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COMORBIDITIES IN HEART FAILURE: HOW TO OPTIMIZE THE TREATMENT?

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In most patients, and particularly in elderly patients, heart failure (HF) is accompanied by a range of comorbidities that play an integral role in its progression and response to treatment. Comorbidity is defined as a chronic condition that coexists in an individual with another condition that is being described. A distinction is made between noncardiac comorbidities and cardiac conditions that are directly related to the presence of HF such as arrhythmias as well as conditions that precede and contribute to its aetiology such as hypertension, diabetes mellitus, and hyperlipidemia. In this article, we will initially focus on noncardiac comorbidities and discuss the general problem of comorbidity in HF. Then we will examine specific comorbidities and how to manage patients with HF in the best way. Finally, we will consider the problem of multidrug therapy when managing patients with comorbidities.

Introduction

Heart failure (HF) represents one of the major public health problems faced by healthcare systems worldwide, and continues to grow largely because of the increasing age of the population. HF is the leading diagnosis at hospital discharge for patients 65 years or older, accounting for more than 600,000 Medicare hospital discharges annually. Among more than 1 million patients hospitalized annually for HF in the USA, over 80 % are 65 years or older, and more than 50 % are 75 years or older. The cost of managing HF is increasing mainly as a consequence of frequent and prolonged hospitalization [1].

Comorbidity refers to chronic conditions that coexist alongside the condition that is being described. Comorbidities in heart failure may be divided into noncardiac comorbidities and cardiac conditions that are directly related to the presence of chronic heart failure (CHF) such as arrhythmias, hypertension, and hyperlipidemia. The first part of this article will focus on noncardiac comorbidities in systolic heart failure and their management as they are very common and contribute to complexity of management of CHF. Additionally, new topics such as diabetes mellitus and physical activity are introduced. This article also examines the complex interactions among noncardiac comorbidities in heart

failure (Figure 1) [2] and summarizes the consequences and available interventions for noncardiac comorbidities in heart failure (Table 1). Literature search was conducted on PubMed with search criteria of «systolic heart failure» AND «COPD», «sleep disordered breathing», «renal dysfunction», «anaemia», «diabetes», «cognitive dysfunction/impairment», «depression» or «arthritis», excluding «heart failure with preserved ejection fraction».

Discussion

The top 10 most common noncardiac conditions were COPD/bronchiectasis (26 %), osteoarthritis (16 %), chronic respiratory failure or other lower respiratory disease excluding COPD/bronchiectasis (14 %), thyroid disease (14 %), Alzheimer's disease/dementia (9 %), depression (8 %), chronic renal failure (7 %), asthma (5 %), osteoporosis (5 %) and anxiety (3 %). The risk of hospitalisation and potentially preventable hospitalisations strongly increased with the number of chronic conditions (figure 1) [2]. After controlling for demographic factors and other diagnoses, comorbidities that were associated consistently with higher risks for CHF hospitalisations and mortality included COPD/bronchiectasis, renal failure, diabetes, depression and lower respiratory diseases. Several reasons may explain why older patients with CHF with greater comorbidity may experience

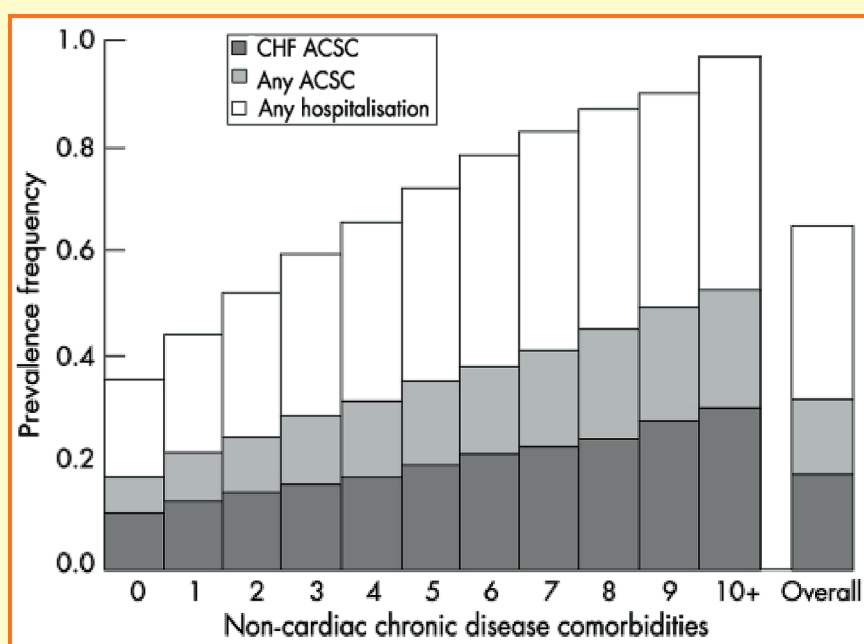


Figure 1. The risk of hospitalisation and potentially preventable hospitalisations strongly increased with the number of chronic conditions (Joel B Braunstein, Gerard F Anderson, Gary Gerstenblith, Wendy Weller, Marlene Niefeld, Robert Herbert and Albert W Wu. Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. Journal of the American College of Cardiology, 2003, Vol. 42, Issue 7, pp. 1226-1233 [<https://www.sciencedirect.com/science/article/pii/S0735109703009471>]).

more adverse events that lead to preventable hospitalisations. These include underutilisation of effective CHF treatments in the presence of other conditions because of safety concerns (eg, use of β -blockers in asthma or ACE inhibitors in renal insufficiency), patient nonadherence to or inability to recall complex medication regimens, inadequate postdischarge care, failed social support and failure to promptly seek medical attention during symptom recurrence.

In the patient with CHF with complex comorbidities, physicians typically face the challenge of managing not a single condition but multiple conditions requiring multiple drugs. A recent study of the chronic drugs prescribed at discharge to patients in the US aged ≥ 65 years hospitalised for CHF revealed that the mean number of drugs was 6.8, representing 10.1 daily doses. Unfortunately, little evidence is available to guide this inevitable polypharmacotherapy in patients with CHF and multiple comorbidities. Typically, most CHF trials, either implicitly or explicitly, excluded older patients and patients with multiple comorbidities. In addition, some trials implement run-in periods to assess tolerance to regimens – an approach that may constrain the applicability of the results. Given the lack of data, how should one approach polypharmacy in CHF? Collaborative disease management programmes that include the careful review of drug lists have been shown to reduce hospital admission rates and reduce the costs of care. Whenever possible, patients with CHF with multiple competing comorbidities and polypharmacy, need to be enrolled in such programmes. Regardless of the availability of disease

management programmes, clinicians need to have systems in place to review medication lists carefully at every visit of a patient, with the goal of eliminating drugs that are not known to provide a clear benefit. When initiating new medications, particular attention needs to be paid to the possibility of adverse drug interactions. In treating coexisting conditions, many commonly used drugs need to be avoided whenever possible in patients with HF, based on known pharmacological principles and recommendations from guidelines.

In conclusion of this part, non cardiac comorbidity frequently complicates CHF care particularly in elderly patients with CHF. Indeed, these are the patients most likely encountered in clinical practice. Underrepresentation of patients with comorbidities in large CHF clinical trials makes generalisation of trial findings to these patients somewhat difficult. Clinical research must adapt to ensure its relevance, and trials need to include not just young patients with systolic dysfunction and little comorbidity.

The comorbidities of hypertension, diabetes mellitus, obesity, hyperlipidemia, and metabolic syndrome are common in patients with heart failure (HF) and affect clinical outcomes [4]. Interestingly, although these comorbidities are associated with the development of incident HF in the general population, in patients with established HF, their contributory roles to clinical outcomes are not predictable, and their management is quite challenging. Recent American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines have addressed the role of lifestyle modification, treat-

Table 1. Summary of consequences and interventions for noncardiac comorbidities in CHF

Comorbidity	Consequences	Interventions
COPD	Increased mortality and hospitalization risk in CHF	Management as per COPD guideline Cardio-selective beta-blockers are safe
SDB	Progression of CHF	CPAP Adaptive servo-ventilation Supplemental oxygen controversial Theophylline not recommended Weight loss if obese CRT
Obesity	Risk of HF, diabetes, SDB, cognitive impairment and arthritis	Physical activity Weight loss
Diabetes	Worse cardiovascular outcomes in CHF Cardiovascular disease Diabetic nephropathy	Management as per diabetes guideline Metformin is safe SGLT-2 inhibitors are currently in trial
Renal dysfunction	Cardiorenal syndrome Increased risk of mortality in CHF Renal anemia	Monitoring of renal function and electrolytes for patients on ACE inhibitor/ARB/aldosterone antagonist CRT
Anemia	Increased mortality and hospitalization risk in CHF	EPO not recommended IV iron in iron deficiency
Cognitive dysfunction	Reduced compliance to treatment Increased mortality and hospitalization risk in CHF	Physical activity Weight loss if obese Screening for cognitive impairment CRT
Depression	Reduced compliance to treatment Increased mortality and hospitalization risk in CHF	Screening for depression CBT Physical activity Monitoring of effect of antidepressant
Arthritis	Physical inactivity	COX-2 inhibitors not recommended TNF inhibitor use in rheumatoid arthritis requires close monitoring

Abbreviations: ARB, angiotensin receptor blocker; CBT, cognitive-behavioral therapy; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; SDB, sleep-disordered breathing.

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ment of blood cholesterol, and management of overweight and obesity in the general population and in patients with increased cardiovascular risk, and a recent report from the Eighth Joint National Committee addressed the management of hypertension. However, these guidelines did not specifically address the management of such comorbidities in patients with HF. Similarly, the most recent ACCF/AHA HF practice guidelines in 2013 addressed the overall management of comorbidities in patients with HF in broad terms, but again, specific and detailed recommendations on how to manage hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome are lacking. The intent of this AHA scientific statement is to summarize data relevant to contributory risk and to provide guidance on the management

of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in the development and prognosis of HF to provide recommendations (table 2) and to foster communication between physicians and other healthcare professionals and patients on the management of these comorbidities. Recommendations in this document are based on published studies and the multidisciplinary expertise of the writing group and harmonized with published practice guidelines from the ACC/AHA and other organizations. Comorbidities are frequent and may be overlooked during routine CHF management. They have great impact on hospitalisations and mortality. The most important comorbidities in heart failure patients are renal insufficiency, diabetes mellitus, chronic obstructive pulmonary disease, sleeping disorders like obstructive and central

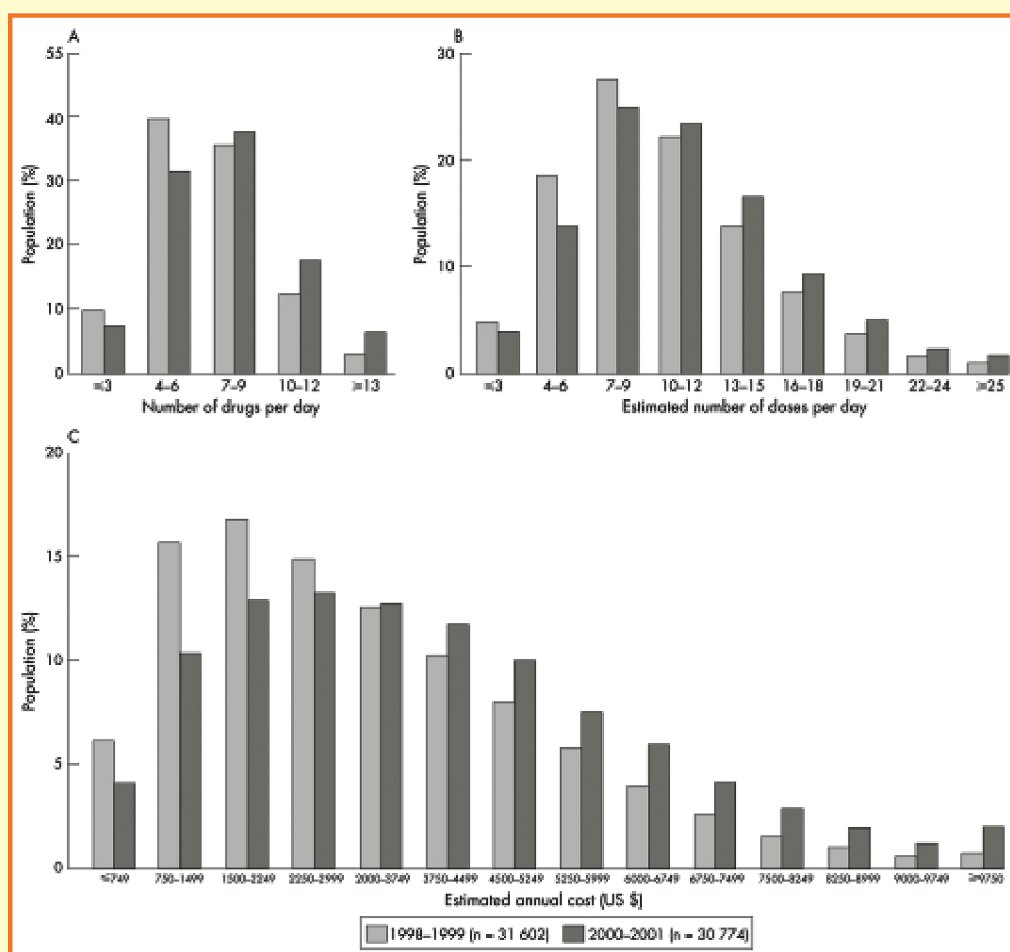


Figure 2. Distribution of the number of longterm prescription medications (A), estimated number of doses per day (B) and estimated annual cost for longterm medications (C) provided at hospital discharge to elderly patients in the US, hospitalised with heart failure [3].

apnea syndrome, and anemia. The most powerful predictor for mortality is renal insufficiency. It's important to recognize the different causes of renal failure. Defining the volume status and the cardiac output is crucial for the guidance of therapy.

The management of diuretic resistance is of special interest and often challenging. Diabetes mellitus is an independent risk factor for heart failure. The benefit of ACE inhibitors and Angiotensin receptor blockers for HF and DM is accepted. The management of Diabetes in HF depends on side-effect profiles of the numerous anti-diabetic drugs. Metformin is safe even in HF patients. Thiazolidinediones should be avoided in NYHA class III/IV because of fluid retention. In COPD patients there is an underuse of beta-blockers and the prediction of mortality with this comorbidity could be partially caused by that.

The principle goal of treatment of sleeping disorders is to avoid hypoxia during night. CPAP therapy improves live quality and HF symptoms. Anemia is often diagnosed, the best therapy – erythropoietin plus iron or iron alone – remains controversial. Iron supplementation without anemia could be an option for better quality of life [6]. To handle all these comorbidities in heart failure patients becomes more and more complex. Heart failure nurses can help us to manage these growing population.

Summary

As addressed in the earlier sections, lifestyle modification and the management of comorbidities remain challenging in patients with HF. Despite intensive lifestyle and medical interventions, the prevention and optimal treatment of hypertension, diabetes mellitus, obesity, and metabolic syndrome have often proved difficult in patients with HF.

- These comorbidities are highly prevalent and are associated with the development of incident HF in the general population.
- However, in patients with established HF, their contributory roles to clinical outcomes are paradoxical; that is, patients with HF with diabetes mellitus, obesity, and hypertension usually are associated with better outcomes than patients without those comorbidities individually, making their management targets and treatment reasons quite challenging.
- Participants in clinical trials receive maximally supportive and evidence-based interventions, yet adherence to standard guideline-directed HF therapy in real-world patients may be limited by the coexistence of chronic HF and comorbid conditions.

	Class I <i>Benefit >>> Risk</i> <i>No additional studies needed</i>	Class IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i>	Class IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i>	Class III <i>Risk ≥ Benefit</i> <i>No additional studies needed</i>
Level A <i>Multiple (3–5) population risk strata evaluated</i> <i>General consistency of direction and magnitude of</i>	Procedure/Treatment SHOULD be performed/administered - Recommendation that procedure or treatment is useful/effective - Sufficient evidence from multiple randomized trials or meta-analyses	IT IS REASONABLE to perform procedure/administer treatment - Recommendation in favor of treatment or procedure being useful/effective - Some conflicting evidence from multiple randomized trials or meta-analyses	IT IS NOT UNREASONABLE to perform procedure/administer treatment - Recommendation's usefulness/efficacy less well established - Greater conflicting evidence from multiple randomized trials or meta-analyses	Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL - Recommendation that procedure or treatment not useful/effective and may be harmful - Sufficient evidence from multiple randomized trials or meta-analyses
Level B <i>Limited (2–3) population risk strata evaluated</i>	Recommendation that procedure or treatment is useful/effective Limited evidence from single randomized trial or non-randomized studies	Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or non-randomized studies	Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or non-randomized studies	Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or nonrandomized studies
Level C <i>Very limited (1–2) population risk strata evaluated</i>	Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard-of-care	Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care	Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care	Recommendation that procedure or treatment not useful/effective and may be harmful Only expert opinion, case studies, or standard-of-care

Table 2. Applying Classification of Recommendations and Level of Evidence Applying Classification of Recommendations and Level of Evidence. «SIZE of TREATMENT EFFECT». (Clyde W. Yancy, Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E. Casey, Mark H. Drazner, Gregg C. Fonarow, Stephen A. Geraci, Tamara Horwich, James L. Januzzi, Mary R. Johnson, Edward K. Kasper, Wayne C. Levy, Frederick A. Masoudi, Patrick E. McBride, John J.V. McMurray, Judith E. Mitchell, Pamela N. Peterson, Barbara Riegel, Flora Sam, Lynne W. Stevenson, W.H. Wilson Tang, Emily J. Tsai, Bruce L. Wilkoff. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2013, Vol. 128, Issue 16, pp. 1810–1852).

- Self-care strategies are limited by HF itself and these competing comorbidities and usually require coordination and different care models.
- Treatment options of these chronic comorbidities in HF are limited and usually without large-scale or definitive clinical trial evidence of improved outcomes in patients with HF.
- Treatment of these comorbidities may be associated with adverse outcomes resulting from overtreatment or side effects of treatment modalities.
- It should be kept in mind that even modest changes in the prevention of comorbidities and risk factors for HF can greatly affect the development of and outcomes in HF.
- These underline the importance of prevention strategies, which probably are the most effective approaches to reduce the burden of HF.
- Furthermore, in recent years, focus has moved from control of a single risk factor to reducing overall cardiovascular risk. Greater benefit may be realized by combining a healthy lifestyle with BP lowering; prevention of diabetes mellitus, insulin resistance, obesity, and ischemic events; and avoidance of cardiotoxic exposure (alcohol, cardiotoxic drugs, and chemotherapy) rather than any single approach alone. Although this approach is likely to be valid, it requires evaluation in well-designed trials.

Complex associations between co-morbidities themselves as well as between co-morbidities and the cardiovascular system lead to the development of HF, both HFpEF and HFrEF. Conversely, HF may give rise to comorbidities, which, in turn, adversely affect outcomes. Prevention of co-morbidities related to HF in the community is of utmost importance. In this regard, measures to decrease obesity and diabetes should be implemented, as both are becoming increasingly prevalent world-wide and are powerful risk factors for almost all major HF-

related co-morbidities. In addition, large, randomized controlled studies with long durations are needed to investigate whether measures to prevent anaemia, which affects roughly a third of the world's population with half of the cases due to iron deficiency, may contribute to a decrease in incident HF. Regarding treatment of prevalent HF, trials that established morbidity and mortality benefits predominantly included non-elderly patients without significant co-morbidities [7].

Assumption of a similar efficacy in elderly HF patients, who usually suffer from additional concomitant morbidities, is mostly based on extrapolations of these data, and the true benefit may be less. Future trials should include HF patients with comorbidities, despite the increased requirements for intensified monitoring and safety evaluations. Moreover, given the recent disappointing results in the majority of HF clinical trials on HF-specific therapies, the hypothesis that targeting comorbidities may improve patient outcomes should be tested. It is encouraging that some of the novel agents used in the treatment of HF-related co-morbidities (e.g. sitagliptin and empagliflozin in diabetes or indacaterol in COPD) seem to have a favourable cardiovascular risk-benefit profile. Finally, a problem related to the management of HF and the frequently of co-existing multimorbidity is the emergence of polypharmacy, especially in the elderly. As polypharmacy can lead to poor compliance with medical therapy and drug-drug interactions, which either increase adverse effects or decrease efficacy of pharmacotherapy, it should be avoided as much as possible. The impact of multi-morbidity-related polypharmacy on the effectiveness of HF management deserves further investigation.

Future trials must also focus on optimal strategies for the comprehensive management of the patient with CHF with multiple comorbidities rather than the isolated effects of single drugs in younger patients with few or no comorbidities.

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