Heart Failure in Older Adults: A Geriatrician Call for Action

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As the population ages, heart failure is becoming a major public health challenge; clinicians need further evidence-based treatments to bridge the existing gap between guidelines and real-world clinical practice.

In 2050, persons aged ≥ 85 years, also known as the oldest old, are projected to reach 18 million, accounting for 4.5% of the US population, up from 2.5% in 2030. These patients are the fastest growing segment of the US population.

Advances in treating cardiovascular (CV) disease over the past 2 decades have led to an increased incidence of heart failure (HF) and hospitalizations among older patients. Total costs of care for persons with HF have exceeded $30 billion annually and are expected to rise to more than $70 billion by 2030 due to growth of the aging population. Moreover, the Framingham Study reported mortality increases with advancing age (HR 1.27 and 1.61 per decade in men and women, respectively).

The prevalence of HF is also high and increasing over time. The National Health and Nutrition Examination Survey reported that about 5.7 million Americans have HF. The prevalence of HF is expected to reach 8 million by 2030. The higher numbers of HF among patients with advanced age is associated with age-related changes in CV structure and function, including reduced responsiveness to β-adrenergic stimulation, impaired left ventricular diastolic filling, and increased vascular stiffness. In addition, age-related changes in other systems might contribute to a HF diagnosis or worsening of the condition.

Older adults experience physiologic changes in pharmacokinetics and pharmacodynamics, including decreased volume of distribution and creatinine clearance, which lead to significant changes in drug concentration and effectiveness.

Geriatric patients aged > 65 years who have comorbidities and those who reside in long-term care settings are underrepresented in clinical trials, leading clinicians to make treatment decisions based on data from younger, community-dwelling individuals. Researchers have questioned whether to include elderly patients and those with comorbidities in clinical trials, given that their diminished response may produce less conclusive results with smaller treatment effects. Exclusion criteria based on comorbid conditions or functional status disqualify many older adults from clinical trials.

This article reviews evidence from major randomized controlled trials over the past 2 decades and explores their applicability to support HF treatment guidelines in patients with advanced age. This article also offers a practical approach to managing HF in these patients while advocating for bridging the gap between research and real-world clinical practice.

PHARMACOTHERAPY FOR HEART FAILURE

Angiotensin-Converting Enzyme Inhibitors

Several randomized clinical trials have found that angiotensin-converting enzyme (ACE) inhibitors improve symptoms in patients with HF. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), demonstrated that enalapril improves survival in patients with New York Heart Association (NYHA) class IV HF with reduced ejection fraction (HFrEF) when added to standard therapy. However, the duration of beneficial effect of reduced mortality could not be assessed because the benefit of enalapril in NYHA class I to III HF was not evaluated, and follow-up data are limited. The average age of patients in the study was 71 years, and individuals with significant comorbidities were excluded.
ACE inhibitors also were found to reduce mortality even in asymptomatic patients with HF/EF in the Studies of Left Ventricular Dysfunction trial (SOLVD).16 Enalapril was found to reduce 4-year mortality by 16% and decrease HF hospitalizations when added to conventional therapy consisting of the short-acting form of metoprolol and nitrates in patients with HF/EF. In this trial, patients aged ≥ 80 years were excluded as well as those with serum creatinine ≥ 2 mg/dL, or other conditions that could cause renal or other adverse impedi-
tancements in a long-term trial.

PARADIGM-HF trial patients with HF/EF were ran-
domized to enalapril or the angiotensin receptor-neprilysin inhibitor LCZ696. After a median of 27 months of follow-up, patients taking LCZ696 who were taking an ACE inhibitor demonstrated greater reduction in CV mortality and HF hospitalizations than enalapril did and was associated with reduced all-cause mortality.17 The trial was stopped early because of evidence of overwhelm-
ing benefit with LCZ696. This study of mainly white men included no patients aged ≥ 75 years.

Angiotensin Receptor Blockers

Although less studied than ACE inhibitors, angiotensin receptor blockers (ARBs) share similar benefits. Among patients with symptomatic HF/EF taking an ACE in-
hibitor, the addition of candesartan reduced the risk of CV death and HF hospitalization as demonstrated in the Candesartan in Heart Failure Assessment of Re-
duction Mortality and Morbidity (CHARM-added and CHARM-alternative trials).18,19 The CHARM-added trial targeted patients with left ventricular ejection fraction (LVEF) < 40%, NYHA II to IV symptoms, who were taking an ACE inhibitor. Adding candesartan reduced CV mortality by 37.9% and HF hospitalization by 42.3% compared with that of placebo.

In the RALES study, spironolactone was found to re-
duce all-cause mortality by 30% and symptoms in NYHA II HF without a significant increase in the risk of seri-
ous hyperkalemia or renal failure.19 Most patients were white men aged < 80 years. This study demonstrated the importance of closely following serum potassium levels after initiating aldosterone antagonists in patients with subclinical renal disease because extensive structural damage within the kidney occurs before serum creatinine increases. Patients with advanced renal failure or those who cannot have close monitoring of serum potassium levels have an unfavorable risk–benefit ratio with aldoste-
rone antagonists. Patients with cancer and liver failure were excluded from this trial.

In the CHARM-Mild Patients Hospitalization and Survival Study in Heart Failure study, (CHARM-MILD Study) eplerenone was found to reduce all-cause mortality and hospitalization for HF/EF.20 Similar to RALES, patients were mostly white men aged < 80 years, and patients had clinically significant, coexisting conditions were excluded.

The 2014 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) randomized 3,445 patients with well-
controlled blood pressure to spironolactone or pla-
ceto.21 Inclusion criteria were LVEF ≥ 45%, findings of HF, and either a HF hospitalization or elevated B-type natriuretic peptide level. There was no difference in the primary composite outcome of CV mortality, aborted

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<td>• Treatment with an angiotensin receptor-neprilysin inhibitor reduces CV mortality and HF hospitalizations when compared with that of enalapril.23</td>
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<td>• ARBs appear to have similar effects as ACE inhibitors in HF/EF, although it is unclear whether there is benefit when added to ACE inhibitors.24</td>
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<td>• Aldosterone antagonists show benefit when combined with ACE inhibitors/ARBs in NYHA III and IV HF.25,26</td>
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<td>• Evidence supports treatment with aldosterone antagonists in HF/EF27 and careful monitoring of serum potassium.28</td>
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| • β-blockers improve mortality in HF/EF and reduce hospitaliza-
tions with some evidence of noninferiority and superiority of different agents.29,30 Some patients experience benefit from ivabradine as an alternative rate-controlling agent.
| • Neither routine anticoagulation with warfarin nor rivaroxaban nor dabigatran exists in the guidelines for HF.31 |
| • Statins do not benefit patients with HF with no other indications for use and nitrate deficiency appears to be inferior to optimized medical therapy in patients with acute cardiac–renal syndrome.32 |
| • Although evidence-based guidelines for HF/EF patients are extensive, little evidence is available for guideline-directed treat-
ment for HFrEF patients in all age groups.33 |
| • Patients aged > 85 years and those with several common comorbidities seldom are included in randomized HF clinical trials. |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.

Mineralocorticoid Receptor Antagonists

Major studies of aldosterone antagonists demonstrated extra benefit when added to ACE inhibitors/ARBs in patients with HF/EF and NYHA class II HF.15,16,17,18 In the RALES study, spironolactone was found to re-
duce all-cause mortality by 30% and symptoms in NYHA II HF without a significant increase in the risk of seri-
ous hyperkalemia or renal failure. Most patients were white men aged < 80 years. This study demonstrated the importance of closely following serum potassium levels after initiating aldosterone antagonists in patients with subclinical renal disease because extensive structural damage within the kidney occurs before serum creatinine increases. Patients with advanced renal failure or those who cannot have close monitoring of serum potassium levels have an unfavorable risk–benefit ratio with aldoste-
rone antagonists. Patients with cancer and liver failure were excluded from this trial.

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure study, (EMPHASIS-HF Study) eplerenone was found to reduce all-cause mortal-
ity and hospitalization for HF/EF.20 Similar to RALES, patients were mostly white men aged < 80 years, and patients had clinically significant, coexisting conditions were excluded.

The 2014 Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT) randomized 3,445 patients with well-
controlled blood pressure to spironolactone or pla-
ceto. Inclusion criteria were LVEF ≥ 45%, findings of HF, and either a HF hospitalization or elevated B-type natriuretic peptide level. There was no difference in the primary composite outcome of CV mortality, aborted

cardiac arrest, or HF hospitalization over the 3.3-year follow-up period. The study found that among patients with HFrEF, spironolactone does not reduce the composi-
tive endpoint of CV mortality, aborted cardiac arrest, or HF hospitalizations compared with that of placebo.21 In the trial, 29% of patients were aged ≥ 75 years, and most were white male. There was no subgroup analysis for differ-
ents. In all 3 trials, patients with kidney injury (serum creatinine of ≥ 2.5 or estimated glomerular filtration rate of ≤ 30 mL/min) were excluded because of the risk of hyperkalemia.

An observational study after the RALES trial demon-
strated a nearly 4-fold increase in admissions for hyper-
kalemia with a 6-fold increase in associated mortality in patients taking spironolactone.22 Therefore, it is important to closely follow serum potassium levels after initiating aldosterone antagonists in older patients with subcli-
renal renal disease. Patients with advanced renal failure or those without close monitoring of serum potassium levels have an unfavorable risk–benefit ratio with aldoste-
rone antagonists.

ANTITHROMBOTIC THERAPY

The large multicenter, double-blind randomized trial WARCEF found no added benefit with warfarin vs aspiri-

Table. Medical Management of Heart Failure: Evidence and Gaps

ACE inhibitors improve symptoms and reduce mortality even in asymptomatic patients with HF/EF. Treatment with an angiotensin receptor-neprilysin inhibitor reduces CV mortality and HF hospitalizations when compared with that of enalapril. ARBs appear to have similar effects as ACE inhibitors in HF/EF, although it is unclear whether there is benefit when added to ACE inhibitors. Aldosterone antagonists show benefit when combined with ACE inhibitors/ARBs in NYHA III and IV HF. Evidence supports treatment with aldosterone antagonists in HF/EF and careful monitoring of serum potassium. β-blockers improve mortality in HF/EF and reduce hospitalizations with some evidence of noninferiority and superiority of different agents. Some patients experience benefit from ivabradine as an alternative rate-controlling agent. Neither routine anticoagulation with warfarin nor rivaroxaban nor dabigatran exists in the guidelines for HF. Statins do not benefit patients with HF with no other indications for use and nitrate deficiency appears to be inferior to optimized medical therapy in patients with acute cardiac–renal syndrome. Although evidence-based guidelines for HF/EF patients are extensive, little evidence is available for guideline-directed treatment for HFrEF patients in all age groups. Patients aged > 85 years and those with several common comorbidities seldom are included in randomized HF clinical trials.
shown a survival benefit for patients with HF. However, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure trial demonstrated survival benefits with metoprolol CR/XL and included patients aged >80 years.32 In the SENIORS study, patients treated with nebivolol had a 4.2% absolute risk reduction in a composite of mortality or hospital admission at a mean follow-up of 21 months.33 It is reasonable to use nebivolol for managing HF in older patients. Careful monitoring of heart rate is necessary when prescribing β-blockers for older patients.

Cardiac Glycosides
Digoxin with diuretics was the first-line treatment for HF for many decades and the mainstay of HF therapy until the first large HF trials were performed in the 1980s. One trial initiated by the Digoxin Investigation Group (DIG) studied patients with HFREF who were already receiving treatment for HF (including 94% taking ACE inhibitors and 82% on diuretics) and randomized them to either digoxin or placebo.34 The study found no significant difference in mortality between the groups at the 3-year follow-up; however, the digoxin group had significantly fewer hospitalizations compared with that of the placebo group.

A post-hoc analysis of patients by age found no difference in mortality between patients aged 70 to 79 years and those >80 years, with a persistent benefit in fewer hospitalizations. Digoxin continues to be recommended as a reasonable medication for treating symptomatic HFREF. However, caution is advised in older patients, especially women, who are at higher risk of digoxin toxicity. No current evidence exists that digoxin adds any benefit to patients with HFpEF of any age and therefore, it should not be used.

Diuretics
Diuretic therapy is important for managing shortness of breath and congestion related to fluid volume overload in patients with HF. Although diuretics have not been shown to reduce mortality in patients with HF, they are the mainstay treatment for patients with HFpEF.35 In a post-hoc analysis of the DIG study, diuretic use was associated with increased risk of mortality and hospitalization in patients aged >65 years.36 Hypotension is one of the most serious adverse effects (AEs) with these agents and occurs in about one-fifth of elderly patients taking diuretics.

In severe cases hyponatremia can cause a range of problems, including weakness, confusion, postural giddiness, postural hypotension, falls, transient hemiparesis, and seizures. In older patients with diminished renal reserve, diuretics are more likely to precipitate prerenal uremia than it does in younger patients. Prerequisites for fracture using an accurate diagnosis, careful monitoring of blood pressure and serum electrolytes, and regular review of their efficacy, AEs, and the need for continued treatment.

Anemia
In patients with iron-deficiency anemia (ferritin 15-100 ng/mL or 100-299 ng/mL with transferrin saturation <20%) and symptomatic HFREF (LVEF < 40% with NYHA II to IV HF), oral iron replacement had no effect on exercise capacity as measured using change in peak oxygen uptake.37 However, IV iron replacement might be a reasonable option to improve functional status and quality of life (QOL) for patients with HF.38 In these studies, participants were aged <73 years, and there is no evidence that treating other types of anemia improves outcomes in patients with HF.

Hypertension
The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that controlling blood pressure to a goal systolic pressure of <120 mm Hg is associated with significant reduction in the mortality in the population with target increased CV risk (aged >75 years, vascular disease, kidney injury, or a Framingham Risk Score >15%).39 The SPRINT study included patients aged >75 (23%); however, the study excluded older adults living in nursing homes and those with diabetes mellitus, symptomatic HF, dementia, or stroke. The subgroup analysis did not stratify patients based on age or provided sufficient evidence regarding treatment targets for this vulnerable population. Therefore, clinicians cannot draw any conclusions about managing hypertension among patients with HF from this study.

Sleep Apnea
Sleep apnea is common among patients with HF. A study of adults with chronic HF treated with evidence-based therapies found that 61% of participants had central or obstructive sleep apnea.39 In elderly patients, sleep apnea is further complicated by insomnia and disturbance of sleep cycle that often occur with the aging process.

It is crucial to differentiate central sleep apnea from obstructive sleep apnea, because the treatment approaches differ. Central sleep apnea is associated with poor prognosis in patients with HF.40 Adaptive servo ventilation for central sleep apnea uses a noninvasive ventilator to deliver servo controlled inspiratory pressure support on top of expiratory positive airway pressure. Adaptive servo ventilation for central sleep apnea is associated with higher all-cause mortality and CV mortality. Continuous positive airway pressure for obstructive sleep apnea improves sleep quality, reduces the apnea-hypopnea index, and improves nocturnal oxygenation.41

Depression
Clinically significant depression occurs in 21% of patients with HF, and the relationship between depression and poor HF outcomes is consistent and strong across several endpoints. However, in a randomized, 12-week study, the selective serotonin reuptake inhibitor sertraline did not improve physical, spiritual, or emotional aspects of quality of life in patients with HF with no evidence of depression.42 Furthermore, studies describing depression treatments among patients with HF are too small and heterogeneous to permit definitive conclusions about intervention effectiveness. These results identify areas requiring further development, raise questions regarding the association between depression and clinical outcomes in patients with HF and provide information on depression prevalence that may help researchers design studies with appropriate depression measures and adequately powered sample sizes.

Frailty
Although frailty is prevalent in the elderly and is independently associated with poor outcomes, there is no standardized definition for frailty. The Fried Frailty Index is a widely used scale that incorporates criteria including weakness, slowness, exhaustion, and low physical activity in the diagnosis of frailty.43 However, these symptoms are common among patients with advanced HF, and frailty is often perceived as fragmented. Polypharmacy negatively impacts HF management by increasing risk of drug nonadherence, drug interactions, and AEs.44

Frailty should be defined collaboratively by the clinician and the patient and should include multidimensional aspects of health, function, and well-being. The treatment goal for patients with HF with frailty is to establish patient-centered goals based on preferences of care.45

DISCUSSION
Although several novel approaches to improve outcomes in patients with HF have been developed, it continues to be the leading cause of cardiovascular death among older patients and the leading cause of hospital admissions.46 About 50% of newly diagnosed patients with HF die within 5 years.47 Current guidelines for managing HF are based on clinical trials that either include few or completely exclude patients aged >80 years, minorities, and patients with comorbidities clinicians encounter daily in clinical practice. Furthermore, most clinical trials are designed with mortality as the primary endpoint, which might be as important to our patients with advanced age as their ability to function with a reasonable QOL and less dependence on caregivers.

Decision making in managing HF in our oldest patients should start with an open discussion of the disease and its prognosis, goals of care, and available treatment options. The discussion should also cover all dimensions ofsuitability, including physical, spiritual, and psychosocial domains. Interventions of patients dying of HF and their caregivers conducted in the United Kingdom identified several communication approaches to treat those specific to treating this population.48 The study revealed in most cases, patients did not recall receiving any written information about the severity of their disease and often did not understand the association among symptoms, such as shortness of breath, edema, and HF. Patients and caregivers did not feel involved in the decision-making process regarding their illness.

The concurrent presence of comorbidity, frailty, and cognitive impairment in our aging population with HF might add to the burden of the primary condition. Care often is perceived as fragmented. Polypharmacy negatively impacts HF management by increasing risk of drug nonadherence, drug interactions, and AEs.45

In an already vulnerable population. There is a need for more
Author disclosures

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REFERENCES