Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction

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Abstract

Heart failure patients are classified by ejection fraction (EF) into distinct groups: heart failure with preserved EF (HFpEF) or heart failure with reduced EF (HFrEF). Although patients with heart failure commonly have multiple comorbidities that complicate management and may adversely affect outcomes, their role in the HFpEF and HFrEF groups is not well-characterized. This review summarizes the role of noncardiac comorbidities in patients with HFpEF versus HFrEF, emphasizing prevalence, underlying pathophysiologic mechanisms, and outcomes. Pulmonary disease, diabetes mellitus, anemia, and obesity tend to be more prevalent in HFpEF patients, but

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renal disease and sleep-disordered breathing burdens are similar. These comorbidities similarly increase morbidity and mortality risk in HFpEF and HFrEF patients. Common pathophysiologic mechanisms include systemic and endomyocardial inflammation with fibrosis. We also discuss implications for clinical care and future HF clinical trial design. The basis for this review was discussions between scientists, clinical trialists, and regulatory representatives at the 10th Global CardioVascular Clinical Trialists Forum.

Keywords

comorbidities; ejection fraction; heart failure

INTRODUCTION

Heart failure (HF) patients often have multiple concomitant diseases that complicate management and may adversely affect outcomes (1,2). Recent data from the Center for Medicare Services demonstrate that 55% of Medicare patients coded with HF have 5 or more chronic comorbidities (3). Data from the European Society of Cardiology Heart Failure Pilot Survey indicate that the majority of chronic HF patients (74%) had at least 1 comorbidity, of which the most common are renal disease, anemia, and diabetes mellitus (DM)(4). In general, more than a quarter of HF patients have comorbid pulmonary or renal dysfunction, which are associated with increased morbidity and mortality in the overall HF population (5–8). Patients are commonly classified by ejection fraction (EF) into heart failure with preserved EF (HFpEF; EF 50%) or heart failure with reduced EF (HFrEF; EF <50%). The role of comorbidities has not been well-characterized in these HF types. In this review, we summarize the role of noncardiac comorbidities in patients with HFpEF versus HFrEF with particular emphasis on prevalence, underlying pathophysiologic mechanisms, and association with outcomes. We focus on chronic obstructive pulmonary disease (COPD), anemia, DM, renal disease, sleep-disordered breathing (SDB), and obesity. We briefly discuss other noncardiac comorbidities, including frailty and arthritis, and highlight the need for future research on these topics, as well as on depression, myopathy, and liver disease. We describe the implications of these data for clinical care and for the design of future HF clinical trials. Cardiac comorbidities including hypertension, coronary artery disease, and atrial fibrillation were recently discussed elsewhere (9) and are beyond the scope of this review. This review is based on discussions between scientists, clinical trialists, and regulatory and industry representatives at the 10th Global CardioVascular Clinical Trialists (CVCT) Forum in Paris, France on December 6, 2013.

Overview of Data Sources

To identify additional relevant articles not discussed at the 10th annual CVCT, we searched MEDLINE (via PubMed) from January 1994 to July 2014 (see Online Appendix for the full search strategy). We used Medical Subject Headings (MeSH) and key words, focusing on the most relevant terms for this topic. We manually searched reference lists of pertinent reviews, including studies and background articles to find any relevant citations that our searches might have missed. We imported all citations into an EndNote X7 database. One

reviewer (J.P.K.) screened and evaluated the retrieved records to select relevant studies. In order to focus on studies with representative patient samples, our search strategy required that publications included more than 500 patients and reported data from multiple sites. Given that entry criteria for clinical trials tend to exclude those with significant comorbidities, we focused on data from large HF registries and cohort studies. We required that the primary papers or supplemental materials included data on noncardiac comorbidities of interest.

In general, the prevalence of comorbidities was high across all studies, as demonstrated in the 3 largest U.S. HF registries (2,10,11), as well as ambulatory HF populations in the United States (12,13), as discussed later in this review. Other world regions demonstrated findings similar to those seen in the United States (14–16). Table 1 presents comorbidity prevalence data from several representative HF registries and epidemiologic cohorts.

HFpEF versus HFrEF: Demographic Differences

Overall, the data suggest that patients hospitalized with HFpEF tend to be 4 to 8 years older than those with HFrEF and are more often female (Table 1). These observations are supported by an analysis from the Framingham Heart Study, which demonstrated that female sex was independently associated with a >2-fold increased risk for HFpEF versus HFrEF (17). Increasing age predicts both HFpEF and HFrEF, but the risk is significantly greater for HFpEF (18). The sex differences in HF phenotype appear largely due to increased HFrEF in men related to previous myocardial infarction (18). Another explanation for these findings relates to a differential response to hypertension in men versus women. Men tend to develop eccentric left ventricular (LV) hypertrophy in response to hypertension, while women tend to develop concentric LV hypertrophy (19). Studies also demonstrate that African Americans have HFpEF less often than HFrEF (2,10,11). These findings are counterintuitive due to the high prevalence of hypertension and LV hypertrophy in this population. The specific reasons for these observations are unknown and require further investigation, but may be related, in part, to ascertainment of the HFpEF diagnosis. It is unclear whether these findings are due to increased complexity in HFpEF detection, particularly in regions where echocardiography or natriuretic peptides are less available. In general, there is a relative paucity of large-scale comparative data regarding the burden of comorbidities in racial and ethnic minority populations with HF (20).

Outcomes Overview

Evidence regarding the outcomes of HFpEF versus HFrEF patients varied in different populations, but overall, the data suggest that HFpEF is associated with substantial morbidity and mortality that approaches or matches that of HFrEF (13,21,22). Interestingly, 1 recent analysis demonstrated that when similar B-type natriuretic peptide (BNP) levels were compared across EF values, the risk for adverse outcomes was similar in HFpEF and HFrEF patients (23). The overall incidence of hospital admission is similar between the 2 groups, but HFpEF patients have a higher incidence of non-HF hospitalizations, while HFrEF patients have a higher incidence of HF hospitalizations (24). Comorbidities, such as COPD, renal disease and DM, are strongly associated with adverse outcomes in HF patients

(25). HFpEF is not merely a disease of old age and multiple comorbidities, but is a distinct entity associated with poor prognosis and severe cardiovascular dysfunction (26,27). However, few studies have explored the differential association between comorbidities and outcomes in HFrEF and HFpEF patients (24,28–30). In general, the increased risk for morbidity and mortality associated with these comorbidities is similar in those with HFpEF and HFrEF.

Pathophysiology

The **Central Illustration** presents pathways linking several comorbidities to disease progression in both HFpEF and HFrEF. These comorbidities interrelate by several common mechanisms, including inflammation and activation of the sympathetic and renin-angiotensin-aldosterone systems (RAAS), as discussed later in this review.

Comorbidities in HFrEF versus HFpEF Patients: Prevalence, Outcomes and Treatments

Chronic Obstructive Pulmonary Disease

COPD occurs in approximately a third of HF patients, with a slightly higher prevalence in HFpEF patients compared with HFrEF patients (5), although the specific rationale for the increased prevalence in HFpEF patients is unclear. Comorbidities such as COPD were suggested to induce a proinflammatory state that causes endothelial and cardiomyocyte dysfunction, with resultant myocardial fibrosis and clinical HFpEF (31). Ongoing smoking was also identified as an independent predictor of HFpEF, but not HFrEF, in epidemiologic studies (18), which supports the inflammatory hypothesis. However, further research is needed because smoking would also be expected to increase risk for coronary events and resultant ischemic cardiomyopathy with reduced EF. An alternative explanation for the close association between COPD and HFpEF involves coupling between impaired LV filling and pulmonary venous changes due to lung parenchymal abnormalities (32). Moreover, HF may result in pulmonary function changes and patient symptoms that mimic COPD. Since they do not have the alternative diagnosis of low EF, patients with preserved EF may be more likely to receive a COPD diagnosis as an explanation for dyspnea (33,34). Despite the potential for bias related to increased COPD diagnosis in HFpEF patients, the consistent observation of increased COPD prevalence in HFpEF patients suggests that concomitant pulmonary and cardiac dysfunction may be particularly important in the preserved EF group.

The primary effect of COPD appears to be increased noncardiovascular mortality during HF hospitalization (6), with similar outcomes in the early period following discharge (35). COPD is associated with increased long-term morbidity (36) and mortality (25). HF patients with COPD are less likely to receive beta-blockers compared with those without COPD (36), possibly due to clinicians' concerns about precipitating bronchoconstriction (33,37,38). The overlapping symptom of dyspnea with both diseases may lead to misapplication of therapy. Given the discordant beta-receptor effects of the different disease treatments, a patient's symptoms and outcome could be adversely affected by the treatment of the comorbid disease. HF patients with COPD also tend to have lower blood pressure, higher creatinine, and underuse of angiotensin converting enzyme (ACE) inhibitors and

mineralocorticoid receptor antagonists (6,35). These characteristics likely contribute to the increased mortality risk associated with COPD in HF patients.

In a recent analysis of the differential association between comorbidities and outcomes in HFrEF and HFpEF patients, COPD was the only comorbidity for which there was a significant interaction (p = 0.01) with EF group and outcomes. COPD contributed to a higher hazard for mortality in patients with HFpEF compared with HFrEF (24). Notably, COPD was an independent predictor of mortality in both groups. These between-group differences are supported by findings from another small study where COPD was highly predictive of death in those with HFpEF, but not HFrEF(39). Data from the Framingham Study support a potential causal role between airflow limitation and HFpEF, but not HFrEF (40). The link between even mild airflow limitation and abnormal LV diastolic filling (41) may explain, in part, the stronger association between COPD and HFpEF.

COPD treatment recommendations focus on prevention, including vaccinations and smoking cessation. Pending randomized trial data, chronic therapy with long-acting anticholinergics is recommended preferentially over inhaled beta-agonists (37). Early intervention in the setting of exacerbations and a multidisciplinary approach may be indicated to balance therapies for both diseases (33). Intravascular volume management may represent an area of particular focus, with the goal of minimizing LV filling pressures and pulmonary interstitial fluid, even in the presence of agents that adversely affect volume status, such as corticosteroids. With respect to beta-blocker use, there is a mechanistic rationale to consider the preferential use of cardioselective agents, such as metoprolol succinate or bisoprolol, rather than carvedilol (37). Evidence from several small studies supports this approach (38,42,43). However, observational studies suggested that there is no differential benefit with cardioselective agents compared with non-cardioselective agents (36,44). Thus, adequately powered prospective studies are needed to investigate the optimal beta-blocker approach in HF patients with COPD.

Anemia

Comorbid anemia is more frequent in HFpEF patients than in HFrEF patients. Prevalence reports vary depending on the specific anemia definition used, but the trends are comparable. Contemporary studies tend to use the WHO classification of anemia as hemoglobin <13 g/dL in men and <12 g/dL in women (24). In the Get With The Guidelines (GWTG) Registry, there was an association between higher EF and increased prevalence of anemia (11). The prevalence of anemia was 22% in patients with an EF 50%, 20% with EF 40% to 49%, and 14% with EF <40%, and there were also sex-specific differences (45). The prevalence of anemia tended to be higher in women in the setting of either reduced or preserved EF. These findings are supported by an analysis from the Organized Program to Initiate Lifesaving Treatment in Patients with Heart Failure (OPTIMIZE-HF), which showed that HF patients (46) with low hemoglobin were older, more often female, and had preserved systolic function. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program, lower hemoglobin was associated with higher EF (47). Furthermore, female sex, DM, and worse renal function were several of the strongest predictors of anemia. These findings suggest a complex relationship between EF

and anemia that likely involves inflammation, hemodilution, bone marrow deficiency, nutritional and metabolic factors, and nephropathy (48). In addition, studies suggest that anemia may increase cardiac output and reduce systemic resistance through nitric oxide-mediated vasodilation (49–51).

Anemia is associated with increased morbidity and mortality in HF patients (52–55). Potential explanations include adverse LV remodeling effects (56), increased neurohormonal and inflammatory cytokines (49), adverse cardiorenal effects (57), and the association with poor nutritional status (47).

Multiple previous studies demonstrated that there is no interaction between EF and outcomes related to anemia status. For instance, in 1 study, anemia was associated with an ~25% increased mortality risk in HFrEF and HFpEF patients (24). Similarly, Felker et al. demonstrated that anemia was independently associated with mortality, and there was no evidence of an interaction with systolic function (28). A recent analysis from the Study of the Effects of Nebivolol Intervention on OUtcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial, which included HF patients irrespective of LVEF, extends these results to morbidity endpoints (58). Anemic patients were at increased risk for the composite of all-cause mortality or cardiovascular hospitalization and mortality, or HF hospitalization, irrespective of underlying HFrEF or HFpEF. Notably, the overall representation of patients with LVEF >50% in SENIORS was modest. The inability to demonstrate a differential relationship between anemia and outcomes in those with HFpEF versus HFrEF may be related, in part, to the number of different etiologies for anemia.

Given the neutral results of recent trials targeting anemia with erythropoietin-stimulating agents in HFrEF patients (59), the optimal treatment of underlying anemia in HF requires further study. Given iron deficiency's relation to anemia status and its potential as a treatable target, this area is of particular interest (60). The prevalence of iron deficiency in HF patients is even greater than the prevalence of clinical anemia. Furthermore, iron deficiency may impact outcomes in HFpEF and HFrEF independent of anemia (61). Iron deficiency leads to worsening HF symptoms, HF progression, and poor outcomes (62). Ongoing and future studies will explore the effect of iron replacement in both HFpEF and HFrEF patients.

Diabetes mellitus

Registry and observational data consistently demonstrate the presence of DM in approximately 40% of HFrEF patients versus 45% of HFpEF patients (2,10,24). DM is associated with the development of myocardial dysfunction, even in the absence of significant coronary artery disease or hypertension (i.e., diabetic cardiomyopathy) (63). Myocardial changes result from insulin resistance and hyperglycemia through mechanisms including increased free fatty acid concentration, mitochondrial dysfunction, abnormal calcium homeostasis, RAAS activation, oxidative stress, and advanced glycation endproducts (63,64). Development of systolic dysfunction may be preceded by myocardial fibrosis and collagen deposition, resulting in diastolic dysfunction (65,66). Importantly, the relationship between DM and HF appears bidirectional, with HF also increasingly the risk for subsequent DM (67). The mechanisms underlying the effect of HF on incident DM or on

DM progression are not completely known, but may involve sympathetic and RAAS activation, with subsequent lipolysis and increased cytokine production (68,69).

DM is associated with increased morbidity and mortality in chronic HF patients (29,70), but its influence as a predictor of long-term outcomes after HF hospitalization is less well-defined. Several acute HF registries have suggested that DM patients are at increased risk for mortality (71,72). However, in the OPTIMIZE-HF registry, DM patients were at increased short-term risk for rehospitalization, but at similar risk for in-hospital and short-term mortality (73). Similarly, in the EVEREST study, DM was associated with increased HF rehospitalization, but not all-cause mortality (74). DM may complicate the clinical course of HF patients through mechanisms including electrolyte disturbances, increased infection risk, and altered medication absorption, as well as through ischemia and other direct adverse effects on the myocardium (1).

The impact of DM in patients with HFpEF versus HFrEF is not well-defined. One recent analysis demonstrated that the point estimate of hazard for mortality associated with DM was greater in HFrEF patients than HFpEF patients, but formal statistical testing did not demonstrate an interaction between the DM and EF groups (24). An analysis from CHARM demonstrated that DM was associated with similarly increased risk for mortality in HFpEF and HFrEF patients (29). In contrast, DM was associated with increased cardiovascular death or HF hospitalization in HFpEF patients compared with HFrEF patients. This difference was due to an increased risk for HF hospitalization associated with DM in HFpEF patients. However, in an analysis from OPTIMIZE-HF, HFpEF patients with DM were not at increased risk for 60-day to 90-day mortality or rehospitalization, in contrast to the increased risk associated with DM in HFrEF patients (interaction p value = 0.0012) (73). Thus, the impact of DM on outcomes in different EF groups is not entirely clear, but may be related to predominant effects on long-term HF rehospitalization, rather than mortality. It is also possible that there are differential effects in patients who had a recent HF hospitalization compared to those with chronic stable HF. The optimal treatment of comorbid diabetes in HF patients is unclear. Several classes of antidiabetic agents such as thiazolidinediones (TZDs) and dipeptidyl peptidase 4 (DPP-4) inhibitors were shown to be associated with increased HF risk (75,76). Alternatively, ongoing studies are investigating whether antidiabetic agents, such as glucagon-like peptide-1 (GLP-1) agonists may improve outcomes in HF patients via benefits on cardiac metabolism (FIGHT; ClinicalTrials.gov Identifier: NCT01800968). Despite metformin's package label warning about its use in HF patients, the occurrence of lactic acidosis is exceedingly low in clinical practice and recent observational data (77) suggest possible benefits on clinical outcomes associated with its use in HF. Ongoing large-scale diabetes studies investigating cardiovascular outcomes, including HF, will inform the management of DM in these patients (EXSCEL; ClinicalTrials.gov Identifier: NCT01144338). Pending the results of these studies, the treatment of DM in patients with HF should preferentially use agents with favorable safety profiles in patients with cardiovascular disease (78). Given the key roles of obesity and metabolic syndrome in the underlying pathophysiology (79), they may also represent important targets in DM patients with HF, particularly those with HFpEF.

Renal Dysfunction

Registry data indicate a similar extent of renal insufficiency in HF patients across the EF spectrum (2,11). The reports vary significantly in different datasets, depending on the specific criteria used, but the figures are similar in patients with HFrEF and HFpEF. The interdependence of heart and kidney dysfunction is captured by the recently described "cardiorenal syndrome" (7,80). Renal dysfunction may worsen HF through multiple mechanisms, including increased sodium and fluid retention, anemia, inflammation, and uremic toxins, as well as RAAS and sympathetic activation. A recent analysis demonstrated a significant association of an increase in urinary markers of renal dysfunction with the risk for new onset HFpEF, but not HFrEF (81). Conversely, HF may lead to renal dysfunction and cardiorenal syndrome through mechanisms related to low cardiac output, accelerated atherosclerosis, inflammation, and increased venous pressure. The multitude of mechanisms that may result in renal dysfunction may, in part, explain its similar prevalence in HFpEF and HFrEF patients. For instance, HFpEF patients may be more likely to have underlying renal dysfunction related to diabetic nephropathy, while atherosclerosis may contribute to renal function changes in patients with HFrEF due to ischemic/nephrosclerotic etiology (16).

Renal dysfunction is an established risk factor for adverse events in patients with HF (82,83). The ADHERE registry revealed that more than half of acute HF patients had at least moderate renal insufficiency on admission, which was associated with increased mortality (84). Importantly, recent data have demonstrated that the association between renal dysfunction and poor outcomes is complex. For instance, *transient* worsening renal function during acute HF hospitalization may not affect post-discharge outcomes (85,86) and aggressive fluid removal leading to hemoconcentration may be associated with lower mortality, despite evidence of worsening renal function (86). Thus, the underlying cause and trajectory of renal dysfunction may play a role in determining the impact on subsequent outcomes. Notably, HF patients with renal dysfunction tend to be older, with lower blood pressures, and higher plasma BNP levels (87). Kidney disease also affects guideline-directed medical therapy in HFrEF patients due to concerns about worsening GFR and hyperkalemia (87).

In addition to similar prevalence in HFrEF and HFpEF patients, the increased risk associated with the comorbidity is similar in both patient groups. Ather et al. demonstrated that renal insufficiency was associated with an approximately 25–30% increase in mortality (24). In a community-based HF patient cohort, worsening estimated glomerular filtration rate was associated with a graded increase in the risk for death and hospitalization, with similar findings in those with HFpEF and HFrEF(30).

The implications of renal insufficiency for treatment of HFpEF and HFrEF patients are severalfold. First, despite concerns related to hyperkalemia, therapies such as ACE inhibitors should be initiated and monitored in accordance with current guidelines (88–89). Recent data suggest that worsening renal function while on an RAAS inhibitor has a better prognosis than on placebo, suggesting that a RAAS inhibitor should not necessarily be discontinued in patients who develop worsening renal function (90). Renal insufficiency may also have important implications related to the management of volume status and

titration of diuretic therapies. For instance, with more severe underlying renal disease, it may be necessary to consider alternative loop diuretics, such as torsemide, or the addition of a thiazide diuretic (91).

Sleep-Disordered Breathing

In recent years, the prevalence and impact of SDB in HF patients is increasingly recognized and multiple ongoing registries are collecting data in this regard (SchlaHF; ClinicalTrials.gov Identifier: NCT01500759). Prior studies demonstrated that SDB is prevalent in both those with HFpEF and those with HFrEF, occurring in upwards of 50 to 80% of patients (92–94). Two primary types of SDB occur and may coexist in HF patients: obstructive sleep apnea (OSA) and central sleep apnea (CSA). HFpEF patients tend to more often have OSA, in comparison to HFrEF patients who tend to have CSA to a greater extent (95). Women with HF are less likely to have SDB compared with men, and its severity may be lower (96). Risk factors for the development of both types of SDB in HF patients include male sex and increased age (97,98). Elevated body mass index is an additional risk factor for OSA, while severe LV impairment and atrial fibrillation increase the likelihood of CSA (97,99). SDB is proinflammatory, with effects on oxidative stress and sympathetic activation (94).

SDB has been associated with increased morbidity and mortality in the general population (100–102); however, its impact on HF patient outcomes is less well-defined. The majority of studies in HF patients focused on HFrEF patients, where SDB was an independent predictor of cardiac readmission (103). In 164 patients with chronic stable HFrEF, untreated OSA was associated with increased mortality on multivariable analysis (104). CSA was also shown to be a predictor of mortality in HFrEF (105). However, not all studies demonstrated a relationship between SDB and outcomes in HFrEF patients (106,107).

To our knowledge, no previous studies scrutinized a differential association between SDB and outcomes in HFrEF versus HFpEF patients. Studies to date in HFpEF patients generally assessed <200 patients, with the emphasis on describing prevalence and patient characteristics, rather than outcomes (95,108). Thus, future research is required to explore the impact of SDB on outcomes in HFpEF. SDB may represent a particularly important comorbidity in HFpEF patients, given the high prevalence of obesity in this patient population.

The primary treatment for OSA is nocturnal continuous positive airway pressure (CPAP). Observational studies in HF patients with OSA suggested potential benefits with CPAP on clinical outcomes (109), yet large-scale randomized studies are needed. The role of CPAP in CSA is even less well-defined. The largest randomized, prospective study of HF patients with CSA (N = 258) found no survival benefit with CPAP, despite improvements in EF and functional status (110). Compared with CPAP devices, minute ventilation-targeted adaptive servo-ventilation (ASV) may treat both CSA and OSA with improved tolerability. Studies have demonstrated benefits on surrogate endpoints with ASV in HF patients (111,112). Survival benefits with ASV in HF patients have not been demonstrated, and randomized trials are ongoing (SERVE-HF and CAT-HF; ClinicalTrials.gov Identifiers: NCT00733343, NCT01953874).

Other Comorbidities

Obesity is common in the general HF population with a higher prevalence in HFpEF patients (Table 1). While increased body weight has been associated with improved outcomes in cardiovascular disease populations (113), recent reports discussed a balanced reappraisal of this obesity paradox (114,115). A higher weight may be associated with better outcomes compared with HF patients with cardiac cachexia and/or nutritional deficiencies. Potential mechanisms for improved outcomes associated with obesity include increased metabolic reserve and lipoprotein pools to serve as scavengers for circulating endotoxins. However, the associations between obesity and metabolic syndrome, glucose intolerance, and diabetes are likely to explain, in part, the link between increased body weight and adverse events in certain circumstances. For instance, a recent study in 4,109 HFpEF patients found a U-shaped relationship between BMI and adverse clinical events. BMI <23.5 kg/m^2 or ≥35 kg/m^2 were each associated with a 27% increase in death or cardiovascular hospitalization, compared with the reference group BMI of 26.5 to 30.9 kg/m^2 (116). Future studies are needed to assess whether treatment strategies targeting appropriate weight gain or weight reduction can improve outcomes in both HFpEF and HFrEF patients.

Additional important comorbidities in HF patients include frailty and arthritis (117). Frailty, limited mobility, and fall risk are increasingly recognized as important predictors of outcomes in HF patients (118). Osteoarthritis is of particular interest, given the inflammatory hypothesis linking comorbidities and adverse cardiovascular outcomes (119). Furthermore, NSAID treatment for osteoarthritis may have direct consequences on fluid retention and the precipitation of acute HF. There is a need for future research on these topics as well as on depression, myopathy, and liver disease, with respect to implications for the management and outcomes of HFpEF and HFrEF patients.

Clinical Practice and Implications for Future Trial Design

Although the presence of multiple comorbid diseases is almost universal in clinical practice, HF guidelines provide little discussion of this, and the evidence base is sparse and mostly observational. Compared to HFrEF patients, those with HFpEF tend to have an increased burden of COPD, DM, and anemia, which are associated with increased morbidity and mortality. Because the development of novel HF therapies has slowed in recent years and most contemporary HF trials have failed to improve outcomes above standard medical therapy (120,121), we suggest the need for a critical reappraisal of treatment strategies in HF where clinicians target comorbidities, in addition to targeting the underlying cardiac dysfunction (Table 2). This approach may be particularly relevant in HFpEF patients where there are no available therapies to reduce the substantial morbidity and mortality. In addition, on the basis of the recent data discussed earlier, improved management of specific comorbidities in HFpEF patients may have an even greater impact than in HFrEF. Most studies to date targeting comorbidities in HF patients focused on the HFrEF population, with few interventions on comorbidities empirically evaluated in HFpEF patients. Given that many of these conditions are closely interrelated and may potentiate each other, targeting comorbidities may represent an important component in the comprehensive management of HF patients.

Another major clinical implication of these data relates to polypharmacy, particularly in the elderly, in whom the prevalence of HF rises sharply. Elderly patients may exhibit variable responses to standard medical HF therapy and are also more prone to experience adverse effects. As the elderly also have more comorbidities requiring specific therapies, polypharmacy is commonplace. Medications with opposing actions may be used simultaneously (e.g., inhaled beta-agonists and beta-blockers) such that medications for non-HF comorbidities may exacerbate HF and vice versa. In general, polypharmacy increases the potential for drug interactions and reduces patients' compliance. Moreover, frailty and cognitive impairment are more common among elderly HF patients and represent additional risks for nonadherence.

Data on the specific role of polypharmacy in HFrEF versus HFpEF are lacking. Given the greater burden of comorbidities in HFpEF, it is, however, reasonable to assume that the negative impact of polypharmacy is at least as great in HFpEF compared with HFrEF. At the same time, HF trials that established morbidity and mortality benefits were predominantly executed in nonelderly cohorts. Assumption of similar efficacy in geriatric populations is mostly on the basis of extrapolation of these data, but the true risk-benefit ratio may be less favorable.

These observations also may have important implications for future HF trial design. As the clinical trial landscape transitions towards more pragmatic trials with broad entry criteria, in some circumstances, study populations may (and perhaps, should) increasingly include those with multiple comorbid diseases. Noncardiologists managing HF patients cite comorbidity and lack of generalizability of prior trials to comorbid patients as a "reason" for not applying standard therapies. Improved generalizability of trial results could translate into increased uptake of evidence-based treatments for both HF and comorbid diseases. While this approach may be possible in HFrEF, given the heterogeneity of the patient population, broad entry criteria for trials in HFpEF may be more likely to fail. Strategies to promote success include use of natriuretic peptide levels for entry criteria, as highlighted by the results of the recent TOPCAT study (122). Importantly, data suggest that the use of different threshold levels for natriuretic peptides may be appropriate in HFrEF versus HFpEF patients, as well as in those with obesity and renal dysfunction (123). Considerations for trial design related to comorbidities are summarized in Figure 1. Importantly, the inclusion of patients with comorbidities in clinical trials may require intensified monitoring and safety evaluations. For instance, there are notable comorbidity-specific adverse effects associated with certain medications (e.g., hyperkalemia with RAAS inhibition in renal dysfunction patients). Finally, given the recent lack of success in HF clinical trials using add-on HF-directed therapies (e.g., direct renin inhibitors (124)), another potential trial approach is to specifically target underlying comorbidities in order to improve overall patient outcomes.

Conclusions

Compared with HFrEF, patients with HFpEF have an increased burden of COPD, DM, anemia, and obesity, but a similarly high prevalence of renal disease and SDB. In general, the increased risk for morbidity and mortality associated with these comorbidities is similar in those with HFpEF and HFrEF. Careful attention to the diagnosis and management of

specific comorbidities in HF patients may help to improve patient outcomes, but further observational and interventional research are urgently required, particularly as noncardiac comorbidity is almost universal in the typical heart failure population.

Acknowledgments

ABBREVIATIONS

COPD	chronic obstructive pulmonary disease
DM	diabetes mellitus
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
SDB	sleep-disordered breathing

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APPENDIX

Appendix

Medline (via PubMed) search strategy.

| Search	Query	Items found
#2	Search "heart failure"[MeSH Terms] OR "heart failure"[TIAB]	139194
#10	Search "preserved ejection fraction"[tiab]	983
#11	Search #2 AND #10	826
#13	Search "reduced ejection fraction"[tiab]	808
#14	Search #2 AND #13	521
#15	Search #14 OR #11	1205
#16	Search (#15) AND ("1994/01/01"[Date - Publication] : "3000"[Date - Publication])	1167
#19	Search #16 NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	1126
#21	Search "pulmonary disease, chronic obstructive"[MeSH Terms] OR "chronic obstructive pulmonary disease"[tiab] OR "COPD"[tiab]	53449
#25	Search "diabetes mellitus"[MeSH Terms] OR "diabetes"[tiab]	439784
#28	Search "sleep apnea syndromes"[MeSH Terms] OR "sleep apnea"[tiab] OR "sleep disordered breathing"[tiab] OR "SDB"[tiab]	29082
#30	Search "kidney diseases"[MeSH Terms] OR kidney disease*[tiab] OR renal disease*[tiab]	428081
#32	Search "anaemia"[tiab] OR "anemia"[MeSH Terms] OR "anemia"[tiab]	179314
#34	Search "obesity"[MeSH Terms] OR "obesity"[tiab]	195364
#36	Search "comorbidity"[MeSH Terms] OR "comorbidity"[tiab] OR "comorbidities" [tiab]	105817
#37	Search #21 OR #25 OR #28 OR #30 OR #32 OR #34 OR #36	1280940
#38	Search #19 AND #37	283
#39	Search #19 AND #37 Filters: English	266
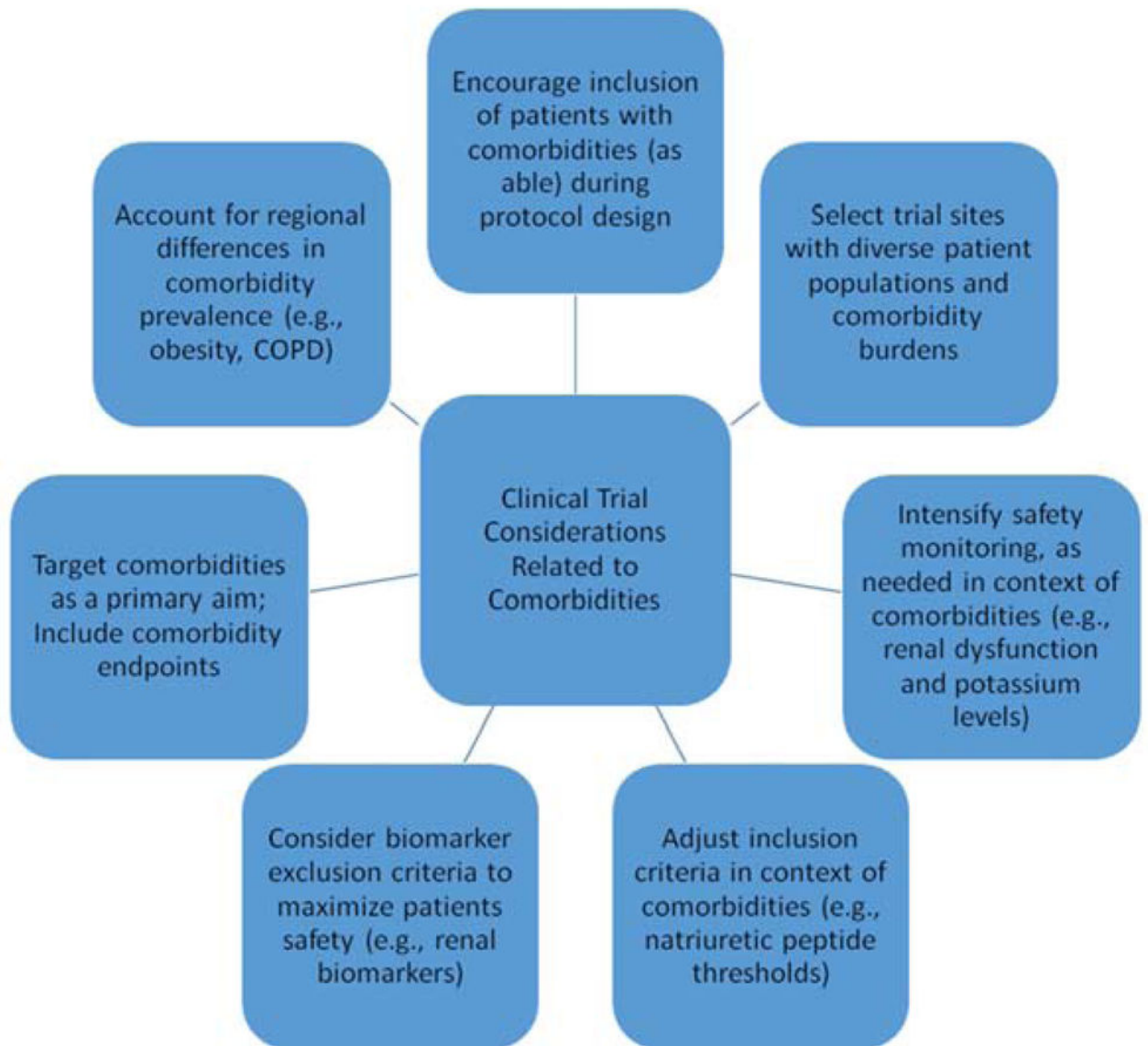
Figure 1. Clinical Trial Considerations Related to Comorbidities
Trial protocols should consider feasibility of encouraging the inclusion of patients with comorbidities (as able). Trial sites should be selected on the basis, in part, of the comorbidity burden of the patient populations. Intensified safety monitoring may be needed in the context of comorbidities. Study entry criteria may need to be adjusted to acknowledge differences in biomarker thresholds in the context of comorbidities such as obesity and/or renal function. Exclusionary biomarker criteria (e.g., renal biomarkers) may offer mechanisms to support patient safety. As able, consider targeting comorbidities as a primary intervention and include comorbidity-specific trial endpoints (e.g., dyspnea relief and beta-blocker usage in context of COPD). Trialists should also take into account regional differences in the prevalence of comorbidities when performing sample size calculations and designing trials (e.g., differential event rates in the presence of comorbid diseases).

Associations Between Preserved Ejection Fraction (HFpEF) and Reduced Ejection Fraction (HFrEF), With Comorbidities
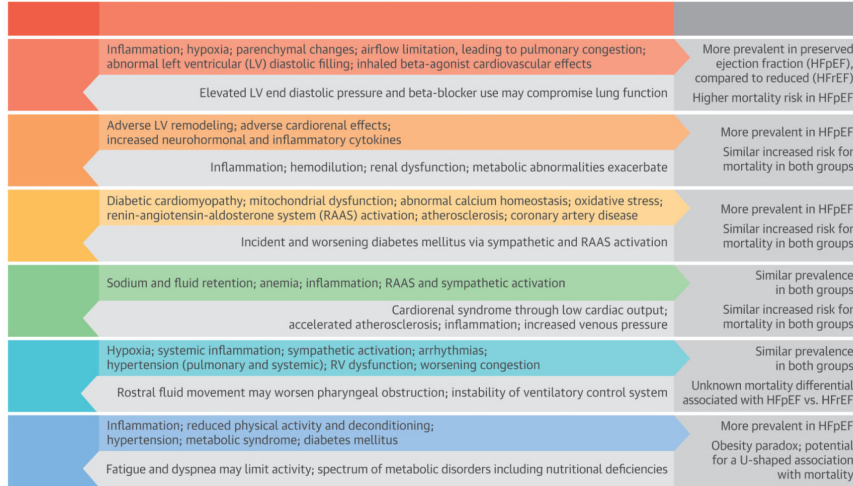
Figure 2. Central Illustration. Associations Between Heart Failure and Comorbidities

Pathways linking several common comorbidities to disease progression in both HFpEF and HFrEF are presented and factors exacerbating other comorbid conditions are highlighted. These comorbidities are interrelated by several common mechanisms, including inflammation and worsening congestion, as well as by sympathetic and renin-angiotensin aldosterone system activation. Heart failure influences each of the comorbidities, demonstrating the bidirectional association.

Abbreviations: COPD = chronic obstructive pulmonary disease; CV = cardiovascular; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system; RV = right ventricular.

Table 1

Demographics and Prevalence of Noncardiovascular Comorbidities in Patients With Acute Heart Failure

	ADHERE Registry (2)		OPTIMIZE-HF Registry (10)		GWTG Registry (11)†		Ather S et al. (24)		Olmsted County 1987–2001		Olmsted County 2003–2005	
	Reduced N = 25,865 50 %	Preserved N = 26,322 50 %	LVSD N = 20,118 49%	Preserved N = 21,149 51%	EF <40% N = 55,083 50%	EF 50% N = 40,354 36%	Reduced N = 6,599 70%	Preserved N = 2843 30%	Reduced N = 2,429 53%	Preserved N = 2167 47%	Reduced N = 248 45%	Preserved N = 308 55%
Population	Acute HF, 274 hospitals*, 2001–2004		Acute HF, 259 hospitals, 2003–2004		Acute HF, 275 hospitals, 2005–2010		Ambulatory HF, US Veterans, 2000–2002		Acute HF, 1987–2001		Inpatients and outpatients with HF	
Age, yrs.	70 ± 14	74 ± 13	70 ± 14	75 ± 13	70 (58– 80)	78 (67– 85)	70 ± 10	71 ± 10	72 ± 12	74 ± 14	73 ± 14	77 ± 13
Female	40%	62%	38%	62%	36%	63%	4%	9%	35%	56%	42%	57%
African American	22%	17%	21%	15%	25%	16%	13%	10%	-	-	-	-
Medical History												
COPD or asthma	27%	31%	-	-	27%	33%	27%	34%	-	-	30%	38%
Renal insufficiency	26%	26%	-	-	48%	52%	52%	49%	-	-	-	-
Anemia	-	-	-	-	14%	22%	28%	33%	-	-	49%	53%
Diabetes mellitus	40%	45%	24% non-insulin/15% Insulin	26% non-insulin/17% insulin	22% oral therapy/18% insulin	24% oral therapy/22% insulin	40%	45%	34%	33%	38%	36%
Obesity (%)or body weight, kg	-	-	78.5 (65.8– 94.0)	78.9 (64.0– 97.5)	25%	33%	35%	51%	36%	41%	-	-
Laboratory Data												
BMI, kg/m²	-	-	-	-	-	-	-	-	28.6 ± 7.0	29.7 ± 7.8	29.1 ± 7.8	29.6 ± 7.5
Hemoglobin, g/dL	-	-	12.5 ± 2.0	11.9 ± 2.0	12.4 (11– 13.8)	11.5 (10.2– 12.9)	-	-	12.5 ± 2.0	11.8 ± 2.1	-	-
Creatinine, mg/dL	1.6 ± 1.3	1.7 ± 1.5	1.4 (1.1–1.9)	1.3 (1.0– 1.8)	1.3 (1– 1.8)	1.3 (1– 1.9)	-	-	1.6 ± 1.0	1.6 ± 1.1	-	-

Presented as mean ± standard deviation, median (interquartile range) or %.

*
274 hospitals included in the analysis cited.

†
Patients with an LVEF between 40–49% were excluded from this table.

Abbreviations: ADHERE = Acute Decompensated Heart Failure National Registry; BMI = body mass index; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; GWTG = Get With The Guidelines; HF = heart failure; LVSD = left ventricular systolic dysfunction; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure..

Table 2

Treatments for comorbidities in Patients With HFpEF and Those With HFrEF

Comorbidity	Recommendations / Comments
COPD	• Emphasis on prevention (e.g., vaccinations, smoking cessation).
	• Consider preferential use of inhaled anticholinergics over beta-agonists pending definitive clinical trials.
	• Early intervention in the setting of exacerbations of either disease.
	• Multidisciplinary management with cardiology and pulmonary.
	• Volume optimization may be particularly important in these patients.
	• Preferential use of cardioselective beta-blockers (metoprolol succinate or bisoprolol) pending additional prospective trials
Anemia	• Thorough evaluation and treatment of underlying cause(s) of anemia.
	• Management of contributing factors such as renal insufficiency and diabetes.
	• Broad application of erythropoietin stimulating agents in HFrEF is not supported by previous studies.
	• Iron deficiency may represent a relevant treatment target.
Diabetes mellitus	• Avoid diabetic therapies that have been associated with increased HF risk (e.g., TZDs, DPP-4 inhibitors).
	• Careful monitoring for other diabetic agents (e.g., metformin) in the setting of HF decompensation and renal dysfunction.
	• Preferential use of metformin may be reasonable pending prospective trials given observational data suggesting benefits for clinical outcomes.
Renal dysfunction	• Appropriate initiation of ACE-inhibitors/ARBs and MRAs, as able, with careful clinical monitoring.
	• Volume status may be a key target of intervention.
	• Alternative loop diuretics (e.g., torsemide) may be indicated.
	• Multidisciplinary management with cardiology and nephrology.
Sleep disordered breathing	• CPAP or ASV device therapy may provide benefits on clinical status (outcomes benefit undefined).

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ASV = adaptive servo-ventilation; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; DPP-4 = dipeptidyl peptidase 4; MRA = mineralocorticoid receptor antagonist; TZDs = thiazolidinediones.