Acute Decompensated Heart Failure: Challenges and Opportunities

Gregg C. Fonarow, MD

Ahmanson-UCLA Cardiomyopathy Center, UCLA Division of Cardiology, Los Angeles, CA

Acute decompensated heart failure (ADHF) represents the most common discharge diagnosis in patients over age 65, and has an exceptionally high mortality and readmission risk. ADHF is characterized by abnormal hemodynamics, including increase in pulmonary capillary wedge pressure and peripheral vasoconstriction, although cardiac index may be reduced, normal, or increased. Myocardial injury, which may be related to decreased coronary perfusion, activation of neurohormones, and/or renal dysfunction, may contribute to short-term and postdischarge cardiovascular events. Recent ADHF registries have provided valuable insights into the characteristics, treatment patterns, and clinical outcomes of these patients. Most patients with ADHF present with either normal systolic blood pressure or elevated blood pressures; hypotension is relatively uncommon. These patients have significant cardiovascular and noncardiovascular comorbidities that may contribute to the pathogenesis and/or adverse outcomes in ADHF. Therapies for ADHF have been targeted to improve symptoms and hemodynamics, as well as preserve or improve renal function, prevent myocardial damage, modulate neurohumoral and inflammatory activation, and manage other comorbidities that may cause and/or contribute to the progression of this syndrome. Concomitant therapies proven to provide long-term benefits in chronic heart failure are also essential. There remains an unmet need for therapeutic approaches for the early management of ADHF that may improve short- and long-term outcomes. Ongoing clinical trials are intended to provide data that will better define the benefits and risks of therapies for ADHF.

[Rev Cardiovasc Med. *2007;8(suppl 5):S3-S12*]

Key words: Acute decompensated heart failure • Clinical trials • Pathophysiology • Registries

Acute decompensated heart failure (ADHF) causes considerable morbidity and mortality and produces a tremendous burden on health care systems worldwide. In the United States, heart failure (HF) as the primary or secondary cause of hospitalization results in almost 3.6 million admissions annually and translates into an annual estimated cost of $29 to $56 billion.[1] In other developed countries, total expenditure on HF ranges between 1% and 2% of the

total health care budget, with 75% relating to inpatient care.[2]

Epidemiology of ADHF

There are various definitions for ADHF, also referred to as *acute HF* or *acute HF syndromes* (AHFS). Acute HF has been defined as the new onset of decompensated HF or decompensation of chronic, established HF with symptoms sufficient to warrant hospitalization.[3] The European Society of Cardiology defined acute HF as the rapid onset of symptoms and signs secondary to abnormal cardiac function.[2] It may occur with or without previous cardiac disease. Cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch.[2] Other definitions include a gradual or rapid change in signs and symptoms compatible with HF, resulting in a need for new and urgent intravenous (IV) therapy or urgent significant augmentation of existing therapy in patients with established or newly developed left ventricular (LV) dysfunction.[4] ADHF represents a broad spectrum of clinical presentations from acute onset of pulmonary edema to gradual worsening of symptoms in a patient with established HF. The clinical classification of patients with ADHF continues to evolve and reflects ongoing changes in the understanding of the pathophysiology of this syndrome.[5]

Studies have shown that ADHF represents a period of high risk for patients, during which their likelihood of death and rehospitalization is significantly greater than for a comparable period of chronic but stable HF. The in-hospital mortality rates reported for ADHF have varied greatly, ranging from 2% to 20%.[3-9] Prognosis is also reported to be very poor after discharge; the mortality risk after hospitalization for acute HF has been reported to be as high as 11.3% at 30 days and 33.1% at 1 year in the United States.[3,4] Analysis of the case fatality rate for patients hospitalized with principal diagnosis of HF in Scotland revealed a median survival of 1.47 years in men and 1.39 years in women.[10] Studies from other countries also reveal high mortality risk. In those with acute pulmonary edema, a 12% in-hospital and 40% 1-year mortality have been reported.[11]

In addition, patients also face a very high risk of rehospitalization. In a study of almost 18,000 Medicare recipients, approximately 44% were rehospitalized 1 or more times in the 6 months following their index hospitalization.[12] A comparative analysis of age-adjusted hospital readmission rates and related utilization in 3 European countries (Finland, Scotland, and the Netherlands) and 3 states in the United States (New York, California, and Washington) showed similar readmission rates for HF in the United States and Europe.[13] Estimates of the risk of death or rehospitalization within 60 days of admission vary from 30% to 60%, depending on the population studied.[2,6] These statistics emphasize the need to develop and implement more effective strategies to manage ADHF.

Ethnic minority groups comprise approximately 30% of all hospital admissions for ADHF.

ADHF Patient Characteristics

Data from the Acute Decompensated Heart Failure National Registry (ADHERE), the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), and the EuroHeart Failure Survey (EHFS) have generated important information concerning the clinical characteristics, laboratories, treatment patterns, and outcomes of patients with ADHF.[14-18]

These registries reveal that over 75% of patients hospitalized with ADHF have worsening of previously diagnosed HF, and 15% to 25% are diagnosed with HF during the index admission. Only a minority (< 2%-8%) have a low-output syndrome.[14-18] The mean age of patients admitted with ADHF is 75 years in the United States (Table 1). Women comprise more than half of these patients, and ethnic minority groups comprise approximately 30% of all admissions.[14-17] Almost two-thirds of ADHF patients have a history of coronary artery disease (CAD), and over 30% of these patients had prior myocardial infarction (MI). Hypertension (72%), diabetes (44%), and renal insufficiency (30%) are very common. A history of atrial fibrillation is seen in 31% of patients. Women admitted with ADHF appear to have less CAD and more hypertension than men, but a similar rate of atrial fibrillation (30%), diabetes (40%), and anemia (35%)[14-17]; 40% of men and 30% of women have bundle branch block or intraventricular conduction delay (QRS > 120 msec).[14,15]

The clinical presentation of ADHF indicates that an estimated 90% of patients have signs of elevated left-sided filling pressures including some degree of dyspnea, and 40% have dyspnea at rest (Table 2).[14-17] Two-thirds have signs of elevated right-sided filling pressures such as pulmonary rales or peripheral edema. Evidence of radiographic congestion is present in 75% of patients admitted with ADHF; nevertheless,

Table 1
Demographic Characteristics and Medical History of ADHERE Enrollees from October 1, 2001–September 30, 2004 (N = 148,126)

Median Age (y)	75.1
Sex	
Male (%)	48
Female (%)	52
Race/Ethnicity	
White (%)	72
Black (%)	20
Hispanic (%)	3
Asian (%)	1
Other (%)	1
HF History	
Prior heart failure (%)	76
Prehospital LVEF assessed (%)	48 (n = 71,104)
< 0.40 or moderate/severe impairment (%)	58
Prior cardiac transplantation (%)	< 1
Listed for cardiac transplant (%)	1
Medical History	
Hypertension (%)	73
Coronary artery disease (%)	57
History of smoking (%)	49
Diabetes (%)	44
Insulin-dependent diabetes (%)	18
Dyslipidemia (%)	36
COPD or asthma (%)	31
Atrial fibrillation (%)	31
Chronic renal insufficiency (%)	30
Myocardial infarction (%)	30
Cardiac valvular disease (%)	22
Pacemaker or ICD (%)	20
PVD (%)	18
Stroke or transient ischemic attack (%)	17
Smoking currently (%)	13
Ventricular tachycardia (%)	8
Chronic dialysis (%)	5
Liver disease (%)	3
LVAD (%)	< 1

ADHERE, Acute Decompensated Heart Failure National Registry; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease.

cardiopulmonary congestion often remains unrecognized and is not appropriately treated in a timely manner during hospitalization for ADHF, which may result in patients being discharged with improved symptoms yet persistently elevated LV filling pressures. This ultimately may contribute to early readmission when symptoms of congestion recur.[19] Most patients admitted to the hospital with ADHF have a normal to high systolic blood pressure (SBP). In ADHERE, half of the patients had an SBP greater than 140 mm Hg on admission. In addition, a strong inverse relation is noted between SBP and in-hospital mortality.[17]

The majority (> 70%) of ADHF events are the result of worsening chronic HF, associated with reduced or preserved LV ejection fraction (LVEF).[15] Other causes of ADHF include new-onset HF (15%-25% of all admissions) due to an acute coronary event such as an MI or a sudden increase in blood pressure superimposed on a noncompliant LV, or the first decompensation in patients with previously asymptomatic LV dysfunction. A smaller proportion of patients present with advanced or refractory HF that is not responsive to therapy associated with hypotension and a continually worsening low output state (5% of all admissions).[14-18]

Almost half of the patients admitted with ADHF have a relatively preserved systolic function (defined by LVEF ≥ 40%).[14-17] If a definition of LVEF greater than 50% is used, approximately one-third of AHFS meet this designation.[15] These patients are older, more likely to be women, and have a higher incidence of hypertension, LV hypertrophy, and diabetes than patients admitted with ADHF and systolic dysfunction.[15] It appears that ADHF patients with relatively preserved systolic function have a similar postdischarge survival and similar readmission rate compared with those who have ADHF and systolic dysfunction.[20]

Treatment of Patients With ADHF

Most patients with HF are admitted to the emergency department (ED).[14-17] Among patients enrolled in the ADHERE database, 78% who are admitted for an acute episode of HF initially present to the ED, whereas only 20% are admitted directly to an inpatient unit.[14] An additional 1% are admitted to an inpatient unit on an observation basis and fewer than 1% are seen in an observation unit as their first point of care. Once hospitalized,

Table 2
Clinical Presentation and Treatment of ADHERE Enrollees from October 1, 2001–September 30, 2004 (N = 148,126)

Any dyspnea (%)	89
Dyspnea at rest (%)	34
Rales (%)	67
Peripheral edema (%)	66
Fatigue (%)	31
SBP assessed (%)	100 (n = 147,469)
SBP < 90 mm Hg (%)	2
SBP 90-140 mm Hg (%)	48
SBP > 140 mm Hg (%)	50
Initial electrocardiogram assessed (%)	94 (n = 139,601)
Atrial fibrillation (%)	14
Other abnormal rhythm (%)	34
Initial chest radiograph assessed (%)	91 (n = 135,026)
Pulmonary congestion (%)	75
Initial serum creatinine concentration measured (%)	98 (n = 145,772)
Creatinine > 1.5 mg/dL (%)	37
Initial BNP concentration measured (%)	48 (n = 70,993)
Median BNP, pg/mL	840
Median N-terminal pro-BNP (pcg/mL)	2822
LVEF assessed (%)	57 (n = 84,606)
< 0.40 or moderate/severe impairment (%)	47
Intravenous Heart Failure Therapy	
Diuretics (%)	88
Any vasoactive therapy (%)	29
Nesiritide (%)	12
Nitroglycerin (%)	9
Dobutamine (%)	6
Milrinone (%)	3
Oral Heart Failure Medications During Hospitalization	
Diuretic (%)	73
ACE inhibitor or ARB (%)	68
β-blocker (%)	63
Aldosterone receptor antagonist (%)	6
Digoxin (%)	35

ACE, angiotensin converting enzyme; ADHERE, Acute Decompensated Heart Failure National Registry; ARB, angiotensin receptor antagonist, BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure; UA, unstable angina.

only 13% of patients are admitted directly to an intensive care unit (ICU) or cardiac care unit (CCU). Hospital care for the vast majority of patients with HF is provided in telemetry units (65%), on the ward (11%), and in step-down units (9%).

Among patients enrolled in the ADHERE database, 88% received IV diuretic therapy (mean duration, 3.0 days) and 29% received IV vasoactive therapy (mean duration, 2.8 days) (Table 3). The most common IV diuretic used was furosemide (84% of patients), followed by bumetanide (7% of patients) and torsemide (2% of patients). The most common IV vasoactive agent used was nesiritide (12% of patients), followed by nitroglycerin (9% of patients), dopamine (6% of patients), dobutamine (6% of patients), and milrinone (3% of patients) (Table 3).[14,15]

There are striking differences in the timing of initiation of treatment between EDs and inpatient units. When diuretics are started in the ED the mean door-to-needle time is 2.1 hours. If the diuretic is not started until the patient is admitted to the hospital, the mean time to initiation of treatment is 16.4 hours. Similarly, if IV vasoactive therapy is started in the ED, the time to treatment is 2.2 hours, compared with 35.9 hours when it is not started until after admission to an inpatient unit.[14] In a covariate adjusted analysis of ADHERE data, it was observed that the length of hospital stay was 3 days shorter when patients had vasoactive

Table 3
Events, Procedures, and Outcomes During the Hospital Stay in ADHERE Patients from October 1, 2001–September 30, 2004 (N = 148,126)

Cardiac catheterization (%)	10
Dialysis (%)	5.6
Mechanical ventilation (%)	4.6
PA catheter insertion (%)	4.1
Defibrillation or CPR (%)	1.5
In-hospital mortality (%)	3.9
Hospital LOS median (days)	4.3
ICU/CCU LOS median (days)	2.5 (n = 26,753)

ADHERE, Acute Decompensated Heart Failure National Registry; CPR, cardiopulmonary resuscitation; ICU/CCU, intensive care unit/coronary care unit; LOS, length of stay; PA, pulmonary artery.

therapy initiated in the ED than when such therapy was initiated only after hospital admission.

During the course of hospitalization there was some improvement in chronic HF treatment regimens prior to discharge. Prior to hospitalization, only 54% of patients with HF were receiving a β-blocker and only 56% were receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor antagonist. Upon discharge from the hospital, these percentages increased to 63% and 68%, respectively. Furthermore, in patients with documented systolic dysfunction and no contraindication to the above-mentioned medications, the frequency of a discharge prescription for a β-blocker and ACE inhibitor was 70% and 74%, respectively.

Invasive hemodynamic monitoring was performed in only 4.1% of the hospitalizations, as shown in Table 3. Diagnostic catheterization was performed in 10% of patients. Electrophysiologic studies were performed in 4% of patients, mechanical ventilation was instituted in 4.6% of patients, and dialysis was performed in 5.6% of patients. The frequency of procedures is higher in patients hospitalized in the ICU but, interestingly, the majority of patients in the ICU were neither mechanically ventilated nor invasively monitored.[14,15]

Clinical Outcomes in ADHF

In ADHERE, 18% of patients received care in the ICU or CCU, with a median length of stay of 2.5 days (Table 3). The median hospital length of stay for all hospitalized patients was 4.3 days. Upon discharge, 50% of patients were asymptomatic at rest and 39% were improved but still symptomatic. Fewer than 1% of patients experienced a worsening of, or no change in, their condition, and status at discharge was not known in 10% of patients. Consistent with these findings, only 50% of patients had a substantial (≥ 5 lb) weight reduction during their hospitalization. Patient outcomes varied tremendously: 60% of patients were discharged home, and a further 13% were discharged home with additional care. Other patients were transferred to other hospitals (2%), to outpatient care (1%), or had unknown status (2%), and 16% went to long-term or hospice care. The in-hospital mortality was 3.9% (Table 3), well above that reported in most clinical trials of patients with acute HF.[14] Among ADHERE-participating hospitals, median hospital length of stay varied from 2.3 to 9.5 days and in-hospital mortality varied from 0% to 11.1%.[21] Similar outcomes were observed in the OPTIMIZE-HF study.[16,17]

According to ADHERE data, in-hospital mortality was significantly higher in men than in women (4.5% vs 3.9%; $P = .0042$).[15] This observation may be explained by the greater incidence in men of systolic dysfunction (25% of men had LVEF > 40% vs 45% of women; $P < 0.0001$) and CAD (66% in men vs 53% in women; $P < .0001$), which harbors a worse prognosis. One unexpected finding showed that, although black patients had greater renal insufficiency, advanced LV dysfunction, and evidence of pulmonary congestion, they had significantly better outcomes than non-black patients. Compared with patients who were not black, mortality was more than 2-fold lower, and hospital stays were shorter ($P < .0001$ for both). Additional analysis of ADHERE data suggests that outcomes such as mortality may vary by treatment. The use of nesiritide or other vasodilators is associated with better outcomes than is the use of inotropic agents, even after extensive adjustments for covariates and treatment propensity matching.[22]

Performance Measures in Patients With ADHF

Among hospitals providing care for patients with ADHF, there is significant individual variability in conformity to quality-of-care indicators and clinical outcomes and a substantial gap in overall performance. Registry data on the Joint Commission quality-of-care indicators show that only 38% of patients were receiving instructions at discharge on diet, weight monitoring, activity level, worsening symptoms, follow-up appointments, and medication management (Joint Commission indicator HF-1). Assessment of LV systolic function (HF-2) was either documented or scheduled in 85% of patients, only 74% of eligible patients with LV systolic dysfunction received an ACE inhibitor at discharge (HF-3), and counseling on smoking cessation for current smokers (HF-4) was given to only 50% of eligible patients. Rates at individual hospitals varied from 0% to 100% with significant differences between academic and nonacademic hospitals.[21]

Temporal Trends in ADHF

A recent study assessed temporal trends in clinical characteristics, treatments, quality indicators, and outcomes among ADHF patients entered into ADHERE.[23] Trends over time were assessed for 12 consecutive quarters (January 2002-December 2004) using data from 159,168 enrollments from 285 ADHERE hospitals. During the study period, patient characteristics at admission were similar or showed only modest changes. Severity of illness by logistic regression analysis was unchanged over all 12 quarters. In-hospital treatment changed significantly over

time, with inotrope use decreasing from 14.7 to 7.9% ($P < .0001$). Nitroglycerin use decreased slightly during the 2002 to 2004 period, whereas nesiritide use rose substantially (all P for trend $< .0001$).[23] IV diuretic use remained high throughout the analysis period (≥ 87%) showing little change over time (P for trend = .09).

During the study period, substantial improvements in quality of care were observed.[23] Discharge instructions increased 133%, smoking counseling 132%, LV function measurement 8%, and β-blocker use 29% (all $P < .0001$), but no significant change in ACE inhibitor or ACE inhibitor/angiotensin receptor blocker use in eligible patients was observed. Clinical outcomes improved over time, including need for mechanical ventilation, which decreased from 5.3% to 3.4% (relative risk [RR] 0.64; $P < .0001$), mean length of stay from 6.3 to 5.5 days, and mortality from 4.5% to 3.2% (RR 0.71; $P < .0001$) (Table 4).

Therefore, over a 3-year period, demographics and clinical characteristics among patients hospitalized with ADHF were relatively similar, but significant changes in IV therapy, enhancements in conformity to quality-of-care measures, and increased administration of evidence-based HF medications occurred. Despite similar baseline risk, substantial and clinically relevant improvements in in-hospital morbidity and mortality over time were observed. These findings suggest that recent innovations in ADHF management may have translated into better clinical outcomes and highlight the need for further efforts to accelerate improvements in the care of patients hospitalized with ADHF.[23]

Prognostic Factors in ADHF

Several clinical trials and observational studies have identified factors that contribute to this high readmission and mortality rate.[17,24-26] Predictive factors include patient age; sex; race; history of previous hospitalization; ischemic etiology; comorbid conditions such as cerebrovascular disease, dementia, chronic obstructive pulmonary disease, hepatic cirrhosis, and cancer; SBP; heart rate; respiratory rate; LVEF; and elevated pulmonary capillary wedge pressure (PCWP) on admission.[17,24-26] Data from the first 33,046 patients enrolled in ADHERE were analyzed to determine predictive factors of in-hospital mortality using classification and regression tree methodology.[24] Three of 45 suspected variables provided the greatest ability to discriminate between survivors and nonsurvivors: blood urea nitrogen (BUN) of at least 43 mg/dL on admission, SBP less than 115 mm Hg on admission, and serum creatinine of 2.75 mg/dL or more on admission (Fig. 1).

The use of biochemical markers as prognostic indicators for ADHF outcomes has expanded. Several recent observational studies using cardiac troponin assays have shown that 30% to 70% of patients hospitalized with ADHF have detectable plasma levels of cardiac troponin at the time of admission in the absence of an acute coronary event.[27,28] These patients have a 2-fold increase in post-discharge mortality and a 3-fold increase in rehospitalization.[27,28] Markers of renal function including BUN and creatinine are highly predictive of clinical outcome in ADHF, whether LV systolic function is reduced or preserved.[15] Mild hyponatremia is also common in ADHF patients.[29,30] In most patients, hyponatremia does not correct during hospitalization and is associated with a 2- to 3-fold increase in in-hospital and postdischarge mortality.[29,30] A recent retrospective analysis also suggested that normalizing serum sodium with vasopressin

In most patients, hyponatremia does not correct during hospitalization and is associated with a 2- to 3-fold increase in in-hospital and postdischarge mortality.

Table 4
In-Hospital Outcomes Over 12 Quarters in ADHERE, 2002–2004

	Quarter 1 (n = 8220)	Quarter 12 (n = 9610)	*P* value
Outcomes			
In-hospital mortality (%)	4.5	3.2	< .0001
Mechanical ventilation (%)	5.3	3.4	< .0001
ICU admissions (%)	18.9	15.2	< .0001
ICU/CCU, median (Q1, Q3)	2.8 (1.4, 5.0)	2.3 (1.3, 4.1)	.0002
Total LOS, median (Q1, Q3)	4.7 (2.9, 7.7)	4.1 (2.8, 6.7)	< .0001

ADHERE, Acute Decompensated Heart Failure National Registry; LOS, length of stay; ICU/ CCU, intensive care unit/coronary care unit; Q, quarter.

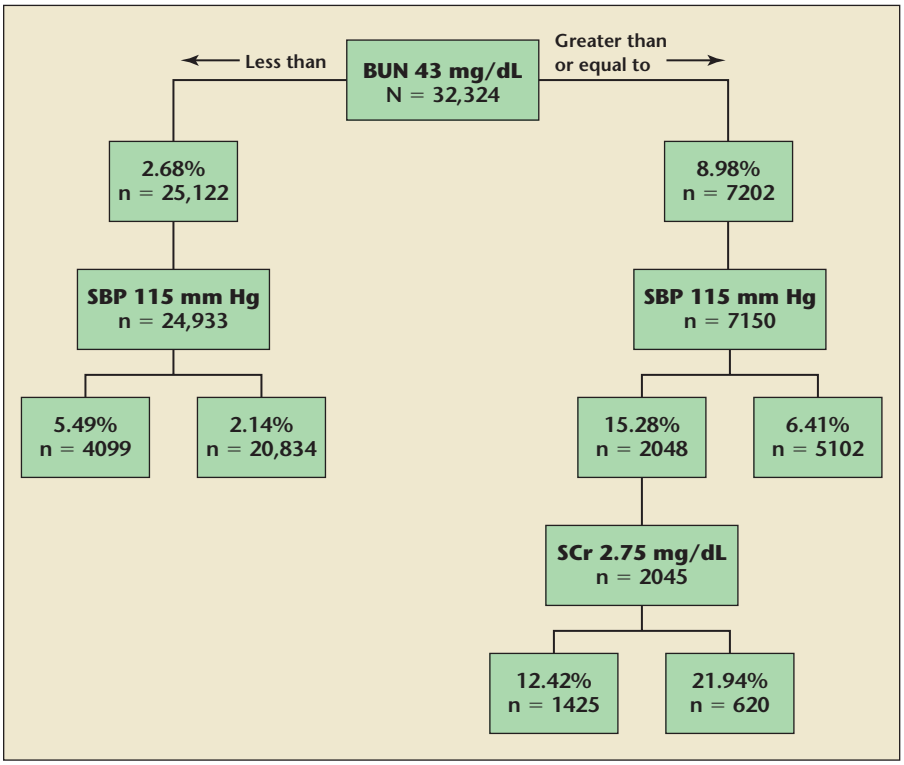

Figure 1. *Predictors of in-hospital mortality and risk stratification identified by classification and regression tree analysis in the Acute Decompensated Heart Failure National Registry (ADHERE). Each node is based on available data from registry patient hospitalizations for each predictive variable presented. Percentages indicate crude mortality for each terminal node. BUN, blood urea nitrogen; SBP, systolic blood pressure; SCr, serum creatinine.*

antagonists during hospitalization may improve outcomes after discharge.[31] Other biomarkers that provide important prognostic information on patients admitted with ADHF include B-type natriuretic peptide (BNP) and N terminal pro-BNP.[32-34] Predischarge functional capacity and anemia are emerging as other important predictors of post-discharge outcomes.[35,36]

Targets for Therapy

Treatment of ADHF has usually been targeted at improving hemodynamics because dyspnea and congestion require immediate attention on presentation to the ED or hospital ward. However, in addition to hemodynamic improvement (LV filling pressure and cardiac index), the potential pathophysiologic targets may include the vasculature (blood pressure), myocardial preservation and coronary perfusion, renal dysfunction, and neurohormonal and inflammatory modulation.[37]

A significant increase in PCWP is present in the vast majority of ADHF patients. This may result in a neurohormonal activation, progressive atrioventricular valvular regurgitation as a result of alteration of ventricular geometry, myocardial stretch-induced increase in intracellular cyclic AMP and calcium, subendocardial ischemia, and myocardial injury, as suggested by elevated levels of troponin in AHFS patients.[38] Persistent elevation of PCWP has been associated with an increased risk of progressive HF or sudden death.[38]

A significant and relatively abrupt increase in SBP (possibly related to a surge of neurohormonal or cytokine activation) may precipitate an episode of ADHF in patients with noncompliant ventricles or diastolic dysfunction.[38] This presentation is more related to vascular failure than a cardiac failure. Accordingly, the target is blood pressure control rather than improvement in cardiac performance and diuresis, particularly when the pulmonary congestion is related to fluid redistribution from the systemic to pulmonary circulation without a significant increase in total body fluid volume.[38]

CAD is one of the major underlying disease states in ADHF.[38] Endothelial dysfunction often accompanies CAD and can lead to reduced responsiveness of blood vessels and changes in blood flow and pressure, thereby increasing vascular resistance. The ischemia associated with CAD results not only in myocardial necrosis and apoptosis, but also in myocardial hibernation. Hibernating myocardium consists of tissue that is viable but noncontractile and may be particularly susceptible to necrosis or apoptosis.[39] In addition, a significant proportion of patients considered to have nonischemic cardiomyopathy have evidence for ischemic damage on cardiac MRI or abnormalities in coronary flow reserve.[38] Thus, the majority of patients with ADHF may have myocardium that is at risk for injury.

Coronary artery disease is one of the major underlying disease states in ADHF.

Several studies have shown that a significant number of patients

hospitalized for ADHF have increased serum troponin levels that correlate with poor long-term prognosis.[28] Although the significance of troponin release in patients with ischemic or primary cardiomyopathy is not well understood, it probably represents myocardial injury.[27,38] This may be an extension of the initial myocardial damage that initiated the ADHF event or may be due to secondary myocardial ischemia, myocardial injury induced by increased LV filling pressures, or a result of the use of certain drugs (eg, inotropic agents), and/or myocardial injury from excessive neurohormonal and cytokine activation. Patients with CAD are also particularly at risk for a decrease in coronary perfusion during an episode of ADHF.[38] In fact, in these patients coronary perfusion is likely to diminish as a result of increase in LV diastolic pressure, activation of neurohormones with further endothelial dysfunction, decrease in blood pressure, and/or increase in heart rate as a result of therapeutic interventions.

Renal dysfunction carries a grim prognosis in patients with ADHF and is at least as powerful an adverse prognostic factor as most clinical variables, including ejection fraction and New York Heart Association functional class.[24, 40-42] Renal function that worsens during hospitalization is a more important predictor of adverse outcomes than baseline renal function. Data from the ADHERE registry have convincingly demonstrated the important role of renal dysfunction in the pathophysiology and adverse outcomes associated with hospitalization for ADHF.[24] Retrospective analyses from other studies have shown that high BUN and BUN/creatinine ratio on admission are associated with a 2-fold increase in 1-year postdischarge mortality.[42]

Other comorbidities, such as type 2 diabetes, anemia, and atrial fibrillation, also have an important impact on the pathophysiology of ADHF.[37,38] Patients with diabetes have a higher risk of myocardial ischemia and reduced renal perfusion. These patients are also more susceptible to infections that may further complicate ADHF. Atrial fibrillation, which affects 20% to 30% of patients with ADHF, can result in reduced cardiac output, thereby exacerbating AHFS and ischemia.[37,38] Anemia is frequently present in patients with ADHF and may contribute via multiple mechanisms in HF disease progression.[36]

Initiation and/or continuation of neurohumoral antagonists during hospitalization for ADHF, including ACE inhibitors, aldosterone antagonists, and β-blockers, may provide cardiovascular protective effects.[5,37] Discharge use of ACE inhibitors and angiotensin receptor blockers has been shown to be associated with improved outcomes in elderly patients hospitalized with HF.[5] Comparisons of patients continued on β-blockers or in whom β-blockers were with held during ADHF hospitalization have shown lower risk-adjusted mortality with continuation of β-blockers. Initiation of β-blockers prior to hospital discharge is associated with substantially lower mortality risk in the first 60 to 90 days following discharge when compared with otherwise eligible patients who were not treated with β-blockers prior to discharge.[16] Early use of aldosterone antagonists in post-MI HF resulted in significant 30-day reductions in the risk of sudden death and all-cause mortality in addition to other standard-of-care therapies.[5]

Guidelines written for the assessment and treatment of ADHF have been released but the therapeutic recommendations focus primarily on the relief of symptoms and no recommendations are made regarding pharmacologic strategies that may change the natural history of ADHF.[5] This gap in our knowledge is a direct result of the paucity of controlled clinical trials evaluating potential therapies. Moreover, the few randomized clinical trials that have been completed have lacked the power to assess the effect of current IV therapies on mortality rates.

IV loop diuretics, the standard treatment for decades, relieve symptoms rapidly and are easily administered. However, no controlled clinical trials have tested the effect of diuretics on ADHF outcomes.[5] IV inotropic agents were introduced more than 2 decades ago, when decreased cardiac contractility was believed to be the principal cause of ADHF.[43] However, both in controlled clinical trials and in observational studies, positive inotropic agents have been associated with higher rates of morbidity, mortality, or both.[22,44]

Acknowledgment of the deleterious effects of inotropes on the failing heart shifted the focus of treatment to vasodilators, principally IV nitroglycerin and nitroprusside.[5] More recent realizations that the production of natriuretic peptides accompanies the neurohormonal activation associated with the progression of HF and that the pleomorphic profile of natriuretic peptides includes attenuation of deleterious neurohormonal signals have prompted development and use of recombinant natriuretic peptides to treat ADHF.[45] Recent analyses of the effects of natriuretic peptides in ADHF have been conflicting.[46-50] Several early trials suggested both a hemodynamic and clinical advantage of natriuretic peptides compared with placebo or active controls.[46,47] To date, only 1 randomized controlled clinical trial has compared the outcomes of inpatients given nitroglycerin with those of inpatients receiving the recombinant

natriuretic peptide nesiritide for ADHF.[46] The findings of that trial demonstrated a greater relief of dyspnea compared with placebo and a greater decrement in pulmonary congestion compared with nitroglycerin.[46] Although these data suggested a clinical benefit, subsequent retrospective analyses that included other databases have generated concerns about acute renal toxicity and a greater risk of death 30 days after initial administration of natriuretic peptides.[48-50] These issues will remain unresolved until randomized controlled trials provide definitive answers.

The Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure (ASCEND-HF) is designed to evaluate whether treatment with nesiritide improves patient outcomes (as measured by reduction in the composite of HF rehospitalization and all-cause mortality through 30 days) and HF symptoms (as measured by subject self-assessed Likert dyspnea scale at 6 hours after study drug initiation) compared with placebo when administered in addition to other standard therapies in patients with ADHF. The study has 2 co-primary hypotheses: 1) that nesiritide administered in addition to standard care is superior to placebo in addition to standard care in the reduction of the composite endpoint of HF rehospitalization, and 2) that all-cause mortality from study drug initiation through day 30 in patients with ADHF and nesiritide administered in addition to standard care is superior to placebo in addition to standard care in relieving dyspnea symptoms as measured by self-assessed Likert scale at 6 hours after study drug initiation in subjects with ADHF. This ongoing clinical trial in ADHF will provide very valuable data when available.

Conclusions

Patients with ADHF represent a population with very high mortality and postdischarge readmission rates. The vast majority of AHFS hospitalizations are related to clinical congestion rather than to a low cardiac output state. Potential targets for treatment include blood pressure control, myocardial preservation, reduction in congestion, preservation of renal function, modulation of neurohumoral and inflammatory activation, control of arrhythmias, and management of other comorbidities that may cause or contribute to the progression of this syndrome. Additional research and large-scale randomized clinical trials testing various treatment strategies are urgently needed to reduce substantial disease burden, disability, and death due to ADHF. ■

Dr. Fonarow is a speaker/consultant for Scios Inc.

References

1. 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). *Circulation*. 2005;112:e154-e235.
2. Nieminen MS, Bohm M, 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.
3. Fonarow GC, Adams KF Jr, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572-580.
4. Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112:3958-3968.
5. Adams KF, Lindenfeld J, Arnold JMO, et al. HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail*. 2006;12:e1-e122.
6. 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;290:2581-2587.
7. Cuffe MS, Califf RM, Adams KFJ, et al; for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541-1547.
8. Clinical Quality Improvement Network Investigators. Mortality risk and patterns of practice in 4606 acute care patients with congestive heart failure. The relative importance of age, sex, and medical therapy. *Arch Intern Med*. 1996;156: 1669-1673.
9. 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;89:615-620.
10. MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66,547 patients

Main Points

- Acute decompensated heart failure represents the most common discharge diagnosis in patients over age 65, and has an exceptionally high mortality and readmission risk.
- Markers of renal function including blood urea nitrogen and creatinine are highly predictive of clinical outcome in acute decompensated heart failure (ADHF), whether left ventricular systolic function is reduced or preserved.
- Data from the ADHERE registry have convincingly demonstrated the important role of renal dysfunction in the pathophysiology and adverse outcomes associated with hospitalization for ADHF.
- Additional research and large-scale randomized clinical trials testing various treatment strategies are urgently needed to reduce substantial disease burden, disability, and death from acute decompensated heart failure.

hospitalized between 1986 and 1995. *Circulation*. 2000;102:1126-1131.
11. Roguin A, Behar D, Ben Ami H, et al. Long-term prognosis of acute pulmonary oedema—an ominous outcome. *Eur J Heart Fail*. 2000;2:137-144.
12. Krumholz HM, Wang Y, Parent EM, et al. Quality of care for elderly patients hospitalized with heart failure. *Arch Intern Med*. 1997;157:2242-2247.
13. Westert GP, Lagoe RJ, Keskimaki I, et al. An international study of hospital readmissions and related utilization in Europe and the USA. *Health Policy*. 2002;61:269-278.
14. Adams KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149:209-216.
15. Yancy CW, Lopatin M, Stevenson LW, et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47:76-84.
16. Fonarow GC, Abraham WT, Albert NM, et al. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Arch Intern Med*. 2007;167:1493-1502.
17. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217-2226.
18. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24:442-463.
19. De Luca L, Abraham WT, Fonarow GC, Gheorghiade M. Congestion in acute heart failure syndromes: importance of early recognition and treatment. *Rev Cardiovasc Med*. 2006;7:69-74.
20. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768-777.
21. Fonarow GC, Yancy CW, Heywood JT. Adherence to Heart Failure Quality-of-Care Indicators in US Hospitals: analysis of the ADHERE Registry. *Arch Intern Med*. 2005;165:1469-1477.
22. Abraham WT, Adams KF, Fonanow GC, et al; for the ADHERE Scientific Advisory Committee and Investigators, and the ADHERE Study Group. Inpatient mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE) registry. *J Am Coll Cardiol*. 2005;46:57-64.
23. Fonarow GC, Heywood JT, Heidenreich PA, et al. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2007;153:1021-1028.
24. Fonarow GC, Adams KF; for the ADHERE Investigators. Risk stratification for in-hospital mortality in heart failure using classification and regression tree (CART) methodology: analysis of 33,046 patients in the ADHERE registry. *JAMA*. 2005;293:572-580.
25. Felker GM, Leimberger JD, Califf RM, et al. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail*. 2004;10:460-466.
26. O'Connor CM, Stough WG, Gallup DS, et al. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail*. 2005;11:200-205.
27. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833-838.
28. Perna ER, Macin SM, Cimbaro Canella JP, et al. Minor myocardial damage detected by troponin T is a powerful predictor of long-term prognosis in patients with acute decompensated heart failure. *Int J Cardiol*. 2005;99:253-261.
29. Klein L, O'Connor CM, Leimberger JD, et al; OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the OPTIME- CHF study. *Circulation*. 2005;111:2454-2460.
30. Gheorghiade M, Hellkamp AS, Pina IL, et al. Hemodynamic characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial [abstract]. *J Am Coll Cardiol*. 2005;45:145A.
31. Gheorghiade M, Adams KF, O'Connor CM, et al. Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) [abstract]. *J Am Coll Cardiol*. 2005;45:145A.
32. Maisel A, Hollander JE, Guss D, et al; Rapid Emergency Department Heart Failure Outpatient Trial investigators. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT): a multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol*. 2004;44:1328-1333.
33. Maisel AS, Krishnaswamy P, Nowak RM, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-167.
34. Bettencourt P, Azevedo A, Pimenta J, et al. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;110:2168-2174.
35. McDermott MM, Feinglass J, Lee PI, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J*. 1997;134:728-736.
36. Felker GM, Gattis WA, Leimberger JD, et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol*. 2003;92:625-628.
37. Gheorghiade M, Zannad F, Sopko G, et al; International Working Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112:3958-3968.
38. Gheorghiade M, De Luca L, Fonarow GC, et al. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol*. 2005;96:11G-17G.
39. Schulz R, Rose J, Martin C, et al. Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation. *Circulation*. 1993;88:684-695.
40. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:681-689.
41. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13-25.
42. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med*. 2004;116:466-473.
43. Loeb HS, Bredakis J, Gunner RM. Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation*. 1977;55;375-378.
44. Cuffe MS, Califf RM, Adams KF, et al. Short term intravenous milrinone for acute exacerbation of chronic heart failure. *JAMA*. 2002;287;1541-1547.
45. Levin ER, Gardner DG, Samson WK. Mechanisms of disease: natriuretic peptides. *N Engl J Med*. 1998;339:321–328.
46. Publication Committee for the VMAC Investigators. Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531-1540.
47. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated CHF: the PRECEDENT study. *Am Heart J*. 2002;144:1102–1108.
48. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure. *JAMA*. 2005;293:1900-1905.
49. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of WRF with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111:1487-1491.
50. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation*. 2004;110:1620-1625.