# Management of Comorbid Conditions in Heart Failure

## A Review

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**KEYWORDS**

• Heart failure • Co-morbid conditions

**KEY POINTS**

- Diabetes mellitus can affect cardiac function at the cellular level through different mechanisms such as myocyte fibrosis, intramyocardial microangiopathy, and cardiac autonomic imbalance, causing diabetic cardiomyopathy.
- Angiotensin-converting enzyme inhibitors have been proved to have mortality benefit in patients with systolic heart failure irrespective of the diabetic status.
- Recent practice guidelines[1] recommend angiotensin-converting enzyme inhibitors and β-blockers as first-line therapy for asymptomatic hypertensive patients with demonstrable left ventricular dysfunction.

### INTRODUCTION

Heart failure is a chronic and progressive condition, and is a major cause of morbidity and mortality worldwide. More than 5.8 million people in United States have a diagnosis of heart failure, and the estimated annual cost of heart failure is around US$37.2 billion.[2] Recent insights have emerged to show that heart failure is a complex clinical condition, particularly in the elderly, that usually interacts with other chronic medical conditions via known and possibly yet unknown mechanisms. This review discusses the common comorbid conditions, their interactions with heart failure, and treatment options. Several major comorbidities that are important in management of heart failure, such as cardiorenal syndrome, atrial fibrillation, and malignancy, are discussed in reviews elsewhere in this issue and are therefore not discussed here.

### EPIDEMIOLOGY OF COMORBID CONDITIONS IN HEART FAILURE

The prevalence of comorbid conditions in heart failure varies depending on study population and severity of heart failure. It may also vary secondary to different definitions

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used in different studies. In a large cross-sectional study involving 122,630 US Medicare beneficiaries who have heart failure and are 65 years or older, Braunstein and colleagues[3] examined the relationship of 20 most common noncardiac comorbidities to potentially preventable hospitalizations and total mortality at 1 year. Forty percent of patients in this sample had 5 or more predefined comorbidities. Also, the risk of hospitalization significantly increased with the number of chronic conditions. The 5 common comorbid conditions in this study, in decreasing prevalence, were hypertension (55%), diabetes mellitus (31%), chronic obstructive pulmonary disease (COPD)/bronchiectasis (26%), ocular disorders (24%), and hypercholesterolemia (21%). Another interesting study evaluated 1395 patients with self-reported heart failure using the National Health and Nutrition Examination Survey (NHANES) database.[4] The proportion of heart failure patients with 5 or more comorbidities increased from 42% to 58% during the past 2 decades. The main comorbid conditions responsible for this increase were hypercholesterolemia, diabetes, obesity, and kidney disease. Although this could represent increasing prevalence of these comorbid conditions during the study period, there has also been better screening for comorbid conditions and recognition of obesity as a chronic health problem in recent years. Wong and colleagues[4] examined the trend in medications during the same period (1988–2008). Although the use of digoxin and calcium-channel blockers decreased over time, they noted that the prescription drug use increased from a mean of 4.1 to 6.4 prescription medications. A separate cost analysis of comorbid conditions investigated 1266 Medicare beneficiaries with heart failure, and demonstrated that the presence of comorbid conditions significantly increased the Medicare expenditure.[5] Furthermore, 81% of patients had at least 1 predefined comorbid condition, and the noncardiac comorbidities that were associated with increased mean expenditure included hemiplegia/paraplegia, renal disease, peripheral vascular disease, and dementia.

## DIABETES MELLITUS

Diabetes mellitus is an independent risk factor for the development of heart failure, which was clearly demonstrated in the Framingham Heart Study involving 5209 subjects.[6] Study investigators noted a 2-fold increase in incidence of heart failure in men and a greater than 5-fold increase in women during a 20-year surveillance. A large, prospective, observational trial from the United Kingdom (UK Prospective Diabetes Study) involving 3642 patients showed that the risk of heart failure decreased by 16% per 1% reduction in hemoglobin A1c.[7] There was also a 14% reduction in myocardial infarction for every 1% reduction in hemoglobin A1c, which is another important predictor of future risk of heart failure. Diabetes also proved to be an independent predictor of mortality in patients with heart failure. The DIAMOND (Danish Investigations and Arrhythmia ON Dofetilide) study investigators[8] evaluated 5491 patients who were hospitalized with heart failure, and identified relative risk of death in diabetic patients in this study as being 1.5 (95% confidence interval [CI], 1.3–1.6, $P<.0001$), even after adjusting for hypertension, ischemic heart disease, and other risk factors. Similar results were shown in the Studies of Left Ventricular Dysfunction (SOLVD) trial in patients with ischemic cardiomyopathy.[9]

Although there is clear evidence of increased risk and poor prognosis with diabetes mellitus, the pathophysiologic mechanism is less clear. Diabetes mellitus can affect cardiac function at the cellular level through differing mechanisms such as myocyte fibrosis, intramyocardial microangiopathy, and cardiac autonomic imbalance, causing diabetic cardiomyopathy.[10] Diabetic cardiomyopathy, along with coexistent myocardial ischemia and hypertension/ventricular hypertrophy, is referred to as the cardiotoxic

triad, which attempts to explain the common mechanisms of poor cardiac function in patients with diabetes mellitus.[11] The choice of glucose-lowering medications may be controversial in patients with heart failure. Although metformin has traditionally been linked to lactic acidosis in heart failure, it was the only antidiabetic agent that was associated with decreased all-cause mortality in a contemporary systematic review.[12] By contrast, thiazolidinedione use has been linked to an increased risk of fluid retention[13] and hence is not used commonly in patients with advanced heart failure.

Angiotensin-converting enzyme (ACE) inhibitors have been proved to have mortality benefit in patients with systolic heart failure, regardless of the diabetic status, in a subgroup analysis of meta-analysis of major clinical trials,[14] which compared 2398 patients with diabetes and 10,188 patients without diabetes. The relative risk (RR) of mortality due to ACE inhibitors was similar in diabetic and nondiabetic patients (RR of 0.84 vs 0.85). The same meta-analysis also evaluated efficacy of β-blockers in patients with and without diabetes. Although β-blockers showed mortality benefit in both groups, relative reduction in mortality was less for diabetic patients (RR of 0.77 vs 0.65), but there was no statistical significance. The historic concern of hypoglycemic unawareness with β-blockers is not well proved[15] and definitely does not outweigh the benefits of β-blockers. The mortality benefit of aldosterone antagonists was similar in patients with and without diabetes.[16]

## HYPERTENSION

Hypertension is one of the two major causes of heart failure.[17] The other cause, coronary artery disease, most often coexists with or is secondary to hypertension, making hypertension the most common risk factor for heart failure. Data suggest that up to 75% of patients with heart failure may have antecedent hypertension.[2] Hypertension as a risk factor for heart failure was demonstrated in a large study that included 5143 subjects aged 40 to 89 years and a mean follow-up of longer than 14 years.[18] Subjects with hypertension had a 2- to 3-fold increased risk of developing heart failure compared with normotensive subjects. Of the major risk factors examined in this study, hypertension had the highest prevalence (60%), but myocardial infarction had the highest hazard ratio for developing heart failure. There are multiple studies, starting from the early years of heart failure investigation, that support the fact that appropriate treatment of hypertension can dramatically decrease the risk of developing heart failure. This was well demonstrated in the Systolic Hypertension in Elderly (SHEP) trial, which randomized 4736 patients to active treatment of hypertension versus placebo.[19] The incidence of left ventricular failure was 50% lower in the treatment group (RR, 0.46; 95% CI, 0.33–0.65). Decreased incidence of myocardial infarction was also noted in the treatment group of this study. Similar results were noted in patients older than 70 years.[20]

Hypertension is the most common cause of left ventricular hypertrophy, which is a strong predictor of adverse cardiac events including heart failure.[21] Pressure overload from systolic hypertension causes myocardial architectural changes such as myocardial hypertrophy and fibrosis.[22] Thereby, hypertension remains an important cause of diastolic dysfunction, which is a contributory factor in a major proportion of patients with heart failure. Diastolic dysfunction could precede systolic dysfunction in hypertensive heart failure.[23] The choice of antihypertensive medications in patients with heart failure is relatively easy, as most of the medications used for the treatment of heart failure also control blood pressure. Recent practice guidelines[1] recommend ACE inhibitors and β-blockers as first-line therapy for asymptomatic hypertensive patients with demonstrable left ventricular dysfunction. In addition, the guidelines

also recommend angiotensin II receptor blockers, aldosterone receptor antagonists, and loop diuretics in patients with symptoms.

## HYPERLIPIDEMIA

Advanced heart failure is commonly perceived as a cachectic disease. However, a history of hyperlipidemia is among the top 5 comorbid conditions in patients with heart failure. Hyperlipidemia is not a predictor of poor prognosis in patients with heart failure, and elevated cholesterol levels were paradoxically associated with a better survival rate. This phenomenon is called reverse epidemiology.[24] Meanwhile, the use of statin therapy in patients with heart failure has been explored. The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) trial[25] randomized 5011 elderly patients with ischemic cardiomyopathy to rosuvastatin and placebo. Despite the reduction in low-density lipoprotein and high-sensitivity C-reactive protein levels, there was no significant difference in the primary end point, but there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group. By contrast, in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Heart Failure (GISSI-HF) trial,[26] 4574 adult patients with heart failure were randomized, but the trial also included patients with nonischemic cardiomyopathy and heart failure with preserved ejection fraction. There was no difference in either primary or secondary end points, including hospitalizations for cardiac reasons.

Coenzyme Q10 (CoQ10) plays an important role in the synthesis of mitochondrial adenosine triphosphate. Low levels of CoQ10 have been shown to be an independent predictor of mortality in patients with heart failure.[27] Because statins are known to decrease CoQ10 levels, there was a concern regarding the use of statins in patients with heart failure, which was addressed in a substudy of the CORONA trial.[28] Although rosuvastatin decreased CoQ10 levels, rosuvastatin treatment was not associated with worse outcomes. Meanwhile, CoQ10 supplementation itself has yet to demonstrate significant long-term benefits. Further randomized controlled trials may be needed to clarify the role of statins and CoQ10 supplementation in patients with heart failure.

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a frequent comorbidity in patients with heart failure, with prevalence ranging from 20% to 30%. COPD and heart failure share common risk factors such as smoking and age. Smoking causes local airway inflammation leading to airway obstruction, but at same time can cause systemic inflammation and endothelial dysfunction. Another hypothesis is that COPD itself causes low-grade systemic inflammation[29] and hence may play an important role in the progression of cardiovascular disease. Because the clinical presentations of these conditions can be similar, there may be a delay in diagnosing the concomitant disease condition. Misdiagnosis or delay in the diagnosis of heart failure causes morbidity and an increase in treatment cost,[30] and vice versa. Although clinical examination will provide clues, plasma B-type natriuretic peptide is increasingly used to differentiate both conditions.[31] It is noteworthy that "cardiogenic wheezing" is also common in advanced heart failure.

COPD was found to be an independent predictor of mortality in patients with heart failure in multiple studies.[32] Forced expiratory volume in 1 second ($FEV_1$) was found to be as important as cholesterol in predicting cardiovascular mortality.[33] Smoking cessation is the mainstay of treatment for COPD, which decreases the incidence of cardiovascular diseases as well.[34] A meta-analysis showed that β-adrenergic agonists that are commonly used to treat COPD significantly increased the risk of cardiovascular events such as tachycardia, atrial fibrillation, myocardial infarction, and heart failure.[35]

Many physicians perceive COPD as a contraindication to β-blockers. However, a Cochrane review of 22 studies evaluating adverse effects of cardioselective β-blockers in patients with COPD found no significant change in $FEV_1$ or respiratory symptoms. Subgroup analysis was done for severe COPD and reversible airway obstruction, and the results were unchanged.[36] Hence, cardioselective β-blockers can be safely prescribed to patients with both COPD and heart failure.

## SLEEP-DISORDERED BREATHING

Sleep-disordered breathing (SDB) is recently gaining recognition in the heart failure literature. The 2 forms of SDB are obstructive sleep apnea (OSA) and central sleep apnea (CSA). The incidence of sleep apnea is likely to increase because of increasing obesity and aging of the general population, while there has been a long-standing association between advanced heart failure and CSA ("Cheyne-Stokes breathing"). There are multiple mechanisms through which OSA may affect the cardiovascular system: intermittent hypoxia, systemic inflammation, negative intrathoracic pressure, and elevated blood pressure.[37] OSA was associated with an increased risk of atrial fibrillation,[38] which itself has a deleterious effect on cardiac function in patients with heart failure. In an observational study involving 4422 patients with OSA, OSA emerged as an independent predictor of coronary artery disease and heart failure in men. In this study, men with an apnea-hypopnea index (AHI: average number of apneas plus hypopneas per hour of sleep) of 30 or higher were 58% more likely to develop heart failure in comparison with those with an AHI of less than 5.[39] A prospective trial from Canada followed 164 systolic patients with heart failure for 2.9 years.[40] In this trial, untreated OSA (AHI $\geq$15) was independently associated with increased mortality risk compared with patients with mild or no OSA.

In patients with undiagnosed SDB, a high index of suspicion is necessary to screen and diagnose SDB. In a recent retrospective study involving 30,719 Medicare beneficiaries, 1263 patients were clinically suspected to have OSA.[41] Patients who were tested and treated for OSA had a better 2-year prognosis than patients who did not undergo testing (hazard ratio, 0.33; 95% CI, 0.21–0.51; $P<.0001$). Also, of the patients who underwent testing, treated patients had a better 2-year survival rate compared with those who were untreated. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study randomly assigned 258 patients with heart failure and CSA to receive continuous positive airway pressure (CPAP) or no CPAP. CPAP improved nocturnal oxygenation, left ventricular ejection fraction, and 6-minute walk distance, but failed to improve survival.[42] The reason for this finding was unclear at the time, but a post hoc analysis published couple of years later showed that mortality benefit was observed in patients whose CSA was well suppressed with CPAP, with no benefit for those patients whose CSA was unsuppressed.[43]

## ANEMIA

The prognostic significance of anemia in multiple other disease states is well established. Prevalence varies widely among studies depending on the definition of anemia and the severity of underlying heart failure. Groenveld and colleagues[44] examined the role of anemia in a large meta-analysis involving 153,180 patients with heart failure; 37.2% of the patients were anemic and crude mortality was significantly higher in anemic patients (odds ratio, 1.96; 95% CI, 1.72–2.21). This difference was noted in both diastolic and systolic heart failure and persisted even after adjustment for known confounders. The cause of anemia is multifactorial, although functional iron deficiency has been

a strong postulate. Chronic inflammation, hemodilution, bone marrow dysfunction, renal dysfunction, and hematinic deficiencies are some mechanisms worthy of note.[45] The renin-angiotensin system plays a role in erythropoiesis, hence ACE inhibitors or angiotensin II receptor blockers may be associated with decreased erythropoietin levels. On the other hand, blood transfusions have been shown to be associated with higher mortality in the setting of acute coronary syndromes, hence blood transfusions are falling out of favor in heart failure also. There is no clear hemoglobin cutoff below which transfusion may be recommended in patients with heart failure.

The interest is diverted toward 2 other possible modes of treatment: intravenous iron and erythropoietin-stimulating agents. A prospective observational study involving 546 stable patients with systolic heart failure found that 57% of anemic patients are iron deficient based on iron studies.[46] Of interest, they also noted that about 32% of patients without anemia also had iron deficiency. Iron-deficiency anemia was an independent predictor of mortality or need for transplantation in this study. The treatment aspect of iron deficiency was examined in the Ferric carboxymaltose Assessment in patients with IRon deficiency and chronic Heart Failure with and without anemia (FAIR-HF) trial,[47] which enrolled 459 patients with systolic dysfunction and iron deficiency. Treatment with intravenous iron improved symptoms, functional capacity, and quality of life, but there was no difference in mortality, and results were the same regardless of the presence of anemia. Meanwhile, the Study of Anemia in Heart Failure Trial (STAMINA-HeFT) randomized 319 patients with systolic heart failure with moderate anemia to receive darbepoetin or placebo. Patients in the darbepoetin arm did not demonstrate significant improvement in exercise duration or quality of life, but there was a trend toward lower all-cause mortality or first heart failure hospitalization.[48] With concerns raised by recent clinical trials on the use of these erythropoietin-stimulating agents,[49] large prospective heart failure clinical trials are ongoing to clarify their potential utility.

## OBESITY

Increasing body mass index (BMI) increases the risk of developing heart failure, which could be due to coexisting cardiovascular risk factors in obese subjects. However, BMI is also known to be an independent risk factor for heart failure. This was demonstrated in 5881 patients from the Framingham Heart Study, in whom there was a 5% to 7% increase in risk of heart failure for every unit increase in BMI.[50] In fact, obesity-related cardiomyopathy (adipositas cordis) was described as early as 1818 by Cheyne.[51] There are multiple mechanisms through which obesity can cause heart failure, including left ventricular hypertrophy, diastolic dysfunction, and systolic dysfunction. Although obesity increases the risk of developing heart failure, the same is not true when it comes to prognosis. At the other end of the spectrum, obesity improves the prognosis of patients with advanced heart failure ("obesity paradox"), as demonstrated in a meta-analysis that included 28,209 patients with heart failure.[52] Overweight and obesity were associated with lower all-cause and cardiovascular mortality in this analysis. The reason for this paradox is unclear, but one of the hypotheses is that obese patients may have higher metabolic reserve to tolerate advanced heart failure, which is a catabolic state causing cachexia.[53] Also, low levels of B-type natriuretic peptide have been noted in obese patients.[54]

## DEMENTIA AND DEPRESSION

Both dementia and heart failure are diseases of old age. There is mounting evidence that heart failure could lead to cognitive impairment in the elderly. This was described

even decades ago as "cardiogenic dementia."[55] The possible mechanisms are chronic cerebral hypoperfusion and possible microembolism from the heart. Also, vascular risk factors associated with heart failure are known to cause vascular dementia, which is the second most common form of dementia after Alzheimer dementia. The increased risk of cognitive dysfunction in heart failure was shown in a systematic review that included 17,785 subjects with and without heart failure. The odds ratio for cognitive impairment was 1.62 in patients with heart failure.[56] The prevalence of mild cognitive impairment is much higher in the chronic heart failure population, and was noted in more than 50% of patients.[57] Only scant evidence exists to support that treatment of heart failure may improve cognitive function,[58] and this has to be proved in larger, well-designed studies before the concept is well accepted. Until then, the authors at least recommend regular screening of patients with heart failure for cognitive impairment.

The coprevalence rate of heart failure and depression varies widely depending on the criteria used to diagnose depression and severity of heart failure.[59] In this analysis, clinically significant depression was noted in at least 1 of every 5 patients with heart failure. Many symptoms of heart failure, such as decreased exercise tolerance, sleep disturbances, and weight gain, could lead to depression. Also, neurohormonal activation[60] and chronic inflammation could play a role in the development of depression. In patients with systolic heart failure, major depression was an independent predictor of mortality at 3 months and 1 year. Depressed patients were more than twice as likely to die when compared with patients without depression. Major depression was also associated with increased hospital readmissions.[61] Compliance with diet and medication regimen is extremely important in the management of heart failure, and there is evidence to suggest that depressed patients are 3 times more likely to be noncompliant.[62] Selective serotonin reuptake inhibitors (SSRIs) are clinically preferable to tricyclic antidepressants in patients with heart failure.[63] Although the preliminary results are not encouraging,[64] results from ongoing clinical studies to evaluate the role of SSRIs in the treatment of depression in patients with heart failure is much awaited.[65]

## SUMMARY

Multiple comorbidities are common in patients in heart failure. Some of them could contribute to the underlying development of heart failure, whereas others may lead to disease progression and may be associated with poor prognosis. It is not only important to diagnose these comorbid conditions early, but also vital to treat such conditions appropriately, which may have a huge impact on the primary disease itself. This review has covered the common conditions, but there are multiple other comorbidities beyond the scope of this article. The authors advise that physicians should try treating "patients as a whole" instead of treating the specific disease, and this may require multidisciplinary care.

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