlled trials. The outlook for vasopressin antagonists may be more promising. Well-designed, controlled clinical trials are urgently needed to evaluate the safety and efficacy of both conventional and investigative pharmacologic approaches to this increasingly prevalent heart failure syndrome.

R. Mills and J. Narula: Dr. Dec has presented an excellent, up-to-date, authoritative review of an important topic. It needs to be emphasized that a patient's presentation to a hospital with ADHF should be considered a failure of the health care delivery system. In the short term, we must strive to deliver good evidence-based management focused on amelioration of symptoms, improvement of hemodynamics, and restoration of neurohormonal balance. In the long term, we must dedicate ourselves to the idea that ADHF should not occur in an effective, comprehensive health care system.

REFERENCES

1. American Heart Association; American Stroke Association. Heart disease and stroke statistics—2005 update. Available at: http://www.americanheart.org/downloadable/heart/1072969766940Hstats2004Update.pdf. Accessed December 1, 2005.
2. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends with the incidence and survival with heart failure. New Engl J Med 2002;347:1397-402.
3. Adams KF. New epidemiologic perspectives concerning mild-to-moderate heart failure. Am J Med 2001;110(supp 7A):6S-13S.
4. Hunt SA, Abraham WT, Chin MH, et al. 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). J Am Coll Cardiol 2005; 46:1116-43.
5. Fonarow GC, for the ADHERE Scientific Advisory Committee. The acute decompensated heart failure national registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003;4(suppl 7):S21-30.
6. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Inter Med 1997; 157:99-104.
7. Polanczyk CA, Rohde LE, Dec GW, et al. Ten-year trends in hospital care for congestive heart failure: improved outcomes and increased use of resources. Arch Intern Med 2000;160:325-32.
8. Smith GL, Masoudi FA, Vaccarino V, et al. Outcomes in heart failure patients with preserved ejection fraction. Mortality, readmission, and functional decline. J Am Coll Cardiol 2003;41:1510-8.
9. Felker GM, Adams KF, Konstam MA, et al. The problem of decompensated heart failure: nomenclature, classification risk stratification. Am Heart J 2003;143(suppl): S18-25.
10. Gheorghiade M, Bebazaa A. Introduction to acute heart failure syndromes. Am J Cardiol 2005;96(suppl):1G-4G.
11. Nieminen MS, Harjola V-P. Definition and epidemiology of acute heart failure syndromes. Am J Cardiol 2005;96(suppl):5G-10G.
12. Gheorghiade M, DeLuca L, Fonarow GC, et al. Pathophysiologic targets in the early phase of acute heart failure syndromes. Am J Cardiol 2005; 96(suppl):11G-17G.

13. Ware LB, Matthay MA. Acute pulmonary edema. New Engl J Med 2005;353: 2788-96.
14. Harlan WR, Oberman A, Grimm R, et al. Chronic congestive heart failure in coronary artery disease: clinical criteria. Ann Intern Med 1997;86:133-8.
15. Stevenson LW, Perloff JK. Limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989;261:884-8.
16. Badgett RG, Lucey CR, Mulrow CE. Can the clinical examination diagnose left-sided heart failure in adults? JAMA 1997;277:1712-9.
17. Yancy CW. Heart failure in African Americans: a cardiovascular enigma. J Card Fail 2000;6:183-6.
18. Adams KF, Lindenfeld JA, Arnold JMO, et al. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guidelines. J Card Fail 2006;12:10-38.
19. Maytin M, Colucci WS. Cardioprotection: a new paradigm in the management of acute heart failure syndromes. Am J Cardiol 2005;96(suppl):26G-31.
20. Perna ER, Macin SM, Parras JI, et al. Cardiac troponin levels are associated with poor short- and long-term prognosis in patients with acute cardiogenic pulmonary edema. Am Heart J 2002;143:814-20.
21. Eichhorn EJ. Prognosis determination in heart failure. Am J Med 2001; 110(7A):14S-35S.
22. Ho KKL, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in the Framingham Heart Study subjects. Circulation 1993;88:107-15.
23. Drazner MH, Rame JE, Stevenson LW, et al. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. New Engl J Med 2001;345:574-81.
24. Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538-43.
25. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J 2002;144:373-6.
26. Lee DS. Austin PC, Rouleau JL, et al. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581–7.
27. Harajai KJ, Tompson HW, Turget T, et al. Simple clinical variables are markers for propensity for readmission in patients hospitalized with heart failure. Am J Cardiol 2001;87:234-7.
28. Chin MW, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. Arch Intern Med 1996;156:1814-20.
29. Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure. Circulation 2005;111:2454-60.
30. Jong P, Vowinckel E, Liu P, et al. Prognosis and determinants of survival in patients newly hospitalized for heart failure. Arch Intern Med 2002;62:1689-94.
31. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12,220 index admissions in Leicestershire 1993-2001. Heart 2003;89:615-20.
32. Felker GM, Benza RL, Chandler AB, et al, 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.
33. Felker GM, Gattis WM, Leimberger JD, et al. Usefulness of anemia as a predictor of death and re-hospitalization in patients with decompensated heart failure. Am J Cardiol 2003;92:625-8.
34. Logeart D, Thabut G, Jourdain P, et al. Pre-discharge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. J Am Coll Cardiol 2004;43:635-41.
35. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-BNP natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168-74.
36. Gheorghiade M, Zannad F, Supko G, et al, for the International Working Group on Acute Heart Failure Syndromes. Acute heart failure syndromes. Current state and framework for future research. Circulation 2005;112:3958-68.
37. Horwich TB, Patel J, MacLellan WR, et al. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality in advanced heart failure. Circulation 2003;108:833-8.
38. Felker GM, Leimberger JD, Califf RM, et al. Risk stratification after hospitalization for decompensated heart failure. J Card Fail 2004;10:460-6.
39. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation and survival in patients with chronic heart failure. Circulation 2000;102:203-10.
40. Weinfield MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J 1999;138:285-90.
41. Gottlieb SS, Abraham W, Butler J, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 2002;8:136-41.
42. Fonarow GC, Adams KF, Abraham WT, et al, for the ADHERE Scientific Advisory Committee, Study Groups and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure Classification and regression tree analysis. JAMA 2005;293:572-80.
43. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA 2002;287:628-40.
44. Nohria A, Tsant SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. J Am Coll Cardiol 2003;41:1797-804.
45. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail 1999;1:251-7.
46. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. Circulation 1997;96:1165-72.
47. ESCAPE Investigators and Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness. The ESCAPE trial. JAMA 2005;294:1625-33.
48. Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J 1998;135: S293-S309.
49. Dec GW. Acute decompensated heart failure. The shrinking role of inotropic therapy. J Am Coll Cardiol 2005;46:65-7.

50. Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. Am J Cardiol 2005;96(suppl):32G-40G.
51. Brater DC. Diuretic therapy. New Engl J Med 1998;339:387-95.
52. Stough WG, O'Connor CM, Gheorghiade M. Overview of current non-inodilator therapies for acute heart failure syndromes. Am J Cardiol 2005;96(suppl): 41G-46G.
53. Abraham WT, Adams KF, Fonarow GC, et al, the ADHERE Scientific Advisory Committee and Investigators, and the ADHERE Study group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications. An analysis form the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57-64.
54. Dormans TP, van Meyel JJ, Gerlag PG, et al. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996;28:376-82.
55. Costanzo MR, Saltzberg M, O'Sullivan J, et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047-51.
56. Weber KT. Aldosterone in congestive heart failure. New Engl J Med 2001; 345:1689-97.
57. Pitt B, Zannad F, Remme WJ, et al, for Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New Engl J Med 1999;341:709-17.
58. White H, Nicolau J, Martinez F, et al, for the EPHESUS Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. J Am Coll Cardiol 2005;46:425-31.
59. Hauptman PJ, Kelly RA. Digitalis. Circulation 1999;99:1265-70.
60. Dec GW. Digoxin is useful in the management of chronic heart failure. Med Clin N Am 2003;87:317-37.
61. Newton GE, Tong JH, Schofield AM, et al. Digoxin reduces cardiac sympathetic activity in severe heart failure. J Am Coll Cardiol 1996;28:155-61.
62. Lee DCS, Johnson RA, Bingham JB, et al. Heart failure in outpatients. A randomized trial of digoxin versus placebo. New Engl J Med 1982;306:699-705.
63. Gheorghiade M, Hall V, Lakier JB, et al. Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin and their combination in patient with severe heart failure. J Am Coll Cardiol 1989;13:134-42.
64. Gheorghiade M, Adams KF, Colucci W. Digoxin in the management of cardiovascular disorders. Circulation 2004;109:2959-64.
65. Rathorne SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. New Engl J Med 2002;347:1403-11.
66. Adams KF, Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the Digitalis Investigator Group trial. A retrospective analysis. J Am Coll Cardiol 2005;46:497-504.
67. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000;101:558-69.
68. Satwani S, Dec GW, Narula J. Beta-adrenergic blockers in heart failure: a review of mechanisms of action and clinical outcomes. J Cardiovasc Pharmacol Therapeut 2004;9:243-55.

69. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. Circulation 2003;107:1570-5.
70. Fonarow GC. Role of in-hospital initiation of carvedilol to improve treatment rates and clinical outcomes. Am J Cardiol 2004;93(suppl):77B-81B.
71. Packer M, Coates AJ, Fowler MB, et al. Carvedilol Prospective Cumulative Survival Study group. Effect of carvedilol on survival in severe heart failure. New Engl J Med 2001;344:1651-8.
72. Gattis W, O'Connor CM, Gallup DS, et al. Pre-discharge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the IMPACT-HF (initiation management pre-discharge process for assessment of carvedilol therapy in heart failure) trial. J Am Coll Cardiol 2003;43:1534-41.
73. Metra M, Nodari S, D'Alaia AK, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure. A randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol 2002;40:1248-58.
74. Shakar SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. J Am Coll Cardiol 1998;31:1336-40.
75. Packer M, Poole-Wilson PA, Armstrong PW, et al, on behalf of the ATLAS Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation 1999;100:2312-8.
76. Cotter G, Metzkor E, Kaluski E, et al. Randomized trial of high-dose isosorbide dinitrate plus low dose furosemide versus high-dose furosemide and low dose isosorbide dinitrate in severe pulmonary edema. Lancet 1998;351:389-93.
77. Exner DV, Dries DL, Domanski MJ, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. New Engl J Med 2001;344:1351-7.
78. Taylor AL, Ziesche S, Yancy C, et al, for the African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. New Engl J Med 2004;351:2049-57.
79. Nieminen MS, Bohm, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005;26:384-416.
80. Guiha NH, Cohn JN, Mikulic E, et al. Treatment of refractory heart failure with infusion of nitroprusside. New Engl J Med 1974;291:587-92.
81. Khot UN, Novaro GM, Popvic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. New Engl J Med 2003;348: 1756-63.
82. Johnson W, Omland T, Hall C, et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators in class IV heart failure. J Am Coll Cardiol 2002;39:1623-9.
83. Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration Cooperative study. New Engl J Med 1982;1129-35.
84. Teerlink JR. Overview of randomized clinical trials in acute heart failure syndromes. Am J Cardiol 2005;96(suppl):59G-67G.

85. Wang DJ, Dowling TC. Meadows D. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. Circulation 2004;110:1620-5.
86. VMAC Publications Committee. Intravenous nesiritide versus nitroglycerin for treatment of decompensated congestive heart failure. A randomized controlled trial. JAMA 2002;287:1531-40.
87. Silver MA, Horton D, Ghali JK, et al. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol 2002;39:798-803.
88. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487-91.
89. Sackner-Bernstein JD, Kowalski MN, Fox M, et al. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA 2005;293:1900-5.
90. Cuffe MS, Califf RM, Adams KR, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.
91. Bayram M, DeLuca L, Massie BM, et al. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. Am J Cardiol 2005;96(suppl):47G-58G.
92. Liang CS, Sherman LG, Doherty JU, et al. Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. Circulation 1984;69:113-9.
93. Biddle TL, Benotti JR, Creager M, et al. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. Am J Cardiol 1987;59:1345-50.
94. Eichhorn EJ, Konstam MA, Weiland DS, et al. Differential effects of milrinone and dobutamine on right ventricular preload, afterload, and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1987;60:1329-33.
95. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: inotropic infusions during hospitalization. Circulation 2003;108:367-72.
96. Nerheim P, Birger-Botkin S, Piracha L, et al. Heart failure and sudden death in patients with tachycardia-induced cardiomyopathy. Circulation 2004;110:247-52.
97. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for treatment. Am J Cardiol 2003;91:2D-8D.
98. Torp-Pederson, Moller M, Bloch-Thomsen PE, et al, for the Danish Investigators of Arrhythmia and Mortality on Dofetilide Study Group. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. New Engl J Med 1999;341:857-65.
99. Strickberger SA, Conti J, Daoud EG, et al. Patient selection for cardiac resynchronization therapy. Circulation 2005;111:2146-50.
100. Abraham WT, Hayes DL. Cardiac resychronization therapy for heart failure. Circulation 2003;108:2596-2603.
101. Rich S, McLaughlin VV. Endothelin receptor blockers in cardiovascular disease. Circulation 2003;108:2184-90.

102. Aaronson D, Burger AJ. Neurohormonal prediction of mortality following admission for decompensated heart failure. Am J Cardiol 2003;91:245-8.
103. Torre-Amione G, Young JB, Colucci WS, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2003; 42:140-7.
104. Coletta AP, Cleland JP. Clinical trials update: highlights of the scientific sessions of the XXIII Congress of the European Society of Cardiology: WARIS II, ESCAMI, PAFAC, RITZ-1, and TIME. Eur J Heart Fail 2001;3:747-50.
105. O'Connor CM, Gattis WA, Adams KF, et al. Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous TeZosentan Study (RITZ-4). J Am Coll Cardiol 2003;41:1452-7.
106. Cotter G, Kaluski E, Stangl K, et al. The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. Eur J Heart Fail 2004;6:601-9.
107. Teerlink JR, McMurray JJ, Bourge RC, et al, for the VERITAS Investigators. Tezosentan in patients with acute heart failure: design of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS). Am Heart J 2005;150:46-53.
108. Packer M. Effects of the endothelin receptor bosentan on the morbidity and mortality in patients with chronic heart failure: results of the ENABLE 1 and 2 trial program. J Am Coll Cardiol 2002;39:101-2.
109. Luscher TF, Enseleit F, Pacher R, et al. Hemodynamic and neurohormonal effects of selective endothelin (ET[A]) receptor blockade in chronic heart failure: the Heart Failure ET(A) Receptor Blockade Trial (HEAT). Circulation 2002;106:2666-72.
110. Kass DA, Solaro RJ. Mechanisms and use of calcium-sensitizing agents in the failing heart. Circulation 2006;113:305-15.
111. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81-6.
112. Slawsky MT, Colucci WS, Gottlieb SS, et al, for the Study Investigators. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:2222-7.
113. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomized double-blind trial. Lancet 2002;360:196-202.
114. Zairis M. The effect of a calcium sensitizer or an inotrope or none in chronic low output decompensated heart failure. J Am Coll Cardiol 2004;43:206A.
115. Garratt C, Packer M, Colucci W, et al. Development of a comprehensive new endpoint for the evaluation of new treatments for acute decompensated heart failure: results with levosimendan in the REVIVE 1 study. Crit Care 2004;8(suppl 1):89.
116. REVIVE II: Multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Presented at the 2005 American Heart Association Scientific Sessions, Dallas, TX, November 14, 2005.
117. The SURVIVE-W trial: Comparison of dobutamine and levosimendan on survival in acutely decompensated heart failure. Presented at the 2005 American Heart Association Scientific Sessions, Dallas, TX, November 16,2005.

118. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. J Am Coll Cardiol 2005;46:1785-91.
119. Orlandi C, Zimmer CA, Gheorghiade M. Role of vasopressin antagonists in the management of acute decompensated heart failure. Curr Heart Fail Rep 2005;2: 131-9.
120. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V_{1a} and V_2 vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 2001;104:2417-23.
121. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V_2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;107:2690-6.
122. Gheorghiade M, Gattis WA, O'Connor CM, et al, for the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effect of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure. JAMA 2004;291:1963-71.
123. Gheorghiade M, Orlandi C, Burnett JC, et al. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Tolvaptan (EVEREST). J Card Fail 2005;11:260-9.