Consensus Statement

Heart Failure in Non-Caucasians, Women, and Older Adults: A White Paper on Special Populations From the Heart Failure Society of America Guideline Committee

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ABSTRACT

The presentation, natural history, clinical outcomes, and response to therapy in patients with heart failure differ in some ways across populations. Women, older adults, and non-Caucasian racial or ethnic groups compose a substantial proportion of the overall heart failure population, but they have typically been underrepresented in clinical trials. As a result, uncertainty exists about the efficacy of some guideline-directed medical therapies and devices in specific populations, which may result in the under- or overtreatment of these patients. Even when guideline-based treatments are prescribed, socioeconomic, physical, or psychologic factors may affect non-Caucasian and older adult patient groups to a different extent and affect the application, effectiveness, and tolerability of these therapies. Individualized therapy based on tailored biology (genetics, proteomics, metabolomics), socioeconomic and cultural considerations, and individual goals and preferences may be the optimal approach for managing diverse patients. This comprehensive approach to personalized medicine is evolving, but in the interim, the scientific community should continue efforts focused on intensifying research in special populations, prescribing guideline-directed medical therapy unless contraindicated, and implementing evidence-based strategies including patient and family education and multidisciplinary team care in the management of patients. (J Cardiac Fail 2015;21:674–693)

Key Words: Heart failure, women, African American, elderly.

See page 687 for disclosure information.

1 Drs Colvin and Sweitzer served as co-chairs of the HFSA writing group for this paper and contributed equally to this paper.

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Heart failure (HF), as a clinical syndrome, is the culmination of pathophysiologic changes precipitated by different disease processes. The clinical presentation, natural history, and response to therapy differ to some extent across populations. Although non-Caucasian ethnic groups, women, and older adults (herein stated as special populations) account for a substantial proportion of the HF population, the number of special population patients enrolled in clinical trials and registries is small.\(^1\)\(^-\)\(^4\) Thus, it is uncertain if the results of these trials can be accurately applied to patients in these special populations. Treatment uncertainty may contribute to underuse of guideline-directed medical therapy in these groups.\(^5\)\(^,\)\(^6\) Furthermore, in the absence of data, it is not possible to assess whether some treatments assumed to be broadly effective might be ineffective or deleterious in subgroups. This paper highlights the challenges of HF management in special populations and provides recommendations for advancing patient care (Table 1).

### Epidemiology, Risk Factors, and Characteristics of Heart Failure

#### Overview

Approximately 5.7 million Americans over the age of 20 years have HF,\(^7\) a figure expected to rise to >8 million by 2030.\(^8\) An estimated 23 million people have HF worldwide. Annually, 870,000 new HF cases are diagnosed in the United States (US).\(^8\) Data from the Framingham Heart Study indicate that 20% of men and women 40 years old and older have HF.\(^7\) HF disproportionately affects African Americans. In the Multi-Ethnic Study of Atherosclerosis (MESA), African Americans had the highest risk of developing HF, followed by Hispanic, Caucasian, and Chinese Americans (4.6, 3.5, 2.4, and 1.0, respectively, per 1,000 person-years).\(^9\)\(^-\)\(^10\) Other reports estimate a higher prevalence of HF among African-American adults compared with Caucasians,\(^1\)\(^0\)\(^-\)\(^1\)\(^1\) and indicate that HF develops at a younger age in African Americans than in Caucasians.\(^1\)\(^2\)\(^-\)\(^1\)\(^3\) The incidence of pediatric dilated cardiomyopathy is also higher among African-American children than among Caucasian children.\(^1\)\(^4\) HF presents at an earlier age in African Americans, and the degree of left ventricular (LV) dysfunction and apparent disease severity tends to be worse at the time of diagnosis.\(^1\) Functional and structural cardiac changes precede the presentation of symptoms by ~10 years.\(^1\)\(^2\)

Nonischemic cardiomyopathy is relatively more prevalent than ischemic cardiomyopathy in African Americans compared with Caucasians.\(^5\)\(^-\)\(^1\)\(^3\) In the Washington DC Dilated Cardiomyopathy study, African-American adults had an increased risk of dilated cardiomyopathy (relative risk [RR] 2.6, 95% confidence interval [CI] 1.6–4.3) compared with Caucasians.\(^1\)\(^0\)\(^-\)\(^1\)\(^5\) The relative prevalence of heart failure with preserved ejection fraction (HFpEF) compared with heart failure with reduced ejection fraction (HFrEF) varies depending on the population studied. In the Atherosclerosis Risk in Communities (ARIC) study, HFpEF composed 73% of the HF cases among middle-aged African Americans.\(^1\)\(^6\)

No single proven causative theory explains the increased prevalence of HF among African Americans. Most likely, many factors contribute to the differences in prevalence and presentation of HF among African Americans, including comorbidities (eg, diabetes, obesity, uncontrolled hypertension,\(^1\)\(^2\) and atrial fibrillation), health literacy, care disparity, and socioeconomic factors. Race provides limited information regarding biologic differences; however, certain trends may be identified within a population. For example, the prevalence of CAD is lower in African-American patients with HF; consequently, nonischemic cardiomyopathy is more common.\(^5\)\(^-\)\(^1\)\(^3\) Hypertensive heart disease is more common in African Americans than in Caucasian patients. Possible explanations for the increased prevalence of hypertension in African Americans include increased salt sensitivity, reduced nitric oxide (NO) bioavailability, increased oxidative stress,\(^1\) impaired vascular function, and increased large artery stiffness, factors that could result in a greater propensity for developing HF.\(^1\)\(^6\)\(^-\)\(^2\)\(^0\) African Americans with hypertension have a more malignant course, with frequent target end organ damage, including LV hypertrophy (LVH), a finding that may provide a potential pathophysiologic link to the higher prevalence of HF in African Americans.\(^2\)\(^1\)

Genetic polymorphisms have been identified that influence the risk of HF, and several polymorphisms may potentially explain some of the pathophysiologic differences noted in African Americans (Table 2), although genetic differences in HF in other non-Caucasian ethnic groups are not as well described. For example, the natriuretic peptide
system regulates blood pressure and moderates the cardiac response to pressure overload via autocrine/paracrine actions. Corin, a transmembrane serine protease, processes natriuretic peptide prohormones into active forms. A corin haplotype defined by 2 loss-of-function mutations (T555I/Q568P) in complete linkage disequilibrium is unique to the African-American population and carried by ~13% of African Americans. It is associated with an increased risk for prevalent hypertension as well as LVH in African Americans.22–24 The genetic substudy of the African-American Heart Failure Trial (A-HeFT), provided a unique presentation in clinical investigations limits the opportunity to expand knowledge.

Table 2. Sampling of Candidate Genes for Polymorphisms and Clinical Implications in African Americans

<table>
<thead>
<tr>
<th>Genetic Polymorphism</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1-Adrenergic receptor; Gly-389</td>
<td>Subsensitive β1-receptor; decreased affinity for agonist and less cAMP generation</td>
</tr>
<tr>
<td>β1-Adrenergic receptor; ARG-389 with α-receptor</td>
<td>Presence of both polymorphisms is associated with increased risk for HF; dual polymorphisms</td>
</tr>
<tr>
<td>eNOS</td>
<td>Subsensitive NO system</td>
</tr>
<tr>
<td>Aldosterone synthase</td>
<td>Excessive fibrosis</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>40% higher TGF-β1 levels; possibly higher endothelin levels and more fibrosis</td>
</tr>
<tr>
<td>G protein 825-T allele (G protein β2-subunit)</td>
<td>Marker of low-renin HTN, LVH, and stroke; associated with greater therapeutic effect of HYD-ISDN</td>
</tr>
<tr>
<td>ACE D allele</td>
<td>May influence LV remodeling and clinical outcomes and may be associated with hypertension</td>
</tr>
<tr>
<td>Corin 1555(S568)</td>
<td>Reduced natriuretic peptide processing capacity; increased risk of death or HF hospitalization ameliorated by HYD-ISDN</td>
</tr>
<tr>
<td>AGTR1(−535)</td>
<td>Associated with hypertension</td>
</tr>
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</table>

Data from epidemiologic studies suggest that Hispanics have higher rates of diabetes, obesity, dyslipidemia, and metabolic syndrome, all of which may contribute to an increased risk of HF.39 There is a higher prevalence of rheumatic heart disease and Chagas disease among immigrants from South and Central America, and a work-up for Chagas disease should be considered in Hispanic patients from these regions presenting with HF symptoms and reduced ejection fraction.39 Hispanics encounter multiple socioeconomic and possibly cultural barriers to health care that may affect disease identification and progression.39 Segments of the Hispanic community may have limited access to health care in the US, may lack English fluency, and may have limited acculturation, which inhibits trust in the medical system and creates additional barriers especially when clinicians lack cultural competence. Finally, the lack of representation in clinical investigations limits the opportunity to expand knowledge.

South Asians have more coronary risk factors than Caucasian patients, and it has been suggested that this group may have a higher risk of premature CAD leading to HF at a younger age.40 Although less well characterized than other populations, South Asian men appear to have impaired endothelial function due to decreased NO bioavailability and impaired circulating progenitor cell mobilization compared with healthy Caucasian men.41 In an analysis of Chinese and South Asian patients who received specialty HF care in Ontario, fewer Chinese patients had a history of CAD, myocardial infarction (MI), surgical or percutaneous revascularization procedures, dyslipidemia, peripheral vascular disease, and chronic obstructive pulmonary disease compared with non-Chinese/non-Asian counterparts. On the other hand, a study from China showed that the risk factors for HF in Chinese adults were similar to a North American population, including hypertension (37%), ischemic heart disease (31%), valvular heart disease (15%), cor pulmonale (27%), and idiopathic dilated cardiomyopathy (4%).42 In contrast, more South Asians had a history of MI.

mutant and wild-type transthyretin cause cardiac amyloid in the general population, the V122 I mutation is rare in individuals who are not of African descent.34 Approximately 4% of African Americans carry the TTR V122 I mutation that confers a high risk for cardiac TTR amyloid deposition. The TTR mutation has been associated with a higher frequency of HF and greater mortality after the age of 65 years. However, despite overexpression of this mutation in African Americans, its true significance and its association with cardiomyopathy have not been established in prospective studies.35–37

Generally, data on HF in non-Caucasian ethnic groups other than African Americans are sparse. A survey by the Centers for Disease Control and Prevention (CDC) found that 26% of Hispanics reported having hypertension, and 27% with high blood pressure were not taking medication regularly.38 Hispanics with HF are more likely to be younger and underinsured than non-Hispanic Caucasians.39

Adapted from Yancy, with permission from Elsevier.
and revascularization compared with non-Chinese/non-Asians.43

**Women**

More than one-half of the 5.7 million people in the United States who have HF are women.7 Younger women with advanced HF generally have severely impaired LV systolic function. The vast majority of women with advanced HF are older adults. HF is a disease of older adults, but women with HF are, on average, 5–10 years older than men.44 The annual incidence of HF was reported to be 8.2 cases per 1,000 population in Caucasian women 65–74 years of age, increasing to 45.6 cases per 1,000 population in Caucasian women ≥85 years of age. In Caucasian men, the annual incidence ranges from 15.2 cases per 1,000 population (65–74 years) to 65.2 cases per 1,000 population (≥85 years of age; Fig 1).7

The lifetime risk for developing HF is 1 in 5 for both women and men,55 but the risk factors of antecedent MI, hypertension, and diabetes differ in their importance for the two sexes. The incidence of MI is lower in women, particularly in younger women, than in men of similar age.46 However, women who have an MI are more likely than their male counterparts to develop HF.47 It is unclear if this increased risk of HF after MI is a function of other differences between men and women with MI, including women exhibiting older age, higher rates of diabetes and renal dysfunction, and delays in the diagnosis and treatment of MI owing to atypical presentations,48 or if the risk is inherently a feature of ischemic heart disease in women. Similarly, a history of hypertension places women at greater risk of HF than men.49 Among the Framingham study subjects, the risk of developing HF was doubled for women who were hypertensive, but the risk was tripled for women compared with similar normotensive subjects.49 Over the past 5 decades, the incidence of HF has decreased in women but not in men.50 More aggressive treatment of hypertension has also led to a decrease in hypertension prevalence, which may be responsible for the decreased incidence of HF in women. Similarly, diabetes increases the risk of HF up to 5-fold in women, compared with a doubling of risk in men with diabetes.51 Once the disease is manifest, however, the presentation of HF does not differ between women and men, with symptoms of fluid retention and dyspnea predominating for both sexes.44

HF in women much more commonly manifests as HFpEF, which likely reflects differences in a range of risk factors and biology and also has implications for treatment.52,53 An analysis of data from Olmsted County, Minnesota, showed that 69% of patients with HFpEF were women and almost one-half were ≥80 years old, whereas in patients with HFrEF, 41% were women, and 38% were ≥80 years old.54 Two studies assessed the clinical characteristics associated with HFpEF and HFrEF in both a university hospital and a community hospital.55,56 In both studies, female sex predicted the presence of HFpEF. In an analysis of data from 8,592 subjects enrolled in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort study, female sex was associated with a higher risk of developing new-onset HFpEF, and male sex was associated with a greater risk of new-onset HFrEF (P < .001 for the interaction).57 Data from the Framingham study showed similar findings.58 A large study of 4 integrated health networks showed that among 23,435 patients with HF, nearly equally divided between HFpEF and HFrEF, women accounted for 61.2% of HFpEF yet only 36.1% of HFrEF.59

Although a large proportion of women who develop HF have CAD, risk factors for progression to HF in this group of women have not been well investigated. An analysis of the participants of the Heart and Estrogen/Progestin Replacement Study (HERS)60 sought to identify predictors of HF among women with coronary disease. Over the course of 6 years, 237 (9.9%) of the 2,391 participants who did not have HF on entry were hospitalized or died of HF. After adjustment for age and medication use, 9 risk factors were identified that were independently associated with the development of HF. Diabetes was the strongest predictor of HF, especially in the setting of concomitant renal insufficiency or morbid obesity. Poorly controlled hypertension, identified as a systolic blood pressure >140 mm Hg, was present in more than one-third of the women studied and was associated with a 2-fold increased risk of developing HF. The combination of diabetes and obesity appeared to be particularly strongly associated with CAD in women compared with men.61

**Older Adults**

Unlike many other diseases, lifetime HF risk does not change with age, remaining 20% at 80 years of age, even though life expectancy is much shorter.7 In contrast, the incidence of HF increases with increasing age (Fig 1),7 reaching ~10% among individuals ≥80 years old.7 In part because more than one-half of HF patients ≥75 years old are women, the majority of older patients have HFpEF. In contrast, ~90% of HF patients under 65 years of age have HFrEF.52

Several specific changes in cardiac structure and function are associated with cardiac aging, and may explain a
number of pathophysiologic and phenotypic features typical of the elderly. With advancing age, there is a decrease both in myocyte number and function. Regenerative mechanisms are impaired and myocardial fibrosis is increased. The prevalence of amyloid also increases with age.

Hypertension is the most common antecedent condition among patients with incident HF. Among older adults, hypertension accounts for ~40% of HF cases in men and ~60% in women.

Moreover, there is a wealth of evidence documenting that antihypertensive therapy reduces HF in older adults with systolic hypertension, including in octogenarians. In the Hypertension in the Very Elderly Trial (HYVET), for example, which randomized 3,845 hypertensive patients ≥80 years of age to diuretic-based therapy with indapamide or to matching placebo, active treatment was associated with a 64% reduction in incident HF (P < .001).

Thus, there is compelling evidence that treatment of hypertension prevents progression from stage B to stage C HF in older adult and elderly patients, including octogenarians. Antihypertensive therapy likely reduces the rate of progression from stage A to stage B HF as well.

### Heart Failure–Related Morbidity and Mortality

Given the differences outlined above, it is not surprising that outcomes also differ between populations. In 2012, HF was listed as the cause of death in 60,341 persons in the US, equivalent to an age-adjusted rate of 17.1 per 100,000 population. The rates of HF death across sex, race, and ethnic groups are presented in Table 3.

#### Non-Caucasian Ethnic Groups

Variable HF clinical outcomes have been reported among non-Caucasian ethnic groups. In general, non-Caucasian ethnic groups with HF appear to have excessive HF-related mortality and morbidity, although contemporary data are less definitive regarding mortality. A subgroup analysis of the Studies of Left Ventricular Dysfunction (SOLVD) database showed that African Americans were at greater risk of death and hospitalization compared with Caucasians.

Although African Americans hospitalized with HF tended to have mortality rates similar to those of Caucasians, after adjustment, functional decline was 50% higher. Among Medicare beneficiaries, African-American and Hispanic patients were more likely to be readmitted but less likely to experience a fatal event compared with Caucasians and Asians.

In the CDC survey, Hispanic HF patients had higher rates of hospitalization and readmissions, but lower in-hospital and short-term mortality rates compared with non-Hispanic Caucasians. Hispanics with HF in the US have longer median life expectancy than other ethnicities.

In other studies, researchers found that race was not an independent predictor of mortality; however, when patients were stratified by etiology of HF and race, African Americans with nonischemic LV dysfunction had worse survival than Caucasians.

Among 1,268 immigrants with HF, lower level of acculturation was identified as a risk factor for 30-day readmission (odds ratio [OR] 1.70, 95% CI 1.07–2.68) but not for 1-year all-cause mortality. Genetic polymorphisms may affect outcome. A polymorphism (−344 T/C) in the promoter region of the aldosterone synthase gene was associated with increased risk of death and hospitalization and worse LV remodeling in African Americans with HF compared with African Americans homozygous for the wild-type allele.

In the A-HeFT trial, an analysis of the corin I555(I555) allele was associated with greater impairments in plasma B-type natriuretic peptide (BNP) processing and increased risk for death or hospitalization for HF in the placebo group receiving treatment with ACE inhibitors or angiotensin receptor blockers (ARBs) and beta-blockers; however, the addition of fixed-dose combination hydralazine and isosorbide dinitrate (HYD-ISDN) completely ameliorated this adverse prognostic impact.

#### Women

After development of HF, women generally have better survival than men with HF, and the cause of death is more likely to be noncardiac in women, perhaps owing to their older age and associated comorbidities.

In determining prognosis in HF patients, high-risk features are the same in men and women and appear to explain most, if not all, of the difference in survival according to sex.
Although studies have documented sex-specific predictors of mortality, the predictors identified across studies depend on the study population and the variables available in the database. In particular, an ischemic etiology, more common in men, carries a clearly worse prognosis than nonischemic causes.40 Despite differences in important HF characteristics between men and women,2,3,8 there were no sex-based differences in in-hospital mortality or in risk factors predictive of mortality among patients treated in Get With the Guidelines registry hospitals, including acutely decompensated patients with either HFpEF or HFpEF.86 Furthermore, the age-adjusted rates of 28- and 365-day case fatality among patients hospitalized for incident acute HF were 10.4% and 29.5%, respectively, and did not differ according to sex or race.71 For patients hospitalized with acute HF and renal dysfunction, length of stay was slightly prolonged in women compared with men, and age-adjusted 180-day mortality was slightly lower in men.85 Despite differences in background characteristics, there were no differences in multivariable risk-adjusted 180-day mortality according to sex.85 When national HF data were used to assess hospitalization and mortality by patient age and sex, men were more likely to be readmitted for HF and were also more likely to have in-hospital mortality in all of the age categories assessed.84 HF hospital stay rates from 2001 to 2009 declined over time among Caucasian men, Caucasian women, and African-American women, but not among African-American men.87 Finally, when race and sex were assessed in 1,264 patients >65 years old with newly diagnosed HF, total mortality and cardiovascular mortality rates were lower in women than in men, regardless of whether race was Caucasian or African American.83 The results were similar after adjustment for covariates.

Older Adults

HF is a leading cause of morbidity and mortality in older adults. Age ≥80 years and a history of HF were 2 of the 5 important factors found to predict risk of rehospitalization within 3 months of discharge in a study of elderly patients hospitalized in internal medicine units.88 The number of noncardiac comorbidities correlates closely with the likelihood of readmission. Furthermore, in a study of 2,033 patients hospitalized with acute HF and renal dysfunction, age and previous HF hospitalization predicted 180-day all-cause mortality.89 Age >65 years was an important predictor of HF hospitalization or mortality only among patients with HFpEF in an analysis of recently hospitalized HF patients enrolled in a self-care study.90 Finally, in a national study of patient outcomes after hospitalization, the relationship between age and in-hospital HF mortality was U-shaped, with patients <25 years old and >64 years old having a higher risk of in-hospital mortality than patients 25–64 years old.84

In a retrospective observational study of mode of death among older adults with HF in Europe, the mean time between diagnosis and death was 48 months. Overall, 28% had sudden cardiac death, 23% had progressive HF, and almost one-half died of other causes.91

Representation in Clinical Trials

Randomized controlled trials are accepted as the most unbiased measure of efficacy for new drugs, devices, or strategies of care. However, eligibility criteria are commonly restrictive. Furthermore, subjective biases and logistical considerations tend to further homogenize study populations. Registries and surveys are generally more inclusive than clinical trials, but they may yield different patient characteristics and outcomes than similar clinical trials. For example, in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), baseline patient characteristics, processes of care, admission and discharge medications, and clinical outcomes differed between patients enrolled in the clinical trial and those enrolled in the registry component of the same study.92 Registry patients were on average 6 years older than trial patients, and they more likely to be female (48% vs 31%).92 In addition, in-hospital mortality was higher in registry patients compared with trial patients (9.3% vs 1.3%).92 Similarly, in a review of 27 clinical trials and 8 prospective epidemiologic studies or registries published from 1987 to 2001, patients enrolled in clinical trials were younger (63 ± 10 years vs 75 ± 11 years; P < .0001), more likely to be male (72% vs 54%; P < .0001), had a lower ejection fraction (26 ± 7% vs 38 ± 15%; P < .0001), and had a lower prevalence of New York Heart Association (NYHA) functional class III-IV (62% vs 75%; P < .0001) than patients encountered in daily clinical practice.93

In general, non-Caucasian ethnic groups, women, and older adults have been underrepresented in HF clinical trials. Even when these groups are included in proportion to the frequency of HF in the general population, small sample sizes limit the ability to conduct reliable subgroup analyses and to extrapolate results to the broader population.

Non-Caucasian Ethnic Groups

There is substantial underrepresentation of non-Caucasians in HF trials, and other than African Americans, ethnic subgroups are frequently not mentioned in clinical trial publications. Enrollment of African Americans in HF clinical trials has varied substantially from 1% to 28% of participants, although they have been underrepresented in the majority of trials.94–106 Barriers to involvement include lack of awareness, communication, economic factors, and mistrust.107

Women

The early Vasodilator Heart Failure Trials108 were conducted in the Veterans Administration and recruited only men. However, in more recent trials, women compose 22%–31% of study participants, consistent with most epidemiologic studies and the sex distribution of
One notable exception was A-HeFT, in which women composed an unprecedented 40% of patients. A greater problem regarding representation of women in HF trials is the relative lack of treatment trials in HFpEF. Of the few major treatment trials of HFpEF that have been conducted, women composed 40%–60% of the study population. None of these trials demonstrated an unqualified benefit of the tested therapy. Thus, data are lacking to guide the treatment of HFpEF, a problem that may affect women to a greater extent than men.

Patients who are approached for participation in clinical research trials but do not consent to participate tend to be older and more often are women. It has been suggested that the low number of women enrolled in clinical trials reflects a reluctance to participate. Although reluctance to participate does not appear to significantly contribute, other factors, such as higher symptom burden and higher psychosocial stress due to lack of caregiver support compared with men, may hinder participation. In addition, women with HF are older and substantially more likely to live alone than men. The motivation to participate in trials may also be different. When women participated in clinical research, they reported participating to attempt to live longer, whereas men reported a desire to contribute to medical science.

### Older Adults

Despite the fact that HF is predominantly a disorder of older adults, the majority of clinical trials have either explicitly excluded older patients or have enrolled relatively healthy older subjects with few comorbidities. Several factors may explain the underrepresentation of older adults in clinical trials. First, older adult patients are less likely to refer to a cardiologist during a hospitalization for acute HF and to receive specialist counseling for outpatient care. Secondly, ~30% of HF trials explicitly excluded elderly patients. Enrollment criteria often focus on age-related conditions, such as comorbidities and life expectancy. Patients enrolled in clinical trials are less likely to have comorbidities commonly encountered in older patients, such as atrial fibrillation (12% vs 31%; P < .0001) and diabetes (22% vs 24%; P < .02). Finally, most trials have concentrated on HFrEF, and the few studies that enrolled patients with HFpEF have failed to demonstrate benefit regarding the primary end point. Therefore, whereas there is a rich body of evidence to guide treatment in middle-aged patients, most of whom have HFrEF, management of older adults, especially those with HFpEF, remains largely empiric.

### Special Issues in the Management of Heart Failure Among Special Populations

#### Non-Caucasian Ethnic Groups

**Access.** Non-Caucasian ethnic groups are more likely than Caucasians to be uninsured, owing to lower rates of job-based insurance; therefore, they have limited access to health care. Non-Caucasian ethnic groups tend to have fewer preventive visits, and Hispanics have the highest uninsured rates of all ethnic groups. Although the Affordable Care Act has succeeded in lowering barriers to care for many racial/ethnic minorities, details of implementation, including the significant coverage gap that exists in states that have not expanded Medicaid, and inability to address the expanding population of undocumented persons with chronic disease have limited its impact. Furthermore, the success (or lack thereof) of the Affordable Care Act on increasing access to care specifically for HF patients has not been well studied.

**Comorbidities.** One of the explanations for the disparities in HF prevalence and outcomes in non-Caucasian ethnic populations is a higher burden of comorbid conditions, as previously discussed. Unhealthy dietary trends correspond to socioeconomic status, and non-Caucasian ethnic groups constitute a higher proportion of the poor in the US. African-American and Hispanic adults and children tend to have higher rates of inactivity and obesity. Understanding the higher prevalence of comorbid conditions that contribute to cardiovascular disease offers opportunities for prevention of HF.

**Response to Pharmacologic Therapy.** In African Americans, the response to neurohormonal blockade has been variable in clinical trials. Interpretation of these findings is complicated by lack of adequate representation of African Americans in these trials, as previously discussed. In the absence of robust data, some have interpreted results of inadequate data to mean that African Americans do not respond to and therefore should not be prescribed evidence-based therapies. Although African Americans have a less robust blood pressure response than Caucasians to enalapril, effects on HF outcomes appear to be similar (Table 4). In SOLVD, treatment with enalapril was associated with a statistically significant reduction in the adjusted risk of hospitalization compared with placebo for Caucasian but not African-American patients, although the study was underpowered to test a difference in treatment response by race. Regarding beta-blockers, bucindolol did not demonstrate benefit in African Americans (and may have had an adverse effect), but the response to carvedilol and metoprolol succinate were similar regardless of race. African Americans were poorly represented in trials of mineralocorticoid receptor antagonists (MRAs) in patients with LV dysfunction; therefore, specific data to describe their responsiveness to these agents are lacking.

The A-HeFT trial provides the best data regarding therapy in self-identified African Americans with HFrEF. Interestingly, the −344 TT allele of aldosterone synthase, which is associated with low-renin hypertension, was associated with a greater response to therapy with HYD-ISDN. The beneficial effect of HYD-ISDN on LV remodeling occurred primarily in the group with a polymorphism in the NOS3 gene, NOS3 Glu298Glu, a highly prevalent polymorphism in African Americans.
African Americans are the only non-Caucasian ethnic group addressed in national and international guidelines owing to the lack of data in other groups. Treatment recommendations are consistent across the general HF population, regardless of ethnicity (except for HYD-ISDN). Furthermore, the combination of HYD-ISDN is considered to be standard therapy in African Americans who are taking beta-blockers and ACE inhibitors or ARBs because of the beneficial effect on survival. However, application of this add-on approach in clinical practice is limited owing in part to the need for 3-times-daily dosing, relatively high rates of drug intolerance and withdrawal, the cost of the combination drug, a lack of data on generic substitution, and, possibly, blood pressure limitations in patients who are already taking multiple agents.

**Response to Rhythm Device Therapy.** Enrollment of non-Caucasian ethnic groups in implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) trials has been low. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), 17% of participants were African American. Despite low enrollment, African Americans experienced a reduction in mortality similar to Caucasians with ICD and CRT with defibrillation (CRT-D), and they exhibited similar rates of both adherence to medical therapy and refusal of ICD implantation after randomization. Nonetheless, African Americans may be less likely to receive ICDs or CRT-D. Genetic factors may also influence the burden of arrhythmia. In African Americans with LV dysfunction and ICDs, a polymorphism of the cardiac sodium channel SCN5A was associated with ICD shocks.

Although the guidelines do not specifically address the application of device therapies in non-Caucasian ethnic populations, there are no data to suggest that these therapies are not beneficial in non-Caucasian ethnic groups. Therefore, ICD and CRT should be considered in the management of all appropriate HF patients.

**Response to Mechanical Circulatory Support and Transplantation.** In the limited data available, African Americans and Caucasians benefit similarly from mechanical circulatory support (MCS). African Americans have traditionally had higher mortality than Caucasians after transplantation. A recent analysis demonstrated that short-term (6-month) mortality was similar in African Americans, Caucasians, and Hispanics, but disparities in long-term outcomes persisted owing to better long-term survival observed in Caucasians but not in African Americans or Hispanics. The causes of this disparity are poorly understood but likely include socioeconomic factors, donor-related issues, and immunologic factors. Nevertheless, MCS and transplantation remain recommended therapies for stage D HF patients of all ethnicities who meet selection criteria.

Because there is a paucity of adequate data regarding HF therapy in non-Caucasian ethnic groups and until it becomes clinically feasible to detect genetic determinants of variable response, standard guideline-directed HF therapy should be prescribed to all medically appropriate patients in the absence of a clear contraindication. Further study regarding contributing comorbid conditions, prevention of HF, socioeconomic stressors, and genomic variations is warranted to determine the best management strategies for specific ethnic populations. Clinical trials that are inclusive and adequately powered are essential to broadening understanding of HF therapies in non-Caucasian ethnic populations.

**Women**

**Response to Pharmacologic Therapy.** Sex-specific reporting of cardiovascular clinical trial results is limited, and rarely prespecified, hampering rigorous statistical analysis of sex differences. Insight into sex differences has been gained through comparative analyses and meta-analyses.

ACE inhibitors remain a cornerstone of HF treatment. Although early studies, such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) 1, with few women patients enrolled, suggested no reduction
in mortality with enalapril for women, later meta-analyses of ACE inhibitor trials demonstrated benefits regardless of sex, although the benefits may be attenuated in women. Sex-related differences have been suggested regarding the treatment of asymptomatic LV dysfunction with ACE inhibitors, with only men receiving benefit. The benefit of beta-blockers appears to be similar regardless of sex.

The role of digoxin in women with HF has been questioned. A post hoc analysis of data from the Digitalis Investigation Group (DIG) study demonstrated that digoxin therapy was associated with an increased risk of death from any cause among women, but not among men, with HFrEF systolic dysfunction. Higher serum digoxin concentrations in women than in men, rather than a more specific sex difference, has been postulated as an explanation for the higher mortality. Higher serum concentrations should be anticipated in women because of their lower body weight, and this should be considered when dosing digoxin. Digoxin is no longer recommended as a first-line therapy in HF guidelines for either men or women, and it should be reserved for those who remain symptomatic despite standard therapies.

In the Randomized Aldactone Evaluation Study (RALES), spironolactone reduced mortality in patients with severe HF when added to therapy with digoxin, diuretics, and ACE inhibitors. However, sex-specific outcomes were not reported, and only 27% of enrolled patients were female. Prespecified subgroup analyses of the efficacy of eplerenone in patients with LV dysfunction after MI and in those with HFrEF and mild symptoms demonstrated similar benefits in women and men.

Sex analyses from A-HeFT showed that fixed-dose HYD-ISDN improved HF outcomes in both men and women. The HYD-ISDN combination significantly improved the primary composite score and event-free survival as well as reduced the risk of first HF hospitalization similarly in both sexes. HYD-ISDN had a slightly greater mortality benefit in women, but treatment interaction by sex was not significant.

In older reports, women were less likely to be prescribed guideline-based HF therapy than men. However, in more recent reports, treatment differences were smaller, even absent for some pharmacologic therapies. Women were as likely as men to be prescribed beta-blockers and ACE inhibitors or ARBs. Fewer women than men received MRAs, but <30% of eligible men and women were prescribed this therapy, which represents a more significant problem than the small sex gap. There are no data to suggest that guideline-based therapy should be applied differently by sex, other than perhaps being sensitive to body weight when selecting an initial dose and monitoring levels of digoxin more closely in women.

Response to Rhythm Device Therapy. In some reports, devices (CRT and ICDs) appear to be underused in women. CRT trials enrolled from 16% to 32% women. In the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) only 25% of the 1,820 patients in the trial were female, but there was a greater benefit of the therapy in women than in men. In MADIT-CRT, women experienced greater reductions than men in the primary end point of HF events or all-cause mortality (women: hazard ratio [HR] 0.31, 95% CI 0.19–0.50; men: HR 0.72, 95% CI 0.57–0.92; interaction P < .01). Women were more likely to have nonischemic disease and left bundle branch block (LBBB), factors known to predict benefit of this therapy. Women had more evidence of reverse remodeling than men in response to CRT.

A Food and Drug Administration (FDA) analysis of individual patient data from 3 randomized, controlled trials of CRT showed similar results. In this analysis, women had a lower risk than men of HF events or death with CRT-D compared with ICD alone, and the effect was most evident in patients with LBBB and QRS duration 130-149 ms (women: HR 0.24, 95% CI 0.11–0.53 [P < .001]; men: HR 0.85, 95% CI 0.6–1.21 [P = .38]). All-cause mortality was lower also for women with LBBB and QRS duration 130-149 ms treated with CRT-D compared with ICD alone, but not for men (women: HR 0.24, 95% CI 0.06–0.89 [P = .03]; men: HR 0.86, 95% CI 0.49–1.52 [P = .60]).

Several analyses evaluated differences in clinical outcome by sex with ICD therapy. No statistically significant interactions between ICD treatment effect and sex were observed in the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial or in SCD-HeFT. However, limited conclusions can be drawn from these data, because the number of women enrolled was relatively small.

Data from the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) were used to evaluate the association between mortality and CRT and ICD therapy in men and women with HF. Both ICD/CRT-D and CRT-pacemaker/CRT-D were associated with lower mortality at 2 years in both men and women. The device-by-sex interactions were not significant.

Response to Mechanical Circulatory Support and Transplant. Data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and individual clinical trials suggest that men and women have similar survival rates after implantation of MCS. In an analysis of the Heartmate II bridge to transplant trial, fewer women than men underwent heart transplantation (40% vs 55%; P = .001), and the duration of support appeared to be longer for women than men (238 days vs 184 days; P = .003). Adverse events appeared to occur similarly in women and men, although neurologic events were reported more frequently in women. Functional capacity and quality of life improved significantly at 6 months in both men and women.

In 1988, women composed 17% of the US transplant population, whereas in 2013, 770 (30.4%) of the 2,531
heart transplants were in women.\textsuperscript{166} Women were much younger than men, on average, at the time of transplantation. In 2013, 55.4\% of the women, versus 37.1\% of men, were <50 years old at the time of transplantation. Of the 446 patients receiving transplants that year who were over the age of 65 years, only 72 (16\%) were women.\textsuperscript{166}

Few studies have examined the effect of sex on outcomes in cardiac transplantation, and results are conflicting. In the majority of series, there was a higher incidence of rejection after transplantation and a poorer survival for women.\textsuperscript{165–167} One proposed reason for poorer outcomes was a greater frequency of autoimmune-mediated diseases in women.\textsuperscript{167} An analysis of patients from the Cardiac Transplant Research Database suggested another contributor: previous pregnancy.\textsuperscript{168} Female transplant recipients were stratified based on their history of childbirth to evaluate the effects of a woman’s parity on rejection and survival. Previous pregnancy, but not the recipient’s sex, was a risk factor for rejection. Another postulated risk includes specific strategies of immunosuppression after transplantation,\textsuperscript{166} but this has not been studied.

Many studies documented referral bias in the diagnosis and treatment of women with CAD. Whether or not such bias exists regarding cardiac transplantation has not been as well explored. Investigators at 1 center examined all patients referred for transplantation evaluation.\textsuperscript{169} Reasons for acceptance and rejection of the procedure were evaluated with particular attention paid to sex differences. Female sex was independently associated with rejection of the procedure largely because women more often than men refused transplant candidacy (29\% vs 9\%), despite a recommendation that transplantation was their best therapeutic option. Whether or not a sex bias exists in the referral of women with HF to a transplant center for evaluation deserves further study.

Response to Exercise. Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACCTION) trial was a randomized trial of formal exercise training versus no exercise training (with optimal medical therapy in both groups) conducted in 2,331 patients with HFrEF (left ventricular ejection fraction $\leq 35\%$), 28\% of whom were women.\textsuperscript{170} In a prespecified subgroup analysis, the hazard ratio (HR) for the end point of all-cause mortality or all-cause hospitalization was 0.83 (95\% CI 0.68–1.00) for women and 0.97 (95\% CI 0.87–1.09) for men (interaction $P = .17$).\textsuperscript{170} In an exploratory analysis, after covariate adjustment, women appeared to benefit from exercise training whereas men did not (women: HR 0.74, 95\% CI 0.59–0.92; men: HR 0.99, 95\% CI 0.86–1.13; interaction $P = .027$).\textsuperscript{171} No differences were observed between men and women in change in peak VO$_2$.\textsuperscript{171} Although not conclusive, these data suggest that women might particularly benefit from exercise training.

Peripartum Cardiomyopathy. Peripartum cardiomyopathy is by definition a disease of women. It occurs once in every 2,500 to 4,000 live births,\textsuperscript{172} although the incidence appears to be increasing in the US.\textsuperscript{173} This entity is defined clinically as the onset of cardiac failure with no identifiable cause in the last month of pregnancy or within 5 months of delivery.\textsuperscript{172} A recent study of >4 million delivering mothers from 6 US states showed that the prevalence of peripartum cardiomyopathy is highest among African Americans and similar among Caucasians and Hispanics.\textsuperscript{175} The prognosis of women with peripartum cardiomyopathy is variable. Although the majority of patients improve rapidly and have recovery of LV function, others may die or require cardiac transplantation.\textsuperscript{176} Left ventricular assist device therapy may also play an important role for selected patients as a bridge to late myocardial recovery or heart transplant.\textsuperscript{177} For women with recovered LV function, there remains a risk of recurrent HF with subsequent pregnancies, and consultation with maternal-fetal medicine physicians and HF cardiologists is recommended. Recent studies suggest a role for prolactin in the pathophysiology of proapoptotic cardiomyopathy, including angiostatic and antiapoptotic properties, as well as the potential role of bromocryptine in treatment.\textsuperscript{178}

Older Adults

Diagnosis and Management. HF in older adults differs in many ways from HF in middle-aged patients (Table 5). Younger patients are more likely to receive care from a cardiologist or HF specialist, whereas older patients, especially the very elderly, are less likely to be managed by an HF specialist. The presentation may be atypical and complicated by the presence of other comorbidities and polypharmacy.

The most common symptoms of HF in older adults include exertional shortness of breath, lower-extremity edema, and impaired activity tolerance, but older patients are also likely to present with atypical symptoms, including fatigue, altered sensorium, irritability or agitation, gastrointestinal disturbances (anorexia, abdominal bloating, altered bowel habits), or failure to thrive. In addition, older patients may not report exertional shortness of breath or activity intolerance because of sedentary lifestyle, cognitive impairment, or presuming that symptoms are due to “old age.” Conversely, typical symptoms of HF may be due to other causes. For example, shortness of breath and exercise intolerance may be due to acute or chronic lung disease, anemia, obesity, or physical deconditioning.

Older patients with HFrEF rarely have an S3 gallop and may not exhibit signs of right HF, such as elevated jugular venous pressure, abdominoujugal reflux, and peripheral edema.\textsuperscript{179,180} Rales may be absent owing to chronicity of the HF itself, chronic lung disease, or atelectasis.\textsuperscript{180–182} Similarly, lower-extremity edema may be due to noncardiac causes, especially venous stasis, or medications, such as calcium channel blockers.

The chest radiograph may be difficult to interpret because of concomitant lung disease, kyphosis, or poor inspiratory effort. Similarly for younger patients, the absence of congestion on chest x-ray does not preclude
the diagnosis of HF. Natriuretic peptide (BNP, N-terminal pro-BNP) levels rise mildly with age, especially in women, so that the specificity for diagnosing HF is reduced in older adults.\textsuperscript{183,184} Echocardiography is less helpful in establishing a diagnosis of HF in older patients because abnormalities of diastolic function and valve function are prevalent in older patients without HF.

**Comorbidities.** HF in older adults almost always occurs in the context of multiple comorbidities, with most patients having 2–6 noncardiac comorbidities and \textasciitilde 25\% having \textasciitilde 6 coexisting chronic illnesses.\textsuperscript{185} Many common comorbidities directly affect the diagnosis, management, and prognosis of HF (Table 5).\textsuperscript{186}

**Polypharmacy.** The high burden of multimorbidity in older HF patients also engenders polypharmacy, most commonly defined as the regular use of \textasciitilde 5 medications. HFrEF is usually treated with \textasciitilde 4 drugs (loop diuretic, ACE inhibitor or ARB, beta-blocker, and MRA), and potentially up to 7 or 8 drugs. Most older adult HF patients have CAD, hyperlipidemia, hypertension, and/or diabetes, and the majority have additional noncardiac comorbidities, as noted previously. For example, nonsteroidal antiinflammatory drugs (NSAIDs), which are the most widely used agents to treat osteoarthritis and are readily available without prescription, promote sodium and fluid retention, may worsen renal function, antagonize the effects of diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors, and lead to increased risk of HF hospitalization.\textsuperscript{187,188} It is not surprising that older HF patients take an average of \textasciitilde 10 medications and that use of \textasciitilde 5 medications is not uncommon.\textsuperscript{189}

“Megapharmacy” in older HF patients has several clinical implications. First, the likelihood that patients are taking their medications as prescribed declines markedly with both the total number of medications and the complexity of the regimen.\textsuperscript{190} Apart from the inherent challenges of managing a very complex medication schedule, even patients with the best intentions may be underadherent or overadherent (ie, inadvertently take extra doses) owing to lack of understanding or clarity on how medications are supposed to be taken. This problem is often further aggravated by subclinical or overt cognitive impairment in older patients.\textsuperscript{190}

A second critical implication of polypharmacy is that the risk of clinically important drug-drug interactions increases progressively with the number of medications used and exceeds 90\% in patients taking \textasciitilde 10 medications (ie, the majority of older HF patients).\textsuperscript{186} Some high-profile drug interactions that affect patients with HF, such as those involving warfarin, digoxin, amiodarone, and NSAIDs, are generally appreciated by most clinicians, but many other common drug interactions (eg, interactions of statins with some antibiotics, calcium channel blockers, and dietary supplements) are less well known.

Finally, the cost of medications is an important consideration for many older patients with limited financial resources. In that context, polypharmacy may lead to nonadherence, which can lead to worsening HF. For all these reasons, clinicians must simplify and consolidate the regimen to the extent feasible, consider medication costs, and use low-cost generic drugs when appropriate.

**Disability, Frailty, and Loss of Independence.** Older patients, especially women, are more likely to live alone or in a long-term care facility, have limited social support, and experience barriers to transportation. Such factors may interfere with medication and dietary adherence, participation in regular exercise, and ability to attend follow-up appointments. These issues are often further complicated by diminished functional status or frailty attributable in part

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**Table 5. Impact of Comorbidities Common in Older Adults on Heart Failure (HF) Diagnosis and Management**

<table>
<thead>
<tr>
<th>Comorbid Condition Common in Older Adults</th>
<th>Impact on HF Diagnosis and Management</th>
</tr>
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<tbody>
<tr>
<td>Reduced creatinine clearance</td>
<td>Contributes to volume overload and attenuates diuresis; may be worsened by diuretics, renin-angiotensin system inhibitors</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Contributes to diagnostic uncertainty and symptom severity; may be difficult to determine volume status</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>May mask symptoms and contribute to deconditioning and disability</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>May mask symptoms and contribute to deconditioning and disability</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>May mask symptoms and contribute to nonadherence</td>
</tr>
<tr>
<td>Depression, social isolation</td>
<td>May contribute to nonadherence and worse prognosis</td>
</tr>
<tr>
<td>Arthritis</td>
<td>May mask symptoms and contribute to deconditioning and disability; NSAIDs may worsen HF and renal function, antagonize medications</td>
</tr>
<tr>
<td>Anemia</td>
<td>May worsen symptoms and prognosis</td>
</tr>
<tr>
<td>Postural hypotension, falls</td>
<td>May be worsened by HF therapies</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Aggravated by diuretics and ACE inhibitor cough; may contribute to nonadherence</td>
</tr>
<tr>
<td>Sensory deficits (visual, auditory)</td>
<td>May interfere with communication and adherence</td>
</tr>
<tr>
<td>Nutritional disorders</td>
<td>Contribute to functional decline and cachexia</td>
</tr>
<tr>
<td>Frailty*</td>
<td>Increased risk for adverse outcomes, including falls; exacerbated by hospitalization, inactivity</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Contributes to nonadherence and drug interactions</td>
</tr>
</tbody>
</table>

NSAIDs, nonsteroidal antiinflammatory drugs; HF, heart failure; ACE, angiotensin-converting enzyme.

*Criteria include unintentional weight loss (\textasciitilde 10 pounds in past year), slow walking speed (lowest quintile adjusted for sex and height), weak handgrip strength (lowest quintile based on sex and body mass index), low physical activity (lowest quintile for men and women), and self-reported exhaustion (based on response to 2 items in the Center for Epidemiologic Studies—Depression scale).

to the aging process (i.e., distinct from age-associated comorbidities). These factors may confound the initial diagnosis of HF and make distinguishing active HF from other potential causes of symptoms or functional decline difficult. Also, patients who are not strictly homebound may be ineligible for home health benefits under current Medicare guidelines, thus falling into a continuity-of-care gap.

HF is common in patients residing in long-term care facilities, with estimated prevalence rates of 20%–30%. Patients living in these controlled environments may be more likely to receive their medications as prescribed. However, multiple “as needed” medications, which are often added to the regimen, may aggravate polypharmacy and the risk for drug interactions. Another challenge of institutional care may be limited dietary options, leading to an inability to adhere to sodium restriction. Institutionalized patients may be less physically active than those living at home, thus contributing to more rapid functional decline.

Functional impairments and frailty become increasingly common with advancing age in the general population as well as in patients with HF. To some extent, these “geriatric syndromes” reflect the cumulative burden of multimorbidity. However, aging processes, including oxidative stress, low-grade inflammation, and telomere shortening, play a fundamental role in progression of disability and development of frailty (see Table 5 notes).

It is important to note that frailty is found in HF patients of all ages, and these issues are relevant in any frail HF patient, no matter the age. However, there are important intersections that exist between HF and frailty in older adults, such that HF is a risk factor for incident frailty, and the presence of frailty is associated with poor response to treatment, worse functional outcomes, and increased mortality in HF patients. HF and frailty likely share some pathogenic mechanisms, including increased oxidative stress and cytokine activation that predispose to cachexia, sarcopenia, and reduced survival.

Response to Pharmacologic Therapy. The relevance and applicability of current HF guidelines to the management of most older adult and very elderly HF patients is uncertain, owing to the differences between older and younger patients as noted previously, which tend to become more pronounced in the very elderly (i.e., ≥85 years). Management of HFpEF is generally similar in older and younger patients. However, data are scant on the use of many therapies in patients >80 years old. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS), nebivolol reduced the primary composite end point of all-cause mortality or cardiovascular hospitalization compared with placebo in patients ≥70 years of age. However, the benefit of beta-blockade observed in the SENIORS randomized trial has not been replicated in observational analyses.

Older adult and very elderly patients are at increased risk for adverse effects from beta-blockers (e.g., bradycardias, fatigue), RAAS inhibitors (e.g., worsening renal function, hyperkalemia), and HYD-ISDN (e.g., orthostatic hypotension), principally due to age-associated changes in the cardiovascular system, kidneys, and other organ systems. Therefore, initial dosages should be lower and dose titration should be slower in older patients, and heightened vigilance is required for detection of adverse effects. In older patients with multiple comorbidities or limited life expectancy, the potential benefits of all drugs should be balanced against the potential risks and the patient’s stated preferences for length of life versus quality of life. In some cases, withholding guideline-directed therapy if the patient perceives that the burden outweighs the benefit may be appropriate.

Diuretics and digoxin are both effective for alleviating symptoms. However, older patients are at increased risk for diuretic-induced electrolyte disturbances and worsening renal function. Therefore, careful dose titration of these medications is required while monitoring symptoms, physical examination, renal function, and electrolytes. In the DIG trial, the benefits of digoxin in reducing HF mortality and hospitalizations were similar in younger and older patients, including octogenarians. Therefore, digoxin remains a useful agent for improving quality of life outcomes in HF patients with persistent symptoms despite optimal therapy. The volume of distribution and clearance of digoxin decline with age; consequently, a daily dose of ≤0.125 mg is therapeutic in most older patients with preserved renal function (i.e., estimated glomerular filtration rate ≥45–60 mL/min). In patients with more severe renal impairment, the digoxin dose should be reduced accordingly. Optimal management of HFpEF in older adults remains undefined.

Response to Rhythm Device Therapy. Device therapy plays an increasingly important role in the management of patients with HFrEF, but data in patients >80 years old are very limited. The benefit of ICDs in reducing all-cause mortality declines with age, in part because older patients are at higher risk than younger patients of dying from noncardiac causes (e.g., pneumonia, hip fracture), and in part because sudden death in the older patient is more likely to be related to pulseless electrical activity, i.e., an arrhythmia not responsive to overdrive pacing, cardioversion, or defibrillation. Thus, the benefits of ICDs in patients >80 years old are unproven, and their use for primary prevention of sudden cardiac death in this age group should be individualized.

Conventional pacemakers for treatment of bradyarrhythmias, with or without HF, are effective for alleviating symptoms and improving quality of life in patients of all ages with appropriate indications. Approximately one-half of all pacemakers in the US are implanted in patients ≥75 years old. In addition, although very few older adult patients were enrolled in the major trials evaluating CRT,
several small observational studies have demonstrated that appropriately selected octogenarians experience reduced symptoms, reverse ventricular remodeling, and improved exercise tolerance and quality of life following CRT implantation.\(^{201}\) Therefore, based on currently available evidence, CRT is a reasonable option in selected patients with persistent HF symptoms despite medical therapy who meet criteria for implantation.

Response to Mechanical Circulatory Support and Transplantation. MCS is also being used increasingly as a bridge to transplant or, more commonly in older patients, as destination therapy.\(^{202}\) Although some older patients benefit from MCS,\(^{203}\) the risk of complications, including gastrointestinal bleeding, stroke, and infections, increases with age.\(^{202}\) In addition, very few patients \(\geq 80\) years old have been treated with MCS, so the value at very elderly ages is unknown. Similarly as for all patients, consideration of MCS in older patients as destination therapy should be undertaken only after detailed discussion of the risks, benefits, and alternatives, including palliative care and hospice. Heart transplantation is rarely considered in patients \(> 70\) years old, in part owing to the scarcity of donor hearts. However, reasonable long-term outcomes can be achieved in carefully selected patients 65–70 years old.\(^{204,205}\)

Response to Exercise. The safety and effectiveness of activity and exercise in older adult patients with HF is often questioned because older or very elderly healthy people have reduced exercise tolerance, decreased LV inotropic reserve, and altered adrenergic responsiveness.\(^{206}\) Furthermore, many patients have a prolonged history of sedentary behaviors. In a systematic review of 7 prospective randomized controlled trials of exercise training in older adult patients with HF (\(n = 530;\) mean age 70–81 years), exercise training led to improved 6-minute walk distance and generic quality of life; however, mortality, hospitalizations, peak oxygen consumption, and HF-related quality of life were similar between exercise and control groups.\(^{207}\) In a small study, exercise training improved exercise tolerance in older patients with HFpEF.\(^{208}\) Regular exercise is recommended for all patients with HF, regardless of ejection fraction or age.\(^{134}\) Improved quality of life associated with exercise may be an important factor to maintaining independent living among older adults.

Quality of Life. Frequently, HF-related quality of life is measured with the use of disease-specific tools (eg, the Minnesota Living With HF questionnaire and Kansas City Cardiomyopathy Questionnaire [KCCQ]) or validated generic tools (eg, the SF-36). Although there are many reports available assessing quality of life in older adults with HF\(^{209,210}\) and the association between quality of life and outcomes,\(^{211–215}\) few reports provided direct evidence of the effects of quality of life on quantity of life. In 1 report, quality and quantity of life among older adults with HF were measured with the use of the EuroQol (EQ-5D), a 5-item tool, and the Seattle HF Model (SHFM), respectively. Increased SHFM scores, reflecting higher mortality, were associated with decreased EQ-5D scores, reflecting worse quality of life in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression domains.\(^{216}\) However, the SHFM has an upper age limit of 85 years. In another study involving patients of general practitioners in the United Kingdom, dying trajectories were studied with the use of the KCCQ. Patients were assessed at set intervals \(\geq 5\) times before death. Researchers learned that there was no typical dying trajectory.\(^{217}\) That study, although small, highlights the point that older HF patients do not have a typical dying trajectory or mode of death that resembles what is seen in patients with other terminal or chronic diseases.

Patient Preferences. Goals of care tend to shift with age, such that middle-aged patients with advanced HF are more often considered to be candidates for aggressive interventions, such as ICDs, MCS, and heart transplantation, to sustain life as long as possible. Conversely, older adult patients may prefer interventions aimed at maximizing quality of life over interventions aimed at maximizing survival. Although it is often stated that older patients value quality of life more than length of life, this is a matter of individual preference. When asked directly, some older patients with HF want to live as long as possible regardless of perceived quality of life, although others would be willing to trade variable amounts of survival time for improved quality of life.\(^{218–220}\) Furthermore, patient surrogates, including spouses and physicians, cannot reliably predict patient preferences. Therefore, these care preferences must be addressed through direct discussion with the patient, preferably with the spouse and/or family in attendance. Because preferences and goals of care may change as illness and health status evolve, reassessment is needed periodically, especially when there has been a significant change in prognosis.

Patients with advanced chronic disease, such as HF, may also have changing preferences regarding site of death. In a retrospective observational study of older adults with HF at end of life, 35% were on opioids and 56% died in their homes.\(^{91}\) There are substantial opportunities for better understanding patient preferences near the end of life.

When appropriate, additional consultation from a geriatrician and/or palliative care service should be obtained. Because noncardiac causes of death may be a large contributor to mortality in older adults, patient-centered integrated cardiac and noncardiac care that is coordinated by a navigator or case manager may aid in improving end-of-life symptoms and quality of life. The evolving discipline of geriatric cardiology places particular emphasis on the intersection of these issues in this specific population.

Future Directions and Conclusion

The care of patients in special populations is challenging because of uncertainties in disease progression and efficacy and safety of individual treatments. There is a growing divide between the results of clinical trials and applying them in clinical practice, owing largely to concerns of generalizability.
HF clinical trials have rarely included sufficient numbers of patients from special populations to provide conclusive evidence of efficacy and safety in those groups. However, the totality of evidence from well-powered trials, meta-analyses, and clinical experience support the position that guideline-based therapy is effective in most patients. In the absence of data suggesting harm, all patients should be prescribed guideline-based therapy, although individualization of therapy (eg, starting dose, titration schedule) is important, particularly in older adults. Large databases of real-world practice show substantial improvements in outcomes when the guidelines are applied universally. Unique models of care delivery to facilitate implementation of guideline-based therapies may be particularly effective for many of these patients.

HYD-ISDN is the only drug combination approved by the FDA for a special population, based on the A-HeFT trial. Future trials should enrich study populations with underrepresented groups and attend to issues of power of pre-specified subgroup analyses to increase the knowledge base regarding treatment effects in these groups. Of particular concern are the populations that have never been enrolled in clinical trials, including the very elderly and patients with multiple comorbidities. These patients present a continual challenge to clinicians, and data are needed to guide treatment decisions. Novel study designs, such as parallel registries for those who do not qualify or are unwilling to participate in a clinical trial, or point-of-care trials could be considered to facilitate enrollment of more diverse populations. The Institute of Medicine has suggested public engagement as a means to educate the public and enhance recruitment for clinical trials. The scientific community has a responsibility to focus efforts on intensifying research in special populations. In the meantime, clinicians should prescribe guideline-directed medical therapy unless contraindicated and should individualize care where appropriate to optimize outcomes of patients in special populations.

Disclosures


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