This paper details the substance and recommendations arising from a meeting convened by the National Heart, Lung, and Blood Institute in August 2009, to assess the challenges and opportunities of emergency department management of acute heart failure syndrome (AHFS). The assembled faculty represented a large cross section of medical professionals spanning the medical management continuum of patients presenting with acute heart failure and included heart failure cardiologists, emergency physicians, laboratory medicine specialists, nurses, and bench scientists. Their recommendations include proposals regarding the design and conduct of emergency department-based clinical trials, suggestions regarding the development of improved methods for early detection and monitoring of AHFS, and potential needs for expanding translational and applied AHFS focused research and biotechnology. We anticipate that this review will serve as a starting point for future investigations across the spectrum of funding sources. (J Am Coll Cardiol 2010;56:343–51) © 2010 by the American College of Cardiology Foundation

All participants agreed that there is a critical need for evidence based management of acute heart failure syndrome (AHFS) in the emergency department (ED). Of 18 Class I recommendations for AHFS treatment, only 1 has Level of Evidence: A data (1). Most AHFS therapies are based on expert opinion (Level of Evidence: C). Furthermore, new therapies/technologies have failed to improve survival or decrease repeat hospital stays. To improve outcomes, it will be necessary to obtain evidence for effectiveness, efficacy, and risks of new and existing therapies. Major strategies that were discussed included: 1) the need for early risk stratification to distinguish between low-risk patients who might return home with an outpatient appointment or be admitted to an observation unit (OU) versus...
higher-risk patients who require hospital admission to an intensive care unit (ICU) in the most severe cases; and 2) that early cardiac and noncardiac (particularly renal) injuries require a better basic understanding of the pathophysiologic contributions and potential therapeutic responses. There was optimism that new diagnostic and therapeutic strategies could be lifesaving if applied during the appropriate time window in the ED and followed by appropriate post-ED management.

Future therapeutic interventions will come from: 1) the basic cardiovascular sciences, including molecular medicine and pharmacology; 2) better understanding of AHFS phenotypes; and 3) the development of new diagnostic techniques and technologic advances. Novel AHFS targeted therapies will require careful testing with study designs focused on timing, route of administration, and co-administration of complementary therapies. This will need collaboration among basic scientists, bioengineers, and diverse clinical disciplines, such as emergency medicine, cardiology, hospital medicine, and critical care.

Recommended actions include:

1. Design and conduct ED based clinical trials. These should focus on emergency AHFS management and should include prospective testing of both existing and new interventions in specifically targeted groups. For optimal conduct, there is a need for coordinated protocols and data management as well as the development of consensus on therapeutic end points and outcomes. Research priorities for funding were recommended, including: 1) biomarkers for early diagnosis and management; 2) early aggressive versus conservative management of congestion; 3) initial versus delayed manipulation of the neurohormonal system; and 4) the discharge strategy of patients after the ED. New initiatives should explore differences among patients across a wide range of ages, sexes, and racial/ethnic populations while focusing on the need to understand the pathophysiology of different syndromes.

2. Develop improved methods for early detection and monitoring of AHFS. These should consider the development and testing of currently available biosensors to monitor physiologic data guiding interventions in “real time.” The development of new technologies is likely to require collaboration between basic and clinical scientists as well as between academia and industry.

3. Expand translational and applied AHFS focused research and biotechnology. These should include collaborative research uniting basic and applied scientists targeting mechanisms of cellular, organ, and systems injury in AHFS. Special areas of interest include: 1) gene expression variation, induction, and regulation in AHFS with a focus on identifying opportunities for early management; 2) the role of the vasculature in AHFS; 3) targeting the kidney with approaches that might protect renal function and enhance the early relief of circulatory congestion; 4) novel approaches for modulating neurohormonal activation; and 5) early introduction of therapies that mitigate progressive cardiac dysfunction and prevent recurrence of AHFS episodes. The latter includes the evaluation of the early use of older interventions (e.g., the use of digoxin for AHFS patients with predominant systolic heart failure [HF]).

**ED Management of AHFS: Challenges and Opportunities**

**Epidemiology.** There are an estimated 3,000,000 annual hospital stays for primary or secondary HF, of which approximately 80% initially present to the ED (2,3). Hospitalized HF patients are a heterogeneous group with a wide range of 30-day mortality (1.7% to 7.2%) and a high post-discharge event rate, approaching 40% at 90 days in some cohorts (4). In fact, HF has the highest readmission rate of any discharge diagnosis.

Acute heart failure syndrome represents a complex, heterogeneous set of clinical conditions with the common denominators of pulmonary congestion and dyspnea. Because most AHFS patients present to the ED with normal or increased blood pressure (only 5% have a systolic blood pressure <90 mm Hg), most receive loop diuretic agents. Although these are reasonably effective at addressing congestion, a number of poorly understood pathophysiologic changes might be more appropriately managed by therapies targeting alterations in hemodynamic, neurohormonal, and endothelial function, as well as myocyte viability, function, and ischemia. The importance of renal deterioration, often as a result of aggressive diuresis, must be emphasized, because worsening renal function is 1 of the most powerful predictors of prognosis. Which specific interventions represent optimal therapy will only be determined after these clinical profiles are studied prospectively.

Currently, there are few high-quality data guiding clinical decision-making. Future trials should distinguish the approach to treatment on the basis of the HF profile. This is analogous to the treatment of ST-segment elevated myocardial infarction and non–ST-segment elevated myocardial infarction; although both represent myocardial infarctions, their optimal treatments differ, and investigations target each individually. A similar approach is necessary for AHFS.

**ED physician’s view of AHFS in the ED.** With annual costs estimated at $20.1 billion, HF hospital stays are 1 of the most expensive U.S. disease expenditures. Because most AHFS admissions are hospitalized via the ED, a systems-wide approach to physiologic success and cost-containment starts in the ED. Improving diagnosis, selection of time-critical interventions, and disposition will produce down-
stream benefits (5). Because early interventions offer a higher likelihood of success, the initial treatment plan is important. The current lack of data and consensus regarding appropriate ED diagnosis, treatment goals, and metrics creates disagreement among caregivers.

Acute heart failure syndrome is a challenging diagnosis, because its dominant symptom of dyspnea is nonspecific, the physical examination is insensitive (6,7), electrocardiograms are inaccurate (8,9), and chest X-ray findings are unreliable (10–12). Even when diagnostic certainty exists, evidence-based ED management options are limited, because few prospective ED interventional AHFS studies have been conducted. Most ED interventions are based on historical or local practices, extrapolating from chronic HF studies, or investigations conducted on hospitalized patients. Thus, early management goals are ill-defined, and definitions of “success” are unclear (13).

In suspected AHFS, the principal responsibilities of care in the ED are, in order of priority: 1) resuscitation; 2) identification and initial management of immediate life threats; 3) symptom relief; and 4) accurate disposition (sorting those requiring inpatient hospital stay from those who might be safely treated and released). The AHFS disposition decisions are predominantly based on physician experience and clinical impressions and involve minimal objective data. Among the challenges to disposition are predicting future intensity of care needs in individual patients—particularly without objective measures to guide decisions—and the multiplicity of options, from discharge to home; transfer to an OU; or admission to a regular medical bed, a step-down unit, or an ICU.

The accuracy of these decisions needs be enhanced through development of risk stratification tools. Accurate identification of low-risk patients (i.e., those with very low [<1%] 30-day death or repeat hospital stay rates) would allow selection of candidates best-suited for early discharge or OU treatment. Although a comprehensive database of chronic HF and large registries of hospitalized patients exist, few identified low-risk patients. Current selection of a low-risk cohort is done by exclusion, driven by the absence of high-risk features and personal experience (Fig. 1) (14–18). Because low-risk patients should have few revisits, successful development of early discharge criteria is essential for a cost-effective ED-based AHFS program. Outcomes associated with coordinated, multidisciplinary efforts to achieve a seamless transition to outpatient management offer a good prospective study target.

Finally, comorbidities play a large role in initial ED management. Most HF patients have comorbid conditions that exacerbate HF or are exacerbated by HF. The ED care approach to these patients must incorporate data regarding potential comorbidities.

Cardiologist’s view of acute HF in the ED. Although multiple AHFS phenotypes exist, there is no consensus of definition (19). Initial triage, treatment, and disposition decisions are typically based on the perceived severity of the presentation. However, long-term risk of any specific phenotype is unknown. We need a better understanding of the natural history of AHFS in patients presenting to the ED to design studies to improve outcomes. Thus, a new AHFS classification scheme based on pathophysiology, severity, and prognosis is critical for both research and clinical management.

Once the diagnosis and phenotype of AHFS have been established and care turned over to the cardiologist or hospitalist, optimal therapy requires reconciliation of many competing goals. Because the underlying pathophysiology of HF predicts the probable course and outcomes and

![Figure 1](image_url)

**Figure 1** Risk Stratification Data Points in ED Patients With Suspected Acute Heart Failure

Note: all superscript numbers relate to the reference numbers 14 to 18. AHFS = acute heart failure syndrome; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; Creat = creatinine; ED = emergency department; Na = sodium; SBP = systolic blood pressure.
guides selection of therapy, defining the predominant presentation is useful clinically. The 2009 American College of Cardiology/American Heart Association Revised Guidelines (1) recognizes 3 types of HF:

1. Volume overload; pulmonary and/or systemic congestion, frequently precipitated by an acute increase in chronic hypertension;
2. Profound depression of cardiac output; hypotension, renal insufficiency, and/or a shock syndrome;
3. Combination of 1 and 2.

The severity and tempo of AHFS and comorbidities impact management strategies for selecting optimal therapies and the probability of attaining clinical improvement. These strategies must also consider long-term prognosis, patient preferences, and the need to modify therapy during the clinical course in response to initial interventions. This includes the patient's hemodynamic stability, the underlying disease state, comorbidities, prognosis, and the availability of suitable inpatient resources. Stratifying AHFS patients by risk of subsequent adverse events is critical to improving care. High-risk patients should be hospitalized to optimize intensity of care (often in an ICU), moderate-risk patients might be candidates for OU transfer, and those at low risk could be discharged from the ED with appropriate follow-up.

It is important to take advantage of the “teachable moment” when an AHFS patient visits the ED or is transferred to an inpatient unit. There is a high rate of recidivism with many patients not practicing adequate self-management. Regardless of where it occurs, improvements in patient and family education and developing tools to enhance self-management skills are likely to result in fewer readmissions.

**Risk Stratification: Rapid and Accurate ED Diagnosis**

Rapid, accurate diagnosis of AHFS is vital. Delayed therapy is associated with increased mortality, as is administration of AHFS treatment to non-AHFS patients (13). Clinical prediction rules prognostic of short-term fatal and nonfatal outcomes have been compared (20) and validated (21). However, performance of these rules is suboptimal. Two National Institutes of Health–sponsored studies, DECIDE (DECision making in acute DEcompensated heart failure) and STRATIFY (STRATIFYing emergency department patients with heart failure)—designed to address the challenges of diagnosis and risk stratification—involves the prospective development of an ED-based risk model that includes variables available during the first 2 h in the ED. These consist of medical history, findings on physical examination, routine laboratory testing, biomarkers of cardiac stress and injury, measures of early therapeutic response, as well as social and demographic factors.

Although natriuretic peptides (NPs) are useful (22,23) and cost-effective (24), they have limitations (18,25,26). As NPs are released in response to myocardial stretch, many non-HF cardiac stress conditions (e.g., myocardial infarction) lead to NP elevation. Thus, although a low NP “rules out” AHFS, a “rule-in” diagnosis of AHFS by NP is complicated by an indeterminate grey zone (27). Additionally, in some AHFS presentations (e.g., flash pulmonary edema, mitral stenosis) early NP levels might be normal (26). Other confounders include determining whether the NP result represents the patient’s wet or dry weight and that levels are increased in renal dysfunction but reduced in obesity. Lastly, recent evidence suggests different structural NP forms in “sick” compared with “normal” subjects (28).

Despite these limitations, NPs are strongly prognostic of future adverse events. The REDHOT (Rapid Emergency Department Heart Failure Outpatient Trial) (29) showed that the 90-day combined event rate (CHF visits and mortality) in patients admitted with B-type NP <200 and >200 pg/ml was 9% and 29%, respectively (p = 0.006). If validated, this NP cutpoint might represent a safe and cost-effective strategy guiding ED disposition. Other candidate markers requiring validation of their prognostic value include mid-regional pro-atrial NP, adenomedullin, copeptin, and ST2. Finally, early data suggest that the infection marker procalcitonin and pro-atrial NP might help differentiate ADHF from pneumonia (30).

Although complex interplay between decreased renal perfusion and renal congestion might contribute to kidney dysfunction, the cardiorenal syndrome is a potent AHFS mortality risk factor (31,32). Although creatinine is traditionally used to assess renal function, cystatin C is more accurate. Sensitive early markers of acute kidney injury, such as neutrophil gelatinase associated lipocalin, kidney injury molecule-1, and interleukin-1 (33,34), might also have clinical value. After acute kidney injury, interleukin-1 exhibits a robust rise that precedes other biomarkers. Combined with B-type NP, it might assist in the early detection of renal dysfunction. Ultimately, a panel of markers for cardiac stress, infection, necrosis/apoptosis/tissue turnover (e.g., high-sensitivity troponin [17]), and acute kidney injury might be the most useful in risk stratification, assessing both prognosis and guiding management.

Finally, cardiac echocardiography as an ED diagnostic and risk stratification tool might be considered. Although there are few controlled and validated echocardiographic studies on the ED evaluation of AHFS—because it is noninvasive, rapid, and increasingly available—it is an attractive technology for future investigations.

**ED Management of AHFS**

To ensure safe, high-quality, and efficient care for AHFS patients during and after hospital stay, comprehensive disease management programs—which include patient and
family education as well as self-monitoring—are needed. Such programs might reduce repeat ED visits and hospital stays. The critical “vulnerable period,” beginning just before ED presentation and extending to a few weeks after discharge, is addressed inadequately by traditional approaches to chronic HF. A personalized AHFS management program, initiated in the ED or OU and continued to after discharge, provides opportunities for outcome improvement. This strategy should include directed intervention with evidence-based, guideline-recommended therapies for patients with correctable disorders (e.g., ventricular dyssynchrony) (19,35). Conversely, patients at low risk for short-term mortality but consuming considerable health care resources offer a target for “systematic individualized nondrug, nondevice” management (e.g., disease-specific education, provision of appropriate cost-limited follow-up, and assistance with transportation or prescription needs) (36–38).

A seamless transition to a personalized disease management program beginning in the ED might improve outcomes. One example might be the OU-based HF model where low-risk patients receive both brief high-intensity therapy and social interventions, education, and delineation of post-discharge care in the ED. Such an approach improves short-term outcomes while avoiding in-patient hospital stay (39). Coupling this strategy with outpatient follow-up under the supervision of an HF specialist and experienced nurse practitioner might yield additional benefits. This could include the creation of Camp Heart Failure or day treatment centers in which patients receive infusion therapy and participate in peer-led support groups. This strategy, although easily inserted into ED/OU operations, could also be incorporated into inpatient post-discharge care. Prospective research is needed to define the management tools for improving outcomes, quality, and costs with this strategy in selected AHFS phenotypes.

**Current and Future Clinical Trials of AHFS**

**Pharmacotherapy.** Despite few prospective ED-based trials of diuretic agents and suggestions of harm with excessive use, diuretic agents are a mainstay of AHFS treatment. NHLBI’s Heart Failure Network is studying this question in the DOSE (Diuretic Optimal Strategy Evaluation in Acute Heart Failure) trial. Critically important unanswered questions include dose, timing, method of administration, and their relative safety in various ED AHFS phenotypes. This data vacuum exemplifies the challenge that new pharmacologics must meet.

Recent AHFS investigations report different outcomes between phase II and III studies. In fact, positive phase III studies are extremely rare. One recent example is rololofylline, where the pilot phase II study (40) showed preservation of renal function, improvement of dyspnea, and a trend (p = 0.055) to decreased 60-day death and cardiac/renal readmissions. However, the larger follow-up PROTECT-2 (A Study of the Selective A1 Adenosine Receptor Antagonist KW-3902 for Patients Hospitalized With Acute HF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial (41) did not confirm the renal or death/readmission benefits, although dyspnea improved through the third day.

Many lessons can be learned from these experiences. Phase III trials with neutral outcomes might be underpowered by accepting frequently overestimated effects of phase II data. Enrolling a cohort with excessive phenotypic heterogeneity in phase III might also result in divergent outcomes. Changing standards of care should be accounted for during trial development and implementation. Trial designs frequently overestimate an intervention’s effect, especially in view of delayed enrollment exposing a patient to ED standard therapy. Promising (albeit hypothesis-generating) beneficial outcome data have been achieved by more recent trials, including the phase II Pre-RELAX-AHF (Relaxin for the treatment of patients with acute heart failure) study (42). They encouraged enrollment as soon as possible after ED presentation. This might enhance the likelihood of success by increasing the study’s effect magnitude while limiting potential confounding from pre-study interventions.

Another research challenge and a fact that complicates the existing pathophysiologic understanding of AHFS is poor linkage between symptomatic improvement and major clinical end points improvement. This is illustrated by the VMAC (Vasodilatation in the Management of Acute CHF) study comparing nesiritide and standard care, which reported reductions in wedge pressure and transient improvements of dyspnea (43). Applying these data to the ongoing phase IV ASCEND-HF (Double-Blind, Placebo-Controlled, Multicenter Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure), required 7,000 patients to evaluate nesiritide’s potential impact on mortality (44). The enormous cost of trials designed to demonstrate small improvements in clinical outcome will have to be considered. Nonetheless, in similarly large trials the mortality of acute myocardial infarction was improved. To achieve benefits in AHFS management, a similar approach might be necessary.

**Diagnostic and hemodynamic devices.** Historically, implanted diagnostic monitoring devices focused on electrophysiologic variables. These devices, such as pacemakers, can provide additional data regarding precipitants of clinical events. Thoracic electrical impedance measurements might reflect clinical status and prognosis, because reduced impedance from excess lung water is associated with increased wedge pressure and longer hospital stays. In the MID-HeFT (Medtronic Impedance Diagnostics in Heart Failure Patients Trial), an inverse relationship was shown between thoracic impedance and hospital stay. In this study, impedance-derived hemodynamic and physiologic markers (e.g., patient activity) declined approximately 2 weeks before hospital stay (45).
Implanted monitors might offer an objective strategy for testing research targets in ED AHFS evaluation.

Future trials might employ the ED interrogation of implantable cardiac-defibrillators, impedance monitors, and resynchronization devices to guide clinical care. These can record heart rate, rhythm, percentage of atrial and ventricular pacing, fluid status, and patient activity (46,47). Potential ED applications might explore the association of heart rate variability changes in the days before hospital stay and the relation of decreased physical activity to admission requirements (46,47). Research demonstrating that device data accessed in the ED predict the need for hospital stay or the intensity of management required would be of significant value.

**Trial Design for AHFS in the ED**

The successful ED trial design will require an integrated approach that incorporates emergency medicine, cardiology, laboratory medicine, other clinical stakeholders, as well as basic research. Prospective studies to define AHFS phenotypes should ideally include an evaluation of cardiac structure and function at ED presentation (potentially with echocardiography or other imaging technology). Because this alone might not be feasible or practical in some ED settings, an evaluation of biomarkers to efficiently characterize the pathophysiology, prognosis, and therapeutic response in individual patients is needed (48). Comparative effectiveness studies of strategies for low-risk AHFS are also deemed important, especially among patients managed in an OU or followed after an ED encounter in an outpatient program (14,49,50).

Although not specific to the ED phase of AHFS management, the clinical value of a multidisciplinary, systems-based approach to the transition of care from initial contact with the medical system until discharge back to the outpatient environment should be ascertained (51,52). The growing and evolving use of OU treatment protocols, in which relatively low-risk AHFS patients or rapid responders to treatment can be discharged directly from the ED (53), provides a unique opportunity to educate patients, initiate important therapies, and organize post-discharge follow-up and management (54,55). Within such a construct, the ED offers a platform serving as an entry portal to a coordinated care process that includes the requisite assumption of individual personal responsibility and institutional partnership. There is also a need to incorporate systematic educational nondrug, nondevice management (e.g., post-discharge educational interventions, home monitoring) as well investigating the impact of a “dose-dependent” effect of these strategies.

In terms of study methodology, there was a consensus that factorial designs (Fig. 2), with concurrent intervention arms, could offer optimal recruitment and intervention efficiencies without sacrificing feasibility and potentially minimizing related costs. Other factors include consideration of ED environmental heterogeneity (e.g., academic vs. community; urban vs. suburban vs. rural) and the requirement of institutional matching. Lastly, there is a need to consider ED relevant end points in trials, such as days alive and out of hospital, which would be highly generalizable and valid in most ED-based studies. A “companion” end point, such as the timely application of evidence-based therapies known to reduce morbidity and mortality, and

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**Figure 2**

*Example of a Factorial Design Study With Concurrent Intervention Arms*

Evaluates the sensitivity of time dependent intervention and the impact of risk-based triage protocols. Abbreviations as in Figure 1.
measures of renal and cardiac dysfunction or damage by biomarkers reflective of these processes, might also be appropriate.

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