Co-morbidities in Heart Failure; Defining a New Unmet Need

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Off label use of medications will be discussed.
The majority of Medicare Beneficiaries with heart failure have 5 or more other major conditions present.
Important Comorbidities in Heart Failure

- **Cardiovascular**
  - Hypertension
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebral vascular disease
  - Hyperlipidemia
  - Atrial fibrillation

- **Non-Cardiovascular**
  - Obesity
  - Diabetes
  - Anemia
  - Chronic kidney disease
  - Thyroid disease
  - COPD / Asthma
  - Smoking
  - Sleep disordered breathing
  - Liver disease
  - Arthritis
  - Cancer
  - Depression

Most Common Comorbidities in Heart Failure


Comorbidities, such as anemia, COPD, diabetes, renal disease are strongly associated with adverse outcomes in HF patients.
## Associations Between HFpEF and HFrEF With Comorbidities

<table>
<thead>
<tr>
<th>COMORBIDITY</th>
<th>BIDIRECTIONAL IMPACT ON DISEASE PROGRESSION</th>
<th>HEART FAILURE SPECIFICS</th>
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</thead>
</table>
| Chronic obstructive pulmonary disease | - Inflammation; hypoxia; parenchymal changes; airflow limitation, leading to pulmonary congestion; abnormal left ventricular (LV) diastolic filling; inhaled beta-agonist cardiovascular effects  
   - Elevated LV end-diastolic pressure and beta-blocker use may compromise lung function | - More prevalent in preserved ejection fraction (HFpEF), compared to reduced (HFrEF)  
   - Higher mortality risk in HFpEF                                                                 |
| Anemia                             | - Adverse LV remodeling; adverse cardiorenal effects; increased neurohormonal and inflammatory cytokines  
   - Inflammation; hemodilution; renal dysfunction; metabolic abnormalities exacerbate | - More prevalent in HFpEF  
   - Similar increased risk for mortality in both groups                                           |
| Diabetes                           | - Diabetic cardiomyopathy; mitochondrial dysfunction; abnormal calcium homeostasis; oxidative stress; renin-angiotensin-aldosterone system (RAAS) activation; atherosclerosis; coronary artery disease  
   - Incident and worsening diabetes mellitus via sympathetic and RAAS activation | - More prevalent in HFpEF  
   - Similar increased risk for mortality in both groups                                           |
| Renal dysfunction                   | - Sodium and fluid retention; anemia; inflammation; RAAS and sympathetic activation  
   - Cardiorenal syndrome through low cardiac output; accelerated atherosclerosis; inflammation; increased venous pressure | - Similar prevalence in both groups  
   - Similar increased risk for mortality in both groups                                               |
| Sleep-disordered breathing         | - Hypoxia; systemic inflammation; sympathetic activation; arrhythmias; hypertension (pulmonary and systemic); RV dysfunction; worsening congestion  
   - Rostral fluid movement may worsen pharyngeal obstruction; instability of ventilatory control system | - Similar prevalence in both groups  
   - Unknown mortality differential associated with HFpEF vs. HFrEF                                  |
| Obesity                            | - Inflammation; reduced physical activity and deconditioning; hypertension; metabolic syndrome; diabetes mellitus  
   - Fatigue and dyspnea may limit activity; spectrum of metabolic disorders including nutritional deficiencies | - More prevalent in HFpEF  
   - Obesity paradox; potential for a U-shaped association with mortality                            |
Polypharmacy in HF Patients is Common and Further Increasing

Number of drugs increased by 12%

Costs increased by 24%

Masoudi, Arch Intern Med 2015
HF, Comorbidities, and Adherence

- Comorbid conditions may impact the tolerability and response to heart failure medications
  - COPD/Asthma for use/tolerability of beta-blockers for HFrEF
  - CKD for use/tolerability of ACEI/ARB/ARNI and MRA for HFrEF
  - AF limiting mortality benefit of beta-blockers for HFrEF

- Treatment of comorbid conditions may substantially increase number of medications/pills and complexity of the medical regimen

- Comorbid conditions may impact adherence/persistence with HF medications
  - Depression and lower rates of medication adherence/persistence
  - Cognitive impairment limiting self care and medication adherence

- Comorbid conditions may cause symptoms that are difficult to distinguish from HF symptoms
  - Anemia contributing to fatigue and exercise intolerance
  - Depression contributing to fatigue
Diabetes and HF

- The two diseases entities are highly co-prevalent (25-44% of HF patients have diabetes)
- Diabetes contributes to disease progression in HF and is associated with worse prognosis
- Standard HF therapies (ACEI or ARB or ARNI, BB, AA, ICD, CRT) provide similar benefits with or without DM
- The optimal HbA1c goals in HF patients has not been defined and HF patients often excluded from DM trials
- Some diabetes medications increase risk of worsened HF and HF hospitalizations
- Certain diabetes medication have emerged that improve outcomes (SGLT 2 inhibitors)
- The optimal glucose-lowering regimen in diabetic HF patients requires further investigation
Empagliflozin is a highly selective inhibitor of SGLT2


7020 adults with type 2 diabetes and established CVD
BMI ≤45 kg/m²; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m² (MDRD)
Obesity and HF

- The vast majority of HF patients in the US are overweight or obese. In recent studies <2% of patients were underweight by BMI.

- Unlike the general population, HF patients in the overweight, obesity I/II categories by BMI have improved survival compared to the healthy weight category, even after adjusting for other factors.

- Weight loss in heart failure (mix of intentional / unintentional) associated with worse outcomes.

- No RTC of weight loss in HFrEF demonstrates benefit.

- Potential benefit in HFpEF on some clinical parameters but not clinical outcomes.
Among obese older patients with clinically stable HFPEF, caloric restriction or aerobic exercise training increased peak VO2, and the effects may be additive.

Neither intervention had a significant effect on quality of life as measured by the MLHF Questionnaire.
Adjusted Survival Curves for All-Cause Death According to the Presence of Significant Weight Loss in Obese Heart Failure Patients

1000 HF patients, of which 27% were obese by BMI
Elisabet Zamora et al. J Am Heart Assoc 2016;5:e002468
Reverse Epidemiology in Heart Failure Patients

- A low (and not a high) **body mass index** is associated with increased morbidity and mortality in heart failure patients.

- A low (and not a high) total serum **cholesterol** is associated with increased morbidity and mortality in heart failure patients.

- A low **blood pressure** is associated with increased morbidity and mortality in heart failure patients.

- A low (and not a high) **calorie and protein intake** may be associated with increased morbidity and mortality among heart failure patients.

Reverse Epidemiology in HF: Potential Clinical Implications

- The targets for BMI, cholesterol, SBP derived from epidemiologic studies of the general population may not apply to HF patients.

- Weight loss, whether intentional or not, should not necessarily be considered beneficial in overweight and obese HF patients. A focus on physical fitness and other healthy behaviors may be more productive.

- Specific targets for BMI, SBP, and cholesterol should be validated in prospective clinical trials in the population they are going to be applied to.

Lessons Learned from Anemia and Sleep Apnea in Heart Failure!

- Anemia is common in patients with HF and associated with symptoms, impaired functional capacity, hospitalizations, and mortality.
- Single center observational studies suggested benefit with treating anemia with ESAs and many clinicians started to used these agents in practice.
- RED-HF trial showed although Hb levels could be increased with ESAs there was no reduction in HF hospitalizations or mortality, plus harm with more thromboembolic events.
- Sleep apnea common in patients with HF and associated with symptoms, hospitalization, and mortality.
- CANPAP trial of CPAP and SERVE-HF with ASV in predominately CSA both stopped early due to excess mortality.
Patients with HF are more likely than the general population to develop AF.

There is a direct relationship between NYHA class and prevalence of AF in patients with HF, progressing from 4% in NYHA class I to >40% in NYHA class IV.

HF and AF can interact to perpetuate and exacerbate each other through mechanisms such as rate-dependent worsening of cardiac function, fibrosis, and activation of neurohormones.

AF can worsen symptoms in patients with HF and conversely, worsened HF can promote a rapid ventricular response in AF.

Trials of the rhythm control strategies using anti-arrhythmic medications have not shown improved outcomes; trials with ablation suggest benefit, but further confirmation needed.
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9.4. Other Multiple Comorbidities

Although there are additional and important comorbidities that afflict patients with HF, how best to generate specific recommendations remains uncertain, given the status of current evidence.

Accounting for All of The Multimorbidity Relationships May Be Needed

Zulman, J Gen Intern Med 2013
Conclusions

- Multiple comorbid conditions are present in the vast majority of heart failure patients
- These comorbid conditions frequently contribute to patients symptoms, functional status limitation, hospitalizations, mortality, and healthcare expenditures
- These comorbid conditions can complicate the use of guideline directed medication and device therapies
- Optimal management of these comorbid conditions in the setting of heart failure have, in most cases, not been well studied
- Current guidelines provide little guidance on effectively managing these comorbid conditions