MONICA COLVIN-ADAMS, MD
Assistant professor of Medicine/Cardiology; medical director, Cardiac Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN

ANNE L. TAYLOR, MD*
Professor of Medicine/Cardiology and associate dean for Faculty Affairs, University of Minnesota Medical School; codirector, University of Minnesota National Center of Excellence in Women's Health; chair, Steering Committee, African-American Heart Failure Trial (A-HeFT)

INTERPRETING THE AFRICAN AMERICAN HEART FAILURE TRIAL (A-HeFT)

Isosorbide dinitrate-hydralazine improves outcomes in African Americans with heart failure

ABSTRACT

The African American Heart Failure Trial (A-HeFT) found that African American patients with advanced heart failure fared better if the fixed-dose combination of isosorbide dinitrate and hydralazine was added to their regimen, which for most of them already included an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), a beta-blocker, and a diuretic (N Engl J Med 2004; 351:2049–2057). This placebo-controlled trial was the first to evaluate a therapy in a specific racial group, and it points the way to a more individualized approach to heart failure therapy.

KEY POINTS

In A-HeFT, more than 90% of patients were receiving an ACE inhibitor or ARB at baseline, and more than 80% were receiving a beta-blocker. Adding fixed-dose isosorbide dinitrate and hydralazine decreased the rates of death and hospitalization for heart failure.

Isosorbide dinitrate and hydralazine may enhance the effect of nitric oxide and reduce oxidative stress.

Low systolic blood pressure is not a contraindication to therapy with isosorbide dinitrate-hydralazine, but physicians should make sure the patient is not volume-depleted and should start with a low dose.

FIXED-DOSE isosorbide dinitrate-hydralazine should be added to the regimen (in addition to an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin-receptor blocker [ARB] plus a beta-blocker) for African American patients with advanced heart failure. This is the conclusion of the African American Heart Failure Trial (A-HeFT),[1] and it has been endorsed by guidelines from several professional organizations.[2,3]

This recommendation may seem like a step backward when we consider that isosorbide and hydralazine have been available for more than 30 years (although a new fixed-dose combination tablet—BiDil—is available for this specific indication). It is a big step forward, however, in our awareness that all subgroups may not respond in the same way to the same drug.

The last 2 decades have witnessed tremendous advances in drugs and devices for managing chronic heart failure that have reduced the mortality rate by as much as 65% and have been proven effective by randomized clinical trials.[4–19] But these trials included few women and people of ethnic minorities, such as African Americans.[20]

Thus, even though we have long known that African Americans bear a heavier burden of heart failure than white people and that the etiology of heart failure is often different in African Americans, until recently we did not know how to apply this knowledge. Now, we are starting to realize that the treatment for heart failure perhaps should be different too.

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AFRICAN AMERICANS BEAR A HEAVIER BURDEN

Important differences between African Americans and whites with heart failure have been consistently noted in numerous databases. Compared with white patients, African Americans:

- Have more heart failure. The prevalence of heart failure is approximately 3% in African American men and women, vs approximately 2% in the general population).[21]
- Present with more advanced heart failure at a younger age.
- Are more likely to have hypertension than coronary artery disease as the cause of their heart failure.[22,23]
- Are hospitalized more for heart failure.
- Are more likely to die at a younger age.[24–26]

The mechanisms responsible for these differences as well as the optimal therapeutic approaches have not, until recently, been explored prospectively in randomized clinical trials.

African Americans present at a younger age with more advanced heart failure

The optimal therapy for heart failure in African Americans has been very controversial in view of findings that African Americans respond less favorably to some heart failure therapies.[26–28] However, these findings have been based on retrospective analyses of clinical trials in which relatively few African Americans were enrolled and are subject to the limitations of retrospective analyses.

WHAT WE KNEW BEFORE A-HeFT

The conceptual basis of the A-HeFT study is rooted in the landmark trials of vasodilators in the 1980s and early 1990s.

V-HeFT: Isosorbide dinitrate-hydralazine is better than placebo or prazosin

In the Vasodilator Heart Failure Trial (V-HeFT),[8] published in 1986, men with mild to moderate heart failure receiving only digoxin and diuretics were randomly assigned to receive one of three treatments: a combination of the vasodilators isosorbide dinitrate and hydralazine, the alpha-blocker prazosin (Minipress), which also has vasodilating properties, or placebo. The two active treatments were chosen to duplicate the balanced hemodynamic profile of intravenous nitroprusside.

At 2 years, the risk of death was 34% lower in the isosorbide dinitrate-hydralazine group than in the placebo group ($P < .028$). Prazosin, which has a similar hemodynamic profile, had no effect on survival, suggesting that improvement in hemodynamic profile alone did not account for the lower mortality rate in the isosorbide dinitrate-hydralazine group.

CONSENSUS: Enalapril is better than placebo in whites

The Cooperative North Scandinavian Enalapril Survival study (CONSENSUS)[10] subsequently showed a 40% lower death rate at 6 months ($P = .002$) and a 31% lower rate at 1 year ($P = .001$) in European patients with severe heart failure treated with the ACE inhibitor enalapril (Vasotec) than in similar patients receiving placebo.

V-HeFT II: Enalapril prevents more deaths than isosorbide dinitrate-hydralazine

The second Vasodilator-Heart Failure trial (V-HeFT II), published in 1991, compared the effects of isosorbide dinitrate-hydralazine and enalapril.[9] At 2 years, the mortality rate was 28% lower in the enalapril group than in the isosorbide dinitrate-hydralazine group ($P = .016$), primarily due to a lower rate of sudden cardiac death, though isosorbide dinitrate-hydralazine resulted in greater improvements in functional capacity and ejection fraction.[8,9]

The results of V-HeFT II suggested that perhaps both enalapril and isosorbide dinitrate-hydralazine could be beneficial in treating heart failure by independent mechanisms. However, ACE inhibitors became the standard of care due to enalapril's greater impact on mortality, while isosorbide dinitrate-hydralazine was used for those who could not tolerate an ACE inhibitor.

Are ACE inhibitors less effective in African Americans?

Although these studies were limited to male veterans, about 28% of the V-HeFT subjects were African American, thus permitting ret-

rospective analysis of outcomes by ethnicity.

These retrospective analyses were prompted by the differences noted above in the patterns of heart failure[22–25] and hypertension[29–32] in African Americans and whites, as well as by data showing ethnic differences in response to ACE inhibitors and beta-blockers used for hypertension.

In a retrospective subgroup analysis of V-HeFT,[27] both white men and African American men had higher survival rates with the isosorbide dinitrate-hydralazine combination than with placebo, but the difference was statistically significant only in the African Americans ($P = .04$). On the other hand, in V-HeFT II, enalapril conferred a survival advantage in white patients, while African Americans had similar outcomes regardless of whether they were treated with enalapril or isosorbide dinitrate-hydralazine.[27]

The two subgroups differed in some of their baseline characteristics.[27] For example, the African Americans had a lower prevalence of coronary artery disease, a greater prevalence of previous hypertension, and a greater cardiothoracic ratio than their white counterparts. In V-HeFT II, the African American men had lower plasma norepinephrine levels, and those with hypertension had lower plasma renin activity, compared with the white men. In response to enalapril, blood pressure fell more and cardiac size decreased more in the white subjects than in the African Americans.

The Studies of Left Ventricular Dysfunction (SOLVD)[28] also suggested, in a retrospective analysis by ethnicity, that ACE inhibitors are less effective in African Americans. In this analysis, white patients had a 44% lower risk of hospitalization for heart failure if they received enalapril than if they got placebo ($P < .001$), but African Americans had no significant reduction. In addition, enalapril was associated with significant blood pressure reductions in white patients but not in African Americans.[25]

In summary, African Americans in V-HeFT and V-HeFT II who received isosorbide dinitrate-hydralazine had a greater reduction in mortality rate than their white counterparts and equivalent survival when isosorbide dinitrate-hydralazine was compared with enalapril. These findings suggested mechanistic differences in the pathophysiology of heart failure between African Americans and whites, which might provide a therapeutic opportunity.

Why might ACE inhibitors work less well in African Americans?

Several mechanisms have been proposed for the lesser responses to ACE inhibitors in African Americans.

Although African Americans and whites appear to have similar ACE levels, the relationship between ACE levels and blood pressure differs. In African American patients, ACE levels tended to be inversely associated with blood pressure, while they tended to be positively associated with blood pressure in whites ($P = .06$), suggesting possible ethnic differences in the way the renin-angiotensin system regulates blood pressure.[29,30]

In addition, ACE inhibitors augment bradykinin levels, which have been associated with improvement in the unfavorable remodeling of the left ventricle in heart failure.[33] Bradykinin appears to exert beneficial effects on the heart via the release of endogenous nitric oxide.[34] Some data suggest that African Americans may have less bioavailable nitric oxide, possibly due to increased oxidative stress,[31,32,35] which could potentially attenuate the response to ACE inhibitors.

Hypertension accounts for more cases of heart failure than ischemia in African Americans

Focus has shifted from hemodynamics to neurohormones

As a result of the V-HeFT, V-HeFT II, CONSENSUS, SOLVD, and other trials, the focus of therapy for heart failure has shifted from hemodynamics to neurohormones. In the new view, heart failure develops in response to an initial insult and progresses by chronic neurohormonal stimulation, which causes intense vasoconstriction, myocyte hypertrophy, fibrosis, and subsequent remodeling of the heart. Large randomized trials have shown that neurohormonal-modifying agents such as ACE inhibitors, beta-blockers, ARBs, and aldosterone antagonists improve outcomes in chronic heart failure[4–12,212,23,33–36] by mechanisms beyond hemodynamic effects.

Other mechanisms that contribute to myocardial remodeling in both experimental

TABLE 1

A-HeFT baseline patient characteristics: Treatment groups were well matched

CHARACTERISTICS	MEN		WOMEN	
	TREATMENT (N = 290)	PLACEBO (N = 340)	TREATMENT (N = 228)	PLACEBO (N = 192)
Age (years)	57 ± 13	57 ± 13	57 ± 13	57 ± 14
Weight (kg)†	95.7 ± 24.8	97.5 ± 26.0	88.4 ± 23.4	88.0 ± 23.3
Primary cause of heart failure (% of patients)				
Ischemic	28.3	23.8	17.1	20.8
Hypertensive	37.2	39.1	43.4	34.4
Idiopathic	23.8	25.3	25.4	31.8
Valvular	2.8	3.2	2.2	3.1
Other	7.9	8.5	11.8	9.9
NYHA class (% of patients)				
II or III‡	96.6	93.2	97.4	97.4
IV	3.4	6.8	2.6	2.6
Diabetes mellitus (% of patients)†	38.6	35.6	52.6	39.6
Renal insufficiency (% of patients)†	20.0	21.1	11.4	12.5
Creatinine (mg/dL)†	1.4 ± 0.57	1.4 ± 0.49	1.1 ± 0.44	1.1 ± 0.38
Atrial fibrillation (% of patients)*	17.9	19.4	12.3	14.6
Ejection fraction (%)†	23.2 ± 7.1	23.2 ± 7.6	24.8 ± 7.6	25.8 ± 7.0
LVIDD/BSA (cm/m^2)§	3.16 ± 0.54	3.10 ± 0.53	3.16 ± 0.56	3.21 ± 0.64
Body mass index (kg/m^2)†	30.7 ± 7.8	31.3 ± 7.8	32.8 ± 8.3	33.2 ± 8.8
Hemoglobin (g/dL)†	13.8 ± 1.6	13.7 ± 1.8	12.7 ± 1.6	12.3 ± 1.8
Blood pressure (mm Hg)				
Systolic*	126 ± 17	125 ± 18	129 ± 17	127 ± 19
Diastolic	77 ± 11	76 ± 11	78 ± 10	75 ± 10
Quality-of-life score†	48 ± 25	50 ± 25	54 ± 25	53 ± 26
Baseline medications (% of patients)				
Diuretic	92.8	91.5	89.5	95.3
ACE inhibitor or ARB	93.4	93.8	90.8	91.7
Beta-blocker	84.5	82.6	82.9	81.3
Digoxin	60.7	60.9	56.1	60.9
Spironolactone	38.6	38.5	42.1	36.5

Plus-minus values represent means ± standard deviations. NYHA = New York Heart Association, LVIDD = left ventricular internal diameter in diastole, BSA = body surface area, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker.
*$P < .05$ and †$P < .01$ comparing men and women; there were no significant sex-by-treatment interactions in baseline characteristics.
‡NYHA class II represented only 1% of the A-HeFT patient population.
§Quality of life was measured with the Minnesota Living With Heart Failure Quality of Life score; lower scores indicate better quality of life.

ADAPTED FROM TAYLOR AL, LINDEFELD J, ZIESCHE S, ET AL. OUTCOMES BY GENDER IN THE AFRICAN-AMERICAN HEART FAILURE TRIAL. J AM COLL CARDIOL. 2006; 48:2263–2267.

and clinical models of heart failure are oxidative stress, impaired bioavailability of nitric oxide, and endothelial dysfunction.[36,37] Thus, it is conceivable that therapy that improves nitric oxide bioavailability could improve heart failure outcomes. Data suggest that organonitrates such as isosorbide are nitric oxide donors, while hydralazine is a potent antioxidant that inhibits the consumption of nitric oxide by reactive oxygen species.[38–40] Thus, the combination may enhance nitric oxide bioavailability.

A-HeFT TRIAL DESIGN

A-HeFT was a randomized, placebo-controlled, double-blind trial that evaluated the effect of isosorbide dinitrate-hydralazine added to standard neurohormonal blockade in African American patients with advanced heart failure.[1] It was designed to prospectively confirm the survival benefit of isosorbide dinitrate-hydralazine in African Americans observed in V-HeFT. Since the V-HeFT trials included only men, it was especially important to include women in A-HeFT.

Patients had class III or IV heart failure

A total of 1,050 patients were included. All were older than 19 years, identified themselves as being African American, had been in New York Heart Association (NYHA) class III or IV heart failure for at least 3 months, and were already receiving neurohormonal blockade therapy (either an ACE inhibitor or an ARB, plus a beta-blocker). Evidence of left ventricular systolic dysfunction had to have been present within 6 months prior to enrollment. Left ventricular dysfunction was defined as an ejection fraction less than 35% or less than 45% with left ventricular dilatation.

Women were excluded if they were pregnant or of childbearing age and not using an effective method of contraception. Also excluded were people with an acute myocardial infarction, acute coronary syndrome, or stroke within 3 months of the trial, cardiac surgery or percutaneous coronary intervention within 3 months or expected during the trial, or uncontrolled hypertension.

Isosorbide dinitrate-hydralazine or placebo was added to baseline treatment

Patients were randomly assigned to receive tablets containing either fixed-dose isosorbide dinitrate 20 mg plus hydralazine 37.5 mg or placebo, three times a day. The isosorbide dinitrate-hydralazine combination was titrated to a target dose of isosorbide 120 mg/day and hydralazine 225 mg/day, ie, two of the fixed-dose combination tablets three times a day. In addition, patients continued to receive their other heart-failure drugs.

End points: Death, hospitalization, change in quality of life

The primary efficacy end point was a composite score based on weighted values for death from any cause, a first hospitalization for heart failure during the follow-up period, and change in quality of life at 6 months assessed by the Minnesota Living With Heart Failure questionnaire.[41]

Secondary end points included individual components of the primary composite score, cardiovascular death, change in B-type natriuretic peptide (BNP) concentration at 6 months, newly recognized need for transplant, and changes in ejection fraction and left ventricular size.

RESULTS

Baseline characteristics by sex and treatment group are shown in TABLE 1. Most patients (95%) were in NYHA class III. Overall, the treatment groups were well matched; however, the active treatment group had more women, more patients with diabetes, and slightly higher diastolic blood pressures.

About 40% of the participants were women: this was the largest percentage of women and the largest absolute number of African American women in any heart failure trial. Although there were some baseline clinical differences between men and women, there were no differences in their baseline heart failure medications.

A-HeFT had more African American women than any other heart failure trial

Of importance, at baseline, patients in both treatment groups were already being well treated with neurohormonal blockers.

Consistent with other databases of African Americans with heart failure, only 23% of the cohort had heart failure attributable to ischemic heart disease. Hypertension was the dominant cause of heart failure in this study, which is consistent with prior studies of African Americans with heart failure.

No patient was lost to follow-up. The target dose of the study medication was achieved in 68% of patients in the treatment group and 89% in the placebo group.

Significant benefit with isosorbide dinitrate-hydralazine

The trial was stopped early (after a mean follow-up of 10 months) on the recommenda-

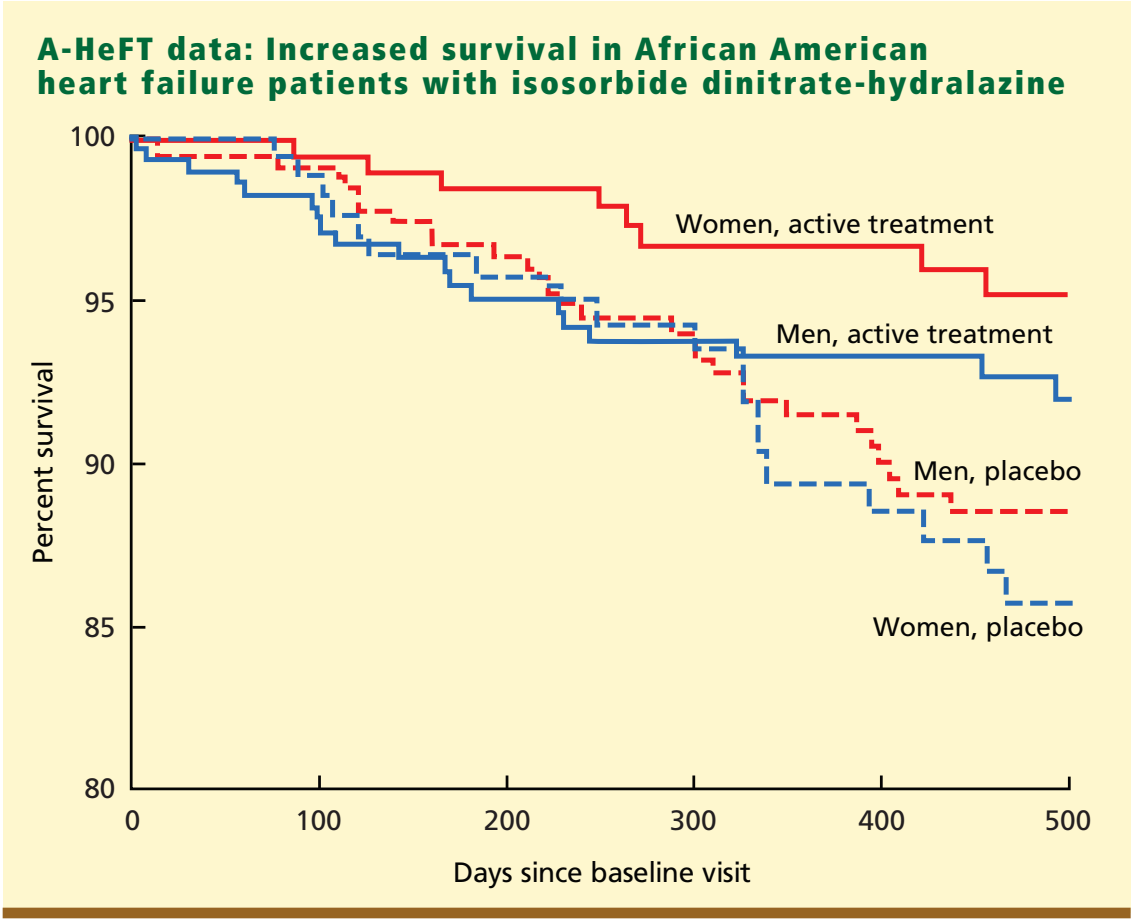

FIGURE 1. Kaplan-Meier curves for survival by sex and treatment groups in the African American Heart Failure Trial

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A-HeFT was stopped early because the mortality rate was significantly lower in the active treatment group

tion of the Data and Safety Monitoring Board because the mortality rate was significantly lower in the active treatment group than in the placebo group: 6.2% vs 10.2% (P = .02). This survival difference emerged at approximately 180 to 200 days and continued to widen over the duration of the trial.

The active treatment group also had significantly:

- Fewer hospitalizations for heart failure (16.4% of the active treatment group was hospitalized at least once vs 24.4% in the placebo group, P = .001)
- Better quality of life
- Higher ejection fractions
- Lower BNP levels[42]
- Fewer heart failure exacerbations.

On the negative side, headache and dizziness were more common in the active treatment group.[1]

Women appeared to benefit slightly more than men in terms of survival (FIGURE 1), but there were no statistically significant interactions of sex and treatment. Hospitalization and event-free survival rates were improved equally in men and women.[43]

APPLYING THE A-HeFT FINDINGS IN CLINICAL PRACTICE

A-HeFT showed that isosorbide dinitrate and hydralazine in a fixed-dose combination significantly increases survival when added to standard heart failure therapy in African American men and women with advanced heart failure.

Reflected in latest guidelines

Current guidelines from the Heart Failure Society of America[2] recommend ACE inhibitors and beta-blockers as first-line therapy for congestive heart failure but also recommend that isosorbide dinitrate-hydralazine be added to ACE inhibitors and beta-blockers for African American patients with left ventricular systolic dysfunction in NYHA functional class II, III, or IV. In addition, the guidelines recommend considering isosorbide dinitrate-hydralazine in patients who are not African American who have left ventricular systolic dysfunction and whose symptoms persist despite optimized therapy.

Guidelines published jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA)[3] state that the "addition of isosorbide dinitrate to a standard medical regimen for heart failure, including [ACE inhibitors] and beta-blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV heart failure."[3]

Both the ACC/AHA and Heart Failure Society of America consider isosorbide dinitrate-hydralazine a reasonable option in those who cannot tolerate an ACE inhibitor or an ARB owing to hypotension, renal insufficiency, cough, or hyperkalemia or as added therapy in patients with persistent symptoms despite optimal management.

Low blood pressure is not a contraindication

Since patients in the A-HeFT trial were already receiving optimal heart failure therapy with neurohormonal-blocking agents, which lower blood pressure, it is important to consider the effect of the added vasodilator on the patient's blood pressure.[3] Blood pressure responses to fixed-dose isosorbide dinitrate-hydralazine varied by baseline blood pressure. In those with systolic blood pressures above the median of 126 mm Hg, blood pressure was reduced. However, isosorbide dinitrate-hydralazine did not significantly reduce blood pressure in the subgroups with systolic blood pressure below the median of 126 mm Hg.[3] Thus, low blood pressure is not a contraindication to therapy.

Of importance, the reductions in death rate and improvement in event-free survival (death or hospitalization) were of equal magnitude whether baseline blood pressure was above or below the mean.[44] However, in patients with low blood pressures, physicians may want to start with one half tablet three times a day after being sure the patient is not volume-depleted.

Future trials should consider minorities

A-HeFT was a landmark trial, the first to examine the efficacy of a therapy in a single racial or ethnic group. It emphasizes the critical importance of including adequate numbers of people of diverse populations in clinical trials to assess population differences in disease patterns and responses to treatment. When such differences are observed, clinical trials are indicated in these populations to define pathophysiologic mechanisms of disease and optimal treatment strategies.

A-HeFT was not a comparison between racial groups but rather a trial to confirm the retrospective observations from the V-HeFT trial that isosorbide dinitrate-hydralazine was particularly effective in African Americans with heart failure. This study demonstrated a clear improvement in survival and quality of life and reduction in hospitalizations for African Americans using this combination. Because the A-HeFT patients were already receiving neurohormonal blockers, the incremental improvement in outcomes strongly suggests that heart failure progresses by mechanisms other than or in addition to neurohormonal stimulation in this population, and these mechanisms are responsive to this combination.

A-HeFT was the first trial to examine the efficacy of a therapy in a single racial or ethnic group

While many clinical trials have failed to clearly and confidently identify best therapy for various populations due to under-representation of those populations, A-HeFT demonstrates the value of following a trail of evidence when differences are observed and then designing focused trials to elucidate the best treatment strategies for specific populations.

The benefit in this population—increased survival, improved quality of life, and fewer hospitalizations—was substantial and strongly suggest that this agent should be added to neurohormonal inhibition in all African Americans with heart failure. A-HeFT now provides the strongest evidence-based data for heart failure treatment strategies in African Americans with advanced heart disease.

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ADDRESS: *Anne L. Taylor, MD, University of Minnesota Medical School, C694 Mayo Memorial Building, Mayo Mail Code 293, 420 Delaware Street, S.E., Minneapolis, MN 55455; e-mail taylo135@umn.edu.*