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*)
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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).[7] Data from the Framingham Heart Study indicate that 20% of men and women 40 years old will develop HF during their lifetime. The incidence of HF approaches 10 per 1,000 population after the age of 65 years.[7] Major HF risk factors include coronary artery disease (CAD), cigarette smoking, hypertension, overweight, diabetes, and valvular heart disease.

Non-Caucasian Ethnic Groups

HF disproportionately affects African Americans. In the Multi-Ethnic Study of Atherosclerosis (MESA), African

Table 1. Outline of Topics*

Epidemiology, Risk Factors, and Characteristics
Heart Failure−Related Morbidity and Mortality
Representation in Clinical Trials
Special Issues in Management
   Diagnosis and Management in the Older Adult
   Access to Care in Non-Caucasian Ethnic Minorities
   Comorbidities
   Response to Pharmacologic Therapy
   Response to Rhythm Device Therapy
   Response to Mechanical Circulatory Support and Transplant
   Response to Exercise in Women and Older Adults
   Polypharmacy
   Disability, Frailty, and Loss of Independence in Older Adults
   Quality of Life
   Patient Preferences in Older Adults
   Peripartum Cardiomyopathy in Women
Future Directions

*Unless otherwise indicated, all 3 special population categories are discussed in a topic category.

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,[10,11] and indicate that HF develops at a younger age in African Americans than in Caucasians.[12,13] The incidence of pediatric dilated cardiomyopathy is also higher among African-American children than among Caucasian children.[14] 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.[4] Functional and structural cardiac changes precede the presentation of symptoms by ∼10 years.[12]

Nonischemic cardiomyopathy is relatively more prevalent than ischemic cardiomyopathy in African Americans compared with Caucasians.[9,11–13] 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.[10,15] 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.[16]

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,[12] 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.[9,10,13] 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,[17] impaired vascular function, and increased large artery stiffness, factors that could result in a greater propensity for developing HF.[18–20] 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.[21]

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

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

Genetic Polymorphism	Clinical Implications
β1-Adrenergic receptor; Gly-389	Subsensitive β1-receptor; decreased affinity for agonist and less cAMP generation
β1-Adrenergic receptor; ARG-389 with α-receptor	Presence of both polymorphisms is associated with increased risk for HF; dual polymorphisms
eNOS	Subsensitive NO system
Aldosterone synthase	Excessive fibrosis
TGF-β1	40% higher TGF-β1 levels; possibly higher endothelin levels and more fibrosis
G protein 825-T allele (G protein β2-subunit)	Marker of low-renin HTN, LVH, and stroke; associated with greater therapeutic effect of HYD-ISDN
ACE D allele	May influence LV remodeling and clinical outcomes and may be associated with hypertension
Corin I555(P568)	Reduced natriuretic peptide processing capacity; increased risk of death or HF hospitalization ameliorated by HYD-ISDN
AGTR1(−535)	Associated with hypertension

cAMP, cyclic adenosine monophosphate; HF, heart failure; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; TGF, transforming growth factor; HTN, hypertension; LVH, left ventricular hypertrophy; HYD-ISDN, hydralazine and isosorbide dinitrate; ACE, angiotensin-converting enzyme; LV, left ventricular.
Adapted from Yancy,[4] with permission from Elsevier.

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 opportunity to explore polymorphisms that influenced remodeling and outcomes in a large cohort of African Americans with HFrEF.[25] Polymorphisms in the angiotensin-converting enzyme (ACE) gene that influences response to spironolactone and affects ventricular remodeling have been well described, although their effect on remodeling and hypertension is controversial.[26] The D/D phenotype has been shown to be associated with LVH, hypertension, and HF risk.[27–29] In African Americans, the deletion allele appears to be associated with hypertension.[30] Furthermore, a number of chromosomal loci associated with risk of HF in African Americans have been identified.[31] Polymorphisms of the α2C-adrenergic receptor (α2CDel322-325) and β1-adrenergic receptor (β1Arg389) are associated with a 10-fold higher risk of HF in African Americans.[32] Polymorphisms in the angiotensin II receptor type I gene AGTR1 (−535) are associated with increased risk of hypertension among African Americans, but not among Hispanics.[33]

Of increasing interest is the amyloidogenic transthyretin (TTR) V122 l mutation in African Americans. Although mutant and wild-type transthyretin cause cardiac amyloid in the general population, the V122 l 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] 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.
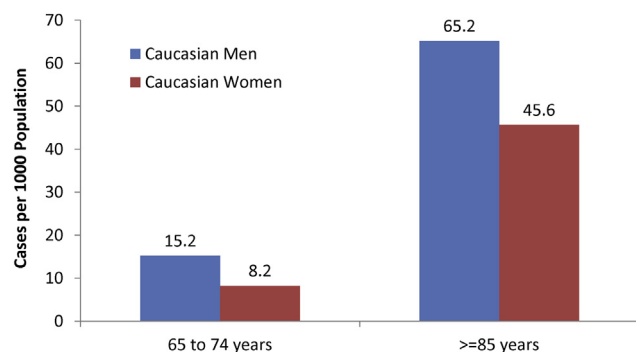
South Asians have more coronary risk factors than Caucasian patients, and it has been suggested that this group may have a higher risk of premature CAD leading to HF at a younger age.[40] Although less well characterized than other populations, South Asian men appear to have impaired endothelial function 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

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,[45] 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 men 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

Fig. 1. The annual incidence of heart failure by age. Based on data from Mozaffarian et al.[7]

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.[62,63] The prevalence of amyloid also increases with age.[64]

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.[49] 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 ($P < .001$).[65] 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.[66]

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.[67] The rates of HF death across sex, race, and ethnic groups are presented in Table 3.[67]

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.[13,15] Although African Americans hospitalized with HF tended to have mortality rates similar to those of Caucasians, after adjustment, functional decline was 50% higher.[68] 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.[69] 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.[39] Hispanics with HF in the US have longer median life expectancy than other ethnicities.[70] In other studies, researchers found that race was not an independent predictor of mortality[71–73]; however, when patients were stratified by etiology of HF and race, African

Table 3. Number and Rate of Heart Failure Deaths According to Age, Sex, Race, and Ethnicity

Characteristic	Number of Deaths	Rate per 100,000 Population
Overall	60,341	17.1*
Age (y)		
55–64	3,094	8.0
65–74	6,387	26.6
75–84	15,028	113.2
≥85	34,229	581.4
Sex		
Male	26,036	19.1*
Female	34,305	15.5*
Race or ethnicity		
Caucasian	53,363	17.2*
African-American	5,922	19.1*
Hispanic	2,404	10.2*
Non-Hispanic	57,827	17.5*
Combined sex and race/ethnicity		
Caucasian male	22,931	19.2*
Caucasian female	30,432	15.7*
African-American male	2,640	22.0*
African-American female	3,282	17.0*
Hispanic male	1,134	11.7*
Hispanic female	1,270	9.1*
Non-Hispanic male	24,846	19.6*
Non-Hispanic female	32,981	16.0*

*Rates are age adjusted.
Data from National Vital Statistics Report.[67]

Americans with nonischemic LV dysfunction had worse survival than Caucasians.[73]

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.[25,74] 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.[25] In the A-HeFT trial, an analysis of the genetic substudy data demonstrated that the corin I555(P568) 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.[75]

Women

After development of HF, women generally have better survival than men with HF,[76–80] and the cause of death is more likely to be noncardiac in women, perhaps owing to their older age and associated comorbidities.[79] 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.[81]

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.[82] In particular, an ischemic etiology, more common in men, carries a clearly worse prognosis than nonischemic causes.[79] Despite differences in important HF characteristics between men and women,[2,83–85] 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 HFrEF 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 women.[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 HFrEF 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 vs 75 ± 11 years; $P < .0001$), were 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 Trials[108] 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

HF.[57,108–110] One notable exception was A-HeFT, in which women composed an unprecedented 40% of patients.[103] 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.[111–115] None of these trials demonstrated 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.[116]

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.[117,118] It has been suggested that the low number of women enrolled in clinical trials reflects a reluctance to participate.[119–121] 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.[117] 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.[122]

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.[1] Several factors may explain the underrepresentation of older adults in clinical trials. First, older adult patients are less likely to be referred to a cardiologist during a hospitalization for acute HF[123] and to receive specialist counseling for outpatient care.[124,125] Secondly, ~30% of HF trials explicitly excluded elderly patients.[1] 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%; $P < .02$).[93] 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.[112,113] 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.[126] Non-Caucasian ethnic groups tend to have fewer preventive visits, and Hispanics have the highest uninsured rates of all ethnic groups.[126] 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).[13,127,128] 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.[127] Regarding beta-blockers, bucindolol did not demonstrate benefit in African Americans (and may have had an adverse effect),[104] but the response to carvedilol and metoprolol succinate were similar regardless of race.[129,130] 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.[103,131] 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.[25] 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.[132]

Table 4. Treatment Responses Among African Americans and Non-African Americans

Treatment	Effect in African Americans
Beta-blockers	
Carvedilol	Similar benefit in AA as in Caucasians
Metoprolol XL	Unclear evidence owing to low enrollment of AA
Bisoprolol	Unclear evidence owing to low enrollment of AA
ACE inhibitors	
Enalapril	Similar benefit in AA as in Caucasians
Other ACE inhibitors (captopril, lisinopril, benazepril, and ramipril)	Low enrollment, ethnicity not mentioned, and/or subgroup analysis not performed
Angiotensin receptor blockers (losartan, valsartan, and candesartan)	Low enrollment, ethnicity not mentioned, and/or subgroup analysis not performed
Aldosterone antagonists	Unclear evidence due to low enrollment of AA
Hydralazine−isosorbide dinitrate	Effective in AA
ICD	Similar benefit in AA as in Caucasians
CRT	Similar benefit in AA as in Caucasians
Heart transplantation	Reduced long-term survival compared with Caucasians
LVAD	Similar survival compared with Caucasians

AA, African Americans; ACE, angiotensin-converting enzyme; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.
Adapted from Sharma et al.[3]

African Americans are the only non-Caucasian ethnic group addressed in national and international guidelines,[133−135] 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.[103] 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.[136] 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.[137,138] Nonetheless, African Americans may be less likely to receive ICDs or CRT-D.[137,139] 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.[140]

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).[141,142] 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.[143] 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,[144,145] 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,[128,146] 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.[128,147]

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.[148] 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.[149,150] 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.[133,134]

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.[101] 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[102] and in those with HFrEF and mild symptoms[151] 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.[152] 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.[152]

In older reports, women were less likely to be prescribed guideline-based HF therapy than men.[153,154] However, in more recent reports, treatment differences were smaller, even absent for some pharmacologic therapies.[44] Women were as likely as men to be prescribed beta-blockers and ACE inhibitors or ARBs.[44] 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.[44] 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.[139,155−157] 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.[158] 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 $P < .01$).[158] 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.[158] 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 [$P = .60$]).[159]

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[160] or in SCD-HeFT.[136,161] 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.[162]

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.[163,164] 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; $P = .003$).[163] Adverse events appeared to occur similarly in women and men, although neurologic events were reported more frequently in women.[163,164] Functional capacity and quality of life improved significantly at 6 months in both men and women.

In 1988, women composed 17%[165] of the US transplant population, whereas in 2013, 770 (30.4%) of the 2,531

heart transplants were in women.[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.[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.[165–167] One proposed reason for poorer outcomes was a greater frequency of autoimmune-mediated diseases in women.[167] An analysis of patients from the Cardiac Transplant Research Database suggested another contributor: previous pregnancy.[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,[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.[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-ACTION) 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 ≤35%), 28% of whom were women.[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 $P = .17$).[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 $P = .027$).[171] No differences were observed between men and women in change in peak VO_2.[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,[172] although the incidence appears to be increasing in the US.[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.[174] 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.[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.[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.[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.[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 HFpEF rarely have an S3 gallop and may not exhibit signs of right HF, such as elevated jugular venous pressure, abdominojugular reflux, and peripheral edema.[179,180] Rales may be absent owing to chronicity of the HF itself, chronic lung disease, or atelectasis.[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

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

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

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

*Criteria include unintentional weight loss (≥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).

For further details and scoring, see: Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–56.

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.[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 ∼25% having >6 coexisting chronic illnesses.[185] Many common comorbidities directly affect the diagnosis, management, and prognosis of HF (Table 5).[186]

Polypharmacy. The high burden of multimorbidity in older HF patients also engenders polypharmacy, most commonly defined as the regular use of ≥5 medications. HFrEF is usually treated with ≥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.[187,188] It is not surprising that older HF patients take an average of >10 medications and that use of ≥15 medications is not uncommon.[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.[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.[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 ≥10 medications (ie, the majority of older HF patients).[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

to the aging process (ie, distinct from age-associated co-morbidities). 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%.[191] HF is also a common reason for discharge from hospital to a transitional care facility. Management of HF in long-term care or transitional care poses unique challenges.[191] 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.[192,193] HF and frailty likely share some pathogenetic 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 (ie, ≥85 years). Management of HFrEF 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.[194] However, the benefit of beta-blockade observed in the SENIORS

randomized trial has not been replicated in observational analyses.[44]

Older adult and very elderly patients are at increased risk for adverse effects from beta-blockers (eg, bradyarrhythmias, fatigue), RAAS inhibitors (eg, worsening renal function, hyperkalemia), and HYD-ISDN (eg, 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.[195] 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.[196,197] 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.[198] 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 (ie, 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.[133,134]

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,[199] in part because older patients are at higher risk than younger patients of dying from noncardiac causes (eg, pneumonia, hip fracture), and in part because sudden death in the older patient is more likely to be related to pulseless electrical activity, ie, 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.[200] Approximately one-half of all pacemakers in the US are implanted in patients ≥75 years old.[46] 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 ≥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 ≥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 prespecified 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

References

1. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med 2002;162:1682−8.
2. Hsich EM, Pina IL. Heart failure in women: a need for prospective data. J Am Coll Cardiol 2009;54:491−8.
3. Sharma A, Colvin-Adams M, Yancy CW. Heart failure in African Americans: disparities can be overcome. Cleve Clin J Med 2014;81:301−11.
4. Yancy CW. Heart failure in African Americans. Am J Cardiol 2005;96:3i−12i.
5. Nallamothu BK, Hayward RA, Bates ER. Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies. Circulation 2008;118:1294−303.
6. Reynolds D, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, McBride ML, et al. Race and improvements in the use of guideline-recommended therapies for patients with heart failure: findings from IMPROVE HF. J Natl Med Assoc 2012;104:287−98.
7. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:e29−322.
8. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606−19.
9. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, et al. Differences in the incidence of congestive heart failure by ethnicity: the Multi-Ethnic Study of Atherosclerosis. Arch Intern Med 2008;168:2138−45.
10. Sosin MD, Bhatia GS, Davis RC, Lip GY. Heart failure—the importance of ethnicity. Eur J Heart Fail 2004;6:831−43.
11. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 2008;101:1016−22.
12. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, et al. Racial differences in incident heart failure among young adults. N Engl J Med 2009;360:1179−90.
13. Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. N Engl J Med 1999;340:609−16.

14. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647−55.

15. Coughlin SS, Labenberg JR, Tefft MC. Black-white differences in idiopathic dilated cardiomyopathy: the Washington DC Dilated Cardiomyopathy Study. Epidemiology 1993;4:165−72.

16. Gupta DK, Shah AM, Castagno D, Takeuchi M, Loehr LR, Fox ER, et al. Heart failure with preserved ejection fraction in African Americans: the ARIC (Atherosclerosis Risk In Communities) study. JACC Heart Fail 2013;1:156−63.

17. Cardillo C, Kilcoyne CM, Cannon RO III, Panza JA. Racial differences in nitric oxide-mediated vasodilator response to mental stress in the forearm circulation. Hypertension 1998;31:1235−9.

18. Morris AA, Patel RS, Binongo JN, Poole J, Al Mheid I, Ahmed Y, et al. Racial differences in arterial stiffness and microcirculatory function between black and white Americans. J Am Heart Assoc 2013;2:e002154.

19. Mulukutla SR, Venkitachalam L, Bambs C, Kip KE, Aiyer A, Marroquin OC, et al. Black race is associated with digital artery endothelial dysfunction: results from the Heart SCORE study. Eur Heart J 2010;31:2808−15.

20. Flack JM, Sica DA, Bakris G, Brown AL, Ferdinand KC, Grimm RH Jr, et al. Management of high blood pressure in Blacks: an update of the International Society on Hypertension in Blacks consensus statement. Hypertension 2010;56:780−800.

21. Wang J, Chen W, Ruan L, Toprak A, Srinivasan SR, Berenson GS. Differential effect of elevated blood pressure on left ventricular geometry types in black and white young adults in a community (from the Bogalusa Heart Study). Am J Cardiol 2011;107: 717−22.

22. Dries DL, Victor RG, Rame JE, Cooper RS, Wu X, Zhu X, et al. Corin gene minor allele defined by 2 missense mutations is common in blacks and associated with high blood pressure and hypertension. Circulation 2005;112:2403−10.

23. Rame JE, Drazner MH, Post W, Peshock R, Lima J, Cooper RS, et al. Corin I555(P568) allele is associated with enhanced cardiac hypertrophic response to increased systemic afterload. Hypertension 2007;49:857−64.

24. Wang W, Liao X, Fukuda K, Knappe S, Wu F, Dries DL, et al. Corin variant associated with hypertension and cardiac hypertrophy exhibits impaired zymogen activation and natriuretic peptide processing activity. Circ Res 2008;103:502−8.

25. McNamara DM, Tam SW, Sabolinski ML, Tobelmann P, Janosko K, Taylor AL, et al. Aldosterone synthase promoter polymorphism predicts outcome in African Americans with heart failure: results from the A-HeFT Trial. J Am Coll Cardiol 2006;48:1277−82.

26. Lindpaintner K, Lee M, Larson MG, Rao VS, Pfeffer MA, Ordovas JM, et al. Absence of association or genetic linkage between the angiotensin-converting-enzyme gene and left ventricular mass. N Engl J Med 1996;334:1023−8.

27. Iwai N, Ohmichi N, Nakamura Y, Kinoshita M. DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy. Circulation 1994;90:2622−8.

28. Raynolds MV, Bristow MR, Bush EW, Abraham WT, Lowes BD, Zisman LS, et al. Angiotensin-converting enzyme DD genotype in patients with ischaemic or idiopathic dilated cardiomyopathy. Lancet 1993;342:1073−5.

29. Schunkert H, Hense HW, Holmer SR, Stender M, Perz S, Keil U, et al. Association between a deletion polymorphism of the angiotensin-converting-enzyme gene and left ventricular hypertrophy. N Engl J Med 1994;330:1634−8.

30. Duru K, Farrow S, Wang JM, Lockette W, Kurtz T. Frequency of a deletion polymorphism in the gene for angiotensin converting enzyme is increased in African-Americans with hypertension. Am J Hypertens 1994;7:759−62.

31. Yu B, Zheng Y, Alexander D, Manolio TA, Alonso A, Nettleton JA, et al. Genome-wide association study of a heart failure related metabolomic profile among African Americans in the Atherosclerosis Risk in Communities (ARIC) study. Genet Epidemiol 2013;37:840−5.

32. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 2002;347: 1135−42.

33. Henderson SO, Haiman CA, Mack W. Multiple polymorphisms in the renin-angiotensin-aldosterone system (ACE, CYP11B2, AGTR1) and their contribution to hypertension in African Americans and Latinos in the multiethnic cohort. Am J Med Sci 2004;328: 266−73.

34. Asl KH, Nakamura M, Yamashita T, Benson MD. Cardiac amyloidosis associated with the transthyretin Ile122 mutation in a Caucasian family. Amyloid 2001;8:263−9.

35. Jacobson D, Tagoe C, Schwartzbard A, Shah A, Koziol J, Buxbaum J. Relation of clinical, echocardiographic and electrocardiographic features of cardiac amyloidosis to the presence of the transthyretin V122I allele in older African-American men. Am J Cardiol 2011;108:440−4.

36. Buxbaum J, Alexander A, Koziol J, Tagoe C, Fox E, Kitzman D. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies. Am Heart J 2010;159: 864−70.

37. Jacobson DR, Gorevic PD, Buxbaum JN. A homozygous transthyretin variant associated with senile systemic amyloidosis: evidence for a late-onset disease of genetic etiology. Am J Hum Genet 1990;47: 127−36.

38. Nwankwo T, Yoon SS, Burt V, Gu Q. Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011−2012. NCHS Data Brief 2013:1−8.

39. Vivo RP, Krim SR, Cevik C, Witteles RM. Heart failure in Hispanics. J Am Coll Cardiol 2009;53:1167−75.

40. Moe GW, Tu J. Heart failure in the ethnic minorities. Curr Opin Cardiol 2010;25:124−30.

41. Cubbon RM, Murgatroyd SR, Ferguson C, Bowen TS, Rakobowchuk M, Baliga V, et al. Human exercise-induced circulating progenitor cell mobilization is nitric oxide−dependent and is blunted in South Asian men. Arterioscler Thromb Vasc Biol 2010; 30:878−84.

42. Sanderson JE, Chan SK, Chan WW, Hung YT, Woo KS. The aetiology of heart failure in the Chinese population of Hong Kong—a prospective study of 730 consecutive patients. Int J Cardiol 1995; 51:29−35.

43. Choi D, Nemi E, Fernando C, Gupta M, Moe GW. Differences in the clinical characteristics of ethnic minority groups with heart failure managed in specialized heart failure clinics. JACC Heart Fail 2014; 2:392−9.

44. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). Am J Cardiol 2009;104:107−15.

45. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, d'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068−72.

46. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129: e28−292.

47. Thomas KL, Velazquez EJ. Therapies to prevent heart failure post−myocardial infarction. Curr Heart Fail Rep 2005;2:174−82.

48. Chieffo A, Buchanan GL, Mauri F, Mehilli J, Vaquerizo B, Moynagh A, et al. ACS and STEMI treatment: gender-related issues. Eurointervention 2012;8(Suppl P):P27−35.

49. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996; 275:1557−62.

50. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397−402.

51. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30−41.

52. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18−28.

53. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2012;5:571−8.

54. Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282−9.

55. McDermott MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, et al. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. Am Heart J 1997;134:728−36.

56. McDermott MM, Feinglass J, Sy J, Gheorghiade M. Hospitalized congestive heart failure patients with preserved versus abnormal left ventricular systolic function: clinical characteristics and drug therapy. Am J Med 1995;99:629−35.

57. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, et al. Incidence and epidemiology of new onset heart failure with preserved vs reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. Eur Heart J 2013;34:1424−31.

58. Ho JE, Lyass A, Lee DS, Vasan RS, Kannel WB, Larson MG, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circ Heart Fail 2013;6:279−86.

59. Saczynski JS, Go AS, Magid DJ, Smith DH, McManus DD, Allen L, et al. Patterns of comorbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. J Am Geriatr Soc 2013;61:26−33.

60. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Hulley SB, Grady D, et al. Predictors of heart failure among women with coronary disease. Circulation 2004;110:1424−30.

61. Pradhan AD, Skerrett PJ, Manson JE. Obesity, diabetes, and coronary risk in women. J Cardiovasc Risk 2002;9:323−30.

62. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2000;35:1628−37.

63. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail 2013;15:717−23.

64. Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, et al. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail 2014;2:113−22.

65. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887−98.

66. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation 1995;91:2573−81.

67. National Center for Health Statistics. Deaths: final data for 2012. Natl Vital Stat Rep 2015:1−85.

68. Vaccarino V, Gahbauer E, Kasl SV, Charpentier PA, Acampora D, Krumholz HM. Differences between African Americans and whites in the outcome of heart failure: evidence for a greater functional decline in African Americans. Am Heart J 2002;143:1058−67.

69. Brown DW, Haldeman GA, Croft JB, Giles WH, Mensah GA. Racial or ethnic differences in hospitalization for heart failure among elderly adults: Medicare, 1990 to 2000. Am Heart J 2005;150:448−54.

70. Arias E. United States life tables, 2010. Natl Vital Stat Rep 2014;63:1−63.

71. Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). Am J Cardiol 2014;113:504−10.

72. Mentz RJ, Bittner V, Schulte PJ, Fleg JL, Pina IL, Keteyian SJ, et al. Race, exercise training, and outcomes in chronic heart failure: findings from Heart Failure−A Controlled Trial Investigating Outcomes in Exercise Training (HF-ACTION). Am Heart J 2013;166:488−95.

73. Thomas KL, East MA, Velazquez EJ, Tuttle RH, Shaw LK, O'Connor CM, et al. Outcomes by race and etiology of patients with left ventricular systolic dysfunction. Am J Cardiol 2005;96:956−63.

74. Peterson PN, Campagna EJ, Maravi M, Allen LA, Bull S, Steiner JF, et al. Acculturation and outcomes among patients with heart failure. Circ Heart Fail 2012;5:160−6.

75. Rame JE, Tam SW, McNamara D, Worcel M, Sabolinski ML, Wu AH, et al. Dysfunctional corin I555(P568) allele is associated with impaired brain natriuretic peptide processing and adverse outcomes in blacks with systolic heart failure: results from the Genetic Risk Assessment in Heart Failure substudy. Circ Heart Fail 2009;2:541−8.

76. Adams KF Jr, Sueta CA, Gheorghiade M, O'Connor CM, Schwartz TA, Koch GG, et al. Gender differences in survival in advanced heart failure. Insights from the FIRST study. Circulation 1999;99:1816−21.

77. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). Circulation 2001;103:375−80.

78. Martinez-Selles M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail 2012;14:473−9.

79. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Circulation 2007;115:3111−20.

80. Vaartjes I, Hoes AW, Reitsma JB, de BA, Grobbee DE, Mosterd A, et al. Age- and gender-specific risk of death after first hospitalization for heart failure. BMC Public Health 2010;10:637.

81. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424−33.

82. Stein GY, Ben-Gal T, Kremer A, Bental T, Alon D, Korenfeld R, et al. Gender-related differences in hospitalized heart failure patients. Eur J Heart Fail 2013;15:734−41.

83. Parashar S, Katz R, Smith NL, Arnold AM, Vaccarino V, Wenger NK, et al. Race, gender, and mortality in adults ≥65 years of age with incident heart failure (from the Cardiovascular Health Study). Am J Cardiol 2009;103:1120−7.

84. Rodriguez F, Wang Y, Johnson CE, Foody JM. National patterns of heart failure hospitalizations and mortality by sex and age. J Card Fail 2013;19:542−9.

85. Meyer S, van der Meer P, Massie BM, O'Connor CM, Metra M, Ponikowski P, et al. Sex-specific acute heart failure phenotypes and outcomes from PROTECT. Eur J Heart Fail 2013;15:1374−81.

86. Hsich EM, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Schwamm LH, Bhatt DL, et al. Sex differences in in-hospital mortal-

ity in acute decompensated heart failure with reduced and preserved ejection fraction. Am Heart J 2012;163:430−7.

87. Chen J, Dharmarajan K, Wang Y, Krumholz HM. National trends in heart failure hospital stay rates, 2001 to 2009. J Am Coll Cardiol 2013;61:1078−88.

88. Ben-Chetrit E, Chen-Shuali C, Zimran E, Munter G, Nesher G. A simplified scoring tool for prediction of readmission in elderly patients hospitalized in internal medicine departments. Isr Med Assoc J 2012;14:752−6.

89. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, et al. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) study. Circ Heart Fail 2014;7:76−87.

90. Mangla A, Kane J, Beaty E, Richardson D, Powell LH, Calvin JE Jr. Comparison of predictors of heart failure−related hospitalization or death in patients with versus without preserved left ventricular ejection fraction. Am J Cardiol 2013;112:1907−12.

91. Rutten FH, Heddema WS, Daggelders GJ, Hoes AW. Primary care patients with heart failure in the last year of their life. Fam Pract 2012;29:36−42.

92. Ezekowitz JA, Hu J, Delgado D, Hernandez AF, Kaul P, Leader R, et al. Acute heart failure: perspectives from a randomized trial and a simultaneous registry. Circ Heart Fail 2012;5:735−41.

93. Badano LP, Di LA, Bellotti P, Albanese MC, Sinagra G, Fioretti PM. Patients with chronic heart failure encountered in daily clinical practice are different from the ''typical'' patient enrolled in therapeutic trials. Ital Heart J 2003;4:84−91.

94. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study. N Engl J Med 1986;314:1547−52.

95. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine−isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303−10.

96. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667−75.

97. MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353: 2001−7.

98. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365: 32−43.

99. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651−8.

100. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759−66.

101. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709−17.

102. Pitt B, Remme W, Zannad F. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309−21.

103. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351: 2049−57.

104. Beta Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med 2001;344:1659−67.

105. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293−302.

106. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685−91.

107. Harris Y, Gorelick PB, Samuels P, Bempong I. Why African Americans may not be participating in clinical trials. J Natl Med Assoc 1996;88:630−4.

108. Jessup M, Pina IL. Is it important to examine gender differences in the epidemiology and outcome of severe heart failure? J Thorac Cardiovasc Surg 2004;127:1247−52.

109. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194−202.

110. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948−55.

111. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781−91.

112. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456−67.

113. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383−92.

114. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure With Preserved Ejection Fraction: a randomized clinical trial. JAMA 2013;1−10.

115. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777−81.

116. Walsh MN, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, et al. Equitable improvement for women and men in the use of guideline-recommended therapies for heart failure: findings from IMPROVE HF. J Card Fail 2010;16:940−9.

117. Feldman DE, Ducharme A, Giannetti N, Frenette M, Michel C, Grondin F, et al. Outcomes for women and men who attend a heart failure clinic: results of a 12-month longitudinal study. J Card Fail 2011;17:540−6.

118. Martin SS, Ou FS, Newby LK, Sutton V, Adams P, Felker GM, et al. Patient- and trial-specific barriers to participation in cardiovascular randomized clinical trials. J Am Coll Cardiol 2013;61:762−9.

119. Ding EL, Powe NR, Manson JE, Sherber NS, Braunstein JB. Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials. Arch Intern Med 2007;167:905−12.

120. Peterson ED, Lytle BL, Biswas MS, Coombs L. Willingness to participate in cardiac trials. Am J Geriatr Cardiol 2004;13:11−5.

121. Sen Biswas M, Newby LK, Bastian LA, Peterson ED, Sugarman J. Who refuses enrollment in cardiac clinical trials? Clin Trials 2007; 4:258−63.

122. Petrie MC, Dawson NF, Murdoch DR, Davie AP, McMurray JJ. Failure of women's hearts. Circulation 1999;99:2334−41.

123. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, et al. Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. Eur Heart J 2009;30:478−86.

124. Johansson S, Wallander MA, Ruigomez A, Garcia Rodriguez LA. Incidence of newly diagnosed heart failure in UK general practice. Eur J Heart Fail 2001;3:225−31.

125. Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. Eur J Heart Fail 2003;5:337−44.

126. Brown E, Ojeda V, Wyn R, Levan R. Racial and ethnic disparities in access to health insurance and health care. Los Angeles: UCLA Center for Health Policy Research and Henry J. Kaiser Family Foundation; 2000.

127. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001;344:1351−7.

128. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol 2003;41:1529−38.

129. Goldstein S, Deedwania P, Gottlieb S, Wikstrand J. Metoprolol CR/XL in black patients with heart failure (from the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure). Am J Cardiol 2003;92:478−80.

130. Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001;344:1358−65.

131. Cohn JN, Tam SW, Anand IS, Taylor AL, Sabolinski ML, Worcel M. Isosorbide dinitrate and hydralazine in a fixed-dose combination produces further regression of left ventricular remodeling in a well-treated black population with heart failure: results from A-HeFT. J Card Fail 2007;13:331−9.

132. McNamara DM, Tam SW, Sabolinski ML, Tobelmann P, Janosko K, Venkitachalam L, et al. Endothelial nitric oxide synthase (NOS3) polymorphisms in African Americans with heart failure: results from the A-HeFT trial. J Card Fail 2009;15:191−8.

133. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:e1−194.

134. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147−239.

135. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787−847.

136. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225−37.

137. Farmer SA, Kirkpatrick JN, Heidenreich PA, Curtis JP, Wang Y, Groeneveld PW. Ethnic and racial disparities in cardiac resynchronization therapy. Heart Rhythm 2009;6:325−31.

138. Mitchell JE, Hellkamp AS, Mark DB, Anderson J, Poole JE, Lee KL, et al. Outcome in African Americans and other minorities in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Am Heart J 2008;155:501−6.

139. Hernandez AF, Fonarow GC, Liang L, Al-Khatib SM, Curtis LH, LaBresh KA, et al. Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure. JAMA 2007;298:1525−32.

140. Sun AY, Koontz JI, Shah SH, Piccini JP, Nilsson KR Jr, Craig D, et al. The S1103Y cardiac sodium channel variant is associated with implantable cardioverter-defibrillator events in blacks with heart failure and reduced ejection fraction. Circ Cardiovasc Genet 2011;4:163−8.

141. Aggarwal A, Gupta A, Pappas PS, Tatooles A, Bhat G. Racial differences in patients with left ventricular assist devices. ASAIO J 2012;58:499−502.

142. Tsiouris A, Brewer RJ, Borgi J, Nemeh H, Paone G, Morgan JA. Continuous-flow left ventricular assist device implantation as a bridge to transplantation or destination therapy: racial disparities in outcomes. J Heart Lung Transplant 2013;32:299−304.

143. Singh TP, Almond C, Givertz MM, Piercey G, Gauvreau K. Improved survival in heart transplant recipients in the United States: racial differences in era effect. Circ Heart Fail 2011;4:153−60.

144. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. Mayo Clin Proc 2007;82:166−70.

145. Kim ES, Carrigan TP, Menon V. Enrollment of women in National Heart, Lung, and Blood Institute−funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. J Am Coll Cardiol 2008;52:672−3.

146. Garg R, Yusuf S, Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273:1450−6.

147. Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). Circulation 2002;105:1585−91.

148. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002;347:1403−11.

149. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol 2005;46:497−504.

150. Eichhorn EJ, Gheorghiade M. Digoxin—new perspective on an old drug. N Engl J Med 2002;347:1394−5.

151. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11−21.

152. Taylor AL, Lindenfeld J, Ziesche S, Walsh MN, Mitchell JE, Adams K, et al. Outcomes by gender in the African-American Heart Failure Trial. J Am Coll Cardiol 2006;48:2263−7.

153. Boyles PJ, Peterson GM, Bleasel MD, Vial JH. Undertreatment of congestive heart failure in an Australian setting. J Clin Pharm Ther 2004;29:15−22.

154. Agvall B, Dahlstrom U. Patients in primary health care diagnosed and treated as heart failure, with special reference to gender differences. Scand J Prim Health Care 2001;19:14−9.

155. Alaeddini J, Wood MA, Amin MS, Ellenbogen KA. Gender disparity in the use of cardiac resynchronization therapy in the United States. Pacing Clin Electrophysiol 2008;31:468−72.

156. Yancy CW, Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, et al. Influence of patient age and sex on delivery of guideline-recommended heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. Am Heart J 2009;157:754−62.

157. Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA. Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death. JAMA 2007;298:1517−24.

158. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, et al. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol 2011;57:813−20.

159. Zusterzeel R, Selzman KA, Sanders WE. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med 2014;174:1340−8.

160. Albert CM, Quigg R, Saba S, Estes NA III, Shaechter A, Subacius H, et al. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156:367–72.

161. Russo AM, Poole JE, Mark DB, Anderson J, Hellkamp AS, Lee KL, et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. J Cardiovasc Electrophysiol 2008;19:720–4.

162. Wilcox JE, Fonarow GC, Zhang Y, Albert NM, Curtis AB, Gheorghiade M, et al. Clinical effectiveness of cardiac resynchronization and implantable cardioverter-defibrillator therapy in men and women with heart failure: findings from IMPROVE HF. Circ Heart Fail 2014;7:146–53.

163. Bogaev RC, Pamboukian SV, Moore SA, Chen L, John R, Boyle AJ, et al. Comparison of outcomes in women versus men using a continuous-flow left ventricular assist device as a bridge to transplantation. J Heart Lung Transplant 2011;30:515–22.

164. Hsich EM, Naftel DC, Myers SL, Gorodeski EZ, Grady KL, Schmuhl D, et al. Should women receive left ventricular assist device support? Findings from INTERMACS. Circ Heart Fail 2012;5:234–40.

165. Fragomeni LS, Kaye MP. The Registry of the International Society for Heart Transplantation: fifth official report—1988. J Heart Transplant 1988;7:249–53.

166. US Department of Health and Human Services. The United Network for Organ Sharing. http://optn.transplant.hrsa.gov/latestData/rptData.asp. Accessed June 24, 2014.

167. Wechsler ME, Giardina EG, Sciacca RR, Rose EA, Barr ML. Increased early mortality in women undergoing cardiac transplantation. Circulation 1995;91:1029–35.

168. Johnson MR, Naftel DC, Hobbs RE, Kobashigawa JA, Pitts DE, Levine TB, et al. The incremental risk of female sex in heart transplantation: a multiinstitutional study of peripartum cardiomyopathy and pregnancy. Cardiac Transplant Research Database Group. J Heart Lung Transplant 1997;16:801–12.

169. Aaronson KD, Schwartz JS, Goin JE, Mancini DM. Sex differences in patient acceptance of cardiac transplant candidacy. Circulation 1995;91:2753–61.

170. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

171. Pina IL, Bittner V, Clare RM, Swank A, Kao A, Safford R, et al. Effects of exercise training on outcomes in women with heart failure: analysis of HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of Exercise Training) by sex. JACC Heart Fail 2014;2:180–6.

172. Givertz MM. Cardiology patient page: peripartum cardiomyopathy. Circulation 2013;127:e622–6.

173. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: a nationwide population-based study. J Am Heart Assoc 2014;3:e001056.

174. Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA 2000;283:1183–8.

175. Kao DP, Hsich E, Lindenfeld J. Characteristics, adverse events, and racial differences among delivering mothers with peripartum cardiomyopathy. JACC Heart Fail 2013;1:409–16.

176. Aziz TM, Burgess MI, Acladious NN, Campbell CS, Rahman AN, Yonan N, et al. Heart transplantation for peripartum cardiomyopathy: a report of three cases and a literature review. Cardiovasc Surg 1999; 7:565–7.

177. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail 2010;12:767–78.

178. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nat Rev Cardiol 2014;11:364–70.

179. Barents M, van der Horst IC, Voors AA, Hillege JL, Muskiet FA, de Jongste MJ. Prevalence and misdiagnosis of chronic heart failure in nursing home residents: the role of B-type natriuretic peptides. Neth Heart J 2008;16:123–8.

180. Kelder JC, Cramer MJ, van Wijngaarden J, van Tooren R, Mosterd A, Moons KG, et al. The diagnostic value of physical examination and additional testing in primary care patients with suspected heart failure. Circulation 2011;124:2865–73.

181. Vyshedskiy A, Alhashem RM, Paciej R, Ebril M, Rudman I, Fredberg JJ, et al. Mechanism of inspiratory and expiratory crackles. Chest 2009;135:156–64.

182. Vyshedskiy A, Ishikawa S, Murphy RL Jr. Crackle pitch and rate do not vary significantly during a single automated-auscultation session in patients with pneumonia, congestive heart failure, or interstitial pulmonary fibrosis. Respir Care 2011;56:806–17.

183. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976–82.

184. Wang TJ, Larson MG, Levy D, Leip EP, Benjamin EJ, Wilson PW, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90:254–8.

185. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 2003;42:1226–33.

186. Schwartz JB, Zipes DP. Cardiovascular disease in the elderly. In: Bonow RO, Mann DL, Zipes DP, Libby P, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Elsevier Saunders; 2011.

187. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 1998;158:1108–12.

188. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med 2000;160:777–84.

189. Gastelurrutia P, Benrimoj SI, Espejo J, Tuneu L, Mangues MA, Bayes-Genis A. Negative clinical outcomes associated with drug-related problems in heart failure (HF) outpatients: impact of a pharmacist in a multidisciplinary HF clinic. J Card Fail 2011;17:217–23.

190. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–97.

191. Jurgens CY, Goodlin SJ, Dolansky M, Ahmed A, Fonarow GC, Boxer R, et al. Heart failure management in skilled nursing facilities: a scientific statement from the American Heart Association and the Heart Failure Society of America. J Card Fail 2015;21:263–99.

192. Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H. Role of frailty in patients with cardiovascular disease. Am J Cardiol 2009;103:1616–21.

193. Murad K, Kitzman DW. Frailty and multiple comorbidities in the elderly patient with heart failure: implications for management. Heart Fail Rev 2012;17:581–8.

194. Flather MD, Shibata MC, Coats AJ, van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–25.

195. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;370:173–84.

196. Beck LH. Changes in renal function with aging. Clin Geriatr Med 1998;14:199–209.

197. Luckey AE, Parsa CJ. Fluid and electrolytes in the aged. Arch Surg 2003;138:1055–60.

198. Rich MW, McSherry F, Williford WO, Yusuf S. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. J Am Coll Cardiol 2001;38:806−13.

199. Santangeli P, Di Biase L, Dello Russo A, Casella M, Bartoletti S, Santarelli P, et al. Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators. Ann Intern Med 2010;153:592−9.

200. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [corrected]. Circulation 2012;126:1784−800.

201. Verbrugge FH, Dupont M, De Vusser P, Rivero-Ayerza M, Van Herendael H, Vercammen J, et al. Response to cardiac resynchronization therapy in elderly patients (≥70 years) and octogenarians. Eur J Heart Fail 2013;15:203−10.

202. Atluri P, Goldstone AB, Kobrin DM, Cohen JE, MacArthur JW, Howard JL, et al. Ventricular assist device implant in the elderly is associated with increased, but respectable risk: a multi-institutional study. Ann Thorac Surg 2013;96:141−7.

203. Adamson RM, Stahovich M, Chillcott S, Baradarian S, Chammas J, Jaski B, et al. Clinical strategies and outcomes in advanced heart failure patients older than 70 years of age receiving the Heartmate II left ventricular assist device: a community hospital experience. J Am Coll Cardiol 2011;57:2487−95.

204. Goldstein DJ, Bello R, Shin JJ, Stevens G, Zolty R, Maybaum S, et al. Outcomes of cardiac transplantation in septuagenarians. J Heart Lung Transplant 2012;31:679−85.

205. Weiss ES, Nwakanma LU, Patel ND, Yuh DD. Outcomes in patients older than 60 years of age undergoing orthotopic heart transplantation: an analysis of the UNOS database. J Heart Lung Transplant 2008;27:184−91.

206. Ferrara N, Komici K, Corbi G, Pagano G, Furgi G, Rengo C, et al. β-adrenergic receptor responsiveness in aging heart and clinical implications. Front Physiol 2014;4:396.

207. Chen YM, Li Y. Safety and efficacy of exercise training in elderly heart failure patients: a systematic review and meta-analysis. Int J Clin Pract 2013;67:1192−8.

208. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659−67.

209. Erceg P, Despotovic N, Milosevic DP, Soldatovic I, Zdravkovic S, Tomic S, et al. Health-related quality of life in elderly patients hospitalized with chronic heart failure. Clin Interv Aging 2013;8:1539−46.

210. Gott M, Barnes S, Parker C, Payne S, Seamark D, Gariballa S, et al. Predictors of the quality of life of older people with heart failure recruited from primary care. Age Ageing 2006;35:172−7.

211. Heidenreich PA, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, Rathore SS, et al. Health status identifies heart failure outpatients at risk for hospitalization or death. J Am Coll Cardiol 2006;47:752−6.

212. Hoekstra T, Jaarsma T, van Veldhuisen DJ, Hillege HL, Sanderman R, Lesman-Leegte I. Quality of life and survival in patients with heart failure. Eur J Heart Fail 2013;15:94−102.

213. Joseph SM, Novak E, Arnold SV, Jones PG, Khattak H, Platts AE, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. Circ Heart Fail 2013;6:1139−46.

214. Kato N, Kinugawa K, Seki S, Shiga T, Hatano M, Yao A, et al. Quality of life as an independent predictor for cardiac events and death in patients with heart failure. Circ J 2011;75:1661−9.

215. Zuluaga MC, Guallar-Castillon P, Lopez-Garcia E, Banegas JR, Conde-Herrera M, Olcoz-Chiva M, et al. Generic and disease-specific quality of life as a predictor of long-term mortality in heart failure. Eur J Heart Fail 2010;12:1372−8.

216. Li Y, Neilson MP, Whellan DJ, Schulman KA, Levy WC, Reed SD. Associations between Seattle Heart Failure Model scores and health utilities: findings from HF-ACTION. J Card Fail 2013;19:311−6.

217. Gott M, Barnes S, Parker C, Payne S, Seamark D, Gariballa S, et al. Dying trajectories in heart failure. Palliat Med 2007;21:95−9.

218. Brunner-La Rocca HP, Rickenbacher P, Muzzarelli S, Schindler R, Maeder MT, Jeker U, et al. End-of-life preferences of elderly patients with chronic heart failure. Eur Heart J 2012;33:752−9.

219. Kraai IH, Vermeulen KM, Luttik ML, Hoekstra T, Jaarsma T, Hillege HL. Preferences of heart failure patients in daily clinical practice: quality of life or longevity? Eur J Heart Fail 2013;15:1113−21.

220. Stevenson LW, Hellkamp AS, Leier CV, Sopko G, Koelling T, Warnica JW, et al. Changing preferences for survival after hospitalization with advanced heart failure. J Am Coll Cardiol 2008;52:1702−8.