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## Acute Heart Failure Syndromes Current State and Framework for Future Research

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**A**cute heart failure syndromes (AHFS) poses unique diagnostic and management challenges. This syndrome has recently received attention from researchers, clinicians, regulatory agencies, and the pharmaceutical industry. However, there is no consensus on its definition, epidemiology, pathophysiology, appropriate therapeutic options, and directions for future research.

This document is the result of the First and Second International Workshop on Acute Heart Failure Syndrome that took place in May 2004 and April 2005. At these workshops, a selected group of physician scientists, epidemiologists, clinicians, regulatory and governmental funding agencies, and industry representatives from North and South America and Europe convened to develop a platform for future investigative approaches and management of AHFS. Subsequently, emergency physicians, who play a pivotal role in the early management of AHFS, contributed to this document.

### Definition

AHFS is defined as gradual or rapid change in heart failure (HF) signs and symptoms resulting in a need for urgent therapy. These symptoms are primarily the result of severe pulmonary congestion due to elevated left ventricular (LV) filling pressures (with or without low cardiac output). AHFS can occur in patients with preserved or reduced ejection fraction (EF). Concurrent cardiovascular conditions such as coronary heart disease (CHD), hypertension, valvular heart disease, atrial arrhythmias, and/or noncardiac conditions (including renal dysfunction, diabetes, anemia) are often present and may precipitate or contribute to the pathophysiology of this syndrome.<sup>1-3</sup>

### Public Health Issues

HF hospitalizations have risen steadily, with >1 million in 2004 in the United States<sup>4</sup>; a similar number has been reported in Europe. In the United States, it is estimated that these hospitalizations account for >75% of the 46 billion dollars spent each year on the care of HF patients.<sup>4</sup> Although much has been accomplished in the management of chronic HF, the absence of evidence-based clinical practice guidelines for AHFS is striking in comparison to the progress made in the treatment of acute myocardial infarction (MI) (Table 1).

The underlying cause of HF hospitalizations has been viewed traditionally as merely a problem of volume overload and/or low cardiac output, usually precipitated by dietary indiscretion and/or medication nonadherence. These hospitalizations were an expected part of the chronic HF continuum. The failure to consider AHFS as a separate entity with distinct epidemiology and pathophysiology may have contributed to the slow progress of its recognition and management. The lack of agreement within the HF community (including regulatory agencies) regarding prognosis and the appropriate goals of therapy (eg, symptom relief versus prevention of repeated hospitalizations and improvement in survival) has also delayed advances in AHFS management. The first randomized placebo-controlled AHFS trials were published as late as 2002.<sup>5,6</sup> None of the placebo-controlled AHFS studies conducted to date has shown either a consistent improvement of in-hospital or postdischarge survival or a decrease in readmissions.

### Epidemiology

Until recently, the clinical characteristics, management patterns, and outcomes of patients hospitalized with AHFS have

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**The online-only Appendix, which contains the names of the Working Group Contributors and/or Meeting participants, can be found in the Data Supplement with this article at <http://circ.ahajournals.org/cgi/content/full/112/25/3958/DC1>.**

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**TABLE 1. Similarities and Differences Between Acute MI and AHFS Resulting in Hospitalization in the United States**

	Acute MI	AHFS
Incidence	1 million per year	1 million per year
Mortality		
Prehospitalization	High	?
In-hospital	3–4%	3–4%
After discharge (60–90 d)	2%	10%
Myocardial injury	Yes	Likely
Pathophysiological target(s)	Clearly defined (coronary thrombosis)	Uncertain
Clinical benefits of interventions in published clinical trials	Beneficial	Minimal/no benefit or deleterious compared with placebo
ACC/AHA recommendations	Level A	None

ACC/AHA indicates American College of Cardiology/American Heart Association.

been poorly defined, being generated from small clinical trials and retrospective analyses of medical records or administrative databases. Data from almost 200 000 patients hospitalized for HF from the Euro-HF survey, the Acute Decompensated Heart Failure National Registry (ADHERE), and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) in the United States provided much-needed information on the epidemiology of AHFS<sup>1–3,7</sup> (Table 2).

### Clinical Classification

AHFS encompasses at least 3 clinical distinct entities: (1) Worsening chronic HF associated with reduced or preserved LVEF (70% of all admissions); (2) de novo HF (eg, after a large MI; sudden increase in blood pressure superimposed on a noncompliant LV) (25% of all admissions); and (3) advanced HF (ie, refractory to therapy) with severe LV systolic dysfunction, associated with a continually worsening low-output state (5% of all admissions).

Although it may be difficult to apply this classification at the time of hospital presentation, this becomes important for in-hospital and postdischarge management.

### Clinical Profile at Presentation

Data from large registries show that AHFS manifestation may vary with 1 or several distinct clinical conditions<sup>1–3,7,8</sup> (Table 3).

### In-Hospital Clinical Profile

After the initial management, AHFS patients can be divided into 2 groups: (1) Those continuing to improve and needing optimization of long-term therapies according to published guidelines and (2) those having recurrent symptoms requiring “rescue therapy,” defined as unplanned or urgent intervention.

### Pathophysiological Targets for Therapy and Research

Traditionally, the primary therapeutic goals for acute HF exacerbation were reduction in pulmonary capillary wedge pressure (PCWP) and/or increase in cardiac output. However,

other therapeutic targets may include blood pressure control, myocardial protection, neurohormonal modulation, and preservation of renal function.

### Hemodynamics

#### High LV Filling Pressure

Increase in LV filling pressure (cardiopulmonary congestion) is the main reason for AHFS admission and readmission.<sup>1–3</sup> Cardiopulmonary congestion leads to further neurohormonal activation,<sup>9</sup> subendocardial ischemia,<sup>10</sup> and progressive mitral and/or tricuspid regurgitation due to altered ventricular geometry. In addition, high right atrial pressures lead to myocardial edema accompanied by a decreased diastolic function and contractility.<sup>11</sup> Although the exact triggers of congestion are not known, excess salt intake, renal dysfunction, neurohormonal and cytokine activation, and medications may contribute to fluid retention.

#### Decreased Cardiac Output

Despite the fact that a decreased cardiac output may be present in AHFS, increasing the cardiac output during hospitalization does not appear to predict outcomes.<sup>12</sup>

#### Elevated Blood Pressure

A significant and relatively abrupt increase in systemic blood pressure occurs in AHFS that may be related to a surge in neurohormonal and cytokine activation. This presentation relates to an acute increase in afterload in the presence of diastolic rather than systolic dysfunction. In this setting, blood pressure optimization rather than diuresis may be the main therapeutic target.

### Myocardial Damage/Injury

Several studies have shown that increased serum troponin levels correlate with poor short- and long-term AHFS prognosis.<sup>10</sup> Preliminary research suggests that cellular hypoxia and activation of the renin-angiotensin, adrenergic, cytokine, and nitric oxide systems lead to cell death (apoptosis/necrosis). Should further research establish the presence and magnitude of myocardial injury in AHFS, preventing or limiting it with acute interventions may result in improvement in long-term outcome.

TABLE 2. Epidemiology of AHFS

	ADHERE (n=110 000)	Euro-HF (n=11 000)	OPTIMIZE-HF (n=48 612)
Important demographic characteristics			
Mean age, y	75	71	73
Women, %	52	47	52
Known heart failure, %	75	65	87
Preserved EF, %	40	54	49
Medical history, %			
CHD	57	68	50
Hypertension	72	53	71
Diabetes	44	27	42
Atrial fibrillation	31	43	31
Renal insufficiency	30	17	30
COPD	31	...	28
Serum sodium <135 mmol/L, %	25	20	25
Conduction delay (QRS >120 ms), %	30	...	...
Clinical profile at presentation			
Mean systolic blood pressure, mm Hg	145	133	142
Systolic blood pressure >140 mm Hg, %	50	29	48
Dyspnea at rest, %	34	40	44
Dyspnea on exertion, %	89	35	61
Rales, %	67	...	64
Jugular venous distension, %	...	...	28
Peripheral edema, %	66	20	65
Outpatient medication use before hospitalization, %			
Diuretics	70	87	66
ACE inhibitors	40	62	40
Angiotensin receptor blockers	12	5	12
$\beta$ -Blockers	48	37	53
Digoxin	28	36	23
Aldosterone antagonists	...	21	7
Hydralazine	...	...	3
Nitrates	26	32	22
In-hospital management, %			
IV diuretics	70	87	66
IV nesiritide	8	...	11
IV inotropes	10	...	9
Pulmonary artery catheter placement	5	...	4
Coronary angiography	10	...	9
Revascularization	2	4	2
ICD/CRT placed	...	...	2
Outcomes			
HF symptoms at discharge, %			
Unchanged/worse	<1	...	<3
Better (symptomatic)	40	...	42
Better (asymptomatic)	50	...	50
>2 kg weight loss at discharge, %	50	...	50
Median length of stay, d	4	8	4
In-hospital mortality, %	4	7	4
60–90 days postdischarge mortality, %	...	6.5	9
60–90 days readmissions, %	...	24	30

COPD indicates chronic obstructive pulmonary disease; IV, intravenous; and ICD/CRT, implanted cardioverter/defibrillator/cardiac resynchronization therapy.

**TABLE 3. Clinical Presentations of AHFS**

Clinical Presentation	Incidence*	Signs and Symptoms	Characteristics
1. Elevated systolic blood pressure	>50%	Usually develop abruptly	Predominantly pulmonary (radiographic/clinical) rather than systemic congestion due to rapid fluid redistribution from systemic to pulmonary circulation; many patients have preserved EF
2. Normal systolic blood pressure	>40%	Develop gradually (days or weeks) and are associated with significant systemic congestion	Despite high ventricular filling pressure, radiographic pulmonary congestion may be minimal because of pulmonary vasculature/lymphatics adaptation due to chronic elevated left atrial pressures
3. Low systolic blood pressure (<90 mm Hg)	<8%	Usually have a low cardiac output with signs of organ hypoperfusion	Many of those patients have advanced or end-stage HF
4. Cardiogenic shock	<1%	Rapid onset	Primarily complicating acute MI, fulminant myocarditis
5A. Pulmonary edema	<3%†	Rapid or gradual onset	Clinical: severe dyspnea, tachypnea, tachycardia, and hypoxemia, requiring immediate airway intervention  Radiographic: present in up to 80% of patients; often not associated with clinical pulmonary edema
5B. "Flash" pulmonary edema	?	Abrupt onset	Precipitated by severe systemic hypertension. Uncorrected, respiratory failure and death ensue. Patients are easily treated with vasodilators and diuretics. After blood pressure normalization and reinstitution of routine medications, patients can be discharged within 24 h
6. Isolated right HF	?	Rapid or gradual onset	Not well characterized; there are no epidemiological data (eg, acute cor pulmonale, right ventricular infarct)
7. Acute coronary syndromes (≈25% of acute coronary syndromes patients have signs/symptoms of HF)	?	Rapid or gradual onset	Many such patients may have signs and symptoms of HF that resolve after initial therapy or resolution of ischemia
8. Post-cardiac surgery HF	?	Rapid or gradual onset	Occurring in patients with or without previous ventricular dysfunction, often related to worsening diastolic function and volume overload immediately after surgery.

\*Of all AHFS admissions.

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

### **Myocardium at Risk**

Viable and noncontractile myocardium is often present in AHFS. Theoretically, the decrease in cardiac contractility that occurs in HF is a compensatory mechanism that lowers energy use by the failing myocardium and thereby improves survival of cardiac myocytes.<sup>13</sup>

In AHFS, high LV diastolic filling pressures, further neurohormonal and cytokine activation, contractility changes, heart rate increase, and/or blood pressure decrease in response to drugs may promote myocardial injury (necrosis or apoptosis), particularly in CHD patients, who often have hibernating myocardium.

### **Coronary Perfusion**

In AHFS, coronary perfusion may be diminished because of an increase in LV diastolic pressure coupled with a decrease in blood pressure and/or tachycardia resulting from certain therapeutic interventions (eg, vasodilators or inotropes) and neurohormonal and cytokine activation that facilitate/amplify further endothelial dysfunction. This may be particularly relevant in CHD patients with stunned/hibernating myocardium.<sup>14</sup>

### **Neurohormonal and Cytokine Abnormalities**

Heightened and/or sustained activation of neurohormones and cytokines deleteriously affects the function and structural integrity of myocytes and vasculature, hemodynamics, coronary perfusion, and renal function.

### **Renal Function**

In AHFS, renal dysfunction carries a poor prognosis.<sup>15,16</sup> A distinction should be made between chronic renal dysfunction resulting from a loss of functioning nephrons and glomerular mass (eg, related to diabetes or hypertension) and "vasomotor nephropathy," defined as transient renal dysfunction related to a afferent/efferent arteriolar perfusion mismatch due to hemodynamic, neurohormonal, and inflammatory factors. This may develop during hospitalization and usually presents with a significant increase in serum urea nitrogen/creatinine ratio in response to diuretic therapy despite continuing presence of fluid overload.<sup>9</sup>

In addition to decreased cardiac output and/or vasodilation that results in altered renal hemodynamics, further activation of neurohormones (renin-angiotensin-aldosterone system, catecholamines, endothelin, vasopressin) and prosta-

**TABLE 4. Prognostic Factors in AHFS**

Prognostic Factors	
Systolic blood pressure	High admission blood pressure is associated with lower postdischarge mortality Readmission rate: 30% at 90 d for both normotensive and hypertensive patients
CHD	Associated with 2-fold increase in postdischarge mortality compared with patients with primary cardiomyopathy In CHD patients there is an increased postdischarge mortality in response to short-term intravenous milrinone compared with placebo
Troponin release	30–70% of patients hospitalized with AHFS have detectable plasma levels of cardiac troponin Associated with a 2-fold increase in postdischarge mortality and a 3-fold increase in rehospitalization rate
BUN	BUN and BUN/creatinine ratio appear to be better prognostic indicators than creatinine Relatively minor increase in BUN is associated with 2- to 3-fold increase in postdischarge mortality
Hyponatremia	≈25% of patients with AHFS have mild hyponatremia Associated with 2- to 3-fold increase in in-hospital and postdischarge mortality
Natriuretic peptides	Levels correlate weakly with elevated LV filling pressures Increased levels are associated with higher postdischarge mortality and repeated hospitalizations
PCWP	Reduction in PCWP during hospitalization, but not an increase in the cardiac output, has been associated with improved postdischarge survival Reduction in PCWP with agents such as milrinone and dobutamine is associated with worse outcomes
Functional capacity	6-minute walk test is emerging as an important predictor of postdischarge outcomes
Other prognostic factors	LVEF, anemia, diabetes mellitus, new sustained arrhythmias, and nonuse of neurohormonal antagonists

BUN indicates blood urea nitrogen.

glandin inhibition contribute to arteriolar glomerular vasoconstriction and urea without creatinine reabsorption in the distal nephron.<sup>14</sup> These neurohormonal effects are exacerbated by diuretic-induced neurohormonal activation and possible intravascular volume depletion.

### Adverse Drug Effects

#### *Non-Potassium-Sparing Diuretics*

Intravenous loop diuretics may improve symptoms and fluid loss initially but also may contribute to renal function decline. This may be related not only to intravascular volume depletion but also to further neurohormonal activation resulting in a vasomotor nephropathy.<sup>11,17</sup> Intravenous loop diuretics may be associated with worse outcomes in AHFS patients.<sup>18</sup>

#### *Inotropic Therapy*

Intravenous inotropes increase myocardial oxygen consumption, causing myocardial damage in the setting of hibernating myocardium.<sup>19</sup> Use of inotropes has consistently been associated with increased mortality.<sup>20</sup>

#### *Vasodilators*

Excessive vasodilatation in AHFS may lead to blood pressure decrease, potentially exacerbating myocardial ischemia and renal hypoperfusion.<sup>21,22</sup>

### Prognostic Factors

Predictive models for mortality and rehospitalization can aid clinical decision making and patient selection for clinical trials. Several recent clinical trials and observational studies have identified emerging prognostic factors in patients admitted with AHFS<sup>8,10,12,16,23–28</sup> (Table 4).

### Evaluation Phases of AHFS Patients

The evaluation of AHFS patients consists of (1) the initial or emergency department (ED) phase; (2) the hospitalization phase; and (3) the predischarge phase (Table 5). The assess-

ments and the management goals differ according to the specific phase.

### Treatment of AHFS Patients

There are 3 phases in the current management of AHFS: The emergency treatment phase, the in-hospital management phase, and the discharge-planning phase. This section briefly addresses the limitations of current therapies and highlights investigational agents.

#### Emergency Treatment Phase

Dyspnea and other symptoms and signs of cardiopulmonary congestion are the primary AHFS manifestations and require immediate attention on presentation to the ED or hospital ward. Patients need to be stabilized initially by early administration of diuretics, vasoactive substances, and/or noninvasive ventilation (eg, continuous positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]).

#### *Non-Potassium-Sparing Diuretics*

Non-potassium-sparing diuretics represent the mainstay of therapy for AHFS and are effective in relieving symptoms acutely. However, despite symptomatic improvement, diuretic therapy may have a deleterious effect on clinical outcomes.<sup>18</sup> A more desirable approach to managing these patients, particularly when hypertension is present, is to administer much lower doses of diuretics in combination with intravenous vasodilators (eg, nitroglycerine) because these patients are not volume overloaded. This strategy has not been tested in large randomized controlled trials.<sup>29</sup>

#### *Intravenous Vasodilators Used in Clinical Practice*

Nitroglycerin reduces LV filling pressures, but its effects on clinical outcomes have not been well studied.<sup>6</sup> Although nitroprusside is being used in AHFS, it may be deleterious when used early in patients with acute MI complicated by severe HF. Nesiritide, a B-type natriuretic peptide, reduces



**TABLE 5. Evaluation phases in AHFS**

Phases	Goals	Available Tools
Initial or ED phase	Establish the diagnosis	Medical history, signs/symptoms, radiographic findings, biochemical markers
	Define the clinical profile	Blood pressure, heart rate, signs (pulmonary congestion and/or peripheral edema), ECG, chest x-ray, renal function (BUN and creatinine), electrolytes, troponin, BNP, pulse oximetry, echocardiography
	Grading severity	No accepted risk-stratification methods are available
Hospitalization phase	Decide subsequent placement	Patient comorbidities, initial response to therapies, workup, social factors
	Monitor clinical condition	Signs/symptoms, heart rate, ECG, blood pressure (orthostatic changes), body weight
	Monitor renal function	BUN and creatinine, electrolytes
	Assess right ventricular and LV filling pressure	Blood pressure (orthostatic changes, Valsalva maneuver), echocardiography, impedance cardiography, BNP/NT pro-BNP, pulmonary artery catheter
	Assess concomitant cardiac and noncardiac conditions	Eg, echocardiography, cardiac catheterization, electrophysiological testing
Discharge phase	Assess myocardial viability	MRI, stress test, echocardiography, radionuclear studies
	Assess functional capacity	6-minute walk test, treadmill
	Evaluate exacerbating factors*; appropriate corrective strategies	Eg, physical therapy, diet control, evaluation for sleep apnea
	Optimize pharmacological therapy	American Heart Association/American College of Cardiology and European Society of Cardiology guidelines
	Establish postdischarge plans	Instructions about weight monitoring, medications, smoking cessation, follow-up

BUN indicates blood urea nitrogen; BNP, B-type natriuretic peptide; and NT pro-BNP, N-terminal pro B-type natriuretic peptide.

\*For example, diet, medication nonadherence, infections, anemia, cardiac arrhythmias, hypertension.

LV filling pressures and dyspnea in AHFS patients.<sup>6</sup> Retrospective analyses have suggested that its use is associated with a decrease in renal function and may increase postdischarge mortality.<sup>21,22</sup>

#### ***Intravenous Vasodilators Under Investigation***

Carperitide (atrial natriuretic peptide) was approved for use in AHFS in Japan and is under clinical development in the United States.

Ularitide, a natriuretic peptide originally isolated from human urine, is under clinical development in Europe and the United States.

#### ***Inotropes Used in Clinical Practice***

Randomized studies indicate that milrinone, dobutamine, and enoximone (used in Europe) should not be used in patients without low-output states.<sup>5</sup> The role of dopamine in AHFS has not been studied. Although digoxin acutely improves hemodynamics both at rest and during exercise and improves the neurohormonal profile, it has not been studied in AHFS.

#### ***Inotropes Under Investigation***

Levosimendan, a calcium sensitizer approved for use in Europe, improves hemodynamics acutely and has been associated with an improvement in survival compared with dobutamine.<sup>30</sup> Two recently presented clinical trials have shown mixed results.<sup>31</sup> The role of levosimendan in AHFS is yet to be determined. Istaroxime is a novel inotropic and powerful lusitropic agent that acts by increasing sarcoplasmic reticulum ATPase activity and by inhibiting the Na<sup>+</sup>,K<sup>+</sup>-ATPase pump. This agent is being studied in phase I/II trials.<sup>32</sup>

#### ***Intravenous Angiotensin-Converting Enzyme Inhibitors***

There are no data on the safety and efficacy of angiotensin-converting enzyme (ACE) inhibitors when used early in AHFS.

Intravenous enalaprilat may have deleterious effects in patients with acute MI, especially when complicated by HF.

#### ***Intravenous $\beta$ -Blockers***

A significant number of AHFS patients present with hypertension and/or atrial fibrillation with a rapid ventricular response. The role of  $\beta$ -blockers in this setting remains to be determined.

#### ***Other Agents Used in Clinical Practice***

Morphine and oxygen supplementation are commonly used in AHFS. The use of morphine, however, may be associated with an increase in adverse events, including mortality.

Noninvasive ventilation (CPAP, BiPAP) may have a role in AHFS treatment, particularly if O<sub>2</sub> saturation is <90%; however, this has not been well studied.

#### ***Other Investigational Agents***

Vasopressin antagonists produce a significant aquaresis and decrease in body weight in AHFS.<sup>33,34</sup> Their role in the AHFS management is being tested in a large, global mortality trial.

Adenosine receptor antagonists induce diuresis via inhibition of sodium absorption in the proximal tubule without reducing renal blood flow and therefore glomerular filtration rate in HF.<sup>35</sup> Their role in AHFS is currently under investigation.

#### ***In-Hospital Management Phase***

This phase begins once the patient is stabilized and dyspnea is improved. Because a significant number of patients continue to have signs and symptoms of HF, the goals of this phase are continued hemodynamic and symptomatic improvement while preventing myocardial and renal injury. Patients who are not treated with ACE inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, or aldosterone antagonists

should receive these therapies, as recommended by recent guidelines.<sup>36–38</sup>

### Discharge-Planning Phase

Despite the clinical evidence supporting the use of implantable cardiac defibrillators and cardiac resynchronization therapy in patients with chronic HF and systolic dysfunction, their role in AHFS patients is not clear.

The available data suggest that a significant number of AHFS patients are not being evaluated for potential beneficial surgical procedures that include myocardial revascularization, LV reconstruction, mitral valve surgery, or cardiac transplantation.<sup>2</sup>

### Directions for Future Research

None of the interventions studied in AHFS clinical trials conducted to date have been shown to improve in-hospital symptoms and postdischarge clinical outcomes compared with placebo. This may be related to the following.

#### Unexpected Findings

Unexpected findings include results such as improvement in the majority of patients randomized to placebo and very poor correlation between targeted hemodynamic changes and clinical outcomes.

#### Incomplete Understanding of the Pathophysiological Process

Remaining questions include the following: What are the pathophysiological differences (if any) between acute and chronic HF? Are the different clinical presentations (eg, high versus normal blood pressure) related to a unique pathophysiological mechanism? Is myocardial preservation an important target for therapy? What is the contribution of different organs or systems to the pathophysiology of AHFS (ie, the role of kidney, liver, and peripheral vasculature)?

#### Timing of Drug Administration

Most trials conducted to date have used interventions initiated from several hours to days after the initial presentation. The lack of efficacy may be related to “late randomization” to agents used as rescue therapy (patients who continue to have severe signs and symptoms after the initial therapies). Early randomization (within hours after presentation) would include a different patient population who (1) is more likely to have severe symptoms and respond rapidly; (2) is less likely to receive large doses of diuretics or other vasoactive agents because of an adequate early response; (3) is less likely to be refractory to treatment; and (4) has higher blood pressure and better renal function.

#### Modalities of Intervention

The effects of the intervention may be determined by the following: Dose and/or duration (eg, too low or too short to have an impact on outcomes); continuous infusion versus “burst” strategy; drug rebound effects; inadequacy of other HF therapies (patients randomized to the active component may be less aggressively managed with other therapies because of initial improvement); and the ease of

implementation of long-term therapies that improve morbidity and mortality (in-hospital-to-outpatient bridge strategy).

### Patient Selection

Patient selection may play a significant role in determining the effects of a given therapy. It is not clear whether either stratification or the performance of separate trials taking into account different characteristics would produce different results with the same intervention. The response to the intervention may be related to the following: Presenting symptoms (eg, presence of dyspnea) or signs (eg, systemic versus pulmonary congestion); slowly versus rapidly developing AHFS; blood pressure level (hypertensive versus normotensive patients); underlying rhythm (eg, atrial fibrillation); LV systolic function; ischemic versus nonischemic etiology; renal function; concomitant drugs; comorbidities (eg, diabetes); and reason for HF presentation (eg, medication noncompliance, worsening underlying disease, acute coronary syndrome).

### End Point Selection

One significant problem in conducting AHFS trial is lack of clarity regarding what to measure, how to measure, and when to measure. There has been a consensus that (1) efficacy end points should be standardized across trials and validated and (2) safety end points should include renal function (estimated glomerular filtration rate [eGFR]) and myocardial injury before discharge (troponin) and long-term safety (repeated hospitalizations/mortality at 60 to 90 days).

#### Efficacy End Points

Efficacy end points should be standardized across trials and validated.

##### *European View*

The preferred efficacy end point for studies conducted in Europe is 30-day mortality. Symptomatic improvement combined with hemodynamic improvement is also an adequate primary end point, providing that there are no deleterious effects in regard to short- and long-term mortality (up to 6 months) on follow-up. Cointerventions as an efficacy end point (even as part of a composite score) are not currently acceptable to European regulatory agencies.

##### *US View*

In the United States, a meaningful clinical benefit that includes an improvement in symptoms, preservation of renal function, and/or reduction in the risk of morbid/mortal outcomes is acceptable as primary end point. The use of B-type natriuretic peptide is not accepted as part of the primary end point, although it can be used as supplemental information. Troponin, accepted as part of the definition for myocardial infarction, is not accepted as an end point in AHFS. However, it may be used as a safety end point. Hemodynamic measurements (ie, PCWP) can be a part of the primary end point; however, hemodynamic measurements should not be the sole factor driving the primary end point in the absence of meaningful clinical benefits. Symptomatic and clinical improvement assessed by the investigator can be used



as a primary end point, providing that the investigator is blinded to the hemodynamic changes that might influence his/her assessment. Renal function is gaining momentum, particularly when combined with a clinical symptomatic improvement for consideration as a coprimary end point.

#### **Safety End Points**

Safety end points include renal function (eGFR) and myocardial injury before discharge (troponin) and long-term safety (repeated hospitalizations/mortality at 60 to 90 days).

#### **Scoring Systems**

Scoring systems should include a combination of symptoms/clinical status (assessed by the patients and/or investigator), need for cointerventions (eg, intravenous diuretics, vasoactive substances), and an objective measurement (eg, B-type natriuretic peptide, PCWP, eGFR). This score should be assessed at multiple time points on the basis of the specific interventions (eg, baseline, 6 and 24 hours, and before discharge).

Taking into consideration the aforementioned issues, we are proposing a stage-based approach for conducting future AHFS trials (using drugs and devices), as follows.

#### **Stage A Trials**

Stage A trials include those therapies targeted at treatment during the initial presentation.

#### **Timing**

Because the delayed timing of study intervention may have been one of the major flaws of previously conducted trials, patients should be enrolled in AHFS trials as soon as possible after presentation to the hospital (ie, 3 to 6 hours, if not earlier).

#### **Patient Selection**

Critically ill patients (eg, shock, acute MI, requiring invasive ventilation) before randomization should be excluded. However, this must be balanced against selection bias that may result from excluding the most critically ill patients. Patients requiring noninvasive ventilation (BiPAP, CPAP) commonly have “flash” pulmonary edema that can be successfully treated with pharmacological intervention and should be included in clinical trials. The response to the study intervention will be less clear when more interventions for HF are used before randomization.

#### **Stratification**

Simple clinical parameters readily available at presentation (eg, blood pressure, renal function, serum sodium) provide opportunity for stratification. The response to different interventions and outcomes may depend on these parameters that possibly signal a different pathophysiological process (similar to the role of ST-segment elevation in acute coronary syndromes).

#### **Duration of Intervention**

Duration of intervention is likely to be at least 24 to 48 hours. A very short administration of the intervention is unlikely to alter the clinical status and outcomes significantly unless it prevents further myocardial damage and/or facilitates institution of longer-term life-saving therapies (such as

thrombolytic therapy in acute MI). In addition, the results may depend on the patient population selected for the study (eg, those with pulmonary edema versus worsening chronic HF).

#### **Efficacy End Point**

The “new” efficacy end point needs to be a multiple component/multiple time end point (clinical composite score). This is based on the fact that the clinical improvement in the placebo groups in AHFS clinical trials conducted to date has been close to 70% when a single component/single time end point has been used. The components of the combined end point should cover different dimensions, such as patient-perceived clinical status (eg, dyspnea), investigator assessment of the patient’s clinical status, and need for cointerventions measured over a period of time.

Ideally, an objective measure should reflect changes in symptoms and outcomes instead of a clinical composite score. To date, there has been a poor correlation between such objective measures (eg, PCWP) and changes in symptoms and outcomes. Additionally, ED-based clinical trials, whereby the impact of early intervention can best be assessed, cannot have hemodynamic measurements included in the study protocol for obvious practical reasons.

Patient self-assessed clinical status and investigator assessment can be quantified (on a 5- or 7-point Likert scale), with improvement being considered when “moderate” or “markedly better” has been achieved in one or both. The investigator assessment should be guided by several clinical findings (such as patient symptoms, vital signs, physical examination) and laboratory data.

The need for cointerventions for worsening HF symptoms, not largely accepted at the present time, might provide an objective way of assessing differences between placebo and study drug. The cointerventions can be defined as use of any unplanned intervention (not routine) for deteriorating cardiac status, such as intravenous vasoactive agents (eg, inotropes), CPAP, intubation, defibrillation, ultrafiltration, and other major interventions. Although the most common cointerventions are intravenous diuretics, it is recognized that they are often prescribed routinely in the hospital setting in patients without deterioration in their cardiovascular status. Therefore, the use of intravenous diuretics as cointervention in AHFS clinical trials needs to be standardized; dose escalation of intravenous diuretics should be used only in response to worsening symptoms, as determined by the objective investigator assessment. Use of cointervention can be classified as better (preplanned [eg, use of prespecified, limited amount of diuretic only]) or worse (urgent or rescue [eg, use of inotropes, escalation of diuretics, intubation]). The efficacy end point should be considered better if moderate or marked improvement is achieved by patient and/or investigator assessment and if the need for cointervention is better.

Routine HF therapies (eg, ACE inhibitors, angiotensin receptor blockers,  $\beta$ -blockers, aldosterone antagonists) should not be considered cointerventions. They should be strongly encouraged during the study period because the acute intervention aim is to stabilize the patient and serve as a bridge to more definitive therapies. Use of long-term

therapies will also prevent the rebound in symptoms that may occur after discontinuation of the investigational intervention.

The composite end point should be assessed at multiple times (eg, 6 hours, 24 hours, and before discharge) to capture status changes and the “true” benefit of the intervention.

### **Safety End Points**

Safety end points need to capture renal, myocardial, and other target organ damage (injury) before discharge and repeated hospitalizations/mortality within 60 to 90 days from randomization.

### **Feasibility of Conducting Stage A Trials**

Most AHFS patients present to the ED. Conduct of such studies requires the ED to develop an appropriate infrastructure, consisting of teams of qualified investigators and research coordinators capable of screening and randomizing patients in early AHFS stages, similar to models of thrombolytic therapy trials for acute MI. Readmission and mortality rates, especially short term (<5 days), of patients discharged with AHFS from an observation unit or the ED could be also explored as a primary end point. One of the key aspects in AHFS research is the recognition that a short-term therapy may not be able to reduce postdischarge mortality. However, the short-term intervention should improve patient status without inducing significant adverse effects that increase long-term mortality (ie, by worsening renal function or causing myocardial injury).

### **Stage B Trials**

Stage B trials would be conducted during the hospitalization, testing medications and/or devices in patients who continue to have HF signs and symptoms despite the initial therapy.

### **Timing**

Patients enrolled in these trials are those in whom the initial therapy fails to produce a desirable clinical and functional improvement after 24 to 48 hours.

### **Stratification**

Because the enrollment will occur after 24 to 48 hours, these patients would have been evaluated already, providing an opportunity to stratify by factors such as LVEF, absence or presence of CHD, and renal dysfunction.

### **Duration of Intervention**

Interventions can be tested either for in-hospital use only or maintained during the outpatient phase.

### **Efficacy End Points**

Efficacy end points need to be validated and standardized across trials. The target is to reach a stable asymptomatic or minimally symptomatic state during exertion. Relevant end points include combination of persistent symptom resolution (functional assessment), sustained global improvement of cardiorenal status, and the total number of days hospitalized for cardiovascular causes or dead within 60 to 90 days of the initial discharge.

### **Safety End Points**

Safety end points need to capture renal, myocardial, and other target organ damage before discharge and repeated hospitalizations/mortality within 60 to 90 days from randomization.

### **Stage C Trials**

Stage C trials would focus on optimization of evidence-based therapies and/or initiation of a therapeutic agent or device to be maintained on an outpatient basis. These trials aim for the critical and vulnerable time period when the immediate postdischarge event rate (within 60 to 90 days) is several-fold higher compared with a similar time period in outpatients with stable chronic HF. Accordingly, demonstration of an intervention benefit may require a smaller sample size.

### **Timing**

These trials can be initiated before or soon after discharge.

### **Stratification**

Different treatment strategies could be used based on factors such as LVEF, absence or presence of CHD, and renal dysfunction.

### **Duration of Intervention**

Interventions are conducted during the outpatient phase.

### **Efficacy End Points**

The target is to maintain a stable asymptomatic or minimally symptomatic state and improve quality of life parameters. The relevant end point should include combination of mortality and worsening HF (defined as hospitalization, unscheduled visits, and unexpected need for HF cointerventions).

### **Study Design for Stages A, B, or C**

There has been a poor correlation in AHFS trials between the encouraging results of the phase II trials and outcomes when the same intervention was used in phase III trials. Studies should be placebo controlled, or, if a control (eg, dobutamine) is used instead of placebo, the effects of an investigational agent on outcomes should be clear and derived from placebo-controlled trials.

### **Quality of Care and Outcome Research**

It is well documented that despite solid clinical data, evidence-based therapies are underused in patients with chronic HF. The OPTIMIZE-HF study<sup>3</sup> has shown that use of algorithms, care maps, and other tools during a hospitalization and at the time of discharge results in more appropriate use of evidence-based therapies. It also appears that having a management strategy in place translates into better outcomes for patients. In an effort to provide the best AHFS care, outcome research must be developed.

### **Conclusions**

AHFS is a complex condition with substantial morbidity and mortality and enormous utilization of health resources and cost. There are numerous challenges in caring for this population. Uniform AHFS classification is currently lacking, and management strategies vary markedly. The International Working Group on AHFS brought together the world's experts to foster an exchange of ideas to facilitate better understanding of pathophysiology, treatment direction, and the future of clinical research in AHFS. There is a general consensus that to reduce mortality, morbidity, and the economic burden of AHFS, systematic research efforts on clinical application and translation of promising basic science

results are needed. Pathophysiologically based interventions (eg, cardiorenal syndrome) may be particularly appealing. A special focus should be on choice of appropriate management strategies, including minimizing the use of drugs with adverse effects and development and validation of known prognostic markers to guide AHFS interventions.

A logical staged approach to implementing clinical management and research strategies is being proposed.

The International Working Group on AHFS continues to work toward the goal of identifying barriers and challenges and addressing both management strategies and research needs and opportunities to significantly decrease the burden of AHFS.

### Disclosures

Dr Gheorghiade reports having received honoraria and/or having served on the Speakers Bureau for GlaxoSmithKline and Medtronic and having served as a consultant and/or on the advisory board for GlaxoSmithKline, Medtronic, Otsuka, Protein Design Labs, Pfizer, and Sigma-Tau. Drs Collins reports having received honoraria and/or having served on the Speakers Bureau for Scios and having served as a consultant and/or on the advisory board for Protein Design Labs. Dr Filippatos reports an affiliation with Metronix and having served as a consultant and/or on the advisory board for Protein Design Labs. Dr Klein reports having served as a consultant and/or on the advisory board for Medtronic and Protein Design Labs. Dr Konstam reports having been employed by Orqis Medical, having an ownership interest in Orqis Medical, having received research support from Otsuka, and having served as a consultant and/or on the advisory board for Otsuka. Dr Massie reports having served as a consultant and/or on the advisory board for Abbott and Scios. Dr Piña reports having received honoraria and/or having served on the Speakers Bureau for Astra-Zeneca and Novartis. Dr Tavazzi reports having received a research grant from Otsuka, having received honoraria and/or having served on the Speakers Bureau for Abbott, and having served as a consultant and/or on the advisory board for Abbott and Protein Design Labs. The remaining authors report no conflicts of interest.

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