Managed Care Interventions for Improving Outcomes in Acute Heart Failure Syndromes

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Abstract

Acute heart failure syndromes (AHFS) are characterized by a gradual or rapid progression of the signs and symptoms of heart failure (HF), resulting in a need for urgent therapy. Patients with AHFS comprise approximately 20% of all HF patients and represent the most severely ill and undermanaged subpopulation of patients with HF. Despite the rising prevalence and costs associated with AHFS, the disease remains largely undermanaged, partially as a result of a failure to initiate treatment with proven therapies, such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, during hospitalization or soon after discharge. Although professional organizations have been striving to improve the state of care for AHFS by providing at least some level of consensus and evidence-based treatment recommendations, the gap between the clinical evidence and actual practice is growing. Appropriate disease assessment, followed by the implementation of life-saving therapies, is the key to improving outcomes. Managed care initiatives, such as improved quality measures, disease management programs, patient education efforts, hospital discharge checklists, and pharmacy-led interventions to enhance medication compliance, provide potential solutions for combating the alarming rise of morbidity, mortality, and costs associated with this disease.

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Acute heart failure syndromes (AHFS) are characterized by a gradual or rapid progression in the signs and symptoms of heart failure (HF), resulting in a need for urgent therapy.[1] As the overall prevalence of HF rises in the United States, so does the prevalence of AHFS, along with the use of costly services in hospitals and emergency departments.[2] AHFS is also associated with extremely high morbidity and mortality following discharge. In fact, patients discharged following admission for AHFS have an event rate as high as 50% within 2 months, including a 10% to 20% mortality rate.[3] It should also be noted that those patients do not represent the 5% of admissions that are related to advanced or refractory HF, nor patients in whom HF is diagnosed for the first time (representing 25% of all admissions).

Despite the rising prevalence and costs associated with AHFS, the disease remains largely undermanaged, partially as a result of a failure to implement the available life-saving therapies during hospitalization or soon after discharge.[1] To some extent this failure is driven by guideline limitations (ie, American College of Cardiology/American Heart Association [ACC/AHA] and Centers for Medicare & Medicaid Services [CMS] quality criteria include only the use of angiotensin-converting enzyme [ACE] inhibitors, measuring ejection fraction [EF], smoking cessation efforts, and patient education) and have yet to incorporate other life-prolonging therapies such as beta-blockers and implantable devices.[1] These issues make AHFS a disease state worthy of significant attention from managed care stakeholders. In fact, considering the alarming current state of care, improving postdischarge outcomes in AHFS should be of highest priority.

Clinical and Financial Impact of AHFS on Managed Care

It is estimated that at least 5.3 million Americans currently have chronic HF, and at least 550,000 new cases of HF are diagnosed every year.[2] Patients with AHFS comprise approximately 20% of all HF patients and represent the most severely ill and undermanaged subpopulation of patients with HF.[1] The percentage of patients hospitalized for HF has risen dramatically of late despite the 171% rise from 1979 (400,000) to 2005 (>1 million).[2] While HF can strike virtually any age group, the elderly are significantly more susceptible, with the risk of developing HF doubling with every decade. In fact, 80% of hospitalizations for HF occur in individuals aged more than 65 years

Table 1. Demographic and Clinical Characteristics of Acute Heart Failure Syndrome Patients (Data on ~200,000 Patients)[1,4,5]

Median age, y	75	History of atrial fibrillation	30%
Women	>50%	Renal abnormalities	30%
History of CAD	60%	SBP >140 mm Hg	50%
History of hypertension	70%	SBP 90-140 mm Hg	45%
History of diabetes	40%	SBP <90 mm Hg	45%
		Preserved ejection fraction	50%

CAD indicates coronary artery disease; SBP, systolic blood pressure.
Adapted from Gheorghiade M, et al. *Circulation.* 2005;112(25):3958-3968.

and 50% among those aged more than 75 years.[2] HF is the most common diagnosis-related group (DRG) for patients aged more than 65 years.[2] In contrast to other cardiovascular disease states, such as coronary artery disease where intensive management has been associated with a reduction in hospital admissions,[2] HF remains a significant public health problem that is increasing in prevalence.[2]

In terms of hospitalizations, AHFS is characterized by chronic persistence, since approximately 30% of patients with AHFS discharged from the hospital are readmitted within 60 to 90 days.[3] Likewise, mortality associated with AHFS is significant, with approximately 10% mortality within 60 to 90 days of discharge.[3]

These clinical challenges of AHFS are accompanied by equally significant economic ramifications for managed care. Hospitalization for patients with AHFS, by far the most costly subpopulation of patients with HF to treat, accounts for more than 75% of the $46 billion spent on HF each year. In fact, the costs associated with the hospitalization of patients with AHFS have made HF the most costly DRG in the United States.[2]

Clinical Presentations. The symptoms of AHFS primarily result from severe pulmonary congestion as a result of elevated left ventricular (LV) filling pressures. This may or may not be accompanied by a low cardiac output.[1] EF may be either preserved or reduced in patients with AHFS, and concurrent cardiovascular conditions, such as hypertension, coronary heart disease, valvular heart disease, and atrial arrhythmias, often precipitate or contribute to the pathophysiology of this condition.[1] Noncardiac conditions, including renal dysfunction, diabetes, and anemia, may also initiate or accelerate the progression to AHFS.[1] An overview of the demographic and clinical characteristics of AHFS is presented in Table 1.[1,4,5]

Three distinct clinical entities comprise AHFS: (1) worsening of chronic HF associated with reduced or preserved EF (70% of all admissions); (2) de novo HF (eg, after a significant myocardial infarction [MI] or sudden increase in blood pressure superimposed on a noncompliant left ventricle) (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).[1]

Somewhat surprisingly, low systolic blood pressure (<90 mm Hg), as might be observed among patients with end-stage cardiomyopathies, is observed infrequently (<8% of admissions). The majority of patients with AHFS present with elevated systolic blood pressure (>50%) or with systolic blood pressure in the normal range (40%).[1] Frank cardiogenic shock is present in less than 1% of AHFS admissions, primarily found in conjunction with acute MI and fulminant myocarditis.[1] Flash pulmonary edema, characterized by acute severe dyspnea, tachypnea, tachycardia, and hypoxemia requiring immediate airway intervention, is present in less than 3% of AHFS patients. This rapid-onset form of pulmonary edema is often precipitated by severe systemic hypertension.[1] Isolated right HF, from pulmonary hypertension, is also present among patients with AHFS, although the prevalence is unknown.[1] Approximately 25% of patients with acute coronary syndromes develop signs and symptoms of HF, but these typically resolve after initial therapy and resolution of ischemia.[1] Finally, an unknown number of patients with AHFS present with HF following cardiac surgery, often related to worsening diastolic function and volume overload immediately after surgery.[1]

Prognostic Factors. There are several important clinical features among patients with AHFS that predict response to therapy and prognosis. High systolic blood pressure at admission is associated with lower postdischarge mortality, but the rate of readmission at 90 days is the same for both normotensive and hypertensive patients.[6] Impaired renal function appears to be very predictive of outcome in AHFS (Figure 1).[7] In the Outcomes

of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial, Klein et al demonstrated that the admission measures of renal function, including blood urea nitrogen (BUN) and estimated glomerular filtration rate (eGFR), in patients hospitalized for worsening HF predict in-hospital outcomes.[8] Both lower admission eGFR and higher admission BUN were associated with an increased risk of death by 60 days after discharge; an increase in BUN (per 5-mg/dL increase) during hospitalization was associated with worse 60-day outcomes (hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.01-1.16).[8] Independent of admission values, an increase of ≥10 mg/dL in BUN during hospitalization was associated with a worse 60-day survival rate: BUN (per 5-mg/dL increase) had an HR of 1.08 (95% CI, 1.01-1.16).[8]

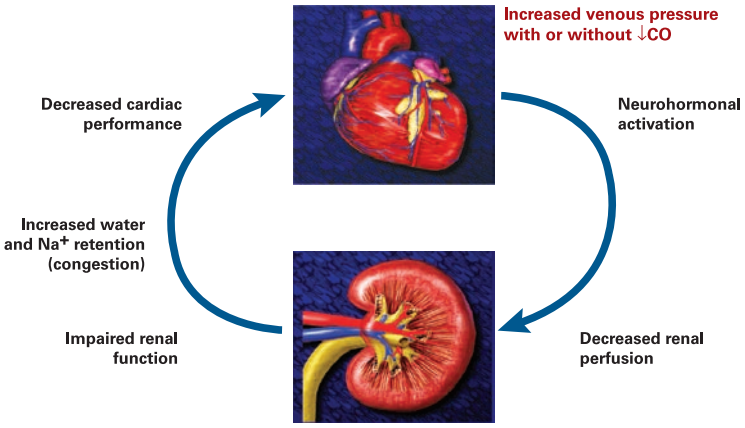
Also in terms of renal function, BUN and BUN/creatinine ratio appear to be better prognostic indicators than creatinine alone, and a relatively small increase in BUN has been associated with a 2- to 3-fold increase in postdischarge mortality.[1] In-hospital mortality has also been linked to BUN, with patients having levels ≥43 mg/dL and serum creatinine levels ≥2.75 mg/dL associated with the highest risk.[9] Furthermore, with each subsequent hospitalization in AHFS, there appears to be a decrement in renal function (**Figure 2**).[10]

Patients with AHFS and CAD have an increased mortality postdischarge when compared with patients without CAD.[11] Troponin release, observed in 30% to 70% of AHFS patients with CAD, is associated with a 2-fold increase in postdischarge mortality and a 3-fold increase in the rate of rehospitalization.[1] Increased natriuretic peptide levels have also been associated with higher postdischarge mortality and rehospitalization.[1]

CAD represents the most common underlying disease in patients in industrialized countries with HF.[12] A series of recent clinical trials have conclusively shown improvements in survival from pharmacologic and device therapy in patients with HF and CAD.[12] Furthermore, the Framingham Heart Study suggested that the most common cause of HF is not hypertension or valvular heart disease as previously thought, but rather CAD.[12]

Low systolic blood pressure (<120 mm Hg) at hospital admission identifies patients who have a poor prognosis despite medical therapy. In patients

Figure 1. Cardiac/Renal Syndrome[a] in Acute Heart Failure Syndrome[7]

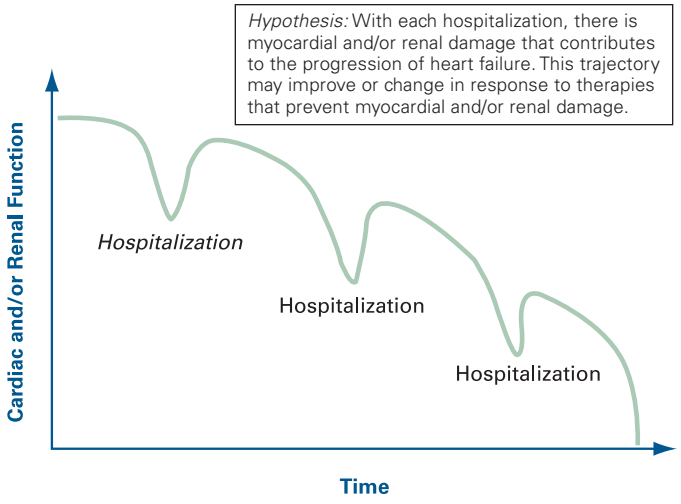


Most patients do not have low cardiac output.
[a]Increasing blood urea nitrogen, in the presence of high filling pressures (edema) often related to high doses of loop diuretics.
Modified from Abraham WT, Schrier RW. *Adv Intern Med.* 1994;39:23-47.

from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) trial, Gheorghiade et al reported that higher systolic blood pressure at admission was associated with lower in-hospital mortality rates: 7.2% (<120 mm Hg), 3.6% (120-139 mm Hg), 2.5% (140-161 mm Hg), and 1.7% (>161 mm Hg) (P <.001 for overall difference).[6] Postdischarge mortality rates in the follow-up cohort by systolic blood pressure at admission were 14.0%, 8.4%, 6.0%, and 5.4%, respectively (P <.001 for overall difference).[6] However, it is important to note that irrespective of systolic blood pressure, the postdischarge rehospitalization rate was 30% at 60 to 90 days.

A prolonged QRS duration is common in patients with reduced EF with AHFS and is another independent predictor of high postdischarge morbidity and mortality.[13] Wang et al reported that during a median follow-up of 9.9 months, all-cause mortality was 18.7% for patients with a normal baseline QRS duration and 28.1% for patients with a prolonged baseline QRS duration (HR, 1.61; 95% CI, 1.38-1.87).[13] The composite of cardiovascular death or hospitalization for HF was 32.4% for patients with a baseline QRS duration less than 120 ms and 41.6% for patients with a baseline QRS duration of 120 ms or greater (HR, 1.40; 95% CI, 1.24-1.58).[13] The increased mortality associated with prolonged QRS duration survived adjustment for multiple variables (HR, 1.24; 95% CI, 1.02-1.50) and the

Figure 2. Acute Heart Failure Syndrome and Heart Failure Progression as Related to Cardiac/Renal Function[10]

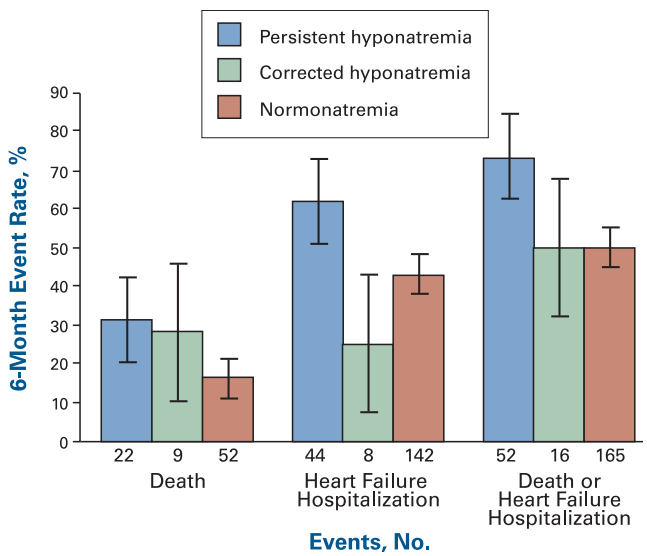


composite of cardiovascular death or hospitalization for HF (HR, 1.28; 95% CI, 1.10-1.49).[13]

Pulmonary capillary wedge pressure (PCWP) has also shown evidence of being a prognostic factor in patients with AHFS. Improvements in postdischarge survival in patients with AHFS have, in some analyses, been demonstrated with a reduction in PCWP but not typically with the use of agents such as milrinone and dobutamine.[1] Functional capacity is a key predictor of postdischarge outcomes, with the 6-minute walk test emerging as the gold standard in this area.[1] Other clinical markers, such as LV ejection fraction, anemia, diabetes mellitus, new sustained arrhythmias, and nonuse of neurohormonal antagonists, may also serve as prognostic factors in patients with AHFS.[1]

Another important prognostic factor in AHFS is hyponatremia. Approximately 25% to 30% of patients with AHFS have mild hyponatremia, defined as a plasma sodium concentration less than 135 mmol/L.[1] Moderate-to-severe hyponatremia, defined as a plasma sodium concentration less than 130 mmol/L, is significantly less common in patients with AHFS. In turn, the neurohumoral changes induced limit both sodium and water excretion in an attempt to normalize perfusion pressure.[14] The severity of the defect in water excretion (due to the neurohumoral activation) and of the associated reduction in the serum sodium concentration parallels the severity of the heart disease.[15] In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, persistent mild hyponatremia was present in 23.8% of patients and was associated with a significantly higher risk of death, HF hospitalization, or the composite end point of death or HF hospitalization when compared with patients without hyponatremia: 6-month mortality (HR, 1.82; 95% CI, 1.03-3.22; P = .04); HF rehospitalization (HR, 1.52; 95% CI, 1.05-2.22; P = .03); and the composite of death or rehospitalization (HR, 1.54; 95% CI, 1.09-2.17; P = .01) (**Figure 3**).[16]

Figure 3. Relationship Between Clinical Events and Patients With Persistent Hyponatremia, Corrected Hyponatremia, and Normonatremia in the ESCAPE Trial[16]



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Furthermore, an analysis of admission serum sodium concentration and clinical outcomes in 48,612 patients from the OPTIMIZE-HF registry demonstrated that hyponatremia in hospitalized patients with HF is relatively common and was associated with longer hospital stays and higher in-hospital and early postdischarge mortality.[17] Specifically, patients with hyponatremia had significantly higher rates of in-hospital and follow-up mortality, and longer hospital stays, although no difference in readmission rates was observed.[17] After adjusting for differences with multivariable analysis, the risk of in-hospital death increased by 19.5%, the risk of follow-up mortality by 10%, and the risk of

Table 2. Risk Prediction Nomogram for Mortality to 60 Days[19]

Find the score that most closely matches for each characteristic. If the value falls between 2 listed, extrapolate to the closest score. Write each score at the bottom of the columns.

Clinical evaluation scores									
Age	Score	Weight (kg)	Score	Systolic Blood Pressure	Score	Sodium	Score	Creatinine	Score
25	0	60	9	80	24	110	12	0	0
35	2	80	7	100	20	115	10	1	5
45	5	100	5	120	17	120	8	2	9
55	7	120	3	140	13	125	6	3	14
65	10	140	2	160	11	130	4	4	19
75	12			180	9	135	2		
85	15			200	8	140	0		
95	17			220	6				
				240	4				
				260	2				
				280	0				
	____	+	____	+	____	+	____	+	____

Add the total number of points for Clinical Evaluation from the above table: _____

Baseline Risk Factors	Score
History of liver disease	8
History of depression	4
History of reactive airway disease	4
Total from clinical evaluation	____
Total score	____

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death or rehospitalization by 8% for each 3-mmol/L decrease in admission serum sodium less than 140 mmol/L.[17]

Looking at several of the aforementioned prognostic factors in unison, Felker et al used multivariable modeling to evaluate admission variables in the OPTIME-CHF study with respect to 60-day mortality or the composite of death or rehospitalization at 60 days.[18] Increased age, lower systolic blood pressure, New York Heart Association class IV symptoms, elevated BUN, and decreased sodium were risk factors for mortality at 60 days.[18] Predictors of the composite of death or rehospitalization within 60 days were the number of HF hospitalizations in the preceding 12 months, elevated BUN, lower systolic blood pressure, decreased hemoglobin, and a history of percutaneous coronary intervention.[18] The researchers stratified patient risk for 60-day mortality according to point values assigned to these prognostic factors, as described in Table 2.[19]

Appropriate Course of Therapy for AHFS and Recommended Treatment Goals

Current treatment approaches for AHFS focus on 3 separate phases:

- Emergency department phase
- In-hospital phase
- Predischarge and early postdischarge phase

Appropriate clinical activities during these individual phases are based on patients' symptoms, course of illness, and progression from admission to discharge, and mirror the AHFS evaluation phases, which delineate how patients should be assessed at different stages of their hospital stay (Table 3).[1]

The overall therapeutic goals and targets in these 3 treatment phases are as follows:

AHFS Therapeutic Goals

- Improve direct hemodynamics (PCWP) without causing myocyte damage (ischemia,

Table 3. Acute Heart Failure Syndrome Evaluation Phases[1]

Phases	Goals	Available Tools
Initial or emergency department 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
	Decide subsequent placement	Patient comorbidities, initial response to therapies, workup, social factors
Hospitalization phase	Monitor medical condition	Signs/symptoms, heart rate, ECG, blood pressure (orthostatic changes), body weight
	Monitor renal function	BUN and creatinine, electrolytes
	Assess right ventricular and left ventricular filling pressure	Blood pressure (orthostatic changes, Valsalva maneuver), echocardiography, impedance cardiography, BNP/NT pro-BNP, pulmonary artery catheter
	Assess concomitant cardiac and noncardiac conditions	For example, echocardiography, cardiac catheterization, electrophysiologic testing
	Assess myocardial viability	MRI, stress test, echocardiography, radionuclear studies
Discharge phase	Assess functional capacity	6-minute walk test, treadmill
	Evaluate exacerbating factors[a]; appropriate corrective strategies	For example, physical therapy, diet control, evaluation for sleep apnea
	Optimize pharmacologic 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; ECG, electrocardiogram; MRI, magnetic resonance imaging; NT pro-BNP, N-terminal pro B-type natriuretic peptide.
[a]For example, diet, medication nonadherence, infections, anemia, cardiac arrhythmias, hypertension.
Reprinted with permission from Gheorghiade M, et al. *Circulation.* 2005;112(25):3958-3968.

necrosis, apoptosis), arrhythmias, hypotension, or renal dysfunction
- Improve hemodynamics indirectly by treating causative conditions (eg, severe hypertension, arrhythmias, and/or ischemia). High wedge pressure may also result from severe hypertension, ischemia, and/or arrhythmias. These conditions and any other precipitants should be treated for optimal results.
- Improve symptoms and achieve euvolemia
- Improve postdischarge outcomes by implementing life-saving therapies (eg, ACE inhibitors, beta-blockers, automatic implantable cardioverter-defibrillator, etc)—this is arguably the most important treatment goal

AHFS Therapeutic Targets

- Myocardial preservation (prevent troponin release)
- Renal preservation (preserve or improve renal function)
- Identification and treatment of dyssynchrony (wide QRS)
- Acute and chronic management of CAD (ischemia, plaque rupture, prevent progression of CAD)
- Normalization of blood pressure in those patients who are hypertensive
- Improvement of neurohormonal profile
- Anticoagulation, if indicated, in patients at high risk for systemic and/or venous thromboembolic events
- Correction of primary valvular abnormalities
- Treatment of severe (<125 mEq/L) or symptomatic hyponatremia

In the emergency treatment phase, the primary manifestations of AHFS, such as dyspnea and other symptoms of cardiopulmonary congestion, require immediate attention.[1] Rapid symptomatic stabilization by early administration of diuretics, vasoactive agents, and/or noninvasive ventilation is the goal of treatment in this phase.[1]

Non–potassium-sparing diuretics, intravenous vasodilators, inotropes, and intravenous beta-blockers comprise the pharmacotherapeutic options available for the patients with AHFS in the emergency treatment phase (**Table 4**, **Figure 4**).[1,20,21] Non–potassium-sparing diuretics, such as hydrochlorothiazide and furosemide, relieve volume overload by removing excess sodium and water from the bloodstream.[1,20,21] However, although these agents assist in symptomatic improvement, they may have a negative

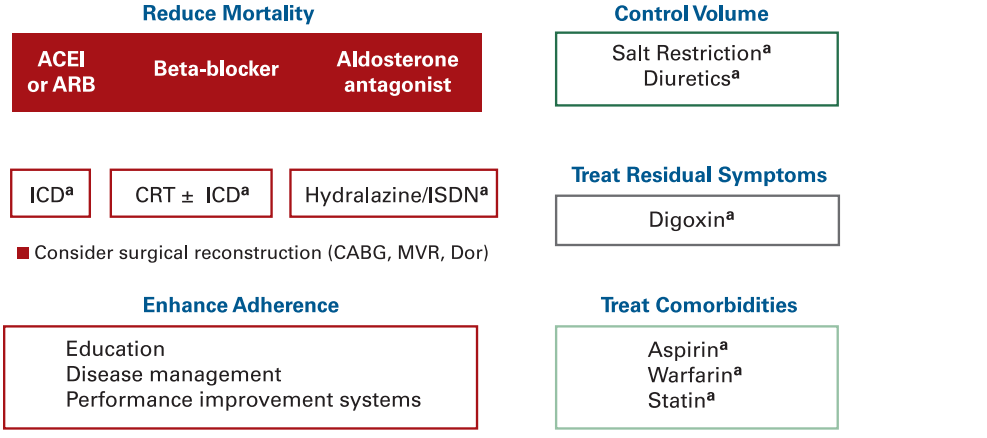
Table 4. Pharmacotherapy for the Emergency Treatment Phase of Acute Heart Failure Syndrome[1,20-22]

Target	Medication Example(s)	Mode of Action	Side Effects
Alleviate congestion	IV furosemide (and other diuretics)	Water and sodium excretion	Electrolyte abnormalities, worsening renal function, activation of neurohormones
Induce vasodilation	Most common IV nitrates (others may be used, such as nitroprusside, nesiritide, etc)	Direct relaxation of vascular smooth muscle cells with various mechanisms	Hypotension, decreased coronary perfusion (ie, with nitroprusside, particularly in patients with CAD)
Improve cardiac performance	Inotropes (other than digoxin): usually dobutamine, milrinone, and levosimendan (the latter in Europe)	Cyclic AMP activators or calcium sensitization resulting in increased contractility; also powerful vasodilators: in effect, inodilators (inotropes with vasodilatory properties)	Hypotension; arrhythmias; myocardial damage, possible increase in postdischarge mortality, particularly in patients with CAD
Reduce heart rate and control blood pressure (ie, in cases of excessive sympathetic tone)	Beta-blockers: IV esmolol may be used when HF is related to atrial fibrillation and RVR and/or severe hypertension; metoprolol may be used, however this agent has a relatively long half-life (4-5 h)	Blockade of beta-1 and beta-2 receptors	Bradycardia, hypotension; however, given short half-life of esmolol (ie, minutes), some of these agents are relatively safe

AMP indicates adenosine monophosphate; CAD, coronary artery disease; HF, heart failure; IV, intravenous; RVR, rapid ventricular response.

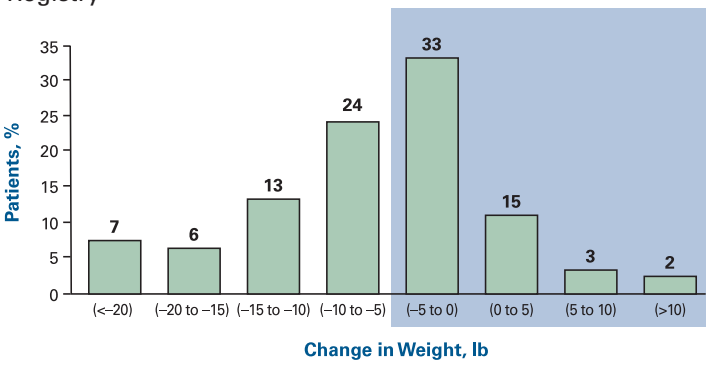
effect on treatment outcomes and contribute to declining renal function.[1] An ideal alternative approach to using high-dose non–potassium-sparing diuretics is to use lower doses in combination with intravenous vasodilators, particularly in hypertensive patients.[1] Intravenous vasodilators, including nitroprusside or nitroglycerine and nesiritide, reduce filling pressures via vasodilation.[1,20-22] Inotropes, such as dobutamine and milrinone, serve to increase myocardial contractility and are reserved for life-threatening situations among patients with reduced cardiac output due to left or right ventricular dysfunction.[1,20-22] Ultrafiltration is also a new modality to remove fluid that is currently being explored. The Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial showed significantly reduced HF rehospitalization rates at 180 days, but further clinical studies are needed for long-term mortality data.[23] There is also a role for intravenous beta-blockers among patients with AHFS who present with hypertension and/or atrial fibrillation with a rapid ventricular response, but this area is poorly studied.[1]

Figure 4. Evidence-Based Therapy Across the Continuum of Left Ventricular Dysfunction and Heart Failure



ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; Dor, Dor procedure; ICD, implantable cardioverter-defibrillator; ISDN, isosorbide dinitrate; MVR, mitral valve replacement.
[a]For select indicated patients.

■ **Figure 5.** Change in Weight Loss[a] Among Heart Failure Patients During Hospitalization According to the ADHERE Registry[28]



[a]More than 50% of patients have little or no weight loss during hospitalization.
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The in-hospital management phase begins once dyspnea has improved and the patient is stabilized.[1] Continued hemodynamic and symptomatic improvement, while avoiding myocardial and renal injury, is the goal of this phase.[1] According to the ACC/AHA guidelines, patients should be treated with agents such as ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, or aldosterone antagonists in this phase.[24]

In the discharge-planning phase, AHFS patients should be evaluated for potentially beneficial surgical procedures, including myocardial revascularization, LV reconstruction, mitral valve surgery, or cardiac transplantation.[1] An appropriate medication regimen on which to be discharged should also be considered for AHFS patients in this phase, potentially including one or more of the previously mentioned life-saving therapies employed during in-hospital management.

Addressing Hyponatremia in the Setting of AHFS

As delineated above, hyponatremia is a well-established marker of poor outcomes in HF. Recently, antagonists of the vasopressin receptor have been noted to improve sodium homeostasis. These agents are informally known as the vaptans, short for vasopressin antagonists. In contrast to diuretics, the antagonists of the vasopressin receptor (V2) induce a highly hypotonic diuresis without substantially affecting the excretion of electrolytes.[16] One member of this class, conivaptan, is approved by the US Food and Drug Administration for the treatment of "euvolemic hyponatremia" but is not indicated for the treatment of HF. Several other compounds in the class are, however, being investigated in the setting of HF.[25] Currently, 4 vasopressin V2-receptor antagonists are under investigation for the treatment of HF: lixivaptan, mozavaptan, satavaptan, and tolvaptan.[25]

Tolvaptan is the most extensively studied vasopressin antagonist in clinical trials for the treatment of HF and can furthermore be considered the most advanced in terms of development.[26-30] As such, the subsequent portion of this review will focus on the use of tolvaptan for treating hyponatremia in AHFS, an area in which the data have begun to accumulate. In a dose-ranging study, 3 doses of tolvaptan and placebo were administered to patients with chronic HF.[26] After a run-in period, 254 patients were randomly assigned to placebo or tolvaptan (30, 45, or 60 mg) once daily for 25 days.[26] Patients were not fluid-restricted and were maintained on stable doses of furosemide.[26] At day 1, when compared with baseline, a decrease in body weight of –0.79 ± 0.99, –0.96 ± 0.93, and –0.84 ± 0.02 kg was observed in the 30-, 45-, and 60-mg tolvaptan groups, respectively, and a body weight increase of +0.32 ± 0.46 kg in the placebo group (P <.001 for all treatment groups vs placebo).[26] Although the initial decrease in body weight was maintained during the study, no further reduction was observed beyond the first day.[26] A decrease in edema and a normalization of serum sodium in patients with hyponatremia were observed in the tolvaptan group but not in the placebo group.[26] No significant changes in heart rate, blood pressure, serum potassium, or renal function were reported by the investigators.[26]

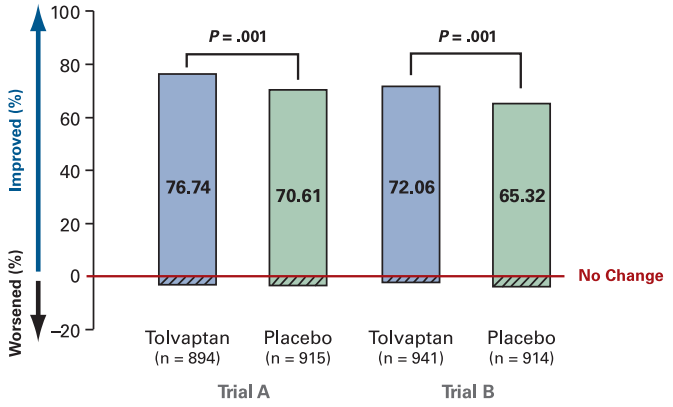
These results prompted the Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) program in which patients were randomized to receive oral tolvaptan (30 mg/day) versus placebo. For regulatory purposes, EVEREST included 2 identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe.[27] A total of 2048 (trial A) and 2085 (trial B) patients were enrolled. The primary end point of the trial was the composite of changes in clinical status and body weight at discharge or hospital day 7.[27] This latter end point was chosen consid-

ering the current treatment standards by which patients are not being relieved of fluid congestion. Although congestion is the main reason for HF hospitalizations, the Acute Decompensated Heart Failure National Registry (ADHERE) data showed that close to 50% of patients have minimal or no weight loss during their hospital stay (Figure 5).[28] While body weight measurement is simply a surrogate for congestion, studies have shown that in the weeks preceding hospitalization for AHFS, increasing signs and symptoms of dyspnea and increasing body weight are closely associated with the need for readmission.[29] Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge). The results of these studies were also combined and reanalyzed to determine the effect of tolvaptan on clinical outcomes.[28]

In EVEREST, tolvaptan demonstrated some promise in the treatment of patients hospitalized with HF and fluid congestion.[27] Mean (SD) body weight reduction was greater with tolvaptan on day 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; P <.001; trial B, 1.82 [2.01] vs 0.95 [1.85] kg; P <.001) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; P <.001; trial B, 3.77 [3.59] vs 2.79 [3.46] kg; P <.001).[27] More patients receiving tolvaptan reported an improvement in dyspnea at day 1 than with placebo (76.7% vs 70.6% in trial A; 72.1% vs 65.3% in trial B; both trials, P <.001) (Figure 6).[27] Furthermore, edema at day 7 or discharge improved significantly with tolvaptan in trial B (P = .02) but did not reach significance in trial A (P = .07).[27]

There was a modest benefit in tolvaptan over placebo in the primary composite end point based on patient-assessed global clinical status and body weight. In the long-term trial, there was no evidence that therapy with tolvaptan was associated with harm, but no evidence of a reduction in mortality at 30 days, or a durable improvement in symptoms (Figure 7).[30] Therefore, a more rapid improvement in dyspnea and a reduction in congestion, as measured by weight loss, are significant findings. It should be noted that unlike intensive diuretic therapy, or other novel therapies like nesiritide, these improvements were not associated with a significant worsening in renal function or other signs of harm. This is somewhat unique among therapies for AHFS where most novel agents such as the inotropes have been associated with increased mortality. It should be noted that despite normalization of serum sodium in patients with hyponatremia (7% of patient population) and reduction of body weight postdischarge with tolvaptan when compared with placebo (standard therapy), there was no improvement in postdischarge outcomes in regard to readmission or mortality.

Figure 6. Change in Dyspnea at Day 1 in EVEREST[27]



Novel Managed Care Interventions to Improve the Quality of Care for AHFS

As outlined previously, HF is the only major cardiovascular disorder that is increasing in prevalence, and the rates of hospitalization for HF have increased dramatically since 1979.[2] The CMS/Hospital Quality Alliance (HQA) and ACC/AHA performance measures for patients hospitalized with

Figure 7. Reduction in Cardiovascular Mortality or Heart Failure Hospitalization With Tolvaptan in EVEREST[30]

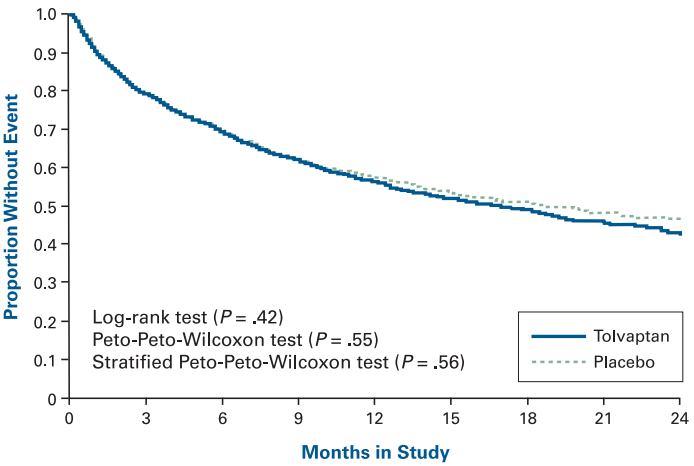


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Table 5. Comparison of Current ACC/AHA Heart Failure Performance Measures Against a Proposed Set for Potential Application in Managed Care[32]

Quality-of-Care Measures	
Current ACC/AHA Measures	**Proposed Managed Care Measures**
Diagnosis/Assessment	**Diagnosis/Assessment**
LV function assessment	LV function, MR severity wall motion abnormalities (LV aneurysm) Congestion assessment (heart rate, blood pressure, orthostatic changes, serial body weights, jugular venous distension, edema, possible BNP or NT-BNP) Exercise capacity prior to discharge (walk in the corridor or 1 flight of stairs)
Treatment	Renal function (blood urea nitrogen, creatinine, eGFR)
Discharge instructions	Serum sodium monitoring
ACE inhibitor or ARB for LVSD	Extent and severity of CAD (assess for ischemia/hibernation)
Adult smoking cessation counseling	Presence and extent of dysfunctional, but viable, myocardium (often present, even in patients without CAD)
Anticoagulant for atrial fibrillation	Ventricular dyssynchrony (QRS duration)
	Treatment (general)
	Address social issues to ensure medication compliance Adult smoking cessation counseling Develop a comprehensive discharge instruction set Early postdischarge outpatient follow-up visit (within 7 days) Heart failure disease management program for high-risk patients ACE inhibitor, ARB, beta-blocker, or aldosterone antagonist for LVSD CRT for dyssynchrony Pneumococcal vaccination and influenza vaccination during influenza season
	Treatment in patients with systolic dysfunction
	For congestion: diuretics, improve cardiac function with ACE inhibitor, ARB, beta-blockers, aldosterone-blocking agents, digoxin[a] For severe MR, LV aneurysm: consider corrective surgery For severe obstructive CAD: consider revascularization (PCI or CABG) For dyssynchrony: consider CRT For atrial fibrillation: anticoagulation unless contraindicated
	Treatment in patients with preserved heart failure
	Aggressively treat the underlying condition (hypertension, CAD, atrial fibrillation, diabetes, and/or renal dysfunction)

ACC/AHA indicates American College of Cardiology/American Heart Association; ACE, angiotenin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVSD, left ventricular systolic dysfunction; MR, mitral regurgitation; NT-BNP, N-terminal B-type natriuretic peptide; PCI, percutaneous coronary intervention.
[a]The best way to improve congestion is to improve cardiac function.

HF most closely approach such AHFS measures.[31,32] The CMS/HQA has 4 measures for monitoring and improving quality of care in patients with HF[31]:

- Discharge instructions
- LV function assessment
- ACE inhibitor or ARB for LV systolic dysfunction
- Adult smoking cessation counseling

The ACC/AHA HF performance measures and the in-patient measure descriptions include the same 4 measures as the CMS/HQA measures, plus a fifth measure for an anticoagulant at discharge for patients with atrial fibrillation.[32]

Whereas these measures focus on key areas of care in the treatment of HF, they are by no means all comprehensive and overlook several crucial therapeutic concerns in the treatment of HF and especially AHFS. In fact, the lack of clinical relevance of these and other similar measures was demonstrated by Fonarow et al in an analysis of the 5 ACC/AHA HF measures against 60- and 90-day discharge results and combined mortality/rehospitalization rates from the OPTIMIZE-HF study.[33] The researchers reported none of the 5 ACC/AHA HF performance measures was significantly associated with reduced early mortality risk, and only ACE inhibitor or ARB use at discharge was associated with 60- to 90-day postdischarge mortality or rehospitalization.[33] However, a potential performance measure not included in the current ACC/AHA measures, beta blockade at the time of discharge, was strongly associated with reduced risk of mortality (HR, 0.48; 95% CI, 0.30-0.79; P = .004) and mortality/rehospitalization during follow-up.[33]

To improve the quality of care in acute HF, a new set of quality measures are in development that more accurately targets the markers for the disease (Table 5). These measures include patient characteristics such as body weight assessment, and an assessment of fatigue. Also included is an assessment of the etiology and severity of HF. In addition, measures monitoring to promote prescription of agents with demonstrated efficacy in the treatment of AHFS, such as diuretics, vasodilators, ACE inhibitors, and beta-blockers, are also necessary.

In an effort to take the aforementioned proposed AHFS quality-of-care measures from concept

to practice, an assessment tool for hospitalists—who interact with AHFS patients to the greatest degree—may prove useful. Specifically, a hospital discharge checklist may be used to ensure that all prognostic factors have been considered and all recommended treatment standards have been employed prior to a patient being discharged from the hospital for AHFS (Table 6).

In recent years, disease management programs have demonstrated promise in the treatment of HF and have introduced multidisciplinary teams and case managers to the list of therapeutic options for the disease. In one study by Capomolla et al, enrolling patients in a hospital-administered HF management program resulted in improved clinical outcomes.[34] Patients discharged by an HF unit were assigned to either usual community care (n = 112) or enrolled in an HF management program delivered by a multidisciplinary team at the hospital and followed for 1 year. Usual care patients were referred to their primary care physician and cardiologists, while HF management program patients received full-time care from a cardiologist, 4 skilled nurses, 2 physiotherapists, and part-time consultation from a dietitian, a psychologist, and a social worker.[34] The members of this team coordinated care efforts and advised on the course of treatment as necessary. Therapy was tailored to the individual patient with the input of the team members, and the nurses and physiotherapists delivered patient education on measures to improve treatment success and physical activity recommendations, respectively.[34] Improvements in several different clinical measures were observed in the HF management group compared with the usual care group. Specifically, HF management program patients were readmitted to the hospital less frequently than were the usual-care group patients (13 vs 78; P <.00001).[34] Furthermore, cardiac death occurred in 17.2% of the usual care group, compared with only 2.7% of the patients in the HF management group (P <.0007).[34] In addition to the HF management program being clinically sound, it was also economically feasible: the cost/utility ratio of the 2 management strategies was similar (usual care, $2409 vs HF management, $2244), and the incremental analysis revealed a cost savings of $1068 for each quality-adjusted life-year gained.[34]

In a similar study of 406 Hispanic and non-Hispanic patients hospitalized for HF, Sisk et al compared a nurse management program with usual care.[35] Patients in the nurse management group received counseling on diet, medication adherence, and self-management of symptoms through an initial visit and regularly scheduled follow-up telephone calls with bilingual nurses.[35] In addition, the nurses facilitated evidence-based changes to medications in discussions with patients' clinicians.[35] Patients in the usual care group received

Table 6. Acute Heart Failure Syndrome Hospital Discharge Checklist

Assessment—Evaluate the patient on the following prognostic criteria prior to discharge:
✔ Heart rate, blood pressure, orthostatic changes, jugular venous distension, edema
✔ Consider BNP or pro-BNP
✔ Exercise/physical activity
✔ Renal function
✔ QRS duration
✔ Presence or absence of coronary artery disease
✔ Any correctable surgical problem (mitral regurgitation, left ventricular aneurysm)
Therapeutic considerations (known to improve outcomes) for each patient prior to discharge:
✔ Diuretics[a]
✔ ACE inhibitors/ARBs
✔ Beta-blockers
✔ Aldosterone-blocking agents
✔ Digoxin[b]
✔ Anticoagulants[b]
✔ Electrical therapy[b]
✔ Surgical correction[b]
✔ Treat underlying comorbidities (ie, "make the patient younger")
Treatment—Implement the following life-saving therapies prior to discharge:
✔ ACE inhibitors/ARBs
✔ Beta-blockers
✔ Aldosterone-blocking agents
✔ Omega-3 fatty acid supplementation
✔ Anticoagulants for atrial fibrillation

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BNP, B-type natriuretic peptide.
Note: It is important to realize that inexpensive interventions may improve outcomes.
[a]Although there is no conclusive data, patients improve symptomatically.
[b]In selected patients, if indicated.

Table 7. The MAWDS® Heart Failure Patient Education Mnemonic[36]

Take your MEDICATIONS
Ensure that patients understand the importance of taking medications, even when they feel better or prescriptions run out
Stay ACTIVE every day
Participation in some form of physical activity every day is important, despite patient fears or lack of assertion
WEIGH yourself daily
Patients must understand that weight gain from fluid retention, not just fat, is a legitimate concern
Follow your DIET
Sodium restriction (<2 g/d) is critical to the management of heart failure
Recognize your SYMPTOMS
Ensure that patients not only recognize and understand the signs and symptoms of heart failure, but also know what to do when experiencing them

Source: Intermountain Healthcare.

care only from their primary care physicians. At 12 months, nurse management patients had had fewer hospitalizations than usual care patients (143 vs 180 hospitalizations, respectively; adjusted difference, –0.13 hospitalization/person-year [95% CI, –0.25 to –0.001 hospitalization/person-year]).[35] In addition, patients in the nurse management group experienced better functioning than patients in the usual care group, with a physical component score on the Short Form-12 of 39.9 versus 36.3, respectively (difference, 3.6 [95% CI, 1.2-6.1]).[35]

In these 2 studies, nurses served a role similar to that of a case manager. Within managed care organizations, case managers can serve to improve care for patients with acute HF as part of a multidisciplinary treatment team. Case managers can promote general health management, assist in patient education activities, and more appropriately screen high-risk patients. Using the MAWDS® mnemonic (Medications, Active, Weigh, Diet, and Symptoms) developed and implemented by Intermountain Healthcare, case managers can facilitate improved medication adherence and healthy lifestyle and diet changes (**Table 7**).[36]

In addition to these primary care initiatives, pharmacy-led interventions such as hospital discharge medication management programs can serve to improve medication adherence and treatment outcomes. These programs involve tracking of prescriptions via pharmacy database monitoring and follow-up with physicians not prescribing according to treatment guidelines by pharmacists and nursing staff. Examples demonstrating the success of such programs in the treatment of cardiovascular disease have been published in a number of instances. One study by Lappé et al examined a hospital-based discharge medication program at Intermountain Healthcare, developed to ensure appropriate prescription of aspirin, beta-blockers, ACE inhibitors, and warfarin by monitoring the pharmacy database.[37] The researchers reported that the rate of prescription of each medication at discharge had improved to greater than 90% (P <.001) and that risk of death and readmission was reduced by 19% and 8%, respectively, postimplementation of the medication management program.[37] Similarly, Fonarow et al reported improved persistence rates for aspirin, beta-blocker, and statin therapy in patients 1 year following admission for an MI after implementation of the University of California-Los Angeles Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) discharge protocol.[38] Prior to the implementation of the CHAMP protocol, persistence rates for aspirin, beta-blocker, and statin therapy in patients 1-year postdischarge for an MI were modest, at 68%, 18%, and 10%, respectively.[38] However, postimplementation, persistence rates for these therapies improved to 94%, 57%, and 91%, respectively.[38] These improved persistence rates resulted in significantly reduced rates of coronary events, such as recurrent MI, hospitalization, and cardiac mortality (P <.05).[38]

Other managed care interventions, such as formulary management and treatment algorithms, may also be employed to ensure proper prescribing practices for clinicians treating patients with AHFS. Provider education efforts can serve to bolster the success of such interventions. In addition, value-based benefit design may prove helpful in ensuring medication access and adherence among patients with AHFS. Value-based benefit design initiatives typically offer reduced copayments on cost- and clinically effective medications for a specific patient population. Conceptually speaking, a value-based benefit design for improving quality in AHFS care would be centered on lower copayment rates on medications for the secondary prevention of AHFS, such as beta-blockers, ARBs, and ACE inhibitors. Value-based benefit designs have recently been introduced by some insurers and tend to focus on

chronic diseases such as diabetes and cardiovascular conditions such as hypertension and HF.

Conclusions

As evidenced by the dramatically rising prevalence, morbidity, and mortality of AHFS, there is a compelling need for immediate action to improve outcomes and control costs. Although professional organizations have been striving to improve the state of care for AHFS by providing at least some level of consensus and evidence-based treatment recommendations, the gap between the clinical evidence and actual practice is growing. Appropriate disease assessment, followed by the implementation of life-saving therapies, is the key to improving outcomes; however, in the current state of care, it is apparent that intervention is necessary to achieve these goals.

Through implementation of the aforementioned interventions, managed care stakeholders will likely be able to improve the quality of care in AHFS and reduce the cost of unnecessary rehospitalizations. It is important to realize that inexpensive interventions may be currently underutilized, such as generic beta-blockers, ACE inhibitors, statins, and other affordable medications, such as coumadin, digoxin, and ASA. Realignment of the goals of therapy of managed care and implementation of these effective and relatively inexpensive drugs may profoundly impact outcomes. Ultimately, a concerted effort by plan management, pharmacists, and physicians will be necessary if managed care is to stem the tide of the HF burden, improving the quality of life for patients in the process.

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