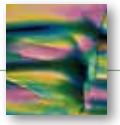

Heart Failure in Older Adults: A Geriatrician Call for Action

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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.[1] 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.[2] 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.[3,4] Moreover, the Framingham Study reported mortality increases with advancing age (HR 1.27 and 1.61 per decade in men and women, respectively).[5]

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.[6] The prevalence of HF is expected to reach 8 million by 2030.[6] 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.[7]

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.[8]

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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 (Table). 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.[9] 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 HFrEF in the Studies of Left Ventricular Dysfunction trial (SOLVD).[10] Enalapril was found to reduce 4-year mortality by 16% and decrease HF hospitalizations when added to conventional therapy consisting primarily of digitalis, diuretics, and nitrates in patients with HFrEF. In this trial, patients aged ≥ 80 years were excluded as well as those with serum creatinine > 2 mg/dL or other conditions that could shorten survival or otherwise impede participation in a long-term trial.

PARADIGM-HF trial patients with HFrEF were randomized to enalapril or the angiotensin receptor-neprilysin inhibitor LCZ696. After a median of 27 months of follow-up, treatment with the angiotensin receptor-neprilysin inhibitor demonstrated greater reduction in CV mortality and HF hospitalizations than enalapril did and was associated with reduced all-cause mortality.[11] The trial was stopped early because of evidence of overwhelming 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 HFrEF taking an ACE inhibitor, the addition of candesartan reduced the risk of CV death and HF hospitalization as demonstrated in the Candesartan in Heart Failure Assessment of Reduction Mortality and Morbidity (CHARM-added and CHARM-alternative trials).[12,13] The CHARM-added trial targeted patients with left ventricular ejection fraction (LVEF) ≤ 40% and NYHA class II to IV HF 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.

The CHARM-alternative study found that use of candesartan in symptomatic HFrEF patients who do not tolerate ACE inhibitors,resulted in a 20% reduction in CV mortality as well as a 40% reduction in hospitalization for HF. Among patients with HF with preserved ejection fraction (HFpEF) and NYHA class II to IV symptoms, adding candesartan modestly reduced the rate of HF-related hospitalizations and had no effect on CV mortality in the CHARM-preserved study.[14] The CHARM trials examined mostly white men, but 26% of patients were aged > 75 years. However, there was no subgroup analysis for patients aged > 75 years. The study excluded patients with serum creatinine > 2 mg/dL.

Other ARB trials included the following:

- The I-PRESERVE trial, which found that irbesartan did not improve outcomes of patients with HF with preserved ejection fraction (HFpEF).[15] The study of mostly white patients did not include patients aged ≥ 80 years.
- A randomized trial of valsartan in HF improved symptoms and mortality in NYHA II to IV HF but showed no benefit when added to ACE inhibitors.[16] The trial had no patients aged ≥ 75 years and excluded those with several common comorbidities.
- A randomized, double-blind trial studied the effects of high-dose vs low-dose losartan on clinical outcomes in 3,846 patients with HF and demonstrated that high-dose losartan (150 mg/d) reduces all-cause mortality and hospitalization for HF more effectively than does low-dose losartan (50 mg/d).[17] The study, however, had several exclusion criteria, and no patients were aged ≥ 75 years.

Mineralocorticoid Receptor Antagonists

Major studies of aldosterone antagonists demonstrated extra benefit when added to ACE inhibitors/ARBs in patients with HFrEF and NYHA class II HF.[18,19]

In the RALES study, spironolactone was found to reduce all-cause mortality by 30% and symptoms in NYHA III HF without a significant increase in the risk of serious hyperkalemia or renal failure.[18] 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 aldosterone 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 mortality and hospitalization for HFrEF.[19] Similar to RALES, patients were mostly white males aged < 80 years, and patients with 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 placebo.[20] 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 HFpEF, spironolactone does not reduce the composite endpoint of CV mortality, aborted cardiac arrest, or HF hospitalizations compared with that of placebo.[20] In the trial, 29% of patients were aged > 75 years, and most were white men. There was no subgroup analysis for older patients.[20] 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 demonstrated a nearly 4-fold increase in admissions for hyperkalemia with a 6-fold increase in associated mortality in patients taking spirolactone.[21] Therefore, it is important to closely follow serum potassium levels after initiating aldosterone antagonists in older patients with subclinical renal disease. Patients with advanced renal failure or those without close monitoring of serum potassium levels have an unfavorable risk–benefit ratio with aldosterone antagonists.

Table. Medical Management of Heart Failure: Evidence and Gaps

- ACE inhibitors improve symptoms and reduce mortality even in asymptomatic patients with HFrEF.[9]
- Treatment with an angiotensin receptor-neprilysin inhibitor reduces CV mortality and HF hospitalizations when compared with that of enalapril. It is also associated with a reduction in all-cause mortality in HFrEF.[11]
- ARBs appear to have same benefits as ACE inhibitors in HFrEF; however, it is unclear whether there is benefit when added to ACE inhibitors.[12,13,16]
- Aldosterone antagonists show benefit when combined with ACE inhibitors/ARBs in NYHA III and NYHA II HFrEF.[18,19] Evidence supports treatment with aldosterone antagonists in HFpEF[20] and careful monitoring of serum potassium.[21]
- β-blockers improve mortality in HFrEF and reduce hospitalizations with some evidence of noninferiority and superiority of different agents.[27,28] Some patients experience benefit from ivabradine as an alternative rate-controlling agent.
- Neither routine anticoagulation with warfarin or rivaroxaban nor treatment with digoxin reduce mortality in HF.[21,31]
- Statins do not benefit patients with HF with no other indications for use and ultrafiltration appears to be inferior to optimized medical therapy in patients with acute cardio-renal syndrome.[34]
- Although evidence-based guidelines for HFrEF patients are extensive, little evidence is available for guideline-directed treatment for HFpEF patients in all age groups.
- 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; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

ANTITHROMBOTIC THERAPY

The large multicenter, double-blind randomized trial WARCEF found no added benefit with warfarin vs aspirin for patients with HFrEF in sinus rhythm.[22] There was no reduced time to first stroke or death, and the reduced ischemic stroke risk was offset by an increase in major hemorrhage. It is not clear whether subgroup analysis for the etiology of patients' HF was performed in WARCEF.

The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial (N = 1,587) found that treatment with warfarin resulted in significantly fewer strokes in patients with ischemic cardiomyopathy.[23] Randomization was not stratified by age group in both trials, and baseline characteristics included mostly white men, and no patients were older than aged > 75 years.

The risk of bleeding with prophylactic aspirin use for CV disease is dose dependent and increases with higher aspirin doses.[24] The use of aspirin, 325 mg/d, in the WARCEF study might have contributed to the increased risk of hemorrhage.

Recently published results of COMMANDER HF found that the addition of rivaroxaban at a dose of 2.5 mg twice daily to standard care, including clinically selected antiplatelet therapies was not associated with a significantly lower rate of the composite primary outcome composite outcome of death, myocardial infarction (MI), or stroke among 5,022 patients with a recent episode of worsening heart failure compared with that of placebo.[25]

Several medical conditions are known to increase bleeding risk, including hypertension, cerebrovascular disease, ischemic stroke, serious heart disease, diabetes mellitus, renal insufficiency, alcoholism, liver disease, and falls.[26] Many of these conditions are common among very old patients and should be considered when estimating risk–benefit ratio of oral anticoagulation therapy.

β-blockers

In several large studies, β-blockers have been shown to be effective in reducing mortality in patients with HFrEF. In the Cardiac Insufficiency Bisoprolol Study II, bisoprolol improved all-cause mortality and all-cause hospitalizations, and reduced sudden death in patients with NYHA III or IV HF.[27] In the Carvedilol or Metoprolol European Trial (COMET), carvedilol was superior to metoprolol in reducing all-cause mortality for patients with NYHA II or IV HF.[28] Both trials included mostly white men; patients with several comorbidities were excluded, and no patients were aged > 80 years.

COMET compared carvedilol with metoprolol tartrate, the short-acting form of metoprolol that has not

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.[29]

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.[30] 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.[31] 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 benefits for 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.[32] In a post-hoc analysis of the DIG study, diuretic use was associated with increased risk of mortality and hospitalizations in patients aged > 65 years.[33] Hyponatremia 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 diuretic use are an accurate diagnosis, careful monitoring of blood pressure and serum electrolytes, and regular review of their efficacy, AEs, and the need for continued treatment.

Statins

The Controlled Rosuvastatin Multinational Trial in Heart Failure demonstrated that low-dose rosuvastatin (10 mg/d) does not improve survival among patients with moderate-to-severe ischemic cardiomyopathy but could reduce the rate of CV hospitalizations.[34] Patients in this study had a mean age of 73 years, and 41% of them were aged ≥ 75 years. However, the study used a low-dose rosuvastatin, and patients with several common comorbidities were excluded. Evidence exists that treatment with other statins may improve outcomes in patients with HF. There is also evidence that among elderly patients with HF, low serum total cholesterol is independently associated with a worse prognosis.[35]

COMORBIDITIES

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.[36] However, IV iron replacement might be a reasonable option to improve functional status and quality of life (QOL) for patients with HF.[37] In these studies, participants were aged < 75 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 among patients with increased CV risk (aged > 75 years, vascular disease, kidney injury, or a Framingham Risk Score >15%).[38] The SPRINT study included patients aged > 75 (25%); 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 nor 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 delivering 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.[41] Continuous positive airway pressure for obstructive sleep apnea improves sleep quality, reduces the apnea-hypopnea index, and improves nocturnal oxygenation.[42]

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 depression symptoms or clinical status among patients with HF.[43] Depression symptoms might overlap with fatigue and low energy expenditure experienced by oldest old patients with HF who do not have depression.

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.[44] However these symptoms are common among patients with advanced HF with and without depression or frailty.

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 of 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 of suffering, including physical, spiritual, and psychosocial domains. Interviews of patients dying of HF and their caregivers conducted in the United Kingdom identified several communication and transition of care challenges 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 in an already vulnerable population. There is a need for more

effective interpersonal and easy to understand communication and resources.

In many situations, support services might be best facilitated by a dedicated palliative medicine team with significant experience in managing patients with HF. Although palliative medicine should always be considered for patients with HF with advanced age, consultations often are not obtained unless the patient decides to forgo medical treatment or until the last month of life.[49]

It is important to note that older adults are not a homogeneous group, and the conventional viewpoint that all patients with HF value symptom control and QOL over longevity may not be true. In a large study three-fourths of elderly outpatients with HF were not willing to trade survival time for improved QOL; and their preferences changed over the course of illness.[50]

Although not all end-of-life symptoms can realistically be palliated, earlier involvement of multidisciplinary palliative medicine specialists may improve symptom control, functional status, and QOL. The team may help patients and caregivers cope with uncertainty, and make informed decisions that are person centered based on value system and beliefs.[51]

CONCLUSION

Randomized control trials as well as thoughtful observational studies of HF in patients with advanced age and comorbidities, although challenging, are needed to create the evidence base for treatment interventions and assessing their impact on mortality, morbidity, and QOL in this rapidly growing segment of our population.

Given the lack of evidence for HF treatment in patients with advanced age, the clinician should weigh the knowledge of the effect of aging on the CV system, and the lived experience of patients with HF, with the evidence that exists for making the best decision to relieve bothersome symptoms and improve outcomes of care as determined by patients and their caregivers.

Often the most important intervention we can offer our patients, especially those nearing the end of life, is dedicating our time to truly and actively listen with empathy, understating, and respect for their autonomy and for their decision making. And in doing so we accept our own limitations with humility.

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