



EDUCATIONAL OBJECTIVE: Readers will try to reduce the incidence of heart failure and exacerbations of heart failure in their African American patients

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Heart failure in African Americans: Disparities can be overcome

ABSTRACT

African Americans are disproportionately affected by heart failure, with a high prevalence at an early age. Hypertension, diabetes, obesity, and chronic kidney disease are all common in African Americans and all predispose to heart failure. Neurohormonal imbalances, endothelial dysfunction, genetic polymorphisms, and socioeconomic factors also contribute. In general, the same evidence-based treatment guidelines that apply to white patients with heart failure also apply to African Americans. However, the combination of hydralazine and isosorbide dinitrate is advised specifically for African Americans.

KEY POINTS

The natural history, epidemiology, and outcomes of heart failure in African Americans differ from those in whites.

Hypertension is the predominant risk factor for heart failure in African Americans, and aggressive management of hypertension may substantially reduce the incidence and consequences of heart failure in this population.

Heart failure in African Americans should be treated according to the same evidenced-based strategies as in the general population. In addition, a combination of isosorbide dinitrate and hydralazine is recommended in African Americans.

Many questions remain unanswered, since African Americans have been markedly underrepresented in clinical trials.

AFRICAN AMERICANS are disproportionately affected by heart failure and have not experienced the same benefit from treatment as white patients have. Much of the disparity can be blamed on modifiable risk factors such as uncontrolled hypertension and on suboptimal health care. When African Americans are treated according to guidelines, discrepant outcomes can be minimized.

In this article, we review the processes contributing to heart failure in African Americans, its management, and challenges with regard to disparities.

HEART FAILURE IS INCREASING

Despite 20 years of progress in understanding the pathophysiology of heart failure and developing medical and surgical therapies for it, its prevalence and associated morbidity are increasing in the United States. In 2010, 6.6 million (2.8%) of the adults in the United States had heart failure,¹ and the prevalence is expected to increase by about 25% by 2030.

DISPARITIES IN INCIDENCE, OUTCOMES

Heart failure is more prevalent in African Americans than in whites, imposes higher rates of death and morbidity, and has a more malignant course.¹⁻⁶

According to American Heart Association statistics, the annual incidence of heart failure in whites is approximately 6 per 1,000 person-years, while in African Americans it is 9.1 per 1,000 person-years.¹ In the Atherosclerosis Risk in Communities study, the incidence of new heart failure was 1.0 per 1,000 person-years in Chinese Americans, 2.4 in whites, 3.5 in Hispanics, and 4.6 in African Americans.²

doi:10.3949/ccjm.81a.13045

Moreover, when hospitalized for heart failure, African Americans have a 45% greater risk of death or decline in functional status than whites.⁷

Heart failure also occurs earlier in African Americans. Bibbins-Domingo et al⁸ reported that heart failure before age 50 was 20 times more frequent in African Americans than in whites. Functional and structural cardiac changes appeared an average of 10 years before the onset of symptoms and were strongly associated with the development of subsequent heart failure.⁸

In the Women's Health Initiative, African American women had higher rates of heart failure than white women, perhaps in part because of higher rates of diabetes.⁹

Heart failure with preserved ejection fraction

About half of patients who have signs and symptoms of heart failure have a normal ("preserved") ejection fraction. The incidence of this condition, previously called diastolic heart failure, appears to be similar between African Americans and whites. However, African Americans appear to have a greater incidence of factors that predispose to it and tend to present later in the course.¹⁰ For example, African Americans have higher left ventricular mass and wall thickness and a higher incidence of left ventricular hypertrophy than white patients.¹¹⁻¹³ In addition, those with heart failure with preserved ejection fraction tend to be younger, female, more likely to have hypertension and diabetes, and less likely to have coronary artery disease, and tend to have worse renal function than their white counterparts.^{14,15} The predisposition to diastolic impairment persists even after adjusting for risk factors.¹¹⁻¹⁵ The mortality rate in African Americans with heart failure with preserved ejection fraction and without coronary artery disease may also be higher than that of comparable white patients.¹⁶

■ WHY DO AFRICAN AMERICANS HAVE MORE HEART FAILURE?

Modifiable risk factors

In African Americans, the higher percentage of cases of heart failure is attributable to modifiable risk factors such as hypertension, hyper-

glycemia, left ventricular hypertrophy, and smoking, and fewer cases are due to ischemic heart disease.^{2,3} Nonischemic cardiomyopathy predominates in African Americans, whereas ischemic cardiomyopathy predominates in whites.

Hypertension, diabetes, obesity, and chronic kidney disease all portend subsequent heart failure and are common in African Americans, but hypertension is the main culprit.^{3,5,8,17-21} The prevalence of hypertension in African Americans is among the highest in the world, and because African Americans are more likely to have poorer control of their hypertension, they consequently have more target-organ damage.²² Indeed, in many hypertensive African Americans who develop heart failure, the hypertension is poorly controlled. However, even after adjusting for risk factors, and particularly blood pressure control, African Americans remain at higher risk of heart failure.²³

The specific mechanistic links between hypertension and heart failure remain to be identified. Despite having a higher prevalence of left ventricular hypertrophy and left ventricular remodeling, African Americans with heart failure tend toward systolic heart failure, as opposed to heart failure with preserved ejection fraction.

Neurohormonal imbalances and endothelial dysfunction

Derangements in the renin-angiotensin-aldosterone and adrenergic axes are likely the main pathophysiologic mechanisms in the genesis of heart failure in all populations. However, other factors may underlie the enhanced disease burden in African Americans.

Impaired endothelial function, as evidenced by impaired digital and brachial artery vasomotion, is very common in African Americans.²⁴⁻²⁶ The small arteries of African Americans are less elastic than those of whites and Chinese.²⁷ The underlying mechanism may be related to increased oxidative stress, decreased nitric oxide availability, exaggerated vasoconstrictor response, and attenuated responsiveness to vasodilators and nitric oxide.²⁸⁻³¹

Genetic polymorphisms

An important caveat in discussing racial differences in heart failure is that "race" is completely arbitrary and is based on sociopolitical

The prevalence of hypertension in African Americans is among the highest in the world

rather than scientific or physiologic definitions. Perceived genetic influences are likely to represent complex gene-gene, gene-environment, and gene-drug interactions.

This is especially true for African Americans, who are a markedly heterogeneous group. The US Office of Management and Budget defines “black” or “African American” as having origins in any of the black racial groups of Africa (www.census.gov/2010census/data). Thus, “African American” includes sixth-generation descendants of African slaves, recently immigrated Jamaicans, and black descendants of French and Spanish people.

Most African Americans have some European ancestry. In one study, the estimated proportion of European ancestry ranged from 7% in Jamaicans of African descent to approximately 23% in African Americans in New Orleans.³²

Nevertheless, several polymorphisms associated with the risk of heart failure may provide insight into some of the “race-based” differences in pathophysiology and response to medications and, it is hoped, may eventually serve as the basis for tailored therapy. Genes of interest include those for:

- Beta 1 adrenergic receptor
- Alpha 2c receptor³³
- Aldosterone synthase³⁴
- G protein
- Transforming growth factor beta
- Nitric oxide synthase³⁵
- Transthyretin.^{36,37}

Socioeconomic factors and quality of care

Heart failure patients—and especially African Americans—have high rates of hospital readmission, and socioeconomic factors have been implicated. In more than 40,000 patients with heart failure, lower income was a significant predictor of hospital readmission.³⁸ Socioeconomic factors in turn could account for delay in seeking treatment for worsening symptoms, failure to recognize symptoms, limited disease awareness, inadequate access to health care, noncompliance with follow-up appointments, and poor adherence to recommended treatment, all of which are common in African American patients.^{38,39}

African Americans also report more discrimination from health care providers, have

more concerns about blood pressure medications, and are more likely to have misperceptions about high blood pressure (eg, that it is not serious), all of which may interfere with optimal blood pressure control.⁴⁰ Managing heart failure in African Americans should include trying to identify and eliminate barriers to attaining treatment goals.

■ PREVENTING HEART FAILURE BY REDUCING RISK FACTORS

The American College of Cardiology Foundation and American Heart Association, in their 2013 guidelines, underscored the progressive nature of heart failure by defining four stages of the disease, from stage A (at risk) through stage D (refractory heart failure) (**FIGURE 1**).⁴¹ They also emphasized the importance of preventing it.

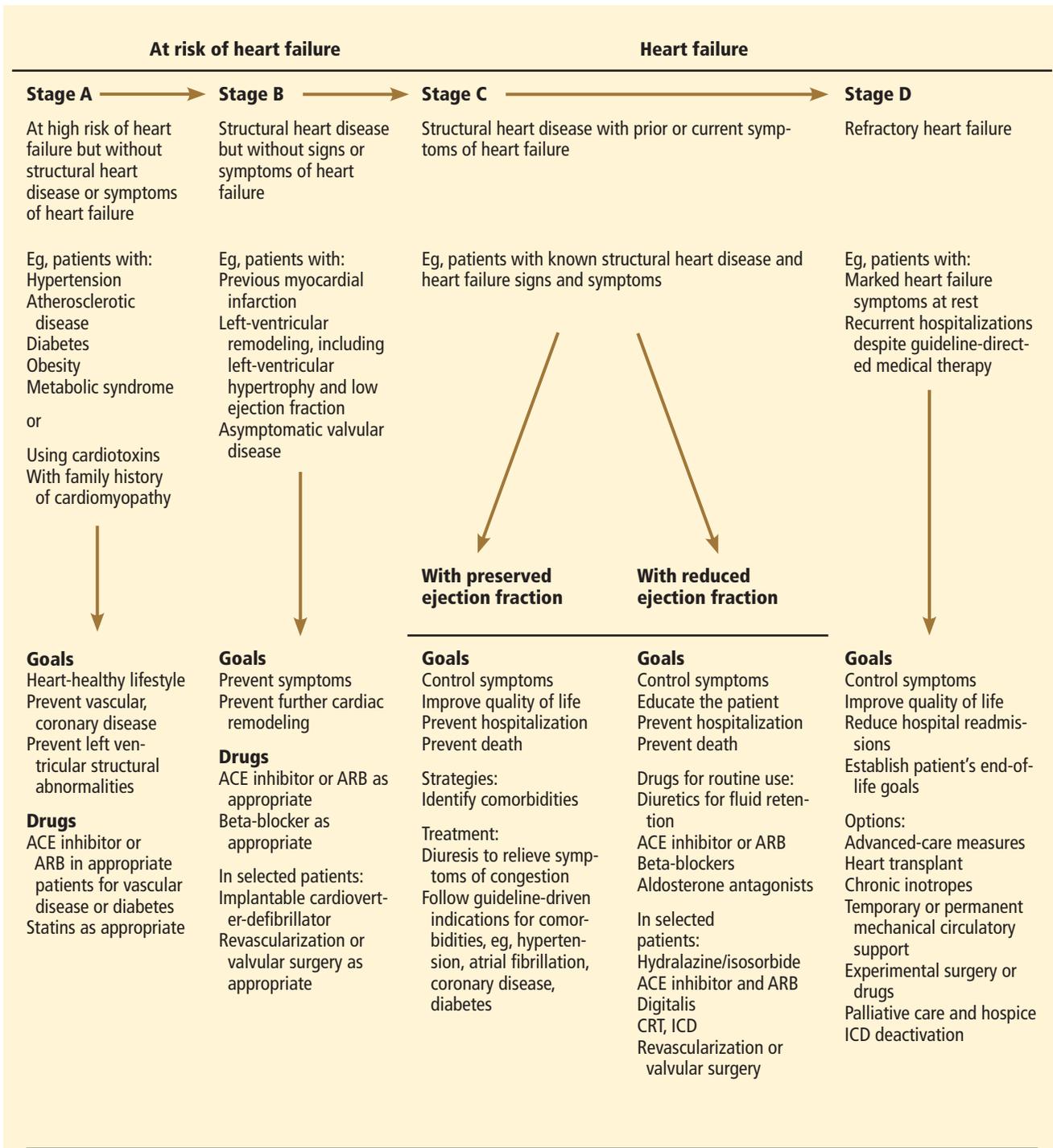
A thorough clinical assessment, with appropriate assessment for risk factors and intervention at stage A, is critical in preventing left ventricular remodeling and heart failure. These risk factors include hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus, valvular disease, obesity, physical inactivity, excessive alcohol intake, poor diet, and smoking.

Hypertension is especially important in African Americans and requires vigorous screening and aggressive treatment. Antihypertensive drugs should be prescribed early, with a lower threshold for escalating therapy with combinations of drugs, as most patients require more than one.

There is considerable debate about the appropriate blood pressure thresholds for diagnosing hypertension and the optimal target blood pressures in African Americans. The 2014 report of the Joint National Committee recommends a similar hypertension treatment target of 140/90 mm Hg for all patients except older adults (for whom 150/90 mm Hg is acceptable), and no separate target for African Americans.⁴² Previous guidelines from this committee recommended thiazide-type diuretics as first-line therapy for hypertension in African Americans⁴³; the new ones recommend thiazide-type diuretics or calcium channel blockers. However, in those with left ventricular systolic dysfunction, hypertension treatment should include drugs shown to

‘Race’ is a sociopolitical rather than a scientific or physiologic concept

HEART FAILURE IN AFRICAN AMERICANS



ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator

FIGURE 1. Stages in the development of heart failure and recommended therapy by stage.

REPRINTED FROM HUNT SA, ABRAHAM WT, CHIN MH, ET AL. 2009 FOCUSED UPDATE INCORPORATED INTO THE ACC/AHA 2005 GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF HEART FAILURE IN ADULTS: A REPORT OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION/ AMERICAN HEART ASSOCIATION TASK FORCE ON PRACTICE GUIDELINES DEVELOPED IN COLLABORATION WITH THE INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION. J AM COLL CARDIOL 2009; 53:E1-E90; COPYRIGHT 2009, WITH PERMISSION FROM ELSEVIER; HTTP://WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/07351097.

TABLE 1

Heart failure treatments in African Americans: Spotty evidence, but recommended

Digoxin may be less effective in African Americans than in whites⁵¹

Angiotensin-converting enzyme (ACE) inhibitors

Enalapril has similar benefit in African Americans as in whites^{5,6,52}

Other ACE inhibitors have insufficient evidence⁵³

Angiotensin receptor blockers have insufficient evidence

Beta-blockers

Bucindolol may be less effective in African Americans than in whites⁵⁶

Carvedilol shows similar benefit in African Americans as in whites^{17,57}

Metoprolol XL has insufficient evidence^{58,59}

Aldosterone antagonists have insufficient evidence⁶⁵

Hydralazine and isosorbide dinitrate is effective in African Americans^{17,66,67}

Implantable cardioverter-defibrillators have similar benefit in African Americans as in whites

Chronic resynchronization therapy has insufficient evidence^{7,75–77}

Heart transplantation—African Americans have lower survival rates than whites^{83–87}

Left-ventricular assist devices—African Americans and whites have comparable survival rates^{91,92}

INFORMATION DERIVED FROM SUBGROUP ANALYSES OF CLINICAL TRIALS

reduce the risk of death in heart failure—ie, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, hydralazine, nitrates, and aldosterone receptor antagonists.

Salt intake should be reduced to less than 3 g per day (1,200 mg of sodium per day), which has been shown to substantially reduce rates of cardiovascular morbidity and mortality and health care costs.⁴⁴ Since most Americans consume 7 to 10 g of salt per day, strict salt restriction should be encouraged as a preventive measure.

Diabetes should be screened for and treated in African Americans per current American Diabetes Association guidelines.

Dyslipidemia should also be screened for and treated per guidelines.⁴⁵

Smoking cessation, moderation of alcohol intake, and avoidance of illicit drugs should be encouraged. Given that African Americans develop heart failure at a relatively early age, the level of vigilance should be high and the threshold for screening should be low.

Healthy neighborhoods, healthy people

Neighborhoods can be designed and built with wellness in mind, incorporating features such as access to healthy food and walkability. Living in such neighborhoods leads to more physical activity and less obesity, although this relationship may be less robust in African Americans.^{46–49}

Environmental factors are multifactorial in African Americans and extend beyond those afforded by the built environment. For instance, lack of safety may hinder the potential benefit of an otherwise walkable neighborhood. These interactions are highly complex, and more investigation is needed to determine the effect of built environments on risk factors in African Americans.

■ DRUG THERAPY FOR HEART FAILURE IN AFRICAN AMERICANS

Use standard therapies

ACE inhibitors, beta-blockers, and aldosterone antagonists are the standard of care in

Assess for hypertension, hyperlipidemia, atherosclerosis, diabetes, valvular disease, obesity, physical inactivity, alcohol intake, poor diet, and smoking

heart failure, with digoxin (Lanoxin) and diuretics used as adjuncts to control symptoms.

African Americans may respond differently than whites to some of these drugs (TABLE 1). However, these findings should be interpreted with caution, since most of them came from subgroup analyses of trials in which African Americans accounted for as many as 28% to as few as 1%.⁵⁰ To date, no data unequivocally show that we should use standard heart failure therapies any differently in African Americans than in whites.

Digoxin: Limited role to control symptoms

Post hoc analysis of the Digitalis Investigation Group trial, in which 14% of the patients were nonwhite, revealed that compared with placebo, digitalis (and achieving a serum digitalis concentration of 0.5 to 0.9 ng/mL) was associated with lower rates of all-cause mortality in most subgroups—except nonwhites.⁵¹

In general, digoxin has a limited role in heart failure, since other drugs are available that substantially modify outcomes. However, it can be considered in patients who have persistent heart failure symptoms.

ACE inhibitors, ARBs are recommended

ACE inhibitors are recommended for patients with New York Heart Association (NYHA) class I, II, III, or IV heart failure (class I recommendation, ie, “recommended”; level of evidence A on a scale of A, B, and C) and as part of standard therapy for African American patients with heart failure with symptomatic or asymptomatic left ventricular systolic dysfunction (class I recommendation; level of evidence C).⁴¹

Although African American patients did not appear to derive any benefit from enalapril (Vasotec) in the Studies of Left Ventricular Dysfunction (SOLVD) trial,⁵² a subsequent analysis that involved the SOLVD Prevention Trial did not find any differences between African Americans and whites in response to this agent.⁶ Similarly, a meta-analysis did not suggest differences in ACE-inhibitor efficacy in reducing adverse cardiovascular outcomes in heart failure between African Americans and non-African Americans.⁵³

Of note: African Americans have a 3% to 4% higher incidence of angioedema from

ACE inhibitors than whites.^{54,55}

Angiotensin receptor blockers (ARBs) can be used as substitute therapy in African Americans who cannot tolerate ACE inhibitors (class IIa recommendation, ie, “reasonable”; level of evidence B).⁴¹

Beta-blockers also recommended

Beta-blockers are recommended in NYHA class I, II, III, and IV heart failure (class I recommendation; level of evidence A) and as part of standard therapy for African Americans with heart failure due to symptomatic left ventricular systolic dysfunction (class I recommendation; level of evidence B) and asymptomatic left ventricular systolic dysfunction (level of evidence C).⁴¹

Carvedilol (Coreg) and metoprolol (Lopressor) are the standard beta-blockers used to treat heart failure, and these drugs should be used in African Americans as well as in whites.^{15,53,56–59} Of interest, however, race-specific differences may exist in the beta-adrenergic pathway.^{60,61}

Aldosterone antagonists: More study needed

Aldosterone antagonists, also called mineralocorticoid antagonists, ie, spironolactone (Aldactone) and eplerenone (Inspra), are recommended in addition to beta-blockers and ACE inhibitors for NYHA class II–IV heart failure, unless contraindicated (class I recommendation; level of evidence A).

However, trials of aldosterone antagonists to date have enrolled few African Americans.^{62–64} The limited data suggest that African Americans with heart failure may be less responsive to the renal effects of spironolactone, demonstrating less of an increase in serum potassium levels, and there are essentially no data to guide the use of these drugs in African Americans with heart failure.⁶⁵ Further study is needed. But in the absence of data to the contrary, these agents, should also be used in African American patients with class III or IV heart failure.

Hydralazine plus nitrates: Recommended for African Americans

Hydralazine plus isosorbide dinitrate (available as BiDil) is recommended as part of stan-

The average salt intake in Americans is 7–10 g/day; the recommended intake is < 3 g/day

standard therapy, in addition to beta-blockers and ACE inhibitors specifically for African Americans with left ventricular systolic dysfunction and NYHA class III or IV heart failure (class I recommendation; level of evidence A), as well as NYHA class II heart failure (class I recommendation; level of evidence B).⁴¹

Preliminary evidence for this combination came from the Department of Veterans Affairs Cooperative Vasodilator-Heart Failure Trials.⁶⁶

Subsequently, the African-American Heart Failure Trial⁶⁷ was conducted in self-identified African American patients with NYHA class III or IV heart failure on standard heart failure therapy, including an ACE inhibitor if tolerated. Patients were randomly assigned to receive a fixed combination of isosorbide 20 mg and hydralazine 37.5 mg, one or two tablets three times a day, or placebo. The target dose of isosorbide dinitrate was 120 mg, and the target dose of hydralazine was 225 mg daily. Follow-up was up to 18 months. The study was terminated early because of a significant 43% improvement in overall survival for the patients in the isosorbide-hydralazine group. In addition, the rate of first hospitalization was 39% lower and the mean improvement in quality-of-life scores was 52% greater with isosorbide-hydralazine than with placebo.⁶⁷

There has been much debate about whether the benefit seen in this trial was the result of a hemodynamic effect, blood pressure response, or neurohormonal modulation. The benefit is less likely from a reduction in blood pressure, as the patients who had low blood pressure derived a mortality benefit similar to those with higher blood pressure, despite no further reduction in their blood pressure.⁶⁸

Treatment for heart failure with preserved ejection fraction

Although there are no data on how to manage heart failure with preserved ejection fraction that are specific to African Americans, the ACCF/AHA guideline⁴¹ recommends treating systolic and diastolic hypertension (class I, level of evidence B) according to published clinical practice guidelines and using diuretics to alleviate volume overload (class I; level of evidence C). Revascularization and management of atrial fibrillation are also “reasonable,”

as are the use of ARBs, ACE inhibitors, and beta-blockers in the management of hypertension (class IIa; level of evidence C). ARBs may also be considered to reduce hospitalization in symptomatic patients with heart failure with preserved ejection fraction (class IIb, ie, “may be considered”; level of evidence B).

For acute decompensated heart failure

One of the greatest challenges in heart failure is treating patients who present with acute decompensated heart failure.

As in the general population, the major precipitating factor for hospitalization with decompensated heart failure in African Americans is nonadherence to prescribed dietary and medication regimens.³⁵ African Americans with acute decompensated heart failure tend to be younger and to have nonischemic cardiomyopathy, hypertension, diabetes, and obesity, but a lower risk of death.^{35,69,70} Up to 44% have uncontrolled hypertension.³⁵

Inotropes and vasodilators have undergone multiple trials in the acutely decompensated state in the general population, but no trial has demonstrated a reduction in the mortality rate, and some showed a higher mortality rate. Thus, the treatment of acute decompensated heart failure remains primarily consensus-guided and symptom-focused.

Loop diuretics have been the mainstay in managing fluid retention and congestion in heart failure. The Diuretic Optimization Strategies Evaluation trial tested low-dose vs high-dose intravenous furosemide (Lasix) given either as a continuous infusion or as intermittent intravenous boluses. All strategies were safe and effective.⁷¹

Although ultrafiltration is an effective method of decongestion in heart failure and has been associated with a reduction in hospitalization, it is also associated with worsening renal function.⁷² The Cardiorenal Rescue Study in Acute Decompensated Heart Failure⁷³ compared ultrafiltration vs stepped diuretic therapy. In this trial, which enrolled approximately 26% nonwhites, stepped diuretic therapy was superior to ultrafiltration in preserving renal function in acute decompensated heart failure, although the efficacy of fluid removal was similar.

Both studies were small, and subgroup anal-

**Neighborhoods
can be built
with wellness
in mind**

yses are not likely to yield useful information. Nevertheless, these data support the use of intravenous diuretics, by continuous infusion or bolus, in acute decompensated heart failure.

Despite no benefit in terms of the mortality rate, inotropes continue to be used in some cases of acute decompensated heart failure, and African Americans appear to have a response to milrinone (Primacor IV) similar to that in whites.⁶⁹

In a nonrandomized study in which most patients were black, high-dose intravenous nitroglycerin appeared to be safe and associated with less need for ventilator support and intensive care unit admission, compared retrospectively with a population that did not receive high-dose nitroglycerin.⁷⁴

Given the different profile of the African American patient with acute decompensated heart failure, prospective studies would be useful in determining the best management strategy.

■ TREATMENTS FOR ADVANCED HEART FAILURE

Cardiac resynchronization and implantable cardioverter-defibrillators

Cardiac resynchronization therapy is indicated for patients with NYHA class II, III, and ambulatory class IV heart failure and left ventricular ejection fraction less than or equal to 35%, sinus rhythm, left bundle branch block, and a QRS duration greater than or equal to 150 ms (class I recommendation; level of evidence A for class NYHA III and IV; level of evidence B for NYHA class II).⁴¹

An implantable cardioverter-defibrillator is recommended in patients with NYHA class II or III heart failure for primary prevention of sudden cardiac death in selected patients with nonischemic dilated cardiomyopathy or ischemic heart disease (class I recommendation; level of evidence A).

However, few members of racial and ethnic minorities were included in trials of implantable cardioverter-defibrillators^{75,76} or cardiac resynchronization,^{7,77,78} so that subgroup analysis is limited. Use of an implantable cardioverter-defibrillator showed similar reduction in mortality between African Americans and whites, and compliance with device implantation and medical therapy was comparable.⁷⁹

Among patients discharged from hospi-

tals in the American Heart Association's Get With the Guidelines–Heart Failure Quality Improvement Program, fewer than 40% of potentially eligible patients received an implantable cardioverter-defibrillator, and rates were significantly lower for African Americans.⁸⁰ When they can get cardiac resynchronization therapy, African Americans appear to experience similar benefit from it.⁸¹

Heart transplantation: Poorer outcomes in African Americans?

Heart transplantation remains the most effective and durable therapy for advanced heart failure. Median survival approaches 14 years.⁸²

However, a retrospective study found that African American recipients had an 11.5% lower 10-year survival rate than whites, which persisted after adjusting for risk, donor-recipient matching by race, and censoring of deaths in the first year.⁸³ Although socioeconomic factors and poor human leukocyte antigen matching have been implicated, a retrospective cohort study showed that African American recipients had a higher risk of death than white recipients even after adjustment for recipient, transplant, and socioeconomic factors.^{84–87} African Americans were more likely to die of graft failure or of a cardiovascular cause than white patients, but were less likely to die of infection or malignancy. Although mortality rates decreased over time for all transplant recipients, the disparity in mortality rates between African Americans and whites remained essentially unchanged.⁸⁴

Among all donor-recipient combinations, African American recipients of hearts from African American donors had the highest risk of death.⁸⁸

Limited access to transplantation persists, particularly for African Americans of lower socioeconomic status. African Americans are more likely than whites to be uninsured, and the funding requirement to be placed on the transplantation list disproportionately affects African Americans.^{89,90}

Left-ventricular assist devices

Left-ventricular assist devices (LVADs) improve survival in heart transplantation candidates and heart failure patients who do not qualify for transplantation. After LVAD

No data unequivocally support using standard heart failure therapies differently in African Americans

implantation, African American patients have similar 1- and 2-year survival rates and no difference in readmission rates compared with whites.^{91,92}

Access to LVAD implantation, however, is significantly influenced by race, and African Americans are significantly less likely to receive one (OR = 0.29).⁹³ Further investigation is required to identify disparities in outcome, access, and contributing factors.

■ DISPARITIES CAN BE MINIMIZED

In general, heart failure in African Americans is characterized by a high prevalence of hypertension as a major risk factor and potentially different pathogenesis than in the general population. Furthermore, heart failure in African Americans is more prevalent, occurs at an early age, and has a more severe course than in whites, perhaps because of a higher prevalence of risk factors such as diabetes mellitus, obesity, and again, hypertension. These disparities are multifactorial and involve a complex interplay between genes, environment, and socioeconomic factors.

For now, heart failure in African Americans should be treated according to standard

evidenced-based strategies, which include a combination of isosorbide dinitrate and hydralazine in addition to other neurohormonal modifying agents (ACE inhibitors, beta-blockers, aldosterone antagonists), a strategy demonstrated to reduce mortality rates in African Americans. When treated according to guidelines, disparities in outcomes can be minimized.

However, many questions about managing heart failure remain unanswered, since African Americans have been markedly underrepresented in clinical trials. Clinical trials need to enroll enough African Americans to answer the questions of interest. Disparities in outcomes must be investigated in a scientific and hypothesis-driven manner. The effect of the built environment on African Americans needs more study as well, as success with these strategies may be impeded by unrecognized factors.

Preventing heart failure should be a priority. Efforts should be directed toward detecting and modifying risk factors early, managing hypertension aggressively, and identifying left ventricular dysfunction early. ■

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