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Heart Fail Clin. Author manuscript; available in PMC 2014 July 01.

Published in final edited form as:
Heart Fail Clin. 2013 July ; 9(3): 359–vii. doi:10.1016/j.hfc.2013.04.003.

Noncardiac Comorbidities and Acute Heart Failure Patients

Robert J. Mentz, MD* and **G. Michael Felker, MD, MHS**
Division of Cardiology, Department of Medicine, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27710, USA

Keywords

Heart failure; Comorbidities; COPD; Renal disease; Diabetes; Anemia; Sleep-disordered breathing

INTRODUCTION

Patients with heart failure (HF) commonly have multiple comorbid diseases that complicate management. Risk factors, such as smoking, obesity, and advanced age, increase the burden of noncardiovascular comorbidities including chronic obstructive pulmonary disease (COPD), sleep apnea, and diabetes mellitus (DM). Registry and trial data suggest that these comorbidities are present in more than 30% of patients with HF (Table 1).[1–3] In addition, patients with HF frequently have kidney disease and evidence of liver dysfunction, which may worsen at the time of HF hospitalization and adversely impact inpatient management and clinical course.[4,5] In one study of Medicare patients, nearly 40% of elderly patients with HF had five or more noncardiac comorbidities and this group accounted for most total hospital days.[6] Thus, the acute HF (AHF) population represents a heterogeneous cohort with multiple interrelated noncardiovascular comorbidities (Fig. 1).

Despite recent advances in the care of patients with chronic HF, the AHF population remains at high risk for adverse events postdischarge. The presence of comorbidities in patients with AHF has been associated with significantly increased morbidity and mortality.[2,7] The risk of hospitalization markedly increases with the number of noncardiac chronic conditions.[6] Rehospitalization rates after AHF are nearly as high for noncardiovascular causes as for HF.[8] Once hospitalized, comorbid pulmonary, renal, and liver dysfunction along with sleep apnea syndromes complicate the management of dyspnea and congestion in AHF (Fig. 2). This article summarizes the impact of comorbidities on the characteristics, treatment, and outcomes of patients with AHF. Attention to the diagnosis and management of these conditions in patients with AHF may help to improve patient outcomes.

COPD

COPD is present in approximately 30% of patients with HF.[9] Patients with HF with COPD tend to have an increased burden of other comorbidities, including hypertension, atrial fibrillation, and coronary artery disease (CAD), compared with those without COPD.[10] The underlying pathophysiology may be caused by the shared risk factor of smoking with low-grade systemic inflammation accelerating disease progression.[11] Patients with AHF with COPD tend to have lower blood pressure, higher creatinine, and underuse of angiotensin-

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*Corresponding author. Duke University Medical Center, 2301 Erwin Road, Durham, NC 27710., robert.mentz@duke.edu.

Disclosures: None.

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converting enzyme (ACE) inhibitors and mineralo-corticoid receptor antagonists (MRAs).[12,13] They are less likely to receive β-blockers compared with those without COPD[10] because of concerns about precipitating bronchospasm.[14–16] The primary effect of COPD may be increased noncardiovascular mortality in the AHF setting[12] with similar outcomes after hospital discharge.[13] However, other studies have suggested an increased long-term risk for morbidity[10] and mortality[6] associated with COPD in chronic HF.

The overlapping symptom of dyspnea with both diseases may confound appropriate diagnosis at the time of disease exacerbation and may lead to misapplication of therapy. Given the discordant β receptor effects of the different disease treatments, a patient's symptoms and outcome could be adversely affected by the treatment of the comorbid disease. For instance, there are observational data demonstrating potential cardiovascular risks with β_2 agonists in patients with HF.[16] However, because worse outcomes in previous studies may be attributed to confounding by indication or COPD severity rather than an adverse effect of therapy, these results should be viewed as exploratory. Alternatively, worsening of one disease process may adversely impact the other disease such that concomitant exacerbations may contribute to clinical deterioration during hospitalization. Careful evaluation of evidence for congestion, edema, and bronchospasm along with natriuretic peptide levels may help determine the relative contribution of each disease process. Thus, therapy can be appropriately targeted in an individual patient to improve his or her symptoms and clinical course.

Anticholinergic bronchodilators may have a more reassuring safety profile compared with β-agonists and may be the preferred first-line agents for patients with COPD with comorbid HF.[14] Conversely, β-blockers do not worsen airway function in most patients with COPD in the chronic setting,[17] yet less is known about their use during hospitalization for pulmonary exacerbation. As a patient's pulmonary exacerbation resolves and there is no evidence of ongoing bronchospasm, it may be possible to initiate β-blockers in patients with HF with COPD. The hospitalized setting may provide the optimal environment for initiation of these therapies, because the patient can be closely monitored for adverse events. Dosages should be carefully titrated to the doses used in clinical trials or to the maximally tolerated dose with monitoring commensurate to the patient's presentation and clinical course. The decision to use a cardioselective versus noncardioselective β-blocker in these patients may not impact outcomes.[10,18]

Taken together, these data highlight the complexities of treating patients with concomitant HF and COPD, and suggest increased risk when the diseases are present together. Because trials investigating the management of patients with COPD have generally excluded patients with significant HF, and vice versa, limited data exist on the management of these patients. We have recently proposed a randomized trial designed to enroll patients with significant COPD and HF to determine the risks and benefits of different bron-chodilator and β-blocker strategies.[16]

RENAL DISEASE

Chronic kidney disease (CKD) is present in approximately 30% of patients with HF. The interdependence of the heart and the kidney is captured in the cardiorenal syndrome.[4,19] Risk factors for the development of HF and vascular disease (eg, hypertension and diabetes) contribute to the prevalence of renal disease in these patients. Patients with AHF with renal dysfunction tend to be older, with lower blood pressure, higher brain natriuretic peptide levels, and more clinical signs of HF.[20] Renal dysfunction is an established risk factor for adverse events in patients with HF.[21,22] The ADHERE registry revealed that greater than half of patients with AHF had at least moderate renal insufficiency (estimated glomerular

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filtration rate [eGFR] <60 mL/min/1.73 m^2) on admission, which was associated with increased mortality.[23]

CKD impacts baseline medication use in patients with HF and complicates in-hospital management. ACE inhibitors and MRAs are frequently underused in patients with HF with renal disease because of concerns about worsening GFR and hyperkalemia.[20] Of the limited data available on the use of ACE inhibitors in patients with AHF who experience worsening renal failure (WRF), an association between their use and WRF has not been demonstrated.[24,25] Recommendations are to use ACE inhibitors and MRAs with caution in those with reduced eGFR and to avoid these classes when eGFR falls below 30 mL/min/1.73 m^2 or in patients with hyperkalemia.[26] In the setting of dynamic fluctuations in renal function during AHF, the degree of monitoring and discontinuation of these agents should be determined based on the clinical situation.[27] Similar to the initiation of β-blockers in patients with COPD with HF, the in-hospital setting may be an ideal time to start ACE inhibitors and MRAs in patients with renal dysfunction after clinical stabilization.

CKD may complicate the ability to successfully decongest patients with AHF and increases the likelihood of experiencing WRF.[28] Renal disease may necessitate increased diuretic dosing to achieve an effect in AHF such that an initial management step is to challenge the patient with higher doses of loop diuretics. Adequate decongestion in this patient population may also be limited by underlying diuretic resistance and the addition of a thiazide diuretic may augment diuresis. Notably, baseline renal dysfunction is a predictor of WRF during AHF, which has been associated with increased mortality.[29–32]

However, recent data exploring the implications of WRF in patients with AHF have questioned the association with worse outcomes. For instance, transient WRF during AHF hospitalization may not impact postdischarge outcomes[33,34] and aggressive fluid removal involving hemoconcentration may be associated with lower mortality despite WRF.[34] Data from the DOSE study suggested that higher doses of diuretics are more efficacious in relieving congestion, at the cost of WRF that does not seem to have long-term consequences.[35] Given that persistent congestion is a predictor of adverse outcomes,[36] transient WRF may be acceptable in exchange for decongestion. Thus, baseline CKD is associated with worse outcomes in patients with AHF, but management strategies that optimize decongestion and prioritize the initiation of guideline-recommended HF medications may lead to improved outcomes.

DIABETES

Approximately 40% of patients with AHF have DM.[1] Patients with AHF with DM are more likely to have hypertension, obesity, ischemic etiology, kidney disease, anemia, and vascular disease.[37–39] In an observational AHF study, patients with DM tended to more frequently present with acute pulmonary edema or acute coronary syndrome compared with those without DM.[38] Although DM is associated with increased cardiovascular morbidity and mortality in ambulatory patients with chronic systolic HF,[40,41] its influence as a predictor of long-term outcomes after AHF is less well defined. The OPTIMIZE-HF registry showed that patients with DM with AHF had longer lengths of stay and increased short-term risk for rehospitalization, but similar in-hospital and short-term mortality.[39] DM was associated with increased HF rehospitalization, but not all-cause mortality in the EVEREST study.[37] However, other AHF registries have suggested that patients with DM are at increased risk for mortality.[38,42]

DM may complicate the clinical course in patients with AHF. For instance, these patients are at increased risk for adverse events during periods of reduced oral intake related to decreased appetite from congestive symptoms and NPO status for procedures. Inconsistent

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caloric intake along with precipitating factors for HF decompensation (eg, infection) may result in wide fluctuations in blood sugars that further perturb mental status, acid-base balance, and serum electrolytes. Long-term complications from DM, such as gastroparesis and peripheral neuropathy, may complicate AHF care by altering medication absorption, compromising nutritional status, and limiting early mobilization. Taken together, these examples highlight the importance of close attention to underlying DM and cautious management during AHF hospitalization.

There remains uncertainty in the optimal management of DM in patients with AHF. Several oral antidiabetic drugs may have harmful cardiac effects.[43,44] Thiazolidinediones (glitazones) cause sodium and water retention and may increase the risk of worsening HF.[26] Metformin initially had a relative contraindication in patients with HF when the drug was first introduced out of concern for lactic acidosis in the setting of renal impairment, but recent studies have suggested a mortality benefit.[45] Insulin use in patients with HF has been associated with increased mortality[46,47]; however, there are concerns that these findings may have been related to disease severity rather than a causal effect of the therapy itself. More recently, patients with AHF requiring insulin were found to have similar risk for adverse events after adjusting for baseline risk factors.[37] Future studies are required to explore the optimal therapeutic approach to DM during AHF hospitalization.

ANEMIA

Anemia is present in 50% to 70% of patients with HF in the ambulatory and hospital setting depending on the definition used.[48] The potential causes of anemia in patients with HF are multifactorial.[48] Patients with HF may experience an absolute or relative iron deficiency, impaired erythropoietin production caused by renal disease, reduced erythrogenesis caused by renin-angiotensin blockade, hemodilution, and anemia of chronic disease caused by the proinflammatory state. Compared with nonanemic patients with AHF, those with anemia tend to be older, with lower blood pressure and higher creatinine and natriuretic peptide levels.[49] CAD, DM, kidney disease, and COPD are more common in those with anemia.

Although a large body of data suggests that anemia is associated with worse HF outcomes,[50–52] studies have been conflicting, particularly after adjustment for baseline characteristics (eg, renal function) and disease onset and severity.[53–56] Most studies were conducted in chronic patients with HF. Thus, less is known about the outcomes of contemporary patients with AHF with baseline anemia.[55] Two recent studies have suggested that baseline anemia during AHF is associated with increased long-term morbidity and mortality.[49,57]

Despite the association between anemia and outcomes, anemia may be a prognostic marker rather than a mediator of risk. Multiple trials in chronic patients with HF, including the recent RED-HF trial,[58] investigating erythropoietin-stimulating agents have failed to demonstrate benefits on outcome.[59,60] Alternatively, the FAIR-HF trial showed that intravenous iron treatment in patients with HF with iron deficiency (with or without anemia) resulted in improved symptoms, functional capacity, and quality of life.[61] Thus, future research is needed to clarify the disconnect between the prognostic implications of anemia and the outcomes associated with treatment.

LIVER ABNORMALITIES

Abnormal liver function tests (LFTs) including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and total bilirubin are common in patients with chronic HF[62] and patients with AHF. An analysis from EVEREST demonstrated that approximately 20% of patients with AHF have abnormalities in these laboratories.[5] The

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prevalence of abnormal LFTs may increase to nearly 50% in patients managed with inotropes.[63] During hospitalization, total bilirubin may be the only liver test that significantly changes; however, most of these laboratory values improve postdischarge. Studies have suggested that elevated bilirubin correlates with higher right atrial pressure and right ventricular dilation.[64] Alkaline phosphatase elevation has also been associated with marked systemic congestion and elevated right-sided filling pressure, whereas elevated AST and ALT has been associated with hypoperfusion.[63] Elevated LFTs are also associated with abnormalities in hemoglobin and natiuretic peptides.[64]

In EVEREST, elevated total bilirubin at baseline and a rise in bilirubin during hospitalization were both associated with increased morbidity and mortality. Similar findings have been demonstrated in chronic patients with HF.[62] Other studies have suggested that alkaline phosphatase and ALT and AST elevation during AHF may also be associated with increased postdischarge mortality.[63]

Abnormal LFTs are common in patients with AHF and may have prognostic relevance, but future investigation is needed to determine the implications for inpatient management. Liver dysfunction during AHF may impact drug metabolism and may further perturb other diseases, such as DM, through alterations in glucose metabolism. More significant elevations in LFTs may limit the use of medications, such as statins and amiodarone, with implications on cardiovascular comorbidities.

SLEEP APNEA

Sleep-disordered breathing (SDB) is common in patients with HF with prevalence estimates of upward of 50% to 75%.[65] Two primary types of SDB occur in patients with HF: obstructive sleep apnea (OSA) and central sleep apnea (CSA)/Cheyne-Stokes respiration. Risk factors for the development of OSA in patients with HF include male sex, elevated BMI, and increased age.[66] Lower-extremity edema has also been shown to lead to SDB, and pulmonary congestion in the setting of worsening HF further increases CSA.[67,68] Chronic SDB causes a series of derangements that may lead to the development or exacerbation of HF. SDB is proinflammatory, with nocturnal oxygen desaturations and hypercapnia seeming to play a pivotal role in the development of oxidative stress and sympathetic activation.[65] Hypertension, CAD, and DM (all well-established HF risk factors) are adversely impacted by SDB. On the other hand, HF may worsen SDB through mechanisms that include nocturnal rostral fluid movement and increased pharyngeal obstruction.[67]

The role of SDB in the clinical course, management, and outcomes of patients with AHF warrants future investigation. Untreated SDB in chronic patients with HF has been associated with increased mortality on multivariable analysis.[69] SDB has been shown to be even more common in patients with AHF than patients with chronic HF and is an independent predictor of cardiac readmission.[70,71] Observational studies assessing the efficacy of continuous positive airway pressure on morbidity and mortality in chronic patients with HF with OSA have suggested potential benefits.[65] Minute ventilation–targeted adaptive servoventilation (ASV) is a distinct form of noninvasive ventilation that automatically adjusts the degree of pressure support in response to the patient's breathing efforts. Minute ventilation–targeted ASV may treat CSA and OSA with improved tolerability compared with continuous positive airway pressure devices. Previous HF studies have demonstrated benefits on quality of life and left ventricular function with ASV[72] and randomized trials of ASV in HF are ongoing. Improved management of SDB in the AHF population may improve clinical outcomes.

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CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

We have highlighted several major noncardiovascular comorbidities in patients with AHF. Other comorbidities, such as frailty, depression, nutritional deficiencies, cancer, and gout may also have direct implications on the management and outcome of patients with AHF. We have identified areas where these comorbidities may complicate HF management. In some circumstances, careful attention to the diagnosis and management of these conditions in patients with AHF may help to improve patient outcomes. As the burden of comorbidities increases in the AHF population, the potential risk for noncardiovascular adverse events increases. These considerations have implications for strategies to improve the outcomes of our patients, and also impact end point selection in clinical trials. Attention to the diagnosis and management of comorbidities represents a critical step in the holistic approach to managing patients with AHF.

Acknowledgments

Funding Support: None.

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KEY POINTS

- The acute heart failure (AHF) population represents a heterogeneous cohort with multiple interrelated noncardiovascular comorbidities.
- Chronic obstructive pulmonary disease, renal disease, diabetes, sleep apnea, and anemia impact the clinical characteristics and outcomes of patients with AHF and complicate in-hospital management.
- Attention to the diagnosis and management of comorbidities in patients with AHF may improve patient outcomes.

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Fig. 1.
Interrelated noncardiovascular comorbidities in patients with acute heart failure. COPD, chronic obstructive pulmonary disease.

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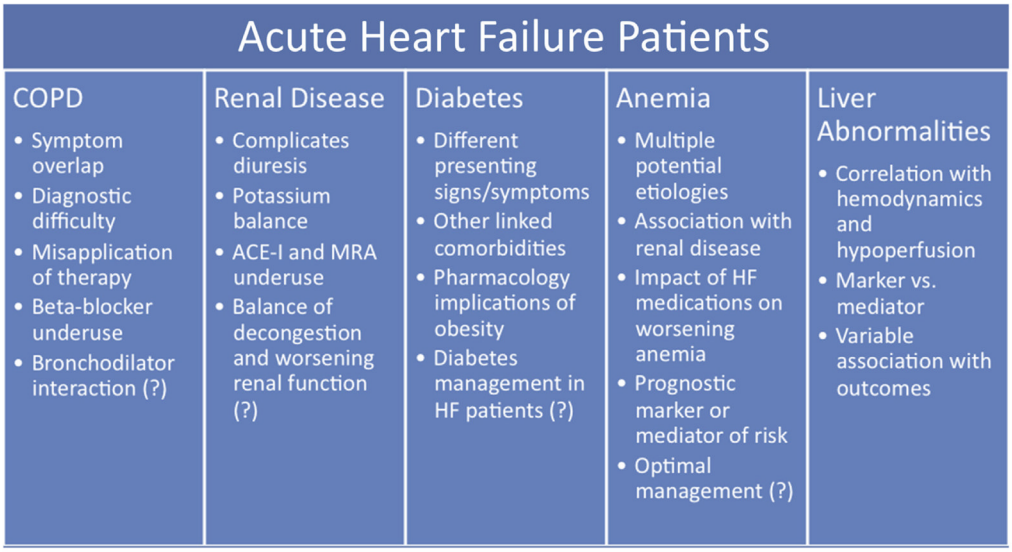

Fig. 2.

Key characteristics associated with different noncardiovascular comorbidities in patients with acute heart failure. ACE-I, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist.

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Table 1

Prevalence of noncardiovascular comorbidities in patients with acute heart failure

	ADHERE (n =187,565)	OPTIMIZE-HF (n =48,612)	EHFS II (n =3580)
Region	United States	United States	Europe
Age (y)	75	73	70
Male (%)	48	48	61
Preserved ejection fraction (%)	53	51	52
Medical history			
COPD	31	28	19
Chronic renal insufficiency	30	20	17
Diabetes mellitus	44	42	33
Anemia	53	18	15
Depression	—	11	—
Liver disease	—	2	—

Abbreviations: ADHERE, Acute Decompensated Heart Failure National Registry; COPD, chronic obstructive pulmonary disease; EHFS II, EuroHeart Failure Survey II; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.