Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims: A Scientific Statement From the American Heart Association

Neal L. Weintraub, Sean P. Collins, Peter S. Pang, Phillip D. Levy, Allen S. Anderson, Cynthia Arslanian-Engoren, W. Brian Gibler, James K. McCord, Mark B. Parshall, Gary S. Francis, Mihai Gheorghiade and on behalf of the American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

Circulation 2010;122;1975-1996; originally published online Oct 11, 2010;
DOI: 10.1161/CIR.0b013e3181f9a223
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

AHA Scientific Statement

Acute Heart Failure Syndromes: Emergency Department Presentation, Treatment, and Disposition: Current Approaches and Future Aims

A Scientific Statement From the American Heart Association

Neal L. Weintraub, MD, Chair; Sean P. Collins, MD, MSc, Co-Chair; Peter S. Pang, MD; Phillip D. Levy, MD, MPH; Allen S. Anderson, MD; Cynthia Arslanian-Engoren, PhD, RN, FAHA; W. Brian Gibler, MD, FAHA; James K. McCord, MD; Mark B. Parshall, PhD, RN; Gary S. Francis, MD, FAHA; Mihai Gheorghiade, MD; on behalf of the American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

With a prevalence of 5 800 000 (≈2% of the entire populace) in 2009 and an estimated yearly incidence of 550 000, the burden of heart failure (HF) in the United States is tremendous.[1] Although HF is largely a condition defined by chronic debility, virtually all patients experience, at some point, acute symptoms that trigger a visit to the emergency department (ED). These symptoms may vary in severity but, for the most part, they necessitate early intervention, often with intravenous medication and, less frequently, respiratory support. As shown by combined data from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), this is a common occurrence; there are nearly 658 000 annual ED encounters primarily for acute HF in the United States—a figure that represents almost 20% of the total HF-specific ambulatory care delivered each year.[2]

It is noteworthy that few settings other than the ED can offer open access to treatment or provide the level and intensity of care required to effectively manage the acute phase of decompensation, also referred to as episodes of acute heart failure syndromes (AHFS). Nearly 80% of those treated for AHFS in the ED are ultimately admitted to the hospital and, accordingly, the ED serves as the principal portal of entry for hospitalized AHFS patients.[3,4] The ED therefore plays a unique role in the continuum of AHFS treatment, functioning for most patients as the initial point of definitive healthcare contact, the location where primary stabilization is achieved, and the site where disposition decisions are generally made.[4] Whereas the ED is a pivotal place for the vast majority of hospitalized patients with acute HF, the evidence base on which this foundation of acute care is built is astonishingly thin. The purpose of this scientific statement, therefore, is to describe current standard practice for HF clinicians, to highlight the knowledge gaps that are present, and to serve as a call to action for ED-based research as a future endeavor for those with a vested interest in AHFS care.

The need for improvement in our approach to AHFS management was recognized in the recently published 2009 Focused Update to the 2005 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Diagnosis and Management of Heart Failure in Adults. For the first time recommendations relevant to the hospitalized AHFS patient were included.[5] Developed using guideline methodology standardized by the ACC/AHA (Table 1),[6] these recommendations represent an important step forward in the ongoing effort to

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on August 11, 2010. A copy of the statement is available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0104). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, Gibler WB, McCord JK, Parshall MB, Francis GS, Gheorghiade M; on behalf of the American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. *Circulation*. 2010;122:1975–1996.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier=3023366.

(*Circulation*. 2010;122:1975-1996.)

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e3181f9a223**

Table 1. Classification of Recommendations and Level of Evidence[6]

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACCF/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

optimize the care of patients with AHFS. With respect to the ED several key points warrant mention: (1) the included procedures and treatments represent a combination that target acute (24 to 48 hours) and subacute (≥48 hours) stages of AHFS and are not specific to the immediate management; (2) although they provide general guidance for treatment, there is limited direction for the care of particular subgroups or phenotypes commonly seen in the ED setting, especially those who have acute hypertension with fluid redistribution rather than excess accumulation[7]; (3) potential applicability of critically important acute interventions typically initiated in the ED, such as noninvasive ventilatory measures[8] and endotracheal intubation, are not discussed; (4) there is no consideration of risk stratification or proposal to provide objective measures for disposition decision making, which has crucial bearing on resource utilization, in particular, for those patients whose condition may be amenable to a short-term, observation stay; and (5) the vast majority of recommendations are considered class I, yet, overall, and in contrast to those presented in the sections for chronic management, only one was based on level A evidence. This final point is perhaps the most pressing and serves to highlight a critical limitation in the quest to develop data-driven, best-practice approaches to the care of AHFS patients in the ED.

Reasons for the lack of definitive evidence for AHFS management are multifactorial but can be largely attributed to the absence of a cohesive research agenda among respective stakeholders. Whereas registry databases such as ADHERE (Acute Decompensated Heart Failure National Registry)[9,10] and OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure)[11,12] have compiled important information on initial

presentation and treatment, large-scale clinical trials, utilizing prospective data collection, have not been designed to recruit patients in the ED setting. Factors contributing to this include a long-standing difficulty establishing consensus on reasonable end points[4] as well as a desire to ensure accurate diagnosis before enrollment. More importantly, there has been a misperception by HF specialists that identification and enrollment of ED patients is problematic.[3] The net result is a lingering uncertainty with regard to the impact of early intervention on outcomes and de facto inclusion of patients who have refractory symptoms.[3,4] The latter, in particular, may be responsible for the predominantly neutral findings associated with the majority of AHFS investigations that have been conducted to date.

As highlighted in this Introduction, a paradigm shift in the clinical practice and investigative agenda surrounding AHFS is warranted. Sensing the urgency of this matter, the National Heart, Lung, and Blood Institute recently convened a multidisciplinary working group of individuals with expertise in AHFS management and tasked them with development of the Institute's future research focus for AHFS.[13] Although the proceedings were published elsewhere, there was firm resolve among all participants regarding the need to improve the evidence base in AHFS by initiating study of these patients in the ED, and that a better understanding of AHFS could only be achieved through broad collaboration.

Organization of Writing Group and Relationships With Industry

Experts in the subject of AHFS were selected and charged with examining subject-specific data and writing this scientific statement. The writing group performed a formal literature review and weighed the strength of evidence for or against existing treatments or procedures using established AHA statement and guideline methodology. Discussion of patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies were considered, as were frequency of follow-up and cost-effectiveness. When available, information from studies on cost was considered; however, review of data on efficacy and clinical outcomes constituted the primary basis for any related recommendations. To ensure that any actual, potential, or perceived conflicts of interest were identified, all members of the writing group, as well as peer reviewers of the document, completed "Relationship with Industry" forms when the writing group was formed. Writing group members were also required to review and update their disclosure information before publication. The writing group used the "Methodology Manual for ACC/AHA Guideline Writing Committees"[14] as a guide for developing this statement. Writing group and reviewer disclosures that are pertinent to this scientific statement are provided at the end of this statement.

What Happens Currently in the ED: Diagnosis, Treatment, and Disposition?

Diagnosis and treatment of AHFS in the ED is a clinical challenge that requires complex decision-making skills to achieve hemodynamic balance, improve functional capacity, and decrease mortality and length of stay.[15–19] This difficult task is further compounded by the organizational structure and operations of most EDs, which tend to be better suited for rapid stabilization, treatment, and disposition of acute emergencies such as shock, arrhythmias, or ST-segment myocardial infarction, as opposed to the timely recognition and treatment of more subtle or complicated forms of AHFS which most often are related to decompensation of underlying, chronic HF.[20] It may be easier to judge how seriously ill patients are when their baseline has deviated from a previously healthy state, than when their condition represents deterioration of a chronic illness that is protean in nature, especially when the emergency physician is unfamiliar with the patient.

The ED phase of AHFS management concludes with a disposition decision (admit to ED observation unit, in-hospital telemetry unit, intensive care unit, or discharge to the outpatient environment).[21] Because it is challenging to identify patients at risk for poor outcomes in the ED, including acute and 30-day adverse cardiac events,[22] and because definitive resolution of symptoms is seldom achieved in the ED, 80% of patients who present to the ED with AHFS are hospitalized.[23] At present, however, there is little evidence to guide disposition decisions, and imprecise risk stratification and uncertainty regarding the etiology of AHFS often prompts the decision to admit for further treatment and testing.[21]

Current Diagnostics

The evaluation of the patient in the ED with possible AHFS includes history, physical examination, chest radiography, 12-lead ECG, cardiac troponin testing (I or T), electrolytes, and a complete blood cell count. The chest radiograph remains a cornerstone for diagnostic testing, but can lack signs of congestion in over 15% of patients, thus limiting its ability as a screening tool.[24] In select cases, liver and thyroid function tests may be considered. The natriuretic peptides b-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP have demonstrated diagnostic utility in this patient population when clinical uncertainty remains after initial history, physical examination, and chest radiography. These biomarkers are generated from a prohormone released from cardiac myocytes in response to ventricular dilatation and pressure overload.[25–27] After release from the cardiac myocyte, the prohormone proBNP is cleaved into BNP, which is metabolically active, and NT-proBNP, which is metabolically inactive. Both BNP and NT-proBNP are elevated in AHFS and the magnitude of marker elevation is correlated with severity of illness.[28–32]

A large study that investigated the diagnostic utility of natriuretic peptides was the Breathing Not Properly trial which enrolled 1586 patients, and evaluated BNP measurement in ED patients with possible AHFS.[28] Using a cutoff of 100 pg/mL, BNP had a sensitivity, specificity, negative predictive, and positive predictive value of 90%, 76%, 79%, and 89%, respectively. In this capacity, BNP is highly useful to exclude AHFS. In a multiple logistic regression analysis including history, physical examination, and chest x-ray findings, an elevated BNP was the strongest independent predictor of AHFS, with an odds ratio of 29.6 (95% confidence interval [CI] 17.75 to 49.37). In a secondary analysis

from this study, BNP correctly classified 74% of the patients with an intermediate probability of AHFS.[33] When BNP was added to clinical judgment after routine evaluation, the area under the receiver operating characteristic curve (AUC) rose significantly from 0.86 to 0.93 ($P<0.0001$). Similarly, a single-center investigation evaluated the diagnostic utility of NT-proBNP in the ED in 600 patients with dyspnea.[31] The AUC rose from 0.90 to 0.96 when NT-proBNP was added to clinical judgment. The authors suggest a single cut point of 300 pg/mL to rule out AHFS, but 2 cut points to rule in AHFS depending on age: <50 years old (>450 pg/mL)and >50 years old (>900 pg/mL). Subsequent studies suggested even further delineation as follows: (1) either an age-independent cutoff of 900 pg/mL, or (2) the more accurate (but more complex) age-stratified approach of 450/900/1800 for patients aged <50/50 to 75/>75 years.[34,35] Other smaller studies have also demonstrated the diagnostic utility of BNP and NT-proBNP for AHFS.[29,30,36,37]

The majority of studies suggest that BNP and NT-proBNP are of equal diagnostic utility. However, subtle differences in patient characteristics may favor one biomarker over the other. BNP and NT-proBNP both can be elevated in patients with renal insufficiency, which is more commonly found in older patients.[38,39] Levels of NT-proBNP appear to be more affected by renal function.[40] Four studies have directly compared the diagnostic utility of BNP and NT-proBNP.[29,36,41,42] Both natriuretic peptides demonstrated similar accuracy in 3 studies, but in 1 study BNP was superior to NT-proBNP.[42] The AUC for the diagnosis of AHFS was 0.80 for NT-proBNP and 0.85 for BNP, $P<0.05$. This was mostly a consequence of the lower specificity of NT-proBNP (76%) when compared with BNP (91%). In this study, only patients >65 years old were enrolled, suggesting that BNP may be superior in older patients. This finding will need to be confirmed in other studies. The natriuretic peptides are particularly good at ruling out AHFS; the negative likelihood ratio of BNP at 100 pg/mL is 0.13,[28] and of NT-proBNP at 300 pg/mL is 0.015.[31] However, the positive likelihood ratio of the natriuretic peptides is more limited (3.8 and 3.1, respectively, for BNP and NT-proBNP) because they can be elevated in numerous conditions including sepsis, pulmonary hypertension, older age, renal insufficiency, atrial fibrillation, and pulmonary embolism.[43–47] Obesity is actually associated with disproportionately low BNP levels.[48] Mechanisms that have been postulated for these low BNP levels include reduced peptide synthesis and/or secretion in subjects with obesity; increased expression of natriuretic peptide clearance receptors in adipose tissue; and increased circulating neutral endopeptidases, which are secreted by adipocytes, may contribute to a lesser extent.[49] Patients with a history of HF can have chronically elevated BNP or NT-proBNP levels. An elevation above their baseline, or dry weight level, may help identify a patient with AHFS. What constitutes a significant change above the baseline level in any particular patient is uncertain at the present time. Biological variability further complicates this situation. Studies suggest that BNP may need to change by at least 70% and NT-proBNP may need to change by 50% to identify a patient with a diagnostically meaningful change.[50–53]

The clinical utility and resource utilization of BNP testing were evaluated in a single-center randomized trial of 453 patients with dyspnea in an ED in Switzerland.[32] Two hundred twenty-five patients were randomly assigned to a standard diagnostic strategy, and 227 patients were randomly assigned to a standard diagnostic strategy plus BNP measurement. In comparison with the standard strategy, BNP testing led to reductions in the number of patients hospitalized (75% versus 85%, $P=0.008$), time to discharge (8.0 days versus 11.0 days, $P=0.001$), cost ($5410 versus $7264, $P=0.006$), and time to treatment (63 minutes versus 90 minutes, $P=0.03$) In a separate analysis from the same trial, the cost-effectiveness of BNP measurement in the ED was maintained at 180 days.[54] However, the dramatically different lengths of stay compared with centers in the United States makes extrapolation of these results problematic. Another trial of 500 patients with dyspnea presenting to EDs in Canada randomly assigned 250 patients to a standard diagnostic strategy and 250 patients to a standard diagnostic strategy plus NT-proBNP measurement.[55] The AUC of the emergency physician's diagnostic accuracy without knowledge of NT-proBNP results was 0.83 (95% CI 0.80 to 0.84), which increased to 0.90 (95% CI 0.90 to 0.93, P<0.001) with knowledge of NT-pro BNP results. Although there were no clinically meaningful differences in ED or hospital length of stay or costs, there was a significant difference in 60-day rehospitalization and costs favoring the NT-proBNP group. However, randomized trials investigating the use of an initial BNP to aid in diagnostic accuracy or serial BNP levels to dictate therapy in the acute setting found no improvement in diagnostic accuracy or clinically important outcomes such as length of stay, mortality, and readmission.[56,57] These randomized trials do not clearly identify whether the potential improved diagnostic accuracy of natriuretic peptides can lead to more appropriate therapy in a cost-effective manner. Further research, preferably in the way of a multicenter trial, is indicated to address this issue.

In summary, the measurement of BNP or NT-proBNP in the ED patient being evaluated for possible AHFS improves diagnostic accuracy when compared with standard diagnostic strategies. Either BNP or NT-proBNP should be measured in patients in whom there is clinical uncertainty concerning the diagnosis.

Current Therapy: Heterogeneous Presentations Met With Homogeneous Therapy

Although dyspnea, the principal symptom in AHFS, is attributed to the common pathophysiologic denominator, increased left ventricular end-diastolic pressure, not all patients have the same etiology or precipitating factor.[58,59] Regardless of the baseline cardiac pathophysiology, critical presenting features such as hemodynamic status, presence (or absence) of myocardial ischemia, and renal dysfunction greatly influence management. Widespread appreciation of this phenotypic variability is lacking,[60–62] perhaps because AHFS is viewed as a single disease entity rather than as a multifaceted disorder.[58]

Furthermore, symptoms related to congestion are what prompt patients with AHFS to seek care.[63] The current goals of ED therapy are to relieve congestion, balance hemodynam-

ics, achieve euvolemia, and avoid harm, such as myocardial and renal injury. Initial stabilization focuses on determining whether the patient requires ventilatory support, either via endotracheal intubation or noninvasive ventilation (NIV). NIV is used as an adjunct to acute pharmacological therapy in patients who present with respiratory distress. Although a large randomized trial suggests no mortality benefit associated with NIV, it does improve dyspnea and reduce preload while other therapies are initiated.[8] Diuretics are a central component of ED therapy, and their use is endorsed by guidelines from both the United States and Europe.[5,64–66] Further studies are needed to resolve the conflicting results as to whether intermittent boluses or a constant infusion is more efficacious.[67,68] Vasodilators, including intravenous angiotensin-converting enzyme (ACE) inhibitors, are frequently used in the treatment of AHFS patients with congestion and normal or elevated blood pressure. In addition to the intravenous form, nitroglycerin is also available in sublingual and topical preparations. Topical nitroglycerin preparations are frequently used in the ED despite limited clinical trial data describing their utility. A highly selective study of patients with AHFS and low cardiac output and monitored by a pulmonary artery catheter suggests that 0.8 mg of sublingual nitroglycerin causes a clinically significant decrease in systemic vascular resistance and an increase in the cardiac index in less than 30 minutes.[69] Similarly, clinically significant improvements in pulmonary capillary wedge pressure and cardiac index were also seen when nitroglycerin ointment (2.5 to 5 cm) was applied topically to patients with AHFS.[70]

ED patients with AHFS can be largely assigned into 2 groups based on presentation blood pressure: (1) hypertensive (>140 mm Hg) and (2) normotensive (<140 mm Hg). Hypotension (<90 mm Hg) and cardiogenic shock are rare and make up less than 5% of ED presentations.[12,65] Those who present with hypertension may appear to be the most acutely ill, but aggressive blood pressure management often results in rapid resolution of symptoms. More importantly, once their acute symptoms are adequately managed, patients presenting with hypertension often have 60- to 90-day mortality rates that are much lower than those who present with normotension.[12,18,71,72] Although both of these subsets have signs and symptoms of pulmonary congestion, the actual mechanisms and volume status may differ. Traditional AHFS models describe fluid accumulation and acute symptoms as being almost synonymous. Recent data suggest that those patients who present with hypertension (ie, vascular crisis) may have congestion caused by a mismatch between rapidly increasing afterload and impaired systolic performance leading to volume redistribution.[7,73–75] Nevertheless, both groups of patients present with similar symptoms and are often treated solely with intravenous diuretics despite differences in underlying pathophysiology and volume status.

Further subcategorization can be made based on underlying etiologies and reasons for decompensation such as AHFS related to dietary and medication nonadherence, ischemia, worsening renal function, arrhythmias, or a concomitant pulmonary process.[76] In select cases this may help direct further therapy such as anitarrhythmics; however, regardless of the etiology, the majority of patients are admitted to the hospital for further therapy targeting congestion reduction.[12,77–79] Very few changes are made to medication regimens during hospitalization, and only a minority of patients receive a therapeutic procedure or device during their inpatient stay.[80–82]

According to the recently completed URGENT (Ularitide Global Evaluation in Acute Decompensated Heart Failure) dyspnea study, the ED approach does improve overt symptoms of breathlessness in most patients by 6 hours.[83] Yet, despite improvement in symptoms by 6 hours, registry data also suggest that only 50% of patients have complete resolution of their congestive symptoms at hospital discharge.[11] Furthermore, there is little randomized evidence of the benefit of diuretics beyond symptomatic improvement, because randomized trials are nonexistent[84] and signals increasingly point to the potential for induction of harm with both acute[85,86] and chronic[87] usage of diuretic medication. Previous studies of diuretics suggest not only an association with adverse outcomes, but also perhaps direct causality.[71,86,88–91] The development of in-hospital acute renal injury has been associated with increased in-hospital mortality.[92–94] Although, for some, diuresis is important and appropriate, could the nearly universal application of homogeneous therapy to an inherently heterogeneous disorder negatively impact the high rates of short-term recidivism[95] and mortality[1] associated with AHFS?[3,58]

AHFS has historically been viewed as a transient event, characterized primarily by systolic dysfunction, low cardiac output, and fluid overload. This pathophysiologic model has been thought to be applicable across all patient groups, varying only by degree of severity.[96–98] Consequently, short-term treatment strategies such as intravenous diuretics, targeted at rapidly alleviating fluid congestion, were adopted without clinical trials evaluating long-term safety and efficacy. It is noteworthy that emerging data from several HF registries have largely challenged the traditional low cardiac output model exemplified by the prototypical male with ischemic heart disease, revealing a more complex and distinct group of pathophysiologic entities.[77,78] Despite the heterogeneous clinical profiles outlined above, suggesting that targeted treatment may be beneficial, the majority of patients with AHFS are treated with homogeneous therapy, namely intravenous diuretics. A next logical step would be to determine whether select subsets of patients, classified via reliable objective measures after initial evaluation, would benefit from targeted therapy aimed at their risk profile, HF etiology, and reason for decompensation.

Emergency Department Disposition Decision Making

The majority of patients who present to the ED with AHFS are admitted to the hospital.[99,100] This approach is largely due to the challenge of identifying ED patients at low risk for poor outcomes. Risk stratification of patients with AHFS is traditionally problematic, not only because of the patients' underlying HF, but also because of their multiple comorbidities. Further, even for patients who exhibit no objective markers of high risk, the subsequent inability to ensure close follow-up, provide bedside HF education, and address the importance of adherence to therapeutic recommendations makes direct ED discharge problematic.

Those patients who present in extremis with significant dyspnea and elevated blood pressures may appear to be at the greatest risk for short-term adverse events. However, once acute symptoms are controlled their intermediate (30- to 60-day) risk of adverse events is low when compared with the cohort of patients with normal blood pressure who often present with less severe symptoms.[12,18,101] Only a minority of patients manifest low-output signs such as diminished urine production or systemic hypoperfusion.[12]

Other admission profiles associated with an increased risk of in-hospital mortality include AHFS related to myocardial infarction or ischemia, worsening renal function, or a concomitant pneumonia.[76] Conversely, as many as one-third of patients decompensate because of medication or dietary nonadherence or as a result of poorly controlled hypertension. These individuals have a better short-term prognosis with a reduced risk of early mortality.[102] Studies over the past decade have recurrently identified several variables and biomarkers as predictors of adverse events: (1) elevated blood urea nitrogen or creatinine, (2) hyponatremia, (3) ischemic electrocardiogram changes, (4) elevated natriuretic peptide levels, (5) elevated troponins, and (6) low systolic blood pressure.[12,65,101,103,104–107] Markers of low-risk AHFS, however, have not been as well delineated. Preliminary work suggests an initial systolic blood pressure over 160 mm Hg and a normal initial cardiac troponin I as markers associated with a decreased risk of adverse events.[22] In a large retrospective analysis of a statewide database that utilized recursive partitioning, 17% of ED patients were identified as low risk.[108] This somewhat complex model also found systolic blood pressure, serum sodium, and creatinine serving to differentiate between low and high risk. This statistical model was subsequently validated in more than 8300 patients. The model had a negative likelihood ratio of 0.24 (0.18 to 0.32) for identification of 30-day mortality or serious complications.[109]

Although markers of low-risk presentations have remained somewhat elusive, alternatives to hospitalization have also been investigated. Because the majority of hospitalizations originate from the ED, emergency physicians have considerable experience stabilizing patients, initiating treatment, and determining disposition in patients with AHFS.[64,110] Because most patients with AHFS are admitted for decongestion as a result of worsening chronic HF, a brief period of management in the ED or an ED-based observation unit may be a reasonable alternative to hospitalization in those patients without high-risk features. Such approaches have proved feasible and have been shown to conserve hospital resources.[111–114] Although close cardiology follow-up as an outpatient is the cornerstone of success in these brief, ED-driven treatment strategies, even better outcomes may be achieved as the ability to effectively risk-stratify patients improves. Ultimately, delineation of low-risk features and identification of AHFS patients with good intermediate-term prognosis is needed. Further prospective study to identify markers of low-risk AHFS patients is therefore necessary.

Post-ED Course

Hospitalization of the patient with AHFS defines a point on the continuum of their disease process. Admission for treatment of both newly diagnosed AHFS or recurrent exacerbations/complications of chronic HF are episodes of profound consequence to the patient. Health, emotional well-being, quality of life, work status, and long-term prognosis are affected by these medical events. Successful treatment via initiation and optimization of medical therapy not only improves patients' immediate symptoms but also their long-term prognosis.[115–117] One of the important keys to success for the practitioner is to ensure that the indicated, evidence-based therapies are administered appropriately and in a timely fashion. After 20 years of clinical trials data, many centers still fall short of this goal. This is probably a combination of the incomplete penetration of recent guidelines into routine medical practice, as well as difficulty in applying guidelines to patients with complex hemodynamic derangements and multiple comorbidities. Furthermore, despite years of HF clinical research, many basic questions remain unresolved. As a result, physicians must still rely on their own clinical experience to treat this prevalent disease.

As mentioned previously, the AHA/ACC guidelines for the management of HF were updated in 2009.[5] Although the evidence base for patients with AHFS is limited, with most recommendations stemming from expert consensus (level C), these guidelines still provide direction for clinicians caring for stabilized AHFS patients as they are being transitioned from the ED to an inpatient bed, and eventually to outpatient care.

Inpatient Therapy for AHFS

Treatment of pulmonary congestion and the resultant symptoms has remained the cornerstone of AHFS therapy for over 50 years. Pulmonary congestion, even though it is sometimes difficult to assess, is a symptom of elevated left atrial pressure. Clinicians currently lack a simple, inexpensive, accurate, reliable, and noninvasive means of assessing this target for therapy. A variety of techniques such as physical examination, echocardiography, pulmonary artery catheterization, implanted hemodynamic monitors, and thoracic impedance have been tested and found to have limited utility in the management of AHFS.[118–123] There remains no reliable means of identifying when to start diuretics and when to withhold them before obvious clinical signs, such as renal dysfunction or hypotension, develop.

Morbidity and Mortality in Hospitalized Patients With AHFS

The average risk of death during hospital admission for AHFS is approximately 4% based on data from both ADHERE and OPTIMZE-HF.[11,63] Patients who are admitted with AHFS and require the administration of vasoactive drugs may have a poorer prognosis and an increased risk of death.[9,124] Patients requiring the use of inotropic agents had a mortality rate of 12% to 13% in ADHERE.[9] Intravenous vasodilators have demonstrated favorable acute hemodynamic effects but the impact on long-term morbidity and mortality remains unclear. The use of vasodilators has been associated with a mortality risk of 4.7% for nitroglycerin and 7.1% for nesiritide.[9] Risk factors for increased mortality during hospitalization include increasing age, elevated heart rate, hyponatremia, hypotension, left ventricular systolic dysfunction, elevated serum creatinine, blood urea nitrogen, natriuretic pep-

tides, and AHFS as the primary cause for admission.[9,34,63,125] An elevated cardiac troponin level has also been associated with nearly a 3-fold higher in-hospital mortality.[126] Several comorbidities have been identified with increased in-hospital mortality. These include liver disease, previous cerebrovascular events, peripheral vascular disease, and chronic obstructive lung disease. Factors associated with a more favorable prognosis during hospitalization for AHFS include hospital admission related to de novo AHFS and prehospitalization therapy with ACE inhibitors or β-blockers.[63]

Readiness for Discharge

Postdischarge morbidity and mortality in the first 60 to 90 days is significant, with patients who were followed up in OPTIMIZE-HF having a mortality rate of 8.6% and a rehospitalization rate of 29.6%.[127] In addition, among Medicare patients, HF is the most common reason for readmission within 30 days of discharge regardless of what prompted the index hospital episode.[95] To minimize postdischarge event rates, a thorough evaluation and consideration of precipitating factors of AHFS is encouraged. Identification of reversible causes, such as coronary artery disease or valvular dysfunction during hospitalization, may shorten hospital lengths of stay and minimize postdischarge morbidity and mortality. However, early, safe objective end points of hospital admissions are lacking. Current ADHF guidelines for ED and hospital disposition are based on limited empirical evidence.[64,110,128,129] This results in a great deal of clinical uncertainty regarding acute treatment and the end points to be achieved to safely discharge patients. The majority of patients are discharged based on the resolution of acute symptoms providing they have not developed high-risk markers such as worsening renal function, hypotension, or elevated troponins.

Beyond the questions of acute management of AHFS, however, lie unequivocal data regarding the benefit of traditional HF medical therapy including ACE inhibitors, angiotensin receptor antagonists, β-blockers, and selective aldosterone receptor antagonists. Early initiation of this therapy, before hospital discharge, with appropriate titration, improves symptoms, reduces hospitalizations, and saves lives. Nevertheless, these therapies remain underutilized[82] and several performance measures currently used to assess medical centers have not been associated with improved clinical outcomes.[130] Performance improvement programs can, however, increase utilization of optimal medical management.[131]

As an episode of AHFS is controlled, guideline-based therapies are initiated and the patient is prepared for discharge. A variety of concerns including economic, health, safety, and resource availability exert pressure to keep the length of stay as short as possible with many benchmarks between 3 and 4 days maximum, although the average length of stay was 4 to 5 days in the OPTMIZE-HF Registry.[63] There is a balance between timely and efficient healthcare delivery and that which results in premature discharge and early readmission. Patients who remain symptomatic from AHFS are at increased risk for repeated decompensation or other complications, including death soon after discharge.[127] Given the high risk of recidivism for AHFS, a planned transition to outpatient status with close follow-up by a HF clinic or specialist may be beneficial. Such a program should begin with education before discharge. Even 1 hour of nurse educator–delivered AHFS education has been shown to improve clinical outcomes, increase self-care, and reduce costs.[132] The optimal design of this follow-up care remains to be defined, but effective programs have included such components as outpatient clinic visits within days of discharge, nurse follow-up by phone or visit, ongoing management in a formal HF clinic, home telemetry devices to monitor vital signs, weight, and symptoms, and perhaps more sophisticated measures like hemodynamic and rhythm monitoring.[133–136]

Postdischarge: Ongoing Assessment and Avoiding Readmission

Patients with chronic HF remain at significant risk for morbidity and mortality despite the range of therapies currently available. These risks may be underappreciated not only by the patient, but also by the treating physician and, thus, objective methods of risk assessment and prognosis could be useful. Historically, prognostic assessments were principally used to identify optimal timing of cardiac transplantation in ambulatory New York Heart Association Class III patients. A number of multivariate prognostic models have been developed to better characterize a patient's ongoing risk. The Heart Failure Survival Score incorporates peak oxygen consumption, heart rate, mean arterial pressure, presence or absence of coronary disease, interventricular conduction defects, serum sodium concentration, and ejection fraction to characterize patients as low, medium, or high risk for 1-year urgent transplant or death without transplant.[137] The Seattle Heart Failure Model incorporates multiple variables with an internet-based risk calculator to estimate 1-, 2-, and 3-year mortality based on disease status and medical interventions.[138] A cardiopulmonary exercise testing score was devised that incorporates not only peak V_{O_2} but also V_E/V_{CO_2} slope, and resting end-tidal CO_2, and oxygen uptake efficiency slope in a multivariate model for predicting 1-year mortality, transplantation, left ventricular assist device implantation, and rehospitalization for AHFS.[139]

Readmission of a patient with chronic HF represents a deterioration in their clinical status that probably has prognostic significance.[140,141]It also represents an opportunity to assess changes in the status of their disease process, inciting factors such as arrhythmias and concomitant diseases such as pneumonia,[76] review of the medical regimen to ensure optimal management including device therapies, and assessment of patient compliance, social support, and patient reeducation. A variety of precipitating factors must be considered including: pulmonary infections, angina, hypertension, arrhythmias, medication nonadherence, diet nonadherence, and other noncardiac medical problems.[142–144] Predictors for repeat hospitalization in an elderly population include a HF admission within the previous year, diabetes mellitus, and serum creatinine >2.5.[127,145] Weight gain following discharge is also predictive of readmission for AHFS.[146] Rehospitalization for HF may also suggest inadequate treatment during a previous stay for AHFS.[147,148]

Integrated Care of the Heart Failure Team

Expertise in Patient Education and Reducing Recidivism: Advanced Practice Nurses, Dieticians, and Pharmacists

Dieticians, pharmacists, nurses, clinical nurse specialists, and nurse practitioners all play a key role in educating hospitalized HF patients and their families on the importance of medication adherence, sodium and fluid restrictions, smoking cessation, and self-care.[149–152] Inpatient education begins in the ED,[153] where the impact of the "teachable moment" may be highest,[154]and continues until discharge.[152] Although initiated in the inpatient setting, this education and counseling continues at outpatient follow-up visits as well. The Joint Commission performance measures mandate that, before being discharged home, all HF patients should receive comprehensive written discharge instructions or other educational materials that address activity level, diet, discharge medications, follow-up appointment, weight monitoring, and plans of what to do should symptoms worsen.[155] Although obligatory, the delivery of discharge information does not necessarily equate with the acquisition of self-care management skills or behaviors[156] fundamental to optimizing patient outcomes.[157]

Those involved in educating must actively engage patients, their family members, and primary caregivers to identify and address barriers to self-care management such as lack of motivation, complex medication regimens, cognitive impairment, low socioeconomic status, low educational level, and inadequate family and social support[157,158] to promote self-care and reduce recidivism.[152] To this end, advanced practice nurses (APNs), as part of a multidisciplinary team, emphasize evidence-based holistic care that integrates the family, the environment, and human responses to health and illness.[159] Strategies enacted by APNs to improve HF self-care management during hospitalization include visiting the patient daily, assessing patient and family knowledge, collaborating with the healthcare team and family, and assessing learning capabilities and style.[160,161] When combined with APN interventions that facilitate discharge planning and home follow-up care, this approach optimizes discharge planning, improves patient-provider communication, and reduces hospital readmission rates, mean costs, and negative outcomes.[160,161]

Shifting the Paradigm: Focused Areas for Future Investigation

Novel Diagnostics

The advent of natriuretic peptides has dramatically altered the diagnostic landscape for AHFS, adding objectivity to what previously had been a problematic approach.[28,31] However, these biomarkers are not devoid of limitations. Because natriuretic peptides are released in response to cardiac myocyte stress regardless of the underlying cause, they lack the specificity necessary to function as absolute indicators of AHFS, even when serum concentrations exceed established thresholds for diagnosis. Detectable quantities are subject to marked variance on the basis of age,[162] sex,[163] body habitus,[164] renal function,[39,165] and abruptness of symptom onset,[166] resulting in the potential for diagnostic errors and, within the context of research, misclassification bias. It has been suggested recently that natriuretic peptide utility can be enhanced through consideration of respective values as continuous rather than as dichotomous measures[167]; however, the incremental benefit of this has yet to be externally validated.[168,169]

The search for additional tools to improve the diagnostic accuracy for patients with undifferentiated dyspnea and possible AHFS remains a high priority. Much of this effort has centered on the identification of new serum biomarkers that enable assessment of neurohormonal activity, systemic inflammation, extracellular matrix composition, subcellular oxidative and metabolic stress, or acute cardiorenal injury. Unlike the natriuretic peptides, however, few of these biomarkers have been rigorously tested in the acute setting and their prospective clinical role, if any, is unclear. Other modalities such as electronic detection of third heart sounds (S_3) using acoustic cardiography,[170–172] noninvasive hemodynamic profiling using impedance cardiography,[173,174] bedside portable chest ultrasound to evaluate for accumulated interstitial lung fluid,[175–177] and quantitative capnometry[178] have been investigated as both stand-alone and adjunct diagnostic measures, but appear to provide little benefit over existing approaches. Cardiovascular response to the Valsalva maneuver has been proposed as an additional method by which ventricular filling pressures and volume status can be assessed[179,180] but its utility in AHFS management has not been well-defined.

Although often overlooked, the quest for novel diagnostics has been hindered by the absence of a uniformly accepted standard for diagnosis of AHFS. In most studies to date, investigators have used retrospectively applied criterion-based standards or blinded cardiology reviews with resolution of disagreement, accounting for approximately 10% of cases, by adjudicated expert consensus. Although practical, such methodology is suboptimal and may contribute to misleading conclusions regarding true test performance. The definitive diagnostic procedure, pulmonary artery catheterization, is simply not feasible in the ED and, given the unfavorable risk-to-benefit ratio,[118,123] unjustifiable for routine management or research-specific purposes in AHFS patients. Existing noninvasive alternatives to pulmonary artery catheterization such as impedance cardiography have not been shown to correlate sufficiently with regard to left ventricular filling pressures[174] and produce unreliable measurements in those with severe dyspnea or diaphoresis. Cardiac MRI is an emerging technology that can provide objective diagnostic information on heart anatomy, contractility and perfusion while enabling assessment of potential acute myocardial injury and residual tissue viability.[181] These attributes hold promise for the future of cardiac MRI as an objective test in patients with AHFS. However, at present, applicability is limited by high acquisition costs, technical demands, sparse availability, and the difficulty of acutely dyspneic patients lying flat for prolonged periods.

Echocardiography can provide a substantial amount of information regarding cardiac structure and function and is considered a critical component of the workup for patients with suspected AHFS.[182,183] Echocardiography also enables categorization of AHFS patients into traditional subgroups based on left ventricular ejection fraction (ie, preserved or reduced) and may provide important information about vol-

ume status by assessing measurements and changes in size of the inferior vena cava.[184–187] Although not included in any of the criterion-based standards, echocardiographic parameters of systolic and diastolic dysfunction may be, in the proper clinical context, highly suggestive of AHFS. Echocardiogram findings clearly contribute to the criterion standard diagnosis in AHFS diagnostic trials. Further, HF with preserved systolic function (HFPSF) is prevalent, accounting for approximately 50% of hospital admissions for AHFS. In-hospital mortality rates appear to be slightly lower (3% in OPTIMIZE-HF and 2.8% in ADHERE) when compared with rates in patients with left ventricular systolic dysfunction. Length of stay and rates of readmission are similar.[11,188] It will be important to enroll and further characterize patients with AHFS and HFPSF to improve the evidence base that influences clinical care.

Despite its clear utility in AHFS, access to formal echocardiography performed in the ED outside of weekday daytime hours is rare. Reasons may vary, but most hospitals across the country simply do not have the available resources and personnel. Over the past decade, however, there has been rapid expansion in point-of-care ultrasound expertise among ED providers. Achievement of basic proficiency is now considered a requisite skill for all emergency medicine residency graduates. Accordingly, there is growing interest among ED providers in the potential applicability of limited cardiac ultrasonography in patients with suspected AHFS. Prior studies have shown that, after a brief period of focused training, emergency physicians can competently estimate ejection fraction[189] and accurately perform Doppler analysis of mitral inflow,[189,190] thereby permitting rapid definition of global cardiac function. This capability would: (a) help direct appropriate intervention to the right patient, (b) delineate structure/function in the heart before the initiation of therapy, and (c) improve understanding of the phenotypes of AHFS.[18] If coupled with thoracic ultrasound[191] and left atrial volume measurement,[192–194] a real-time, noninvasive depiction of lung fluid burden as it relates to underlying cardiac dysfunction and acute left ventricular filling pressure could be obtained. Interpreted within the context of ED blood pressure, which is both a primary manifestation of AHFS etiology[186,195–197] and a critical determinant of outcome,[12,103] and information derived from interrogation of implanted monitoring devices, if present, a phenotype-oriented approach to management may be achievable.[60,61]

Novel Approaches to Therapy

Based on an improved understanding of AHFS pathophysiology, lessons learned from largely disappointing clinical trials (Table 2), and the high postdischarge event rate, it is clear that novel approaches and strategies are needed.[198] Such strategies should be aligned with appropriate end points that are based on the mechanism of action and goals of the intervention. Furthermore, they should be designed to address the potential time-dependent nature of AHFS management, the importance of which, in contrast to acute coronary syndrome (ACS) care, has not been well explored. Previous retrospective studies suggest that time to treatment may be important in AHFS, but it must be prospectively studied to determine its impact on outcomes.[199–200] It is important to note that past clinical trials in AHFS have largely bypassed the ED phase of management, enrolling patients 24 to 48 hours after admission. Depending on the drug's pharmacodynamic properties, it is possible that a therapeutic window exists beyond which apparent efficacy is diminished. For dyspnea relief, a key end point in AHFS,[83,202] this may be particularly true. Current therapeutic trials targeting dyspnea relief have significantly shortened the time window of enrollment to capture patients when symptoms are most severe—on ED presentation.[202,203]

Goals of ED Management

Although preliminary data suggest that prompt ED intervention impacts outcomes in terms of in-hospital morbidity and mortality,[200,201] it is not clear whether this extends to more intermediate-term outcomes, such as 30- to 60-day rehospitalization, or mortality. After addressing immediate life-threatening conditions, the current approach to ED management moves quickly to a focus on symptomatic improvement, which drives subsequent therapeutic decisions. Intermediate-term goals therefore become a secondary priority. It is possible, however, that such outcomes could be influenced by ED management, especially if it were to produce either of the following: (1) sufficient interruption of a pathophysiologic process that actively contributes to the acute, decompensated state; or (2) significant unwanted downstream effects such as renal or myocardial injury. Although existing data regarding these considerations are limited, understanding how acute therapy impacts underlying cardiorenal function and hemodynamic end points is critical to the development of more progressive, outcome-oriented AHFS care.

Patient Characterization

A more complete understanding of patients at the time of presentation and their response to current management is needed to better target future research. Current clinical profiles are largely based on inpatient hospital registries[204–206] but these do not include important information on acute cardiac function, which may be available via focused bedside echocardiogram, nor do they provide data on immediate and short-term responses to standard ED therapy. Consequently, the natural history of ED patients hospitalized for AHFS is not well described. We are in need of comprehensive clinical, laboratory, and neurohormonal data from the time of ED presentation through the postdischarge phase. A prospective observational database that includes these parameters, as well as the ability to investigate novel cardiac and renal injury biomarkers, would help address this knowledge gap and add substantially to our current appreciation of AHFS. Results could then be used as a guide to define clinical profiles and guide short-term management (Table 3).[4,21] Nitrates, for example, might be used in higher relative doses to diuretics in the hypertensive profile, or ultrafiltration could be used in the diuretic-resistant patient.[207,208] Conversely, inotropic agents should be considered in the rarer cases of advanced/low-output HF. Several different profiles have been suggested for future subcategorization.[5,21] The European Society of Cardiology[66] suggests that patients can be categorized into 6 possible profiles, with overlap between categories: (1) worsen-

Table 2. Summary of Previous AHFS Clinical Trials From the Past Decade

Study Acronym	Year of Publication	Primary End Point	Key Secondary End Points
VMAC[240]	2002	Coprimary 1. Change in PCWP at 3 h 2. Change in dyspnea (Likert) at 3 h	PCWP at 24 h, dyspnea at 24 and 48 h, global clinical status
OPTIME-CHF[241]	2002	Cumulative days of hospital stay for cardiovascular cause or days dead within 60 d after random selection	Proportion of cases in which therapy failed because of adverse events or worsening heart failure (sustained SBP ≥80 mm Hg, myocardial ischemia, arrhythmias, persistent CHF, inadequate diuresis, organ hypoperfusion), HF score, global health (VAS)
ESCAPE[118]	2005	Days alive and out of hospital during the first 6 mo	Adverse events related to catheter use, 6-min walk duration, QOL via time trade-off, and MLHF
VERITAS[242]	2007	Coprimary 1. Change in dyspnea (at 3, 6, and 24 h with VAS 0–100) over 24 h (area under the curve) 2. Death or worsening heart failure (pulmonary edema, shock, new or 1 intravenous therapy, mechanical cardiac or pulmonary support, renal replacement therapy) at 7 d	Death or major cardiovascular events at 30 d; improved hemodynamic measures over 24 h; LOS; days hospitalized within 30 d; 6-mo mortality
SURVIVE[243]	2007	All-cause mortality at 180 d	All-cause mortality at 31 d; days alive or out of hospital at 180 d; cardiovascular mortality at 180 d; change in BNP level at 24 h; dyspnea at 24 h; patient-assessed global assessment at 24 h
REVIVE-II[244]	Not yet published (presented 2005)	Composite of clinical signs and symptoms of HF over 5 d expressed as 3-stage end point: 1. Better (moderately or markedly improved global assessment at 6 h, 24 h, and 5 d with no worsening) 2. Same 3. Worse (death from any cause, persistent or worsening HF requiring intravenous diuretic agents, vasodilators, or inotropes at any time; or moderately or markedly worse patient global assessment at 6 h, 24 h, or 5 d)	Change in BNP; mortality at 90 d
EVEREST[80,245]	2007	Short-term composite: changes in global clinical status (by VAS) and body weight at day 7 or discharge. Long-term dual end points: 1. All-cause mortality (superiority and noninferiority) 2. Cardiovascular death or HF hospital stay (superiority only)	Composite components in isolation at days 1 and 7 or discharge; dyspnea at day 1; peripheral edema at day 7 or discharge; KCCQ at 1 wk and 6 mo; body weight; changes in serum sodium
ASCEND-HF[246]	Enrolling	Coprimary 1. Composite of all-cause mortality and HF repeat hospital stay through 30 d 2. Dyspnea at 6 and 24 h	Overall well-being (Likert) 6 and 24 h; days alive and outside of hospital within 30 d
PROTECT I and II[247]	Completed, presented 2009 not yet published	Composite of clinical signs and symptoms of HF over 7 d expressed as 3-stage end point: 1. Better (moderately or markedly improved global assessment at 24 and 48 h with no worsening) 2. Same 3. Worse (death from any cause, persistent or worsening heart failure through day 7, or creatinine increase ≥0.3 mg/dL at 7 and 14 d)	Safety; within trial costs

PCWP indicates pulmonary capillary wedge pressure; SBP, systolic blood pressure; CHF, congestive heart failure; QOL, quality of life; MLHF, Minnesota Living with Heart Failure Questionnaire; VAS, Visual Analog Scale; LOS, length of stay; BNP, b-type natriuretic peptide; and KCCQ, Kansas City Cardiomyopathy Questionnaire.

Adapted from Allen et al,[198] with permission from Elsevier. Copyright 2009, American College of Cardiology.

Table 3. Presenting Profiles in Emergency Department Patients With AHFS

Clinical Presentation	Incidence*	Characteristics	Targets† and Therapies‡
Elevated BP (>160 mm Hg)	≈25%	Predominantly pulmonary (radiographic/clinical) with or without systemic congestion. Many patients have preserved EF	Target: BP and volume management Therapy: vasodilators (eg, nitrates§, nesiritide, nitroprusside) and loop diuretics
Normal or moderately elevated BP	≈50%	Develop gradually (days or weeks) and are associated with systemic congestion. Radiographic pulmonary congestion may be minimal in patients with advanced HF	Target: volume management Therapy: loop diuretics±vasodilators
Low BP (<90 mm Hg)	<8%	Mostly related to low cardiac output and often associated with decreased renal function.	Target: cardiac output Therapy: inotropes with vasodilatory properties (eg, milrinone, dobutamine, levosimendan); consider digoxin (intravenous and/or orally)±vasopressor medications±mechanical assist devices (eg, IABP)
Cardiogenic shock	<1%	Rapid onset. Primarily complicating acute MI, fulminant myocarditis, acute valvular disease.	Target: improve cardiac pump function Therapy: inotropes±vasoactive medications±mechanical assist devices, corrective surgery
Flash pulmonary edema	3%‖	Abrupt onset. Often precipitated by severe systemic hypertension. Patients respond readily to vasodilators and diuretics.	Target: BP, volume management Therapy: vasodilators, diuretics, invasive or NIV, morphine¶
ACS and AHFS	≈25% of ACS have HF signs/symptoms	Rapid or gradual onset. Many such patients may have signs and symptoms of HF that resolve after resolution of ischemia.	Target: coronary thrombosis, plaque stabilization, correction of ischemia Therapy: reperfusion (eg, PCI, lytics, nitrates, antiplatelet agents)
Isolated right HF from pulmonary HTN or intrinsic RV failure (eg, infarct) or valvular abnormalities (eg, tricuspid valve endocarditis)	?	Rapid or gradual onset due to primary or secondary PA hypertension or RV pathology (eg, RV infarct). Not well characterized with few epidemiological data.	Target: PA pressure Therapy: nitrates, epoprostenol, phosphodiesterase inhibitors, endothelin-blocking agents, coronary reperfusion for RV infarcts, valve surgery
Postcardiac surgery HF	?	Occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery and the subsequent early postoperative interval. Can also be caused by inadequate intraoperative myocardial protection resulting in cardiac injury.	Target: volume management, improve cardiac performance (output) Therapy: diuretic or fluid administration (directed by filling pressures and cardiac index), inotropic support, mechanical assistance (IABP, VAD)

ACS indicates acute coronary syndromes; AHFS, acute heart failure syndromes; EF, ejection fraction; HTN, hypertension; IABP, intraaortic balloon pump; MI, myocardial infarction; NIV, noninvasive ventilation; PA, pulmonary artery; RV, right ventricle; VAD, ventricular assist device.

*Of all AHFS admissions.

†Treating etiology or precipitant is of equal of greater importance (eg, arrhythmia, ACS, infection).

‡Represents initial therapies for early management and should be tailored to each patient's unique presentation.

§Probably preferred in patients with ACS or history of CAD.

‖Its incidence may be related to the definition used (clinical vs radiographic).

¶Avoid if retaining CO_2.

Data from Gheorghiade and Pang[4] and Gheorghiade et al.[58]

ing or decompensated chronic HF, (2) cardiogenic pulmonary edema, (3) hypertensive AHFS, (4) cardiogenic shock, (5) isolated right HF, and (6) AHFS with ACS.[66] Although specific goals for each phenotype have not been well-established, increasing evidence suggests that hypotension and tachycardia should be avoided, especially in patients with coronary artery disease.[209,210] Whether management by profile leads to improved short- or long-term outcomes versus current management requires further study before broad implementation.

Importantly, clinical profiles may not take into account the underlying substrate or etiology of the patient's chronic HF. For example, a common clinical profile is hypertensive HF, but should the presence or absence of systolic dysfunction or coronary artery disease further refine management? It has recently been suggested that patients be further classified according to the ACC/AHA stages of HF (Table 4).[5,211] These stages account for the underlying substrate and promote certain therapeutic options and considerations but whether this is important to consider in the early phase of management is not known. Further, detailed echocardiographic data regarding cardiac structure and function may not be available on all patients, limiting the feasibility of directing therapy based on HF stages.

Table 4. ACC/AHA Stages of Heart Failure

A: At high risk for HF but without structural heart disease or symptoms of HF
B: Structural heart disease but without signs or symptoms of HF
C: Structural heart disease with prior or current symptoms of HF
D: Refractory HF requiring specialized interventions

Novel Risk Stratification: Low-Risk, Not High-Risk Markers Are Necessary

Previous and ongoing research continues to identify individual markers of high risk associated with adverse events. The recurrent theme is obvious—hypotension, hyponatremia, renal dysfunction, increased troponin levels, and elevated natriuretic peptides all portend a poor prognosis.[12,31,34,103,104,107,126,142,212,213] Unfortunately, markers of high risk rarely impact acute decision making, especially when prognosticating for events 6 to 12 months in the future. Although we know that these markers identify patients at risk for subsequent events, how does this impact disposition decisions? When risk is not immediate (ie, in-hospital morbidity or mortality), such markers have little bearing on the administration of acute therapy or the triage level for inpatient care. Stated another way, when emergency physicians are already admitting 4 of every 5 patients with AHFS to the hospital, will markers of high risk really alter practice patterns? Such data may prompt initiation of life-saving therapies such as β-blockers or ACE inhibitors before hospital discharge, but these efforts would only modify intermediate- to long-term risk.

In essence, the absence of high-risk markers does not, by default, define a low-risk patient. Decision making for this large cohort of patients without high-risk features (ie, those with normal troponins, serum sodium, and renal function) has not been well studied. Can they be safely discharged directly from the ED or should they be managed in an observation unit? What if they have poor social support or lack access to timely outpatient follow-up? Biomarkers have emerged over the past decade as an effective means of stratifying patients with AHFS and, to varying degrees, may be useful for determination of immediate or short-term risk. According to Morrow and de Lemos for a biomarker to be clinically useful it must meet the following 3 criteria: (1) accuracy on repeated measurements and available at a reasonable cost, (2) provision of additional information not already available from careful clinical assessment, and (3) the measured level should aid in decision making.[214] Millions of dollars are spent and many papers are published in an attempt to delineate criteria 1 and 2; however, when 80% of patients are ultimately admitted, it appears that few if any AHFS prognostic biomarkers have fulfilled criteria 3 in terms of risk stratification. We clearly need to identify sensitive, meaningful markers with strong negative likelihood ratios that can identify patients who are truly at low risk for adverse events and can be safely discharged home.

Predictive Instruments May Be the Answer

Although physicians and nurses exhibit intermediate accuracy for prediction of postdischarge death, their ability to estimate other metrics of risk such as need for subsequent rehospitalization is poor.[215] Given the heterogeneity of the AHFS population, it is unlikely that any single biomarker will supersede others to such a degree that it will be the sole discriminator of discharge eligibility. Predictive instruments represent the most likely method of successfully defining low-risk AHFS patients. "Medical decision making" is the science of statistically examining detailed clinical data to develop mathematical models or predictive instruments to guide appropriate clinical care of patients with complex diseases.[216–219] By accounting for commonly overlooked factors such as socioeconomic status and healthcare access, such predictive instruments can reduce the margin of error and increase the likelihood that clinicians will successfully identify those who are truly at low risk. Because such predictive instruments are meant to aid, not replace, clinical decisions, they can complement the often relied on gestalt approach to patient care, supporting (or refuting) physician beliefs regarding stability for outpatient management. An example of the potential utility of an AHFS predictive instrument was recently published by Hsieh and colleagues. They retrospectively analyzed an administrative database to derive and validate a predictive instrument that identified 19.2% of AHFS patients at low risk for 30-day adverse events.[109] Their validated model incorporated vital signs, renal function, white blood cell count, and glucose as risk predictors. Events were infrequent in the low-risk cohort with inpatient mortality, in-hospital complication, and 30-day mortality rates of 0.7%, 1.7%, and 2.9%, respectively.

These results notwithstanding, a prospectively derived, multicenter, ED risk stratification model for patients with signs and symptoms of HF is needed. Data suggest that emergency physicians would be comfortable discharging a patient if there was a combined overall risk of in-hospital events or 30-day mortality of $<2\%$.[220] Prospectively performed studies collecting ED-based data are needed to confirm preliminary findings and facilitate safe, early ED discharge. Such an approach, which is the focus of 2 ongoing National Heart, Lung, and Blood Institute grants being directed by emergency medicine investigators,[223] has proven effective at safely decreasing admissions for low-risk patients with other disease processes such as acute coronary syndromes[222–224] and community-acquired pneumonia.[225–227] Inherent to this is the need to alter risk-stratification standards from prediction of remote adverse events (eg, 90 days, 1 year), which are highly dependent on subacute to chronic care and patient behavior, to those which occur sooner (eg, within 14 days) and are more likely to be associated with the patient's acute HF episode.[106,142,145,228–232] Similar to the use of repeat troponin measurement or assessment of myocardial viability for acute coronary syndromes,[224] incorporation of objective, evidence-based end points into evolving predictive instruments will provide important information regarding near-term risk that could, at last, be appropriately used in the acute setting to identify AHFS patients who are safe for early ED, observation unit, and hospital discharge.

ED Enrollment of Patients With AHFS

It has become clear that there are many unanswered questions regarding ED care of the patient with AHFS. Evidence-based guidelines are needed for diagnostic, therapeutic, and disposition decision making. To conduct the clinical trials necessary to develop the foundation for an adequate evidence base, researchers will have to enroll patients early in their AHFS presentation,

while they are still in the ED. Some view the ED as too chaotic of an environment to successfully screen, consent, and enroll patients. This is often the reason identified as the primary barrier to conducting clinical trials in the ED.[3] However, this has been found to be largely untrue. Careful planning is necessary so that identification and enrollment in the ED is followed by transition of the patient to an inpatient research team that assumes or shares the trial duties with the ED team. An example of this team approach is the Emergency Management and Research Group in Acute Heart Failure (EMERG-HF).[3] This model, in general, uses 2 physicians to lead an interdisciplinary team of emergency physicians, cardiologists, research nurses, study coordinators, and research assistants. The emergency medicine team is responsible for screening, consenting, and performing randomization, as well as providing the initial care and data collection. Although dependent on bed availability, when the patient is admitted to the hospital, the care and trial responsibilities are transferred to the cardiology team.

Depending on departmental research infrastructure, there are a few different ED methods of screening and enrolling patients. One cost-efficient process of enrollment uses study assistants to perform the initial screening. Once the patient passes initial screening, the study team (nurse and/or physician) is activated to complete the screening process and consent and enroll the patient. Another alternative is to have a research nurse perform both screening and enrollment. This model is usually used when there are multiple research protocols going on simultaneously, allowing the research nurse to screen for more than one trial, and maximizing opportunities for enrollment.

Another issue to consider is a patient's capacity to provide informed consent, which may impede enrollment depending on the severity of the acute illness. However, these issues are surmountable with proper planning before trial initiation. Over the past decade processes for satisfying regulatory requirements have gone through rigorous review and are now well developed.[3,83,170,221] In extreme cases, when a patient's decision making capacity is expected to be so impaired as to impede the consenting process, exception from informed consent may be necessary. Exception from informed consent requires significant resource allocation to obtain community input regarding the trial, but allows inclusion of patients who otherwise could not be enrolled.

Successful ED enrollment requires a coordinated effort involving the physicians, nurses, and study assistants of both emergency medicine and cardiology. Delineation of responsibilities and coordination of an on-call schedule for the study team is critical for success. These processes often require several weeks of meetings before trial commencement. However, once the infrastructure is put into place, it can be easily adapted from one trial to the next.

Summary

The economic burden of HF and AHFS on the healthcare system continues to increase. The vast majority of patients hospitalized for AHFS present to the ED. As a result, emergency medicine physicians have become the gatekeepers for patients with AHFS. It is clear there are many unanswered questions about the optimal workup, treatment, and disposition of the ED patient with AHFS. Although there have been significant life-sustaining advancements in the outpatient management of chronic HF, with the exception of natriuretic peptide testing, there have been no significant breakthroughs in AHFS care in the past several decades. Despite the profound heterogeneity in AHFS presentations, therapeutic options for patients with AHFS have remained largely unchanged during this time period; AHFS therapy continues to focus on fluid removal with intravenous diuretics. Even though this produces early and sustained improvement in symptoms in the majority of ED patients with AHFS, its downstream impact on renal and myocardial function, hemodynamics, and short-term outcomes has not been rigorously studied in the acute setting.

Table 5. A Comparison of Characteristics, Pathophysiologic Targets of Therapy and Evidence in Management of Patients With ACS and AHFS

	ACS	AHFS
Incidence	1 million/y	1 million/y
Mortality		
Prehospital	High	?
In-hospital	3%–4%	3%–4%
60–90 d	2%	10%
Targets of therapy	Clearly defined-thrombosis	Unclear
Clinical trial results	Beneficial	Minimal, no benefit, harmful
ACC/AHA Guidelines	Level A	Minimal level A/B, mostly C

Several possible reasons exist for the lack of improvement in AHFS care and the disappointing results of clinical trials.[3] However, a common link among all of these trials has been a universal paucity of ED enrollment. Although acute therapy and symptomatic improvement occurs in less than 6 hours in the vast majority of patients, patients are typically randomly assigned to therapeutic trials long after this time.[83] Initial therapy remains largely unaccounted for in trial design despite its impact on symptoms and its association with untoward events such as renal insufficiency and hypotension.[7,89–91] Disease management programs have targeted the high-risk hospitalized patient, but have failed to enroll the ED patient who may be discharged home, where socioeconomic barriers are also prevalent and result in a high 30-day recidivism.[230,233]

ED patients have not been enrolled in AHFS trials largely because of a misconception about the inability to enroll patients in the ED early in their course of therapy. This view has been found to be largely inaccurate. Emergency physicians have a track record of enrolling complex patients in a variety of therapeutic trials for ACS, major trauma, acute ischemic stroke, and recently AHFS.[72,203,234–236] This critical momentum needs to continue through partnerships with cardiology, which will ensure continuity in clinical trial management and improvement in AHFS care as patients transition from the ED through hospitalization to hospital discharge. These collaborations need to begin at the local level and extend to national and international trial design and conduct.

Our current approach to AHFS is similar to the approach to ACS preceding the understanding of coronary artery pathophysiology (Table 5). Elucidation of the pathophysiology, in conjunction with ED-based intervention trials of

thrombolytic therapy and angioplasty, has resulted in a marked improvement in patient outcomes.[237–239] Our diagnostic, treatment, and disposition decision making has changed dramatically over the past 20 years, resulting in many patients with low-risk ACS features being evaluated and discharged either directly from the ED or after a brief stay in an ED-based observation unit. Given the complexity of AHFS patients, the pathophysiologic target is likely multifactorial, but we need a systematic approach to understanding the interaction between AHFS management decisions and their impact on outcomes. As the number of patients with HF and AHFS continues to grow, it is imperative that ongoing therapeutic trials and management strategies address the significant knowledge gaps that currently exist in AHFS care if we expect to deliver evidence-based care and improve clinical outcomes.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Neal L. Weintraub	University of Cincinnati	None	None	None	None	None	None	None
Sean P. Collins	University of Cincinnati	Abbott Point of Care†; Brahms Diagnostics*; NIH/NHLBI†	None	None	None	None	Abbott Point of Care*; Bayer Pharmaceuticals*; The Medicines Co.*	None
Allen S. Anderson	University of Chicago Medical Center	None	None	Johnson & Johnson/Scios*	Medical malpractice case review on cardiac transplant prognosis*	None	None	None
Cynthia Arslanian-Engoren	University of Michigan School of Nursing	Blue Cross Blue Shield of Michigan†	None	None	None	None	None	None
Gary S. Francis	University of Minnesota	None	None	None	None	None	Sanofi-Aventis*	DSMBs for Novartis*; Corthera*
Mihai Gheorghiade	Northwestern University	None	None	None	None	None	Bayer Schering Pharma AG†; DebioPharm S.A.†; Medtronic†; Novartis Pharma AG†; Otsuka Pharmaceuticals†; Sigma Tau†; Solvay Pharmaceuticals†; PeriCor Therapeutics†	None
W. Brian Gibler	University of Cincinnati College of Medicine	AstraZeneca†; Bristol-Myers Squibb†; Sanofi-Aventis†; Schering Plough†	None	None	None	Inovise*	AstraZeneca*; Daiichi Sankyo/Lilly*; Schering Plough*	None
Phillip D. Levy	Wayne State University	Astellas Pharm Inc.*; Corthera Inc.*; Nile Therapeutics*; Solvay Pharmaceuticals*	None	The Society of Chest Pain Centers*	None	None	Bayer Schering Pharma AG*; Corthera, Inc*; EKR Therapeutics*; The Medicines Co.*	None
James K. McCord	Henry Ford Health System	Brahms Diagnostic*; Nanosphere*; Siemens*	None	Biosite Diagnostics*	None	None	None	None
Peter S. Pang	Northwestern Memorial Faculty Foundation	Merck†	None	Corthera Inc.*; Supplement sponsored by Otsuka and Abbott*; The Society of Chest Pain Centers*	Provided expert witness review of a case involving sepsis management (1 case only)	None	Astellas†; Bayer†* Johnson & Johnson*; Palatin Technologies*; PeriCor Therapeutics*; Solvay Pharmaceuticals†	DSMB for the Medicines Co.*
Mark B. Parshall	University of New Mexico	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Brian Hiestand	Ohio State University	Biosite Inc.*; Inovise Medical*; Medtronic*; The Medicines Company*	Inovise Medical*	None	None	None	newMentor, a medical writing/editing company that makes frequent use of the ACC/AHA guidelines*	None
Jim Januzzi	Massachusetts General Hospital	Roche Diagnostics†; Siemens†; Critical Diagnostics*	None	None	None	None	Roche Diagnostics*; Critcal Diagnostics*	None
Donna Mancini	Columbia University	None	None	None	None	None	Celladon†	None
Frank Peacock	Cleveland Clinic Foundation	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "Significant" if (a) the person receives $10 000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.

*Modest.

†Significant.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2010 Update: a report from the American Heart Association. *Circulation.* 2010;121:e46–e215.
2. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2006. *Natl Health Stat Report.* 2008;1–29.
3. Collins SP, Levy PD, Lindsell CJ, Pang PS, Storrow AB, Miller CD, Naftilan AJ, Thohan V, Abraham WT, Hiestand B, Filippatos G, Diercks DB, Hollander J, Nowak R, Peacock WF, Gheorghiade M. The rationale for an acute heart failure syndromes clinical trials network. *J Card Fail*. 2009;15:467–474.
4. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol*. 2009;53:557–573.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009; 119:e391–e479.
6. Gibbons RJ, Smith S, Antman E; American College of Cardiology; American Heart Association. American College of Cardiology/American Heart Association clinical practice guidelines: part I: where do they come from? *Circulation.* 2003;107:2979–2986.
7. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure–is it all about fluid accumulation? *Am Heart J*. 2008;155:9–18.
8. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359:142–151.
9. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J; ADHERE Scientific Advisory Committee and Investigators; ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol*. 2005;46:57–64.
10. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M, ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:1943–1950.
11. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. 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.
12. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217–2226.
13. Peacock WF, Braunwald E, Abraham W, Albert N, Burnett J, Christenson R, Collins S, Diercks D, Fonarow G, Hollander J, Kellerman A, Gheorghiade M, Kirk D, Levy P, Maisel A, Massie BM, O'Connor C, Pang P, Shah M, Sopko G, Stevenson L, Storrow A, Teerlink J. National Heart, Lung, and Blood Institute working group on emergency department management of acute heart failure: research challenges and opportunities. *J Am Coll Cardiol*. 2010;56:343–351.
14. ACC/AHA Task Force on Practice Guidelines. *Manual for ACC/AHA Guideline Writing Committees: Methodologies and Policies from the ACC/AHA Task Force on Practice Guidelines.* Available at: http://www.americanheart.org/presenter.jhtml?identifier=3039684. Accessed December 26, 2009.
15. Kapoor JR, Perazella MA. Diagnostic and therapeutic approach to acute decompensated heart failure. *Am J Med*. 2007;120:121–127.
16. Gheorghiade M, Mebazaa A. The challenge of acute heart failure syndromes. *Am J Cardiol.* 2005;96:86G–89G.
17. Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. *Am J Cardiol.* 2005;96: 32G–40G.
18. Mebazaa A, Gheorghiade M, Pina IL, Harjola VP, Hollenberg SM, Follath F, Rhodes A, Plaisance P, Roland E, Nieminen M, Komajda M, Parkhomenko A, Masip J, Zannad F, Filippatos G. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med*. 2008; 36(suppl):S129–S139.
19. Neuenschwander JF 2nd, Baliga RR. Acute decompensated heart failure. *Crit Care Clin.* 2007;23:737–758, vi.
20. Peacock WF, Soto-Ruiz KM. Risk stratification for suspected acute coronary syndromes and heart failure in the emergency department. *Acute Card Care.* 2009;11:138–145.
21. Collins S, Storrow AB, Kirk JD, Pang PS, Diercks DB, Gheorghiade M. Beyond pulmonary edema: diagnostic, risk stratification, and treatment challenges of acute heart failure management in the emergency department. *Ann Emerg Med*. 2008;51:45–57.
22. Diercks DB, Peacock WF, Kirk JD, Weber JE. ED patients with heart failure: identification of an observational unit-appropriate cohort. *Am J Emerg Med*. 2006;24:319–324.
23. Peacock WF. Using the emergency department clinical decision unit for acute decompensated heart failure. *Cardiol Clin.* 2005;23:569–588, viii.
24. Collins SP, Lindsell CJ, Storrow AB, Abraham WT. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. *Ann Emerg Med*. 2006;47:13–18.

25. Bruneau BG, Piazza LA, de Bold AJ. BNP gene expression is specifically modulated by stretch and ET-1 in a new model of isolated rat atria. *Am J Physiol*. 1997;273(pt 2):H2678–H2686.
26. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med*. 1998;339:321–328.
27. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, Ogawa H, Okumura K, Mukoyama M, Nakao K. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation.*1994;90:195–203.
28. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161–167.
29. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol*. 2003;42:728–735.
30. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol*. 2001;37:379–385.
31. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, Tung R, Cameron R, Nagurney JT, Chae CU, Lloyd-Jones DM, Brown DF, Foran-Melanson S, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol*. 2005;95:948–954.
32. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647–654.
33. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, Duc P, Westheim A, Omland T, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation.* 2002;106:416–422.
34. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006;27:330–337.
35. Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *Am J Cardiol*. 2008;101:29–38.
36. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. *Heart.* 2005;91:606–612.
37. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, Gordon G, Bagg W, Oxenham H, Yandle T, Richards M, Sharpe N. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol*. 2003;42:1793–1800.
38. Januzzi JL Jr, Sakhuja R, O'Donoghue M, Baggish AL, Anwaruddin S, Chae CU, Cameron R, Krauser DG, Tung R, Camargo CA Jr, Lloyd-Jones DM. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. *Arch Intern Med*. 2006;166:315–320.
39. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS; Breathing Not Properly Multinational Study Investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis*. 2003;41:571–579.
40. Lamb EJ, Vickery S, Price CP. Amino-terminal pro-brain natriuretic peptide to diagnose congestive heart failure in patients with impaired kidney function. *J Am Coll Cardiol*. 2006;48:1060–1061.
41. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardman SM, Dargie HJ, Cowie MR. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail*. 2005;7:537–541.
42. Ray P, Arthaud M, Birolleau S, Isnard R, Lefort Y, Boddaert J, Riou B. Comparison of brain natriuretic peptide and probrain natriuretic peptide in the diagnosis of cardiogenic pulmonary edema in patients aged 65 and older. *J Am Geriatr Soc*. 2005;53:643–648.
43. Brueckmann M, Huhle G, Lang S, Haase KK, Bertsch T, Weiss C, Kaden JJ, Putensen C, Borggrefe M, Hoffmann U. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. *Circulation.* 2005;112:527–534.
44. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation.* 2000;102:865–870.
45. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg G, Westheim A, Knudsen CW, Perez A, Kazanegra R, Bhalla V, Herrmann HC, Aumont MC, McCullough PA; BNP Multinational Study Investigators. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J*. 2004;147:1078–1084.
46. Tulevski II, Hirsch A, Sanson BJ, Romkes H, van der Wall EE, van Veldhuisen DJ, Buller HR, Mulder BJ. Increased brain natriuretic peptide as a marker for right ventricular dysfunction in acute pulmonary embolism. *Thromb Haemost.* 2001;86:1193–1196.
47. Knudsen CW, Clopton P, Westheim A, Klemsdal TO, Wu AH, Duc P, McCord J, Nowak RM, Hollander JE, Storrow AB, Abraham WT, McCullough PA, Maisel AS, Omland T. Predictors of elevated B-type natriuretic peptide concentrations in dyspneic patients without heart failure: an analysis from the breathing not properly multinational study. *Ann Emerg Med*. 2005;45:573–580.
48. McCord J, Mundy BJ, Hudson MP, Maisel AS, Hollander JE, Abraham WT, Steg PG, Omland T, Knudsen CW, Sandberg KR, McCullough PA. Relationship between obesity and B-type natriuretic peptide levels. *Arch Intern Med*. 2004;164:2247–2252.
49. Bayes-Genis A, DeFilippi C, Januzzi JL Jr. Understanding amino-terminal pro-B-type natriuretic peptide in obesity. *Am J Cardiol*. 2008;101:89–94.
50. O'Hanlon R, O'Shea P, Ledwidge M, O'Loughlin C, Lange S, Conlon C, Phelan D, Cunningham S, McDonald K. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *J Card Fail*. 2007;13:50–55.
51. Wu AH, Smith A, Apple FS. Optimum blood collection intervals for B-type natriuretic peptide testing in patients with heart failure. *Am J Cardiol*. 2004;93:1562–1563.
52. Wu AH, Smith A. Biological variation of the natriuretic peptides and their role in monitoring patients with heart failure. *Eur J Heart Fail*. 2004;6:355–358.
53. Wu AH. Serial testing of B-type natriuretic peptide and NTpro-BNP for monitoring therapy of heart failure: the role of biologic variation in the interpretation of results. *Am Heart J*. 2006;152:828–834.
54. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med*. 2006;166:1081–1087.
55. Moe GW, Howlett J, Januzzi JL, Zowall H; Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) Study Investigators. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation.* 2007;115:3103–3110.
56. Singer AJ, Birkhahn RH, Guss D, Chandra A, Miller CD, Tiffany B, Levy P, Dunne R, Bastani A, Thode HC Jr, Hollander JE. Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II): a randomized controlled trial of the effect of serial B-type natriuretic peptide testing on patient management. *Circ Heart Fail*. 2009;2:287–293.
57. Lokuge A, Lam L, Cameron P, Krum H, de Villiers S, Bystrzycki A, Naughton MT, Eccleston D, Flannery G, Federman J, Schneider HG. B-type natriuretic peptide testing and the accuracy of heart failure diagnosis in the emergency department. *Circ Heart Fail.* 2010;3:104–110.

58. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L. Acute heart failure syndromes: current state and framework for future research. *Circulation.* 2005;112:3958–3968.
59. Zannad F, Mebazaa A, Juilliere Y, Cohen-Solal A, Guize L, Alla F, Rouge P, Blin P, Barlet MH, Paolozzi L, Vincent C, Desnos M, Samii K; EFICA Investigators. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: The EFICA study. *Eur J Heart Fail*. 2006;8:697–705.
60. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure: different phenotypes of the same disease? *Eur J Heart Fail*. 2007;9: 136–143.
61. De Keulenaer GW, Brutsaert DL. The heart failure spectrum: time for a phenotype-oriented approach. *Circulation.* 2009;119:3044–3046.
62. Yancy CW. Vasodilator therapy for decompensated heart failure. *J Am Coll Cardiol*. 2008;52:208–210.
63. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Coordinators. Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *J Am Coll Cardiol*. 2008; 52:347–356.
64. Heart Failure Society of America. HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail*. 2006;12:e1–e2.
65. Peacock WF, Fonarow GC, Ander DS, Maisel A, Hollander JE, Januzzi JL Jr, Yancy CW, Collins SP, Gheorghiade M, Weintraub NL, Storrow AB, Pang PS, Abraham WT, Hiestand B, Kirk JD, Filippatos G, Gheorghiade M, Pang PS, Levy P, Amsterdam EA. Society of Chest Pain Centers Recommendations for the evaluation and management of the observation stay acute heart failure patient: a report from the Society of Chest Pain Centers Acute Heart Failure Committee. *Crit Pathw Cardiol*. 2008;7:83–86.
66. European Society of Cardiology; Heart Failure Association of the ESC (HFA); European Society of Intensive Care Medicine (ESICM), Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Bohm M, Corra U, della Bella P, Elliott PM, Follath F, Gheorghiade M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL, Verheugt FW, Zamorano JL, Zannad F. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA). *Eur J Heart Fail*. 2008;10:933–989.
67. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. *J Card Fail.* 2010;16:188–193.
68. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev.* 2005(3):CD003178.
69. Haude M, Steffen W, Erbel R, Meyer J. Sublingual administration of captopril versus nitroglycerin in patients with severe congestive heart failure. *Int J Cardiol*. 1990;27:351–359.
70. Kawai C, Kambara H, Nakano T, Hirota Y, Saito M, Kagoshima T, Nobuyoshi M, Tsuruha Y. Multicenter studies of 2% nitroglycerin ointment in patients with heart failure. *Clini Ther*. 1984;6:677–688.
71. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, Moshkovitz Y, Zaidenstein R, Golik A. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet.* 1998;351: 389–393.
72. Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, Dunne R, Zalenski R. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. *Ann Emerg Med*. 2007;50:144–152.
73. Lewin J, Ledwidge M, O'Loughlin C, McNally C, McDonald K. Clinical deterioration in established heart failure: what is the value of BNP and weight gain in aiding diagnosis? *Eur J Heart Fail*. 2005;7: 953–957.
74. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure–re-distribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail*. 2008;10:165–169.
75. Balmain S, Padmanabhan N, Ferrell WR, Morton JJ, McMurray JJ. Differences in arterial compliance, microvascular function and venous capacitance between patients with heart failure and either preserved or reduced left ventricular systolic function. *Eur J Heart Fail*. 2007;9: 865–871.
76. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW, Young JB. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med*. 2008;168:847–854.
77. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP; ADHERE Scientific Advisory Committee and Investigators. 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.
78. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J; Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. 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.
79. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J.* 2006;27:2725–2736.
80. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA.* 2007;297:1332–1343.
81. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW; ADHERE Scientific Advisory Committee and Investigators. 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.
82. Fonarow GC, Yancy CW, Heywood JT; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE Registry. *Arch Intern Med*. 2005;165:1469–1477.
83. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, Andre S, Mark Courtney D, Hasa J, Spinar J, Masip J, Frank Peacock W, Sliwa K, Gayat E, Ilippatos G, Cleland JG, Gheorghiade M. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. *Eur Heart J.* 2010;31:832–841.
84. Guglin M. Reappraisal of the role of diuretics in heart failure. *Cardiol Rev.* 2009;17:56–59.
85. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail*. 2002;8:136–141.
86. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail*. 2007;9:1064–1069.
87. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J*. 2006; 27:1431–1439.
88. Jhund PS, McMurray JJ, Davie AP. The acute vascular effects of frusemide in heart failure. *Br J Clin Pharmacol*. 2000;50:9–13.

89. Gottlieb SS, Brater DC, Thomas I, Havranek E, Bourge R, Goldman S, Dyer F, Gomez M, Bennett D, Ticho B, Beckman E, Abraham WT. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation.* 2002;105:1348–1353.
90. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999;138(pt 1):285–290.
91. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation.* 1999;100:1311–1315.
92. Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail*. 2007;13:599–608.
93. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, Horwitz RI. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. *Am J Cardiol*. 2000;85:1110–1113.
94. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail*. 2003;9:13–25.
95. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009; 360:1418–1428.
96. Gheorghiade M, De Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol.* 2005;96:11G–17G.
97. Gheorghiade M, Mebazaa A. Introduction to acute heart failure syndromes. *Am J Cardiol.* 2005;96:1G–4G.
98. Cotter G, Moshkovitz Y, Milovanov O, Salah A, Blatt A, Krakover R, Vered Z, Kaluski E. Acute heart failure: a novel approach to its pathogenesis and treatment. *Eur J Heart Fail*. 2002;4:227–234.
99. Graff L, Orledge J, Radford MJ, Wang Y, Petrillo M, Maag R. Correlation of the Agency for Health Care Policy and Research congestive heart failure admission guideline with mortality: peer review organization voluntary hospital association initiative to decrease events (PROVIDE) for congestive heart failure. *Ann Emerg Med*. 1999;34(pt 1):429–437.
100. Smith WR, Poses RM, McClish DK, Huber EC, Clemo FL, Alexander D, Schmitt BP. Prognostic judgments and triage decisions for patients with acute congestive heart failure. *Chest.* 2002;121:1610–1617.
101. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*. 2007;28:980–988.
102. Ambardekar AV, Fonarow GC, Hernandez AF, Pan W, Yancy CW, Krantz MJ; Get With the Guidelines Steering Committee and Hospitals. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: findings from Get With The Guidelines-Heart Failure (GWTG-HF). *Am Heart J*. 2009;158:644–652.
103. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005; 293:572–580.
104. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, O'Connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail*. 2007;13:360–364.
105. Formiga F, Chivite D, Manito N, Casas S, Riera A, Pujol R. Predictors of in-hospital mortality present at admission among patients hospitalised because of decompensated heart failure. *Cardiology*. 2007;108:73–78.
106. Chin MH, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med*. 1996;156:1814–1820.
107. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290:2581–2587.
108. Auble TE, Hsieh M, Gardner W, Cooper GF, Stone RA, McCausland JB, Yealy DM. A prediction rule to identify low-risk patients with heart failure. *Acad Emerg Med*. 2005;12:514–521.
109. Hsieh M, Auble TE, Yealy DM. Validation of the Acute Heart Failure Index. *Ann Emerg Med*. 2008;51:37–44.
110. Silvers SM, Howell JM, Kosowsky JM, Rokos IC, Jagoda AS. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute heart failure syndromes. *Ann Emerg Med*. 2007;49:627–669.
111. Storrow AB, Collins SP, Lyons MS, Wagoner LE, Gibler WB, Lindsell CJ. Emergency department observation of heart failure: preliminary analysis of safety and cost. *Congest Heart Fail*. 2005;11:68–72.
112. Peacock WF IV, Albert NM. Observation unit management of heart failure. *Emerg Med Clin North Am*. 2001;19:209–232.
113. Peacock WF IV, Remer EE, Aponte J, Moffa DA, Emerman CE, Albert NM. Effective observation unit treatment of decompensated heart failure. *Congest Heart Fail*. 2002;8:68–73.
114. Collins S, Schauer D, Gupta A, Brunner H, Storrow A, Eckman M. Cost-effectiveness analysis of ED decision making in non-high-risk heart failure patients. *Am J Emerg Med.* 2009;27:293–302.
115. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med.* 1992;327:685–691.
116. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM, on behalf of the SAVE investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327: 669–677.
117. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation.* 2002;106:2194–2199.
118. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, Stevenson LW, Francis GS, Leier CV, Miller LW; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625–1633.
119. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM Jr, Magalski A, Zile MR, Smith AL, Smart FW, O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW; COMPASS-HF Study Group. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. *J Am Coll Cardiol*. 2008;51:1073–1079.
120. Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A, Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail*. 2008;1:170–177.
121. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH, Mullens W, Borowski AG, Curtin RJ, Thomas JD. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation.* 2009;119:62–70.
122. Packer M, Abraham WT, Mehra MR, Yancy CW, Lawless CE, Mitchell JE, Smart FW, Bijou R, O'Connor CM, Massie BM, Pina IL, Greenberg BH, Young JB, Fishbein DP, Hauptman PJ, Bourge RC, Strobeck JE, Murali S, Schocken D, Teerlink JR, Levy WC, Trupp RJ, Silver MA; Prospective Evaluation and Identification of Cardiac Decompensation by ICG Test (PREDICT) Study Investigators and Coordinators. Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. *J Am Coll Cardiol*. 2006;47:2245–2252.
123. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM, Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA*. 2005;294:1664–1670.
124. Costanzo MR, Johannes RS, Pine M, Gupta V, Saltzberg M, Hay J, Yancy CW, Fonarow GC. The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized

patients with acutely decompensated heart failure: A propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. *Am Heart J*. 2007;154:267–277.
125. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee and Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:1943–1950.
126. Peacock WF 4th, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH; ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358:2117–2126.
127. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, Greenberg BH, Yancy CW, Young JB, Fonarow GC. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008;156:662–673.
128. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2005;46:1116–1143.
129. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M, Thygesen K; ESC Committee for Practice Guideline (CPG). 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.
130. Fonarow GC. Acute decompensated heart failure: challenges and opportunities. *Rev Cardiovasc Med.* 2007;8(suppl 5):S3–S12.
131. Fonarow GC, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. 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.
132. Koelling TM, Johnson ML, Cody RJ, Aaronson KD, Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation.* 2005;111:179–185.
133. de la Porte PW, Lok DJ, van Veldhuisen DJ, van Wijngaarden J, Cornel JH, Zuithoff NP, Badings E, Hoes AW. Added value of a physician-and-nurse-directed heart failure clinic: results from the Deventer-Alkmaar heart failure study. *Heart.* 2007;93:819–825.
134. Atienza F, Anguita M, Martinez-Alzamora N, Osca J, Ojeda S, Almenar L, Ridocci F, Valles F, de Velasco JA; PRICE Study Group. Multicenter randomized trial of a comprehensive hospital discharge and outpatient heart failure management program. *Eur J Heart Fail*. 2004;6:643–652.
135. Phillips CO, Wright SM, Kern DE, Singa RM, Shepperd S, Rubin HR. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. *JAMA.* 2004;291:1358–1367.
136. Gonseth J, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. *Eur Heart J.* 2004;25:1570–1595.
137. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation.* 1997;95:2660–2667.
138. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation.* 2006;113:1424–1433.
139. Myers J, Arena R, Dewey F, Bensimhon D, Abella J, Hsu L, Chase P, Guazzi M, Peberdy MA. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156:1177–1183.
140. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007;154:260–266.
141. Ko DT, Alter DA, Austin PC, You JJ, Lee DS, Qiu F, Stukel TA, Tu JV. Life expectancy after an index hospitalization for patients with heart failure: a population-based study. *Am Heart J*. 2008;155:324–331.
142. Chin MH, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. *Am J Cardiol*. 1997;79:1640–1644.
143. Opasich C, Febo O, Riccardi PG, Traversi E, Forni G, Pinna G, Pozzoli M, Riccardi R, Mortara A, Sanarico M, Cobelli F, Tavazzi L. Concomitant factors of decompensation in chronic heart failure. *Am J Cardiol*. 1996;78:354–357.
144. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart.* 1998;80:437–441.
145. Krumholz HM, Chen YT, Wang Y, Vaccarino V, Radford MJ, Horwitz RI. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J*. 2000;139(pt 1):72–77.
146. Blair JE, Khan S, Konstam MA, Swedberg K, Zannad F, Burnett JC Jr, Grinfeld L, Maggioni AP, Udelson JE, Zimmer CA, Ouyang J, Chen CF, Gheorghiade M; EVEREST Investigators. Weight changes after hospitalization for worsening heart failure and subsequent re-hospitalization and mortality in the EVEREST trial. *Eur Heart J*. 2009;30:1666–1673.
147. Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, Jegou A, Bauer F, Trochu JN, Bouzamondo A, Tanguy ML, Lechat P; B-CONVINCED Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;30:2186–2192.
148. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Coordinators. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. *J Am Coll Cardiol*. 2008;52:190–199.
149. Rodgers JE, Stough WG. Underutilization of evidence-based therapies in heart failure: the pharmacist's role. *Pharmacotherapy.* 2007;27(pt 2):18S–28S.
150. Coons JC, Fera T. Multidisciplinary team for enhancing care for patients with acute myocardial infarction or heart failure. *Am J Health Syst Pharm*. 2007;64:1274–1278.
151. Naylor MD, Bowles KH, Brooten D. Patient problems and advanced practice nurse interventions during transitional care. *Public Health Nurs.* 2000;17:94–102.
152. Paul S. Hospital discharge education for patients with heart failure: what really works and what is the evidence? *Crit Care Nurse*. 2008;28:66–82.
153. Konick-McMahan J, Bixby B, McKenna C. Heart failure in older adults: providing nursing care to improve outcomes. *J Gerontol Nurs*. 2003;29:35–41.
154. Williams S, Brown A, Patton R, Crawford MJ, Touquet R. The half-life of the 'teachable moment' for alcohol misusing patients in the emergency department. *Drug Alcohol Depend*. 2005;77:205–208.
155. The Joint Commission. Performance measurement initiatives. Heart failure core measure set. Available at: http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/Heart+Failure+Core+Measure+Set.htm. Accessed November 9, 2009.
156. Albert NM. Promoting self-care in heart failure: state of clinical practice based on the perspectives of healthcare systems and providers. *J Cardiovasc Nurs*. 2008;23:277–284.
157. Moser DK, Watkins JF. Conceptualizing self-care in heart failure: a life course model of patient characteristics. *J Cardiovasc Nurs*. 2008;23:205–218.
158. Dunbar SB, Clark PC, Quinn C, Gary RA, Kaslow NJ. Family influences on heart failure self-care and outcomes. *J Cardiovasc Nurs*. 2008;23:258–265.

159. Arslanian-Engoren C, Hicks FD, Whall AL, Algase DL. An ontological view of advanced practice nursing. *Res Theory Nurs Pract*. 2005;19: 315–322.
160. Naylor MD, Brooten DA, Campbell RL, Maislin G, McCauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *J Am Geriatr Soc*. 2004;52: 675–684.
161. McCauley KM, Bixby MB, Naylor MD. Advanced practice nurse strategies to improve outcomes and reduce cost in elders with heart failure. *Dis Manag*. 2006;9:302–310.
162. Berdague P, Caffin PY, Barazer I, Vergnes C, Sedighian S, Letrillard S, Pilossof R, Goutorbe F, Piot C, Reny JL. Use of N-terminal prohormone brain natriuretic peptide assay for etiologic diagnosis of acute dyspnea in elderly patients. *Am Heart J*. 2006;151:690–698.
163. Krauser DG, Lloyd-Jones DM, Chae CU, Cameron R, Anwaruddin S, Baggish AL, Chen A, Tung R, Januzzi JL Jr. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy. *Am Heart J*. 2005;149:744–750.
164. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, Maisel AS. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J*. 2006;151:999–1005.
165. Anwaruddin S, Lloyd-Jones DM, Baggish A, Chen A, Krauser D, Tung R, Chae C, Januzzi JL Jr. Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll Cardiol*. 2006;47:91–97.
166. Logeart D, Saudubray C, Beyne P, Thabut G, Ennezat PV, Chavelas C, Zanker C, Bouvier E, Solal AC. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. *J Am Coll Cardiol*. 2002;40:1794–1800.
167. Steinhart B, Thorpe KE, Bayoumi AM, Moe G, Januzzi JL Jr, Mazer CD. Improving the diagnosis of acute heart failure using a validated prediction model. *J Am Coll Cardiol*. 2009;54:1515–1521.
168. Brophy J. ACP Journal Club. A model combining clinical assessment and NT-proBNP level accurately predicted heart failure in ED patients with dyspnea. *Ann Intern Med*. 2010;152:JC1–JC13.
169. Dickstein K. Diagnosing acute heart failure: the mathematician and the clinician. *J Am Coll Cardiol*. 2009;54:1522–1523.
170. Collins SP, Peacock WF, Lindsell CJ, Clopton P, Diercks DB, Hiestand B, Hogan C, Kontos MC, Mueller C, Nowak R, Chen WJ, Huang CH, Abraham WT, Amsterdam E, Breidthardt T, Daniels L, Hasan A, Hudson M, McCord J, Naz T, Wagoner LE, Maisel A. S3 detection as a diagnostic and prognostic aid in emergency department patients with acute dyspnea. *Ann Emerg Med*. 2009;53:748–757.
171. Collins SP, Lindsell CJ, Peacock WF, Hedger VD, Askew J, Eckert DC, Storrow AB. The combined utility of an S3 heart sound and B-type natriuretic peptide levels in emergency department patients with dyspnea. *J Card Fail*. 2006;12:286–292.
172. Peacock WF, Harrison A, Moffa D. Clinical and economic benefits of using AUDICOR S3 detection for diagnosis and treatment of acute decompensated heart failure. *Congest Heart Fail*. 2006;12(suppl 1):32–36.
173. Peacock WF, Summers RL, Vogel J, Emerman CE. Impact of impedance cardiography on diagnosis and therapy of emergent dyspnea: the ED-IMPACT trial. *Acad Emerg Med*. 2006;13:365–371.
174. Kamath SA, Drazner MH, Tasissa G, Rogers JG, Stevenson LW, Yancy CW. Correlation of impedance cardiography with invasive hemodynamic measurements in patients with advanced heart failure: the BioImpedance CardioGraphy (BIG) substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial. *Am Heart J*. 2009;158:217–223.
175. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. *Cardiovasc Ultrasound*. 2008;6:16.
176. Gargani L, Frassi F, Soldati G, Tesorio P, Gheorghiade M, Picano E. Ultrasound lung comets for the differential diagnosis of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. *Eur J Heart Fail*. 2008;10:70–77.
177. Soldati G, Gargani L, Silva FR. Acute heart failure: new diagnostic perspectives for the emergency physician. *Intern Emerg Med*. 2008;3: 37–41.
178. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary disease as cause of acute dyspnea in pre-hospital emergency setting: study of diagnostic accuracy. *Croat Med J*. 2009;50:133–142.
179. Felker GM, Cuculich PS, Gheorghiade M. The Valsalva maneuver: a bedside "biomarker" for heart failure. *Am J Med*. 2006;119:117–122.
180. Sharma GV, Woods PA, Lambrew CT, Berg CM, Pietro DA, Rocco TP, Welt FW, Sacchetti P, McIntyre KM. Evaluation of a noninvasive system for determining left ventricular filling pressure. *Arch Intern Med*. 2002;162:2084–2088.
181. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. *J Am Coll Cardiol*. 2009;54:1407–1424.
182. Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA). *Eur Heart J*. 2008;29: 2388–2442.
183. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. *J Am Coll Cardiol*. 2007;50:381–396.
184. Goonewardena SN, Blair JE, Manuchehry A, Brennan JM, Keller M, Reeves R, Price A, Spencer KT, Puthumana J, Gheorghiade M. Use of hand carried ultrasound, B-type natriuretic peptide, and clinical assessment in identifying abnormal left ventricular filling pressures in patients referred for right heart catheterization. *J Card Fail*. 2010;16: 69–75.
185. Sasaki T, Kubo T, Miyamoto T, Komamura K, Honda K, Miyatake K. Clinical significance of measuring inferior vena cava dimension in patients with acute exacerbation of chronic heart failure [in Japanese]. *J Cardiol*. 2001;37:309–313.
186. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*. 2009;119:3070–3077.
187. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259.
188. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47:76–84.
189. Randazzo MR, Snoey ER, Levitt MA, Binder K. Accuracy of emergency physician assessment of left ventricular ejection fraction and central venous pressure using echocardiography. *Acad Emerg Med*. 2003;10:973–977.
190. Nazerian P, Vanni S, Zanobetti M, Polidori G, Pepe G, Federico R, Cangioli E, Grifoni S. Diagnostic accuracy of emergency Doppler echocardiography for identification of acute left ventricular heart failure in patients with acute dyspnea: comparison with Boston criteria and N-terminal prohormone brain natriuretic peptide. *Acad Emerg Med*. 2010;17:18–26.
191. Liteplo AS, Marill KA, Villen T, Miller RM, Murray AF, Croft PE, Capp R, Noble VE. Emergency thoracic ultrasound in the differentiation of the etiology of shortness of breath (ETUDES): sonographic B-lines and N-terminal pro-brain-type natriuretic peptide in diagnosing congestive heart failure. *Acad Emerg Med*. 2009;16:201–210.
192. Arques S, Jaubert MP, Bonello L, Sbragia P, Nicoud A, Paganelli F. Usefulness of left atrial volume for the diagnosis of diastolic heart failure: an echocardiographic-catheterization study. *Int J Cardiol*. March

16, 2009. doi:10.1016/j.ijcard.2009.03.005. Available at: http://www.sciencedirect.com/science/journal/01675273.
193. Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: implication for diagnosis of diastolic heart failure. *Eur J Heart Fail*. 2006,8:38–45.
194. Tripepi G, Mattace-Raso F, Mallamaci F, Benedetto FA, Witteman J, Malatino L, Zoccali C. Biomarkers of left atrial volume: a longitudinal study in patients with end stage renal disease. *Hypertension.* 2009;54:818–824.
195. Adamopoulos C, Zannad F, Fay R, Mebazaa A, Cohen-Solal A, Guize L, Juilliere Y, Alla F. Ejection fraction and blood pressure are important and interactive predictors of 4-week mortality in severe acute heart failure. *Eur J Heart Fail*. 2007;9:935–941.
196. Styron JF, Jois-Bilowich P, Starling R, Hobbs RE, Kontos MC, Pang PS, Peacock WF. Initial emergency department systolic blood pressure predicts left ventricular systolic function in acute decompensated heart failure. *Congest Heart Fail.* 2009;15:9–13.
197. Uriel N, Torre-Amione G, Milo O, Kaluski E, Perchenet L, Blatt A, Kobrin I, Turnovski A, Kaplan S, Rainisio M, Frey A, Vered Z, Cotter G. Echocardiographic ejection fraction in patients with acute heart failure: correlations with hemodynamic, clinical, and neurohormonal measures and short-term outcome. *Eur J Heart Fail*. 2005;7:815–819.
198. Allen LA, Hernandez AF, O'Connor CM, Felker GM. End points for clinical trials in acute heart failure syndromes. *J Am Coll Cardiol*. 2009;53:2248–2258.
199. Wuerz RC, Meador SA. Effects of prehospital medications on mortality and length of stay in congestive heart failure. *Ann Emerg Med*. 1992;21:669–674.
200. Peacock WF, Emerman C, Costanzo MR, Diercks DB, Lopatin M, Fonarow GC. Early vasoactive drugs improve heart failure outcomes. *Congest Heart Fail*. 2009;15:256–264.
201. Maisel AS, Peacock WF, McMullin N, Jessie R, Fonarow GC, Wynne J, Mills RM. Timing of immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. *J Am Coll Cardiol*. 2008;52:534–540.
202. Pang PS, Cleland JG, Teerlink JR, Collins SP, Lindsell CJ, Sopko G, Peacock WF, Fonarow GC, Aldeen AZ, Kirk JD, Storrow AB, Tavares M, Mebazaa A, Roland E, Massie BM, Maisel AS, Komajda M, Filippatos G, Gheorghiade M; Acute Heart Failure Syndromes International Working Group. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. *Eur Heart J*. 2008;29:816–824.
203. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, Marmor A, Katz A, Grzybowski J, Unemori E, Teichman SL, Cotter G. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet.* 2009;373:1429–1439.
204. Adams JKF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. 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.
205. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, O'Connor CM, Yancy CW, Young J. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J*. 2004;148:43–51.
206. Diercks DB, Fonarow GC, Kirk JD, Emerman CL, Hollander JE, Weber JE, Summers RL, Wynne J, Peacock WF IV; ADHERE Scientific Advisory Committee and Investigators. Risk stratification in women enrolled in the Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM). *Acad Emerg Med.* 2008;15:151–158.
207. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:675–683.
208. Costanzo MR, Saltzberg MT, Jessup M, Teerlink JR, Sobotka PA; Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) Investigators. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. *J Card Fail.* 2010;16:277–284.
209. Beohar N, Erdogan AK, Lee DC, Sabbah HN, Kern MJ, Teerlink J, Bonow RO, Gheorghiade M. Acute heart failure syndromes and coronary perfusion. *J Am Coll Cardiol*. 2008;52:13–16.
210. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, Liu PP, Konstam MA, Greenberg B, Mehra MR, Breithardt G, Pang PS, Young JB, Fonarow GC, Bonow RO, Gheorghiade M; Acute Heart Failure Syndromes International Working Group. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. *J Am Coll Cardiol*. 2009;53:254–263.
211. Pang PS, Komajda M, Gheorghiade M. The current and future management of acute heart failure syndromes. *Eur Heart J*. 2010;31:784–793.
212. Maisel A, Hollander JE, Guss D, McCullough P, Nowak R, Green G, Saltzberg M, Ellison SR, Bhalla MA, Bhalla V, Clopton P, Jesse R; 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.
213. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med*. 2007;167:1998–2005.
214. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. *Circulation.* 2007;115:949–952.
215. Yamokoski LM, Hasselblad V, Moser DK, Binanay C, Conway GA, Glotzer JM, Hartman KA, Stevenson LW, Leier CV. Prediction of rehospitalization and death in severe heart failure by physicians and nurses of the ESCAPE trial. *J Card Fail*. 2007;13:8–13.
216. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. *N Engl J Med*. 1985;313:793–799.
217. Wasson JH, Sox HC. Clinical prediction rules. Have they come of age? *JAMA*. 1996;275:641–642.
218. Goldman L, Weinberg M, Weisberg M, Olshen R, Cook EF, Sargent RK, Lamas GA, Dennis C, Wilson C, Deckelbaum L, Fineberg H, Stiratelli R. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med*. 1982;307:588–596.
219. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. *JAMA*. 1997;277:488–494.
220. McCausland JB, Machi MS, Yealy DM. Emergency physicians' risk attitudes in acute decompensated heart failure patients. *Acad Emerg Med.* 2010;17:108–110.
221. Storrow AB, Collins S, Lindsell CJ, Disalvo T, Han J, Weintraub NL. *Improving Heart Failure Risk Stratification in the ED: Stratify 1R01HL088459-01; Treatment Endpoints in Acute Decompensated Heart Failure 1K23HL085387-01A2*. Vanderbilt University and University of Cincinnati: National Heart, Lung, and Blood Institute; 2007.
222. Tatum JL, Jesse RL, Kontos MC, Nicholson CS, Schmidt KL, Roberts CS, Ornato JP. Comprehensive strategy for the evaluation and triage of the chest pain patient. *Ann Emerg Med*. 1997;29:116–125.
223. Gibler WB, Runyon JP, Levy RC, Sayre MR, Kacich R, Hattemer CR, Hamilton C, Gerlach JW, Walsh RA. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med*. 1995;25:1–8.
224. Storrow AB, Gibler WB. Chest pain centers: diagnosis of acute coronary syndromes. *Ann Emerg Med*. 2000;35:449–461.
225. Yealy DM, Auble TE, Stone RA, Lave JR, Meehan TP, Graff LG, Fine JM, Obrosky DS, Edick SM, Hough LJ, Tuozzo K, Fine MJ. The emergency department community-acquired pneumonia trial: methodology of a quality improvement intervention. *Ann Emerg Med*. 2004;43:770–782.
226. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA*. 2000;283:749–755.

227. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336:243–250.
228. Villacorta H, Rocha N, Cardoso R, Gaspar S, Maia ER, Bonates T, Kopiler D, Dohmann HJ, Mesquita ET. Hospital outcome and short-term follow-up of elderly patients presenting to the emergency unit with congestive heart failure [in Portuguese]. *Arq Bras Cardiol*. 1998;70: 167–171.
229. Ghali JK, Kadakia S, Cooper R, Ferlinz J. Precipitating factors leading to decompensation of heart failure: traits among urban blacks. *Arch Intern Med*. 1988;148:2013–2016.
230. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med*. 1995;333: 1190–1195.
231. Ashton CM, Kuykendall DH, Johnson ML, Wray NP, Wu L. The association between the quality of inpatient care and early readmission. *Ann Intern Med*. 1995;122:415–421.
232. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med*. 1997;157:99–104.
233. Stewart S, Marley JE, Horowitz JD. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study. *Lancet.* 1999;354:1077–1083.
234. Roe MT, Christenson RH, Ohman EM, Bahr R, Fesmire FM, Storrow A, Mollod M, Peacock WF, Rosenblatt JA, Yang H, Fraulo ES, Hoekstra JW, Gibler WB; EARLY Investigators; Emergency Medicine Cardiac Research and Education Group. A randomized, placebo-controlled trial of early eptifibatide for non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2003;146:993–998.
235. Moore EE, Johnson JL, Moore FA, Moore HB. The USA Multicenter Prehosptal Hemoglobin-based Oxygen Carrier Resuscitation Trial: scientific rationale, study design, and results. *Crit Care Clin.* 2009;25: 325–356.
236. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, del Zoppo G, Kleindorfer D, Woo D, Khatri P, Castaldo J, Frey J, Gebel J Jr, Kasner S, Kidwell C, Kwiatkowski T, Libman R, Mackenzie R, Scott P, Starkman S, Thurman RJ; CLEAR Trial Investigators. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke.* 2008;39:3268–3276.
237. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet.* 1988;2:349–360.
238. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation.* 1977;56:786–794.
239. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet.* 1996;348:771–775.
240. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531–1540.
241. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M; 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.
242. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainisio M, Kobrin I; VERITAS Investigators. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA*. 2007;298:2009–2019.
243. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Poder P, Kivikko M; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA*. 2007;297:1883–1891.
244. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail*. 2006;8:105–110.
245. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST Outcome Trial. *JAMA*. 2007;297:1319–1331.
246. Hernandez AF, O'Connor CM, Starling RC, Reist CJ, Armstrong PW, Dickstein K, Lorenz TJ, Gibler WB, Hasselblad V, Komajda M, Massie B, McMurray JJ, Nieminen M, Rouleau JL, Swedberg K, Califf RM. Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF). *Am Heart J*. 2009;157:271–277.
247. Cleland JG, Coletta AP, Yassin A, Buga L, Torabi A, Clark AL. Clinical trials update from the European Society of Cardiology Meeting 2009: AAA, RELY, PROTECT, ACTIVE-I, European CRT survey, German pre-SCD II registry, and MADIT-CRT. *Eur J Heart Fail.* 2009;11:1214–1219.

KEY WORDS: AHA Scientific Statements ■ acute care ■ diagnosis ■ emergency medicine ■ heart failure ■ outcomes ■ prognosis ■ treatment