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STATE-OF-THE-ART PAPER

Acute Heart Failure Syndromes

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Heart failure resulting in hospitalization represents a significant and growing health care burden. Heterogeneity characterizes this group in terms of mode of presentation, pathophysiology, and prognosis. The vast majority of patients symptomatically improve during hospitalization; however, their early post-discharge rehospitalization and mortality rates continue to be high. Worsening signs and symptoms, neurohormonal, and renal abnormalities occurring soon after discharge may contribute to these high post-discharge event rates. Currently available assessment modalities combined with recent advances in cardiovascular therapies provide present-day opportunities to improve post-discharge outcomes. Further investigation into pathophysiologic targets and novel approaches to clinical trial design are needed. Improving post-discharge outcomes is the single most important goal in the management of acute heart failure syndromes. (J Am Coll Cardiol 2009;53:557–73) © 2009 by the American College of Cardiology Foundation

Hospitalization for acute heart failure syndromes (AHFS) is 1 of the most important predictors of post-discharge mortality and readmission in patients with chronic HF (1,2). Over 1 million hospitalizations with a primary diagnosis of HF occur each year in the U.S. (3). As a diagnosis at hospital discharge, HF has tripled over the last 3 decades. This trend will likely continue due to an aging population, improved survival after myocardial infarction (MI), and better prevention of sudden cardiac death (3,4).

Management of AHFS is challenging given the heterogeneity of the patient population, absence of a universally accepted definition, incomplete understanding of its pathophysiology, and lack of robust evidence-based guidelines. The majority of patients appear to respond well to initial therapies consisting of loop diuretics and vasoactive agents (5–7). However, post-discharge mortality and rehospitalization rates reach 10% to 20% and 20% to 30%, respectively, within 3 to 6 months (6,8). Although this may reflect the severity of HF, myocardial injury and/or renal impairment occurring in AHFS may contribute to this grim prognosis. Improving post-discharge mortality and prevention of readmissions are the most important goals in AHFS.

This review reflects concepts developed by the International Working Group on AHFS that met annually for the last 5 years, composed of cardiologists, hospitalists, emergency physicians, industry, and governmental agencies (5).

Definitions

AHFS can be defined as new onset or gradual or rapidly worsening HF signs and symptoms requiring urgent therapy (5). Irrespective of the underlying cause (e.g., ischemic event) or precipitant (e.g., severe hypertension), pulmonary and systemic congestion due to elevated ventricular filling pressures with or without a decrease in cardiac output is a nearly universal finding in AHFS (5). Coronary artery disease (CAD), hypertension, valvular heart disease, and/or atrial fibrillation, as well as noncardiac conditions such as renal dysfunction, diabetes, anemia, and medications (i.e., nonsteroidal anti-inflammatory drugs, glitazones), may also contribute to these abnormalities (5,9–11). The majority of AHFS patients have worsening chronic HF; after initial management resulting in stabilization, they should no longer be considered acute but chronic HF (11).

Patient Characteristics

Heart failure afflicts over 5 million Americans and 15 million Europeans (3,11–13). The cost in the U.S. is over 34 billion dollars per year, mainly related to hospitalizations, with similar financial burdens for many European countries (3,11–13). Over 1 million hospital discharges for HF occurred in 2005 in the U.S., an increase of 171% compared with discharges in

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AHFS = acute heart failure syndromes
ARB = angiotensin receptor blocker
BNP = B-type natriuretic peptide
BP = blood pressure
BW = body weight
CAD = coronary artery disease
CRT = chronic resynchronization therapy
EF = ejection fraction
HF = heart failure
IV = intravenous
LVFP = left ventricular filling pressure
MI = myocardial infarction
PCWP = pulmonary capillary wedge pressure
PSF = preserved systolic function
SBP = systolic blood pressure

1979 (12). Approximately 3.8 million hospital diagnoses of HF occurred in 2004 (3). Between 1992 and 2001, there were 10.5 million U.S. emergency department visits for AHFS, with an average increase of 18,500 visits each year (4). AHFS resulting in hospitalization is the most common diagnosis-related group for Medicare patients and in total, the most expensive (3,12–14). Only recently, AHFS registries from Europe and the U.S. provided us with an accurate characterization and prognosis of these patients (6,7,9,10,15–20). However, less is known from other geographical regions.

Patient characteristics. The majority of AHFS patients have worsening chronic HF resulting in hospitalization, with the remaining 15% to 20% diagnosed with HF for the first time. The mean age is 75 years and over one-half are women. Dyspnea and signs of congestion manifested by jugular venous distention and edema are common (9,15,21). At presentation, approximately 25% of patients are hypertensive (systolic blood pressure [SBP] >160 mm Hg), <10% are hypotensive, most are taking diuretics, 40% take angiotensin-converting enzyme (ACE) inhibitors, 10% take angiotensin-receptor blockers, 50% take beta-blockers, and 20% to 30% take digoxin (9,18,21). A history of CAD is present in 60%, hypertension in 70%, diabetes in 40%, atrial fibrillation in 30%, and moderate to severe renal impairment in 20% to 30% (22).

Approximately 50% of AHFS patients have a relatively preserved systolic function (PSF) (6,7,9,15,23). They are older and more likely to be female. They are also more likely to have a history of hypertension and atrial arrhythmias, and present with severe hypertension (6,7,23) (Table 1).

Precipitants for admission. Hospitalization commonly results from congestion or fluid overload and not a low cardiac output (9,24). Congestion, due to an increase in left ventricular filling pressure (LVFP) (hemodynamic congestion) often results in jugular venous distention, peripheral edema, and/or an increase in body weight (BW) (clinical congestion). This often starts days if not weeks before admission (25,26). Hospitalization for HF, in itself, is 1 of the most important predictors for rehospitalization (1,2). Both in the U.S. and Europe, uncontrolled hypertension, ischemia, arrhythmias, exacerbation of chronic obstructive pulmonary disease with or without pneumonia, and noncompliance (dietary and/or medication) are major precipitants for admission (27). In patients presenting with de novo HF, a significant number are diagnosed with acute coronary syndrome (19).

Clinical course. Most patients have rapid symptomatic improvement with loop diuretics and have a relatively short hospital stay (4,9,15,18). Although systemic and pulmonary congestion is the main reason for hospitalization, many do not have a decrease in BW during hospitalization and are often discharged with HF signs and/or symptoms (7,28,29). Often a comprehensive assessment is not performed (e.g., cardiac catheterization, assessment for viable, but dysfunctional myocardium). This may result in underutilization of evidence-based therapies (5,28,30,31). In patients admitted with worsening chronic HF, except for diuretic dose escalation, introduction of new or up-titration of evidence-based therapies (e.g., ACE inhibitors, beta-blockers) is <5% to 10%. In fact, they are often discharged on the same pre-admission medications (8,15,32).

The mean length of stay in the U.S. is ~6 days (median: 4 days) (9,18). In-hospital mortality (~2% to 4%) may reach 20% for those patients with severe renal impairment and low SBP. However, this group represents <2% to 5% of the overall AHFS population (6). Post-discharge mortality varies at 60 to 90 days from 5% to 15% depending on BP at presentation (the higher the BP, the lower the mortality). The readmission rate is approximately 30%, independent of SBP at presentation (21). Risk for these events is highest in the first few months following discharge (2,31). Recent data suggests an association between early events and worsening symptoms, renal function, and neurohormonal profile during the first few weeks after discharge (33). Among patients admitted with chronic HF and low ejection fraction (EF), approximately 40% will die from progressive HF and 30% will die suddenly and unexpectedly post-discharge (31). Approximately 50% of readmissions are not related to HF. Early post-discharge events in PSF patients appear similar to those with reduced EF, although the mode of death and reason for rehospitalization has not been studied in these patients (6). It is possible that a significant number of morbid events in the AHFS/PSF population are related to coexisting cardiac or noncardiac comorbidities, such as CAD, hypertension, atrial fibrillation, renal insufficiency, or stroke (34,35).

Clinical Classification

Patients may be classified into HF presenting for the first time (de novo) or worsening chronic HF (5) (Fig. 1). In both groups, the presence and extent of CAD may determine the initial, in-hospital, and post-discharge management (36). The EF may influence post-discharge rather than initial management, which should be based on the presenting clinical profile. Of the approximately 80% of AHFS patients with chronic HF resulting in hospitalization, <5% to 10% have advanced HF. Low blood pressure, renal impairment, and/or signs and symptoms refractory to standard therapy characterize

Table 1 Preserved Versus Reduced Systolic Function Patient Characteristics

Characteristics at Admission	Patients With LVSD (n = 20,118)	Patients With PSF (n = 21,149)
Demographics		
Age, yrs	70.4 ± 14.3	75.1 ± 13.1
Male	62%	38%
Caucasian	71%	77%
African American	21%	15%
Medical history		
Diabetes, insulin-treated	15%	17%
Diabetes, noninsulin-treated	24%	26%
Hypertension	66%	76%
Hyperlipidemia	34%	32%
Atrial arrhythmia	28%	33%
Vital signs on admission		
Body weight, kg	78.5 [65.8, 94.0]	78.9 [64.0, 97.5]
Heart rate, beats/min	89 ± 22	85 ± 21
SBP, mm Hg	135 ± 31	149 ± 33
DBP, mm Hg	77 ± 19	76 ± 19
Etiology		
Ischemic	54%	38%
Hypertensive	17%	28%
Idiopathic	18%	21%
Findings on admission		
Acute pulmonary edema	3%	2%
Chest pain	23%	24%
Uncontrolled hypertension	9%	12%
Dyspnea at rest	44%	44%
Dyspnea on exertion	63%	62%
Rales	63%	65%
Lower extremity edema	62%	68%
Jugular venous distention	33%	26%
Left ventricular EF, %	24.3 ± 7.7	54.7 ± 10.2
Laboratory values		
Serum sodium, mEq/l	137.7 ± 4.6	137.9 ± 4.8
Serum creatinine, mg/dl	1.4 [1.1, 1.9]	1.3 [1.0, 1.8]
Serum hemoglobin, g/dl	12.5 ± 2.0	11.9 ± 2.0
BNP, pg/ml	1,170.0 [603.0, 2,280.0]	601.5 [320.0, 1,190.0]
Troponin I, ng/ml	0.1 [0.1, 0.3]	0.1 [0.0, 0.3]
Medications on admission		
ACE inhibitor	45%	36%
ARB	11%	13%
Amlodipine	5%	10%
Aldosterone antagonist	10%	5%
Beta-blocker	56%	52%
Loop diuretic	63%	58%
Digoxin	30%	17%
Aspirin	42%	38%
Antiarrhythmic	13%	8%
Hydralazine	3%	3%
Nitrate	22%	21%
Statin*	40%	39%

Data presented as percent, mean ± SD, or median [25th, 75th percentiles]. Adapted and reproduced, with permission, from Fonarow et al. (6). *Statin use among patients with coronary artery disease, cerebrovascular disease/transient ischemic attack, diabetes, hyperlipidemia, or peripheral vascular disease.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; DBP = diastolic blood pressure; EF = ejection fraction; LVSD = left ventricular systolic dysfunction; PSF = preserved systolic function; SBP = systolic blood pressure.

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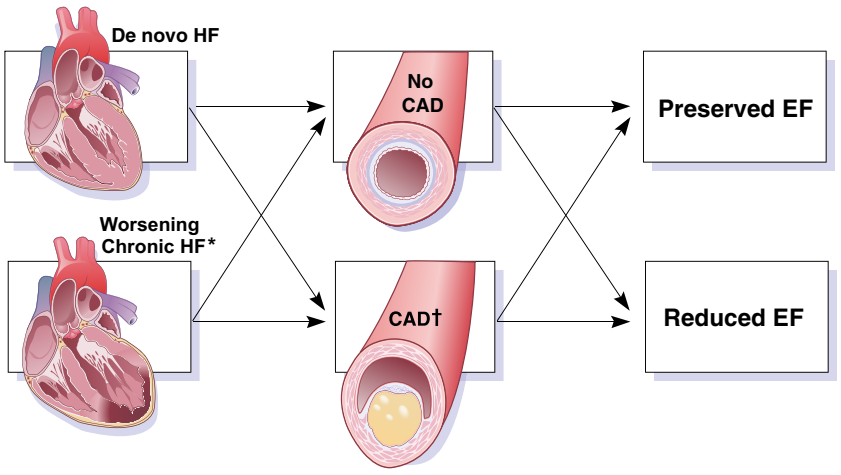

Figure 1 General Clinical Classification

Broad general classification proposed for AHFS patients representing key factors that may influence management. *Advanced HF is a subset of chronic HF. †With or without acute coronary syndromes. Figure illustration by Rob Flewell. CAD = coronary artery disease; EF = ejection fraction; HF = heart failure.

advanced HF. De novo HF represents the remainder of AHFS and may be further divided into those with pre-existing risk for HF (e.g., hypertension, CAD) without evidence of prior LV dysfunction or structural abnormalities and those with pre-existing cardiac structural abnormalities (e.g., reduced EF) (13).

Pathophysiology

AHFS are characterized by severe hemodynamic and neurohormonal abnormalities that may cause myocardial injury and/or renal dysfunction or may be a result of it (11,37,38). These abnormalities may be caused or precipitated by ischemia, hypertension, atrial fibrillation, other noncardiac conditions (e.g., renal insufficiency), or untoward drug effects (11,39–42).

Congestion. High LV diastolic pressure resulting in pulmonary and systemic congestion with or without low cardiac output is the main reason for presentation in the majority of patients (5,9,24,37,43,44). Pulmonary congestion may be defined as pulmonary venous hypertension (increased pulmonary capillary wedge pressure [PCWP]) often resulting in pulmonary interstitial and alveolar edema. Systemic congestion manifests clinically by jugular venous distention with or without peripheral edema and gradual increases in BW are often seen (11) (Table 2). Occasionally, severe pulmonary congestion develops abruptly when precipitated by a rapid increase in BP (afterload), particularly in patients with diastolic dysfunction (45–48). Renal impairment, severe neurohormonal or endothelial abnormalities, dietary indiscretion, and certain medications such as nonsteroidal anti-inflammatory drugs, glitazones, and first generation calcium-channel blockers, may also contribute to fluid overload (5,27,49–52).

High LV diastolic pressure, by itself, may contribute to the progression of HF by further causing activation of neurohormones, subendocardial ischemia, and/or changes in LV size and shape (remodeling) that often results in mitral insufficiency (24,53–55). Increased systemic venous pressure (high right atrial pressure), most commonly caused

Table 2 Assessment of Congestion

BW	Increase in BW predicts hospitalization (26,33). However, a reduction in BW in response to different therapies may not necessarily result in decreased hospitalization or mortality.
Heart rate and rhythm	Both bradyarrhythmias and tachyarrhythmias can contribute to congestion.
BP	Either no change in BP or an increase in BP from supine to the upright position or during Valsalva maneuver usually reflects a relatively high LV filling pressure (113).
Jugular venous pressure	Equals RA pressure. In a chronic state, the RA pressure correlates with PCWP/LVDP.
Rales	Associated with increase in PCWP when present with other signs of elevated filling pressure (e.g., JVD, S_3), but is nonspecific by itself.
Edema	Peripheral edema, only when associated with JVD, indicates right-sided failure that is usually associated with left-sided HF. During hospitalization, may move from dependent periphery to the sacral area.
Orthopnea test	Patients often do not tolerate lying flat when there is a rapid increase in filling pressure. However, in a chronic state, this position may be tolerated in spite of a relatively high filling pressure.
BNP/NT-proBNP	Marker of increased LV filling pressures.
Chest X-ray	Pulmonary congestion (cephalization, interstitial edema, alveolar edema, pleural effusions) may be absent in spite of a very high PCWP in patients with severe but chronic HF. However, when present, it indicates a high PCWP.

Exercise testing to assess functional classification might aid in assessment of residual congestion.
BNP = B-type natriuretic peptide; BP = blood pressure; BW = body weight; HF = heart failure; JVD = jugular venous distention; LV = left ventricle; LVDP = left ventricular diastolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCWP = pulmonary capillary wedge pressure; RA = right atrium.

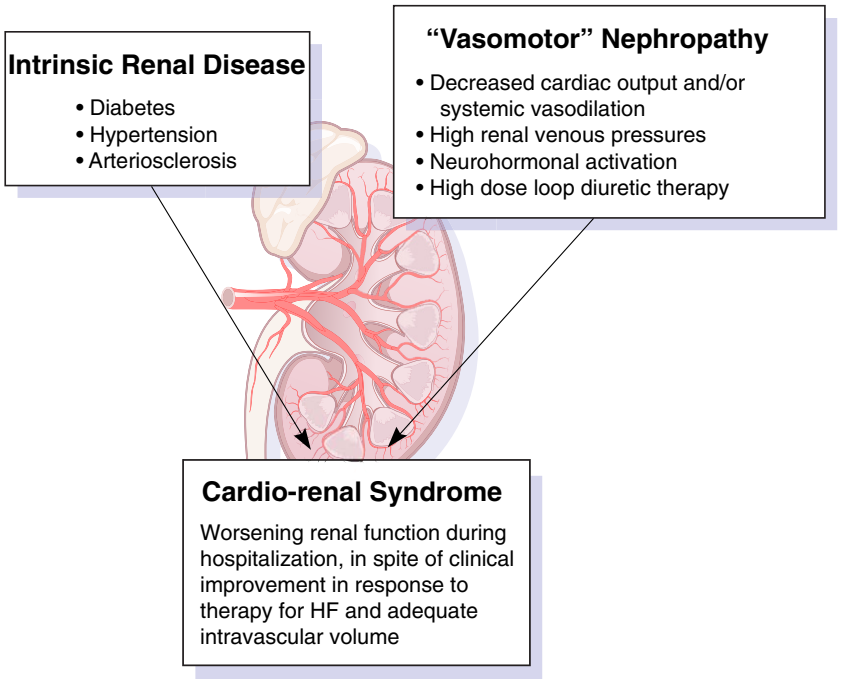

Figure 2 The Cardio-Renal Syndrome

Both intrinsic/pre-existing structural kidney disease and potential contributors to renal injury from acute heart failure (HF) syndromes characterize the cardio-renal syndrome. Figure illustration by Rob Flewell.

by high left-sided pressures (PCWP), may contribute to the development of the cardio-renal syndrome (56–59).

Body weight is often used as a marker of congestion in both inpatient and outpatient settings. However, recent data suggest a more complex relationship among BW, congestion, and outcomes. Although an increase in BW predicts hospitalization (26,33), a reduction in BW in response to different therapies may not necessarily result in decreased hospitalization or mortality. For example, vasopressin antagonists and non–potassium-sparing diuretics appear to decrease BW effectively, however, their use has not always been associated with an improvement in mortality or rehospitalization (60,61).

Myocardial injury. Troponin release often occurs in AHFS, particularly in patients with CAD (14,62,63). This likely reflects myocardial injury, which may be related to hemodynamic and/or neurohormonal abnormalities or the result of an ischemic event (MI). Injury may also be the consequence of a high LV diastolic pressure, further activation of neurohormones, and/or inotropic stimulation, resulting in a supply and demand mismatch (increased myocardial oxygen demand and decreased coronary perfusion) (38). These conditions may precipitate injury, particularly in patients with CAD, who often have hibernating and/or ischemic myocardium (36). This is supported by experimental data in dogs where stimulation of hibernating myocardium with low-dose dobutamine resulted in myocardial necrosis (64). The importance of myocardial injury in AHFS has not been well studied and remains an area of investigation.

Renal impairment. In AHFS, renal abnormalities promote sodium and water retention (59). Structural renal dysfunction due to diabetes, hypertension, and arteriosclerosis, are common. Worsening renal function occurs in 20% to 30% of patients during hospitalization (65,66). Recent data suggests that approximately 20% of patients have worsening renal function soon after discharge (67). This worsening during or after discharge may result from further neurohormonal and hemodynamic abnormalities (low cardiac output and/or high venous pressure), which may be aggravated by high-dose loop diuretics (56–59,66,68) (Fig. 2). Renal dysfunction resulting from neurohormonal or hemodynamic abnormalities (vasomotor nephropathy) may be preventable or reversible and it is often referred as the cardio-renal syndrome. In a given patient, distinguishing between vasomotor nephropathy from abnormalities related to intrinsic kidney disease is often difficult and remains an important area for research.

Untoward drug effects. Non–potassium-sparing intravenous (IV) loop diuretics are first-line agents to alleviate congestive symptoms. However, those beneficial effects may be associated with electrolyte abnormalities, further activation of neurohormones, and worsening renal function (68,69). High-dose administration of IV loop diuretics has been associated with worse outcomes in HF patients.

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Table 3 Prognostic Indicators and Potential Targets of Therapy in AHFS*

SBP	Admission and early post-discharge SBP inversely correlates with post-discharge mortality. The higher the BP, the lower both in-hospital and post-discharge mortality. However, the readmission rate of approximately 30% is independent of the SBP at time of admission (21).
CAD	Extent and severity of CAD appears to be a predictor of poor prognosis (36).
Troponin release	Results in a 3-fold increase in in-hospital mortality, a 2-fold increase in post-discharge mortality, and a 3-fold increase in the rehospitalization rate (14,79).
Ventricular dyssynchrony	Increase in QRS duration occurs in approximately 40% of patients with reduced systolic function and is a strong predictor of early and late post-discharge mortality and rehospitalization (31).
Renal impairment	Associated with a 2- to 3-fold increase in post-discharge mortality. Worsening renal function during hospitalization or soon after discharge is also associated with an increase in in-hospital and post-discharge mortality (33,66,70,80).
Hyponatremia	Defined as serum sodium <135 mmol/l, occurs in approximately 25% of patients, and is associated with a 2- to 3-fold increase in post-discharge mortality (30,94,95).
Clinical congestion at time of discharge	An important predictor of post-discharge mortality and morbidity (24,44).
EF	Similar early post-discharge event rates and mortality between reduced and preserved EF (6).
BNP/NT-proBNP	Elevated natriuretic peptides associated with increased resource utilization and mortality (81).
Functional capacity at time of discharge	Pre-discharge functional capacity, defined by the 6-min walk test, is emerging as an important predictor of post-discharge outcomes (82,83).

Adapted and modified, with permission, from Gheorghiade et al. (5). *This is not an all-inclusive list. CAD = coronary artery disease; other abbreviations as in Tables 1 and 2.

However, this association may be a marker of the severity of HF, rather than a cause of increased mortality (61,68,70).

Dobutamine, milrinone, and levosimendan improve hemodynamics; however, these effects may be associated with increased myocardial oxygen consumption (tachycardia and increased contractility) and hypotension due to their vasodilatory effects (71,72). Decreasing coronary perfusion due to hypotension in the presence of increased myocardial oxygen demand may result in myocardial injury, particularly in patients with CAD who often have ischemic or hibernating myocardium (38).

Hypotension associated with the use of vasodilators may also result in myocardial and renal hypoperfusion and possibly injury (38,40–42,73).

Prognostic Factors

Recent clinical trials and observational studies have identified emerging prognostic factors in patients admitted with AHFS (74–83) (Table 3).

BP. Systolic BP on admission and early post-discharge is emerging as an important predictor of in-hospital and post-discharge mortality (21,33). It correlates inversely with mortality; high SBP at time of admission is associated with a substantially lower in-hospital and post-discharge mortality (21). However, the 60- to 90-day readmission rate remains high and appears independent of presenting BP (21).

CAD. Patients with AHFS and CAD often have a worse prognosis than other patients. This may be related to the extent and severity of CAD but also to the presence of other comorbidities that are more common in these patients (36). Hibernating and/or ischemic myocardium is a therapeutic target for medical therapy and/or revascularization (36) (Fig. 3). Unstable angina appears to be an important cause for hospitalization in patients with chronic HF and PSF (84).

Ventricular dyssynchrony. A prolonged QRS complex, a marker of ventricular dyssynchrony, is present in approximately 40% of patients with reduced systolic function hospitalized for worsening HF. This is associated with an increase in early and late post-discharge mortality and hospitalization (31). Although chronic resynchronization therapy (CRT) appears to be beneficial in patients with chronic HF and reduced systolic function with a prolonged QRS, this was not studied in AHFS (31,85). The prognostic value of QRS duration in patients with AHFS and PSF has not been studied.

Arrhythmias. New sustained ventricular or atrial arrhythmias developing during hospitalization are uncommon; however, when present, they predict an increase in post-discharge mortality (86).

Renal impairment. Renal impairment is often present at time of admission (22). Approximately 30% of patients with AHFS have worsening renal function during hospitalization (87,88). Markers of renal impairment, either blood urea nitrogen, Cr, blood urea nitrogen/Cr ratio, estimated glomerular filtration rate, and/or cystatin C all have important prognostic significance (22,66,87–93). Emerging data suggests that an increase in blood urea nitrogen during the early post-discharge period is 1 of the most important predictors of early mortality (33,67).

Hyponatremia. Mild hyponatremia occurs in ~25% of patients with AHFS, irrespective of systolic function, and usually remains uncorrected during hospitalization (30,94,95). These hyponatremic patients have the same hemodynamic and clinical response as those with normonatremia, yet demonstrate a significantly greater risk of death post-discharge (95). Although vasopressin antagonists (e.g., tolvaptan and conivaptan) effectively correct hyponatremia, their use has not been associated with improved outcomes (43,60,96).

Other prognostic factors. Troponin release, elevated natriuretic peptide levels, elevated PCWP, liver disease, anemia, severe symptoms, older age, and increased heart rate appear to be markers of increased post-discharge mortality risk (62,63,74,97–103). In contrast, the use of beta-blockers, aldosterone antagonists, and ACE inhibitors is associated with an improved prognosis (6). Recently, cardiac catheterization has been associated with improvement in post-discharge outcomes. This improvement was related to implementation of evidence-based therapy for CAD during hospitalization (105).

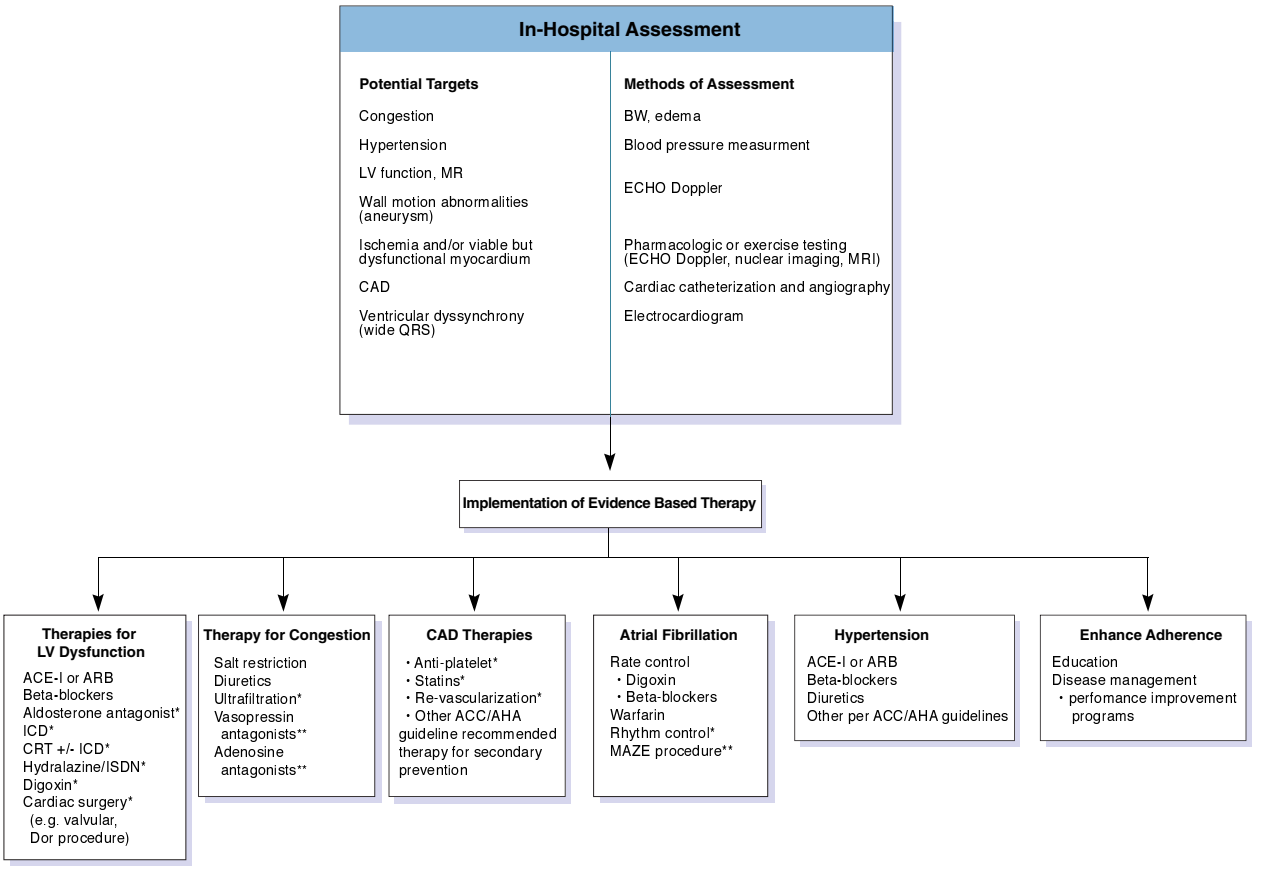

Figure 3 Assessment and Targeted Implementation of Evidence-Based Therapy in AHFS

Chart recommends assessment methods and ways to implement therapy. *Select patients; **investigational agents. ACC = American College of Cardiology; ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AHA = American Heart Association; ARB = angiotensin receptor blocker; CRT = chronic resynchronization therapy; Dor procedure = ventricular reconstructive surgery to restore aneurysmal left ventricle to its normal, elliptical shape; ECHO = echocardiography; ICD = implantable cardiac-defibrillator; ISDN = isosorbide dinitrate; LV = left ventricle; MAZE = Cox maze procedure to eliminate atrial fibrillation; MR = mitral valve regurgitation; MRI = magnetic resonance imaging; other abbreviations as in Figure 1.

Evaluation Phases of AHFS Patients

Four phases of hospital evaluation and management of AHFS are proposed: 1) initial or early phase (i.e., emergency department); 2) in-hospital phase; 3) pre-discharge phase; and 4) early post-discharge phase (5).

Early phase. This phase of AHFS management typically takes place in the emergency department, where 80% of all hospitalized patients initially present (15,16,18). Evaluation and management often proceeds concomitantly (Table 4). After stabilization/treatment of life-threatening conditions, improving hemodynamics and symptoms are key goals. Abnormal hemodynamics often results from conditions such as hypertension, ischemia, and/or arrhythmias. These conditions, as well as any other precipitants of HF, should be treated for optimal results.

The downstream impact of early therapy on outcomes for AHFS has not been well studied (106). Intravenous loop diuretics with or without vasoactive agents (inotropes and/or vasodilators) improve symptoms in most patients (106–109). The potential deleterious effects of these therapies, if any, on the myocardium and kidney have not been well studied (5). IV inotropes and vasodilators that initially improve signs and symptoms may adversely affect post-discharge outcomes (39,41,42,71,109,110). Determining if injury to key organs such as the heart or kidney occurs early or begins prior to presentation may shift the therapeutic window upstream.

Clinical profiles at presentation. Initial management should be based on clinical profiles (Table 5). The presence and severity of underlying CAD may affect early management decisions, because these patients may require additional therapies or may be adversely affected by other therapies (e.g., inotropes) (39).

A universally accepted risk-stratification method applicable at the time of admission and a classification similar to the Killip scoring system for acute MI is needed. In general, risk stratification should consider baseline variables, clinical course, and variables measured during the

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Table 4 Initial Management for AHFS*

1. Treat immediate life-threatening conditions/stabilize patient	Life-saving measures may precede or parallel diagnostic evaluation (i.e., unstable arrhythmia, flash pulmonary edema, STEMI)
2. Establish the diagnosis	Based on medical history, signs (JVD, S_3, edema), symptoms (dyspnea), biomarkers (e.g., BNP) and CXR
3. Determine clinical profile and begin initial treatment	Key components include HR, BP, JVP, presence of pulmonary congestion, ECG, CXR, renal function, troponin, BNP, pulse oximetry, history of CAD
4. Determine and manage the cause or precipitant	Such as ischemia, hypertension, arrhythmias, acute valvular pathologies, worsening renal function, uncontrolled diabetes, and/or infectious etiologies is critical to ensure maximal benefits from HF management
5. Alleviate symptoms (e.g., dyspnea)	Usually a diuretic with or without other vasoactive agents. Morphine may also be used for pulmonary edema†
6. Protect/preserve myocardium and renal function	Avoid hypotension or increase in HR, particularly in patients with CAD. Use of inotropes should be restricted to those with low-output state (low BP with organ hypoperfusion)
7. Make disposition	Majority are admitted to telemetry, with a small number discharged home. Robust evidence to support risk stratification and disposition identifying the low-risk patient for safe discharge with close outpatient follow-up is lacking

*These steps usually occur in parallel, not series. †Retrospective data suggests morphine is associated with worse outcomes.
CXR = chest X-ray; ECG = electrocardiogram; HR = heart rate; JVP = jugular venous pressure; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Tables 1, 2, and 3.

early post-discharge period. Severity of initial signs and symptoms may not always correlate with outcomes (33,76,77,102). Patients with severe signs of HF (pulmonary edema) as a result of severe systemic hypertension may have better post-discharge outcomes than advanced HF patients with low EF who may present with less severe symptoms (11).

In-hospital phase. Further improvement of signs and symptoms, achieving euvolemia, and targeted initiation and/or up-titration of evidence-based therapies for chronic HF based on a comprehensive assessment are the goals of this phase (11,13,48,111). Monitoring for potential cardiac injury and renal function is important. The role of serial B-type natriuretic peptide (BNP)/N-terminal

Table 5 Clinical Profiles

Clinical Presentation	Incidence*	Characteristics	Targets† and Therapies‡
Elevated BP (above 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 (e.g., 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 (e.g., milrinone, dobutamine, levosimendan); consider digoxin (intravenous and/or orally) ± vasopressor medications ± mechanical assist devices (e.g., 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 (e.g., PCI, lytics, nitrates, antiplatelet agents)
Isolated right HF from pulmonary HTN or intrinsic RV failure (e.g., infarct) or valvular abnormalities (e.g., tricuspid valve endocarditis)	?	Rapid or gradual onset due to primary or secondary PA hypertension or RV pathology (e.g., RV infarct). Not well characterized with little epidemiological data.	**Target:** PA pressure **Therapy:** nitrates, epoprostenol, phosphodiesterase inhibitors, endothelin-blocking agents, coronary reperfusion for RV infarcts, valve surgery
Post-cardiac 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 post-operative interval. Can also be caused by inadequate intra-operative 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)

Adapted and modified, with permission, from Gheorghiade et al. (5). *Of all AHFS admissions. †Treating etiology or precipitant is of equal of greater importance (e.g., 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 versus radiographic). ¶Avoid if retaining CO_2.
ACS = acute coronary syndromes; AHFS = acute heart failure syndromes; HTN = hypertension; IABP = intra-aortic balloon pump; MI = myocardial infarction; NIV = noninvasive ventilation; PA = pulmonary artery; RV = right ventricle; VAD = ventricular assist device.

pro-BNP measurements in this setting remains to be determined.

Because dissociation between clinical (dyspnea, edema) and hemodynamic congestion (high LVFP) may be present after initial therapy, assessment of filling pressures is important. Measurement of jugular venous pressure, if done properly, is an important bedside measurement of right atrial pressure (112,113). This is particularly important because high right atrial pressure is a sign of elevated left-sided pressure. Orthostatic BP changes and the response during Valsalva maneuver or sublingual nitroglycerin may aid in assessment of LVFP (24,113). Routine pulmonary artery line-guided therapy in patients with severe HF does not result in improved outcomes (114). However, a pulmonary artery line may be considered for refractory signs and symptoms, particularly in the presence of worsening renal function. The level of BNP/N-terminal pro-BNP has also been proposed as a "measure" of congestion. A tailored approach with evidence-based therapy in response to BNP levels in chronic HF was associated with better outcomes in the outpatient setting (115). This approach remains to be investigated in AHFS. Currently, evidence and/or guidelines to assess congestion during hospitalization or pre-discharge are not well established.

Refractory or advanced HF should be managed according to published guidelines (13,111,116). Thromboembolic events and myocardial ischemia should be considered in patients not responding to standard therapy.

A thorough assessment to ensure implementation of evidence-based guidelines (pharmacological, surgical, interventional, and implantable cardiac-defibrillator/CRT) should occur during this phase or soon after discharge (Fig. 3). The ADHERE (Acute Decompensated National Heart Failure Registry) and OPTIMIZE-HF (Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients with Heart Failure) registries demonstrated the relative paucity of comprehensive assessment (6,28). Hospitalization presents opportunities to optimize management, given the resources available in-hospital versus outpatient. The traditional focus during hospitalization has been on alleviating congestion (e.g., improving symptoms and decreased BW), rather than optimization of therapies known to improve outcomes in patients (37,117). Appropriate management of comorbidities (e.g., CAD, atrial fibrillation, hypertension, diabetes mellitus) based on evidence-based guidelines may also improve post-discharge outcomes (35).

Of current HF quality measures (ACE inhibitor/angiotensin receptor blocker [ARB], anticoagulant at discharge for HF patients with atrial fibrillation, assessment of EF, smoking cessation, and adequate discharge instructions), only ACE inhibitor/ARB has been shown to improve outcomes in AHFS (8,118,119). It is doubtful that those measures alone will have a significant impact on post-discharge outcomes, given the complex pathophysiology and heterogeneity of this patient population. Implementation of evidence-based therapies (pharmacological, electrical devices, and surgical) based on comprehensive assessment may improve outcomes (13,120–125) (Fig. 3). This important hypothesis remains to be tested.

Pre-discharge phase. Goals at discharge: 1) improve signs and symptoms; 2) appropriate management of precipitants; 3) euvolemia with successful transition to oral diuretics; 4) implementation or planned implementation of current HF guidelines; and 5) post-discharge planning and education involving patients and family have been established, with clear instruction regarding weight monitoring, medications, and telephone and clinic follow-up. Formal assessment of functional capacity (e.g., 6-min walk test) before discharge has not been well studied, and this may not be feasible or specific in many older patients.

Discharge criteria, which account for the heterogeneity of the patient population and incorporate different strategies of care, should be developed. Strategies for discharge after complete resolution of signs and symptoms compared with earlier discharge with residual symptoms and close follow-up for further optimization should be studied.

Early post-discharge phase ("vulnerable" phase). Recent data demonstrates deterioration in signs and symptoms, neurohormonal profile, and renal function during the first few weeks after discharge in patients who die or are rehospitalized within 60 to 90 days (33). This deterioration occurs despite standard therapy, including beta-blockers, ACE inhibitors, or ARB, and often aldosterone-blocking agents (33). Assessment of these variables in the early post-discharge period may provide unique opportunities to further optimize standard therapy (up-titration) and/or introduce additional therapy known to improve outcomes (e.g., hydralazine/nitrates, aldosterone-blocking agents, CRT). In addition, the use of novel intravenous therapies (126,127) that are known to improve hemodynamics or to preserve myocardial and renal function should be studied in this vulnerable period.

Transitioning From Acute to Chronic HF

Approximately 80% of patients hospitalized with worsening HF have chronic HF. For the vast majority who stabilize after initial management, they should be considered as chronic HF and be treated according to published guidelines (11,13,48,111,116,120,123–125,128–130).

Available data highlight gaps in utilization/optimization of evidence-based therapies, such as beta-blockers, ACE inhibitors, aldosterone-blocking agents, ARB, and electrical devices (5,8,11,17,28,128,131). Recent analysis from the GWTG-HF (Get With the Guidelines–Heart Failure) database showed variations by age, race, geographic region, and comorbidities on CRT uptake as well as differences between clinical trials and guideline recommendations (131). Initiation or up-titration of evidence-based chronic HF therapies during hospitalization or soon after, absent

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contraindications, will likely improve post-discharge event rates (128).

Early Pharmacologic Management

Pharmacologic therapies have been reviewed extensively elsewhere (126,127,132,133). Dyspnea, along with other symptoms and signs of AHFS, require urgent attention upon presentation. In this setting, dyspnea is related to high PCWP. The increase of PCWP may be the result of different pathophysiological processes (e.g., hypertension, ischemia, arrhythmias, valvular disease), which often require specific therapies. Precipitants (e.g., dietary indiscretion, pneumonia, pulmonary embolism) may aggravate or worsen the clinical profile and need to be taken into consideration and treated.

Fluid removal. Loop diuretics are the mainstay of therapy in AHFS and effectively relieve symptoms. Continuous infusion has been recommended for improved efficacy and for diuretic-resistant patients (11). Combination therapy with thiazide diuretics may also be considered (11,134). It is prudent, however, not to rely totally on diuretics for fluid removal, as many patients are left with signs of HF despite symptomatic improvement. The addition of vasodilators and/or digoxin should be considered (46,135). The clinical value of new or emerging therapies for fluid removal, such as ultrafiltration, vasopressin antagonists, and/or adenosine-blocking agents, remains to be determined.

In spite of their clinical benefits, non–potassium-sparing diuretics may cause further neurohormonal and renal abnormalities (61,68). The potential negative effects of non–potassium-sparing diuretics, as well as the optimal dose and duration, however, have not been well studied and are currently being investigated in a large National Heart, Lung, and Blood Institutes trial (DOSE-AHF [Diuretic Optimal Strategy Evaluation in Acute Heart Failure] study) (136).

Aldosterone-blocking agents may be particularly useful in patients with AHFS, because the majority of patients have evidence of right-sided failure, often resulting in liver congestion. This is often associated with increased serum concentrations of aldosterone despite standard therapies (e.g., ACE inhibitor) (33). Accordingly, both their neurohormonal and diuretic effects (with higher doses) may be of benefit. However, use of aldosterone-blocking agents in AHFS has not been studied.

ULTRAFILTRATION. Ultrafiltration effectively removes fluid, reduces BW without improving dyspnea, and is associated with a decrease in readmission rates (137). These promising results need to be confirmed in a larger clinical trial.

VASOPRESSIN ANTAGONISTS. Tolvaptan, a vasopressin-2 antagonist, when added to standard therapy in patients admitted with worsening chronic HF and reduced EF modestly improves hemodynamics, signs, and symptoms (e.g., BW, dyspnea) and normalizes serum sodium in hyponatremic patients (43,107,138). Continuation of fixed doses of tolvaptan after discharge decreased neither mortality nor readmission rates, in spite of a reduction in BW when compared with standard therapies (60,107). Conivaptan, a vasopressin-1 and -2 antagonist, has been approved by the Food and Drug Administration only for treatment of hyponatremia. Although it has a similar hemodynamic profile when compared with tolvaptan, it does not improve signs and symptoms in patients admitted with HF (138,139). The role of vasopressin antagonists in the management of AHFS remains to be determined.

ADENOSINE ANTAGONISTS. Adenosine antagonists induce diuresis via inhibition of sodium absorption in the proximal tubule, block tubuloglomerular feedback, and therefore preserve or increase glomerular filtration rate in HF (126,127,140–144). The PROTECT (Effects of Rolofylline, a New Adenosine A1 Receptor Antagonist, on Symptoms, Renal Function, and Outcomes in Patients With Acute Heart Failure) pilot trial suggested that rolofylline, a selective A1 receptor antagonist, may improve symptoms and post-discharge outcomes, and is now being tested in a large outcome trial (145).

Pre-load and afterload reducers. NITROGLYCERIN. Nitroglycerin reduces LVFP, but its effects on clinical outcomes have not been well studied, although small studies suggest benefit (106,146). It may be particularly useful in patients with AHFS and underlying CAD or acute coronary syndrome complicated by HF.

NITROPRUSSIDE. Nitroprusside is a powerful systemic vasodilator, usually requires hemodynamic monitoring, and appears useful in patients with advanced HF (147). However, retrospective analysis demonstrated increased mortality when used early in patients with acute MI complicated by severe HF, even when hemodynamics were monitored with a pulmonary artery catheter (40). The safety and efficacy of nitroprusside in AHFS has not been well studied.

NESIRITIDE. Nesiritide was approved for the treatment of AHFS in the U.S. in 2001, but not in Europe. It improves hemodynamics and dyspnea (109). Retrospective data raised the hypothesis that it may worsen renal function and increase post-discharge mortality (41,42). The safety and efficacy of nesiritide is being tested in a large international trial (ASCEND-HF [Double-Blind, Placebo-Controlled, Multicenter Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure] trial) (148).

INTRAVENOUS ACE INHIBITORS. The American College of Emergency Physicians guidelines support the use of intravenous ACE inhibitors for initial AHFS therapy, although as a Level C recommendation, while European Society of Cardiology guidelines do not support their use (11,48,149). Intravenous enalaprilat may adversely affect outcomes when used early in patients with acute MI (73). The role of IV ACE inhibitors remains to be determined.

RELAXIN. Relaxin, an investigational vasodilator identical to the native human neurohormone, appears in animal and pilot clinical studies to be a potent vasodilator (150). It is currently being investigated in AHFS patients.

ULARITIDE. Ularitide, a natriuretic peptide composed of 32 amino acid residues originally isolated from human urine, has been evaluated in an early clinical trial (151,152). It improves hemodynamics and signs and symptoms, without worsening renal function when compared with placebo treatment. Severe hypotension, however, occurred at higher doses (151,152).

Inotropes. Inotropes with vasodilatory properties, such as dobutamine, milrinone, and levosimendan (available in Europe) are known to improve hemodynamics (71,72,110). Short-term use of IV milrinone without a bolus, when added to standard therapy, does not improve signs and symptoms, or reduce the total number of hospital days, and was associated with severe hypotension and arrhythmias (71). In retrospect, it appeared to increase post-discharge mortality in patients with CAD (39). These findings raised the hypothesis that short-term administration of drugs may affect post-discharge outcomes, possibly by causing myocardial injury due to decreased perfusion and/or increased myocardial oxygen demand, particularly in patients with CAD who may have ischemic and/or hibernating myocardium (38).

In AHFS, the short-term use of levosimendan improved symptoms and reduced the need for cointervention for worsening HF; however, it was associated with significant side effects (hypotension, ventricular tachycardia) and a trend toward increased early mortality (110). In patients admitted with very severe HF, levosimendan was not superior to dobutamine in terms of post-discharge mortality that was very high in both groups (72). In general, inotropes with vasodilator properties should be reserved for those patients with a low output state, defined as low BP with sign of organ hypoperfusion, who do not respond to other therapies (13,111,116).

DIGOXIN (IV). Digoxin improves hemodynamics in HF without activating neurohormones or negatively affecting heart rate, BP, or renal function (135,153,154). These effects are seen when used alone or in combination with other vasoactive agents, including ACE inhibitors (135,153). Its chronic use has been shown to decrease hospitalization when added to a diuretic and ACE inhibitor (155). Although IV digoxin has all the properties of an ideal agent in AHFS, its effects in AHFS in patients with or without AF have not been studied (135).

ISTAROXIME. Istaroxime, an investigational inotrope with lusitropic properties, improves hemodynamics. In contrast to current inotropes, it increases SBP and decreases heart rate in AHFS (156). This agent appears promising for patients presenting in a low-output state, manifested by a low BP (157). It is currently being tested in a larger clinical trial.

CARDIAC MYOSIN ACTIVATORS. Cardiac myosin activators, in the early stages of clinical investigation, target myocardial myosin adenosine triphosphatase, generating force to improve contractility without changing intracellular concentrations of calcium (126,127). This molecule is currently undergoing further investigation in clinical trials (158,159).

Other therapies. A number of other treatments are commonly given, although randomized clinical trial data are lacking. These therapies include morphine and oxygen supplementation. The use of morphine in the ADHERE registry retrospectively points toward an association between morphine and worse outcomes (160). Noninvasive ventilation relieves dyspnea in AHFS (161). Although its use has been associated with decreased resource utilization and mortality, in the largest noninvasive ventilation trial to date, no mortality benefit was seen over oxygen for either continuous or bilevel noninvasive ventilation (161,162). However, this trial was not stratified by severity of presenting illness (161). Adenosine-regulating agents are an emerging therapy aimed to enhance endogenous adenosine-mediated cardioprotective mechanisms (163). Soluble guanylate cyclase activators represent another emerging therapy; early data suggest beneficial arterial and venous vasodilatory effects (164). Direct renin inhibitors will be explored in AHFS in the ASTRONAUT (Aliskerin Trial on Acute Heart Failure Outcomes) trial.

Clinical Trials in AHFS

Overall, clinical trial results have disappointed in terms of efficacy and/or safety (41,42,60,71,72,107–109). In the last 15 years, only nesiritide has been approved for the treatment of AHFS; however, post-approval questions of safety arose (41,42). These disappointing results may have been related to the drug itself, failure to target the appropriate pathophysiologic process, patient selection, and/or end points chosen. For the majority of agents being studied in AHFS, gaps in our knowledge exist (Table 6). In addition, demonstration of early symptomatic benefit beyond that of standard therapy alone is difficult given the significant beneficial response to available therapies (107–109). A reassessment of how to conduct clinical trials in AHFS is being investigated (5,165).

Dividing trials into stages has been proposed: Stage A is early intervention (i.e., emergency department); Stage B involves in-hospital management; and Stage C is before or soon after discharge (5).

Improving post-discharge outcomes is the most important goal in AHFS; as such, future clinical trials should address this issue. At the same time, both patients and physicians desire therapies that improve signs, symptoms, and/or quality of life, assuming an acceptable safety profile. Expecting therapies used for 48 h to improve outcomes at 2 to 6 months in a complex, heterogeneous substrate such as HF may set the bar too high. This may negatively affect research of therapies that may safely improve patient reported outcomes (e.g., dyspnea). Another consideration

Table 6 Therapies for AHFS

	Symptomatic Improvement	HR	Hypotension	LVFP	Cardiac Output	Arrhythmia	Coronary Perfusion	Effect on Viable But Dysfunctional Myocardium	Myocardial Injury (Tn)	Renal Function	Neurohormonal Activation	Effects on Mortality and/or Rehospitalization
Fluid removal												
Diuretics (IV)	Yes	Var	Poss	↓	Var	?	?	?	?	?↓	Yes	?
K-sparing diuretics	Poss	⇔	No	?	?	No	?	?	?	?	? No	↓*
Fluid removal—experimental												
Vasopressin antagonists (orally)	Yes	⇔	No	↓	⇔	No	?	?	?	⇔	?†	⇔
Adenosine antagonists (IV)	?↑	⇔	?	?	?	?	?	?	?	?↑	?	?↓
Vasodilators												
Nitroglycerin (IV)	Yes	Var	Poss	↓	No	No	?↑	?	?	?	?↑	?
Nitroprusside (IV)	Yes	Var	Yes	↓	Var	No	?↓	?	?	?	?	?
Nesiritide (BNP) (IV)	Yes	Var	Poss	↓	No	No	?	?	?	?↓	?	?↑
Enalaprilat (IV)	?	⇔	Poss	↓	No	No	?	?	?	?↓	↓	?
Vasodilators—experimental												
Ularitide (urodilatin)	Poss	⇔	Poss	↓	?↑	?	?	?	?	?⇔	?	?
Relaxin (IV)	?	?	Poss	↓	?	?	?	?	?	?	?	?
Inotropes												
Digoxin (IV)	?	↓	No	↓	↑	No‡	?	?	?	⇔	↓	↓
Dopamine (IV)	?	↑	No	Dose dependent	Dose dependent	Dose dependent	?	?	?	?	?	?
Dobutamine (IV)	? Yes	?↑	Poss	↓	↑	↑	?	?↓ (may cause injury)	Poss	?	?	?↑
Levosimendan (IV)	Yes	↑	Poss	↓	↑	↑	?	?	?	?	?	?↑
Enoximone	Poss	↑	Poss	↓	↑	↑	?	?	?	?	?	?
Milrinone (IV)	⇔	↑	Poss	↓	↑	↑	?	?	?	?	?	?↑ in CAD
Inotropes—experimental												
Cardiac myosin activators	?	?	?	?	↑	?	?	?	?	?	?	?
Istaroxime	?	↓	No	↓	↑	May	?	?	?	⇔	No	?
Endothelin antagonists												
Tezosentan	⇔	⇔	Yes	↓	↑	No	?	?	?	⇔	?	⇔

Adapted and reproduced, with permission, from Shin et al. (127). *Aldosterone antagonists only. †Elevates vasopressin levels. ‡At proper therapeutic levels.

↓ = decrease; ↑ = increase; ⇔ = no change or neutral; ? = unknown; IV = intravenous; K = potassium; LVFP = left ventricular filling pressure; May = may worsen or improve; Poss = possible; TN = troponin; Var = variable response; other abbreviations as in Tables 1 and 5.

would be to create a novel end point, emphasizing the importance of bridging to evidence-based therapies. For example, in-hospital therapy with an investigational agent, which improves hemodynamics and symptoms, protects or preserves the heart and/or kidneys, has a strong safety profile, and improves uptake of known life-saving therapies (e.g., ACE inhibitors, beta-blockers), might represent an excellent short-term goal. Subsequently, this may result in improved post-discharge outcomes.

A significant number of patients with early events have worsening hemodynamics and neurohormonal and renal abnormalities in the first few weeks after discharge. Accordingly, early intervention during this vulnerable phase with intravenous (e.g., adenosine-blocking agents, guanylate cyclase activators, natriuretic peptides) or oral (e.g., vasopressin antagonists, renin inhibitors) and/or other therapeutic interventions (e.g., CRT, ultrafiltration) should be explored in future clinical trials. Novel applications of existing therapies (e.g., aldosterone-blocking agents, digoxin) should also be explored during this phase.

The present model of clinical development programs follows a stepwise progression, from in vitro to animal modeling to first-in-human into clinical trials. Given the still-limited understanding of the pathophysiology of AHFS, a "bidirectional" research approach may be in order. For example, during early clinical studies, new hypotheses may emerge; in partnership with scientists, novel therapies would go back to animal models to try to answer these questions for both efficacy and safety, which would then lay the foundation for clinical studies.

Conclusions

Hospitalization for AHFS represents a significant and growing health care burden. Heterogeneity characterizes this group in terms of mode of presentation, pathophysiology, and prognosis. The vast majority of patients symptomatically improve during hospitalization; however, their early post-discharge rehospitalization and mortality rates continue to be extremely high. Worsening signs and symptoms and neurohormonal and renal abnormalities occurring soon after discharge may contribute to these high post-discharge event rates. Currently available assessment modalities combined with recent advances in cardiovascular therapies provide present-day opportunities to improve post-discharge outcomes. Further investigation into pathophysiologic targets and novel approaches to clinical trial design are needed. Improving post-discharge outcomes is the most important goal in the management of AHFS.

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