

Race, exercise training, and outcomes in chronic heart failure: Findings from Heart Failure - A Controlled Trial Investigating Outcomes in Exercise Training (HF-ACTION)

Robert J. Mentz, MD,^a Vera Bittner, MD, MSPH,^b Phillip J. Schulte, PhD,^c Jerome L. Fleg, MD,^d Ileana L. Piña, MD, MPH,^e Steven J. Keteyian, PhD,^f Gordon Moe, MD,^g Anil Nigam, MD, MSc,^h Ann M. Swank, PhD,ⁱ Anekwe E. Onwuanji, MD,^j Meredith Fitz-Gerald, RN, BSN,^b Andrew Kao, MD,^k Stephen J. Ellis, PhD,^c William E. Kraus, MD,^a David J. Whellan, MD, MHS,^l and Christopher M. O'Connor, MD^a
Durham, NC; Birmingham, AL; Bethesda, MD; New York, NY; Detroit, MI; Toronto, and Montreal, Canada; Louisville, KY; Atlanta, GA; Kansas City, MO; and Philadelphia, PA

Background The strength of race as an independent predictor of long-term outcomes in a contemporary chronic heart failure (HF) population and its association with exercise training response have not been well established. We aimed to investigate the association between race and outcomes and to explore interactions with exercise training in patients with ambulatory HF.

Methods We performed an analysis of HF-ACTION, which randomized 2331 patients with HF having an ejection fraction $\leq 35\%$ to usual care with or without exercise training. We examined characteristics and outcomes (mortality/hospitalization, mortality, and cardiovascular mortality/HF hospitalization) by race using adjusted Cox models and explored an interaction with exercise training.

Results There were 749 self-identified black patients (33%). Blacks were younger with significantly more hypertension and diabetes, less ischemic etiology, and lower socioeconomic status versus whites. Blacks had shorter 6-minute walk distance and lower peak VO_2 at baseline. Over a median follow-up of 2.5 years, black race was associated with increased risk for all outcomes except mortality. After multivariable adjustment, black race was associated with increased mortality/hospitalization (hazard ratio [HR] 1.16, 95% CI 1.01-1.33) and cardiovascular mortality/HF hospitalization (HR 1.46, 95% CI 1.20-1.77). The hazard associated with black race was largely caused by increased HF hospitalization (HR 1.58, 95% CI 1.27-1.96), given similar cardiovascular mortality. There was no interaction between race and exercise training on outcomes ($P > .5$).

Conclusions Black race in patients with chronic HF was associated with increased prevalence of modifiable risk factors, lower exercise performance, and increased HF hospitalization, but not increased mortality or a differential response to exercise training. (Am Heart J 2013;166:488-495.e1.)

African American or black populations are at an increased risk for developing heart failure (HF), which occurs at an earlier age and may be associated with

increased morbidity and mortality compared with whites.¹⁻⁴ Elderly black Medicare patients were recently shown to have increased 30-day readmission rates for HF compared with whites.⁵ However, several studies during the 1990s in the Veterans Affairs health care system^{6,7} and in Medicare patients⁸ demonstrated better survival in black patients with HF compared with white patients. Recent registry data from patients hospitalized with acute HF have also suggested that blacks may have comparatively lower in-hospital mortality and similar short-term outcomes.⁹⁻¹¹

Importantly, none of these studies investigated the strength of race as an independent predictor of long-term outcomes in a diverse, contemporary chronic HF population, and the association between race and exercise training response has not been well established.

From the ^aDuke University, Durham, NC, ^bUniversity of Alabama at Birmingham, Birmingham, AL, ^cDCRI, Durham, NC, ^dNHLBI, Bethesda, MD, ^eMontefiore-Einstein Medical Center, New York, NY, ^fHenry Ford Hospital, Detroit, MI, ^gSt Michael's Hospital, Toronto, Canada, ^hMontreal Heart Institute and University of Montreal, Montreal, Canada, ⁱUniversity of Louisville, Louisville, KY, ^jMorehouse School of Medicine, Atlanta, GA, ^kSaint Luke's Mid-America Heart Institute, Kansas City, MO, and ^lThomas Jefferson University, Philadelphia, PA. Hector O. Ventura, MD served as guest editor for this article.

Submitted April 11, 2013; accepted June 4, 2013.

Reprint requests: Robert J. Mentz, MD, 2301 Erwin Road, Durham, NC 27710.

E-mails: robert.mentz@duke.edu, rob.mentz@gmail.com

0002-8703/\$ - see front matter

© 2013, Mosby, Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.ahj.2013.06.002>

Although there was no evidence of a significant race and treatment interaction for all-cause mortality/hospitalization in the HF-ACTION study,¹² further investigation is warranted of the disease-specific outcomes of cardiovascular morbidity and mortality. We investigated the association between race and outcomes following multivariable adjustment and explored interactions with exercise training in patients with ambulatory HF enrolled in the HF-ACTION study.

Methods

The design and results of the HF-ACTION study have been published (ClinicalTrials.gov, NCT00047437).¹²⁻¹⁴ HF-ACTION was a trial of exercise training versus usual care in patients with an ejection fraction (EF) $\leq 35\%$ and New York Heart Association (NYHA) class II to IV symptoms despite optimal HF therapy for at least 6 weeks. Race was documented by self-report (ie, white, black/African American, American Indian/Alaska native, Asian, and/or native Hawaiian/Pacific Islander). The protocol was approved by the institutional review boards/ethics committees for each of the sites and the coordinating center. All patients voluntarily provided written informed consent with randomization between April 2003 and February 2007.

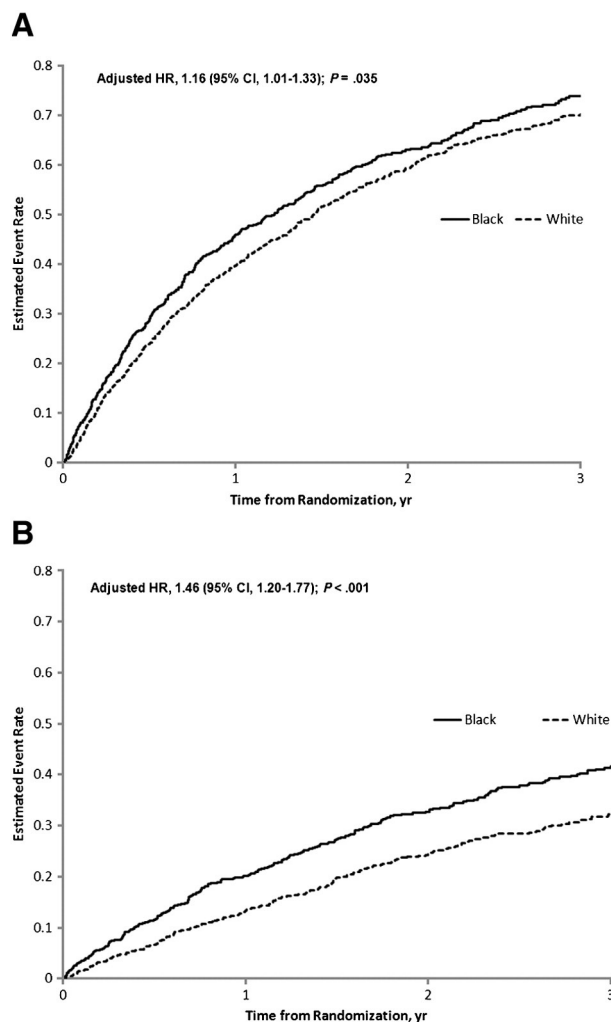
Patients were scheduled to complete a cardiopulmonary exercise (CPX) test, 6-minute walk, and health status surveys at baseline and were subsequently randomized to aerobic exercise training + usual care or usual care alone. Patients randomized to aerobic exercise were scheduled to participate in 3 supervised exercise sessions/wk for 3 months. Patients exercised using a treadmill or stationary cycle ergometer as their primary training mode. Patients were encouraged to begin home-based exercise after 18 supervised sessions and to fully transition to home exercise after 36 supervised sessions. The primary index of adherence was weekly volume of self-reported exercise. After the trial started, it was decided that full adherence was to be defined as ≥ 90 min/wk of exercise during months 1 to 3 and ≥ 120 min/wk during subsequent months. Patients were instructed to continue home-based exercise training, along with one supervised session every 3 months, throughout follow-up. The primary end point was all-cause mortality/hospitalization. An independent clinical events committee adjudicated deaths and cardiovascular hospitalizations until the first HF hospitalization. Exercise and health status measures were repeated 3 months after baseline. Median follow-up was 2.5 years.

Statistical methods

Patients were grouped as white, black, or other. Baseline characteristics including health status (eg, Kansas City Cardiomyopathy Questionnaire [KCCQ]) and exercise parameters (eg, peak oxygen consumption [VO_2] and CPX duration) were described. Continuous variables were summarized with the median and 25th and 75th percentiles and compared for black vs. white using the Wilcoxon rank sum statistic. Categorical variables are presented as percentages and compared for black vs. white with a Pearson χ^2 statistic or exact test when appropriate.

Given the small sample size of nonblack minorities ($n = 121$), results are restricted to white and black subgroups; "other race" was included in statistical models. The primary outcome was time to mortality/hospitalization in black versus white patients.

Figure



Adjusted event curves for all-cause mortality/hospitalization* (**A**) and cardiovascular mortality/HF hospitalization[†] (**B**). *Adjusted for peak VO_2 by Weber class, KCCQ symptom stability score, blood urea nitrogen, country, EF, sex, β -blocker dosage, mitral regurgitation (MR) grade, and ventricular conduction. [†]Adjusted for loop diuretic dose, EF, MR grade, ventricular conduction, KCCQ symptom stability score, blood urea nitrogen, sex, age, peak VO_2 by Weber class, and V_E/VCO_2 .

We evaluated the secondary outcomes of time to cardiovascular mortality/HF hospitalization and all-cause mortality as well as the components of the composite outcome. Results for the composite endpoint of cardiovascular mortality/cardiovascular hospitalization were similar to the results for cardiovascular mortality/HF hospitalization and thus not presented here. We investigated the relationship between race and outcomes using Cox proportional hazards models, including adjustment for a comprehensive set of predictors. The adjustment variables were developed for the data set and have been used in the post hoc HF-ACTION analyses.¹⁵ In brief, baseline predictors (Figure footnote) were selected using a stepwise variable selection based

on a bootstrapped-backward selection process. As a secondary analysis, we further independently adjusted for socioeconomic status (income, education, marital status, and employment status) based on previous work.¹⁶ Proportional hazards assumptions were checked and verified for race with all outcomes; no violation was suggested. Adjusted event curves for black vs. white race were plotted for mortality/hospitalization and CV mortality/HF hospitalization using the group prognosis method.

An adjusted Cox proportional hazards model was used to assess the relationship of the interaction of race and exercise treatment with time to the clinical end points. In addition, the change in exercise and health status variables (baseline to 3 months) was examined in the study arms stratified by race. Linear regression modeling, adjusted for baseline covariates selected using backward selection, was used to explore an interaction between race and treatment as a predictor of the change in exercise and health status variables. To account for missing data at 3 months, subjects in the linear regression model were inversely weighted by their estimated probability of having a missing response conditional on their baseline characteristics. The analysis plan specified that the *P* value would be reported for the interaction of black race and exercise therapy for clinical outcomes and the change in exercise and health status variables. If these *P* values for interaction were significant, then the hazard ratio (HR) for the clinical end point (or the estimate of the change at 3 months for the health status or exercise parameter) and 95% CI for treatment within each racial category would be reported. We also explored the relationships between exercise volume¹⁷ and adherence with race. A *P* value <.05 was considered statistically significant for all analyses. All analyses were performed by the Duke Clinical Research Institute using SAS (Cary, NC) system version 9.2.

The HF-ACTION study was funded by the National Heart, Lung, and Blood Institute, but no extramural funding was used to support the current analysis. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the manuscript, and its final contents.

Results

Of patients who self-reported race (*n* = 2,296), 33% (*n* = 749) were black. [Table I](#) presents baseline characteristics. Blacks were younger, were more often female, and had less ischemic etiology and lower socioeconomic status versus whites. Blacks also tended to have higher body mass index (BMI) and more hypertension and diabetes but less atrial fibrillation. Blacks had shorter 6-minute walk distance and lower peak VO₂ at baseline; ([Table II](#)). Differences in these exercise-testing parameters remained significant after adjustment for sex differences (both *P* < .01). More than 90% of black and white patients were receiving angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers, with approximately half as many receiving aldosterone antagonists. Combination hydralazine/nitrate use was greater in blacks than in whites. Blacks were less likely to have an implanted cardioverter/defibrillator (ICD) or cardiac resynchronization therapy (CRT) device; however, there were significant differences in conduction

pattern by race. Specifically, more blacks had normal ventricular conduction, and fewer blacks had bundle-branch block morphology (14.7% vs 22.9%).

Adherence to exercise training by exercise minutes per week during the first 3 months and months 10 to 12 was 63 (18-106) in blacks versus 86 (50-125) in nonblacks (*P* < .001) and 68 (6-167) versus 108 (26-208) (*P* < .001), respectively. Median exercise volume in the exercise training arm was lower in blacks than in whites (2.9 [1.0-5.0] vs 4.4 [2.4-6.6] MET-h/wk, respectively, during months 1-3).

Overall adverse events were similar in patients of different race (online [Appendix Supplementary Table D](#)), with the exception of more worsening HF in blacks than in whites (36% vs 24%).

Mode-specific event rates for death and hospitalization are presented in the online [Appendix Supplementary Table II](#). Over a median follow-up of 2.5 years, all-cause mortality was 17.9% in blacks and 15.8% in whites. Hospitalization occurred in 67.0% of blacks versus 62.1% of whites. Nearly half of all hospitalizations were for HF in blacks (48.4%) compared with approximately a third in whites (33.9%). Black race was associated with increased mortality/hospitalization and cardiovascular mortality/HF hospitalization ([Table III](#)). All-cause mortality was similar in black and white patients. Cardiovascular mortality was similar between groups (*P* = .21), whereas black race was associated with increased hazard for HF hospitalization (HR 1.62, 95% CI 1.37-1.92) (online [Appendix Supplementary Table III](#)).

After multivariable adjustment for the adjustment model covariates, black race remained associated with increased mortality/hospitalization and cardiovascular mortality/HF hospitalization ([Table III](#)). [Figure 1](#) displays adjusted event curves for the endpoints of mortality/hospitalization, and cardiovascular mortality/HF hospitalization. Exploring the individual components of these end points suggested increased risk, associated with black race for HF hospitalization (adjusted HR 1.58, 95% CI 1.27-1.96), but similar risk for cardiovascular mortality (adjusted *P* = .18).

After adjustment for additional socioeconomic covariates, black race was no longer associated with a significant increase in mortality/hospitalization (*P* = .09). The increased risk of cardiovascular mortality/HF hospitalization ([Table III](#)) and the individual component of HF hospitalization associated with black race remained statistically significant (HR 1.55, 95% CI 1.22-1.97) (online [Appendix Supplementary Table III](#)).

There was no interaction between race and assignment to exercise training on clinical outcomes ([Table IV](#)). However, there was evidence for an interaction between black race and exercise training for change in 6-minute walk distance (adjusted *P* = .02). The estimated improvement in 6-minute walk distance with exercise training versus usual care at 3 months was +26 m (95% CI, +18 to +34) in whites versus

Table I. Baseline characteristics of the study cohort based on race

Variable	Race		P
	Black (n = 749)	White (n = 1426)	
Age (y)	55 (47-64)	62 (54-70)	<.001
Female sex	41	22	<.001
Income			<.001*
<25,000	49	30	
\$25,000-\$49,999	26	27	
\$50,000-\$99,999	10	25	
\$100,000 or more	3	8	
Decline	12	10	
Education			<.001*
<High school	14	12	
High school graduate/equivalent	35	25	
Some college/no degree	27	26	
Completed associate degree	8	9	
College graduate	11	18	
Completed graduate school	5	10	
Marital status			<.001*
Married	41	66	
Widowed	12	9	
Divorced	17	14	
Separated	6	2	
Single/Never married	20	7	
Living with partner	4	3	
Employment status			<.001*
Employed full-time	17	19	
Employed part-time	5	6	
Disabled	41	25	
Unemployed	8	4	
Retired	27	43	
Other	2	3	
Ischemic etiology	32	61	<.001
NYHA III-IV	39	36	.23
EF (%)	25 (20-31)	25 (20-30)	.63
Ventricular conduction			<.001
Normal	54.3	32.3	
LBBB	11.8	19.1	
RBBB	2.9	3.8	
IVCD	14.4	11.5	
Paced	14.8	27.4	
Unknown	1.7	3.0	
History of myocardial infarction	24	51	<.001
Hypertension history	77	51	<.001
Diabetes history	36	30	.003
Atrial fibrillation/flutter	14	25	<.001
BMI (kg/m ²)	32 (27-38)	29 (26-34)	<.001
Systolic blood pressure (mm Hg)	114 (102-130)	110 (100-124)	<.001
Heart rate (beats/min)	72 (64-78)	69 (62-76)	.003
Sodium (mmol/L)	139 (138-141)	139 (137-141)	.02
Creatinine (mg/dL)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	.61
Blood urea nitrogen (mg/dL)	18 (13-25)	22 (17-30)	<.001
ACE inhibitor/angiotensin receptor blocker	95	94	.22
β-Blocker	96	94	.15
β-Blocker type			<.001
Atenolol	2.7	2.5	
Bisoprolol	1.0	4.9	
Carvedilol	60.1	60.3	
Metoprolol XL	29.9	23.1	
Metoprolol immediate release	5.6	8.4	
Other	0.7	0.8	
Dose (mg/d), carvedilol equivalent	50 (25-50)	31 (19-50)	<.001

(continued on next page)

Table I (continued)

Variable	Race		P
	Black (n = 749)	White (n = 1426)	
Aldosterone antagonist	49	43	.007
Hydralazine [†]	34	7	<.001
Nitrates [‡]	26	23	.059
Hydralazine + nitrates	15	3	<.001
Loop diuretic	84	74	<.001
Digoxin	46	44	.28
Implantable cardioverter/defibrillator	31	45	<.001
Biventricular pacemaker	12	22	<.001

Expressed as median (interquartile range) or %.

* P values for the dichotomized comparison of each variable as follows: income: <\$25,000 vs ≥\$25,000; education: <high school vs ≥high school; marital status: current or prior partner (married, living with partner, widowed) vs no partner (single, divorced, separated); employment status: employed, volunteer, student, homemaker, or retired vs unemployed or disabled.

† Includes combination therapy with nitrates.

‡ Includes combination therapy with hydralazine.

Table II. Baseline health status and exercise parameters by race

Variable	Black (n = 749)	White (n = 1426)	P
Beck Depression Inventory II score	8 (5-16)	8 (4-14)	.059
Kansas City Cardiomyopathy Questionnaire Overall Score	66 (48-81)	69 (53-84)	<.001
6-min walk distance (m)	348 (277-416)	383 (309-445)	<.001
CPX test duration (min)	8.7 (6.1-11.0)	10.0 (7.3-12.5)	<.001
Peak VO ₂ (mL kg ⁻¹ min ⁻¹)	13.2 (10.6-16.5)	15.0 (12.3-18.2)	<.001
VE/VCO ₂ slope	32 (28-38)	33 (29-39)	<.001
% with respiratory exchange ratio >1.10	34	48	<.001
Heart rate at peak exercise (beats/min)	122 (107-138)	118 (103-132)	<.001

Expressed as median (interquartile range) unless noted.

Table III. Association between black race and outcomes in chronic HF (reference = white race)

	HR (95% CI)	P
All-cause mortality or all-cause hospitalization		
Unadjusted	1.15 (1.03-1.28)	.013
Adjusted for HF-ACTION model covariates* (n = 1727)	1.16 (1.01-1.33)	.035
Adjusted for HF-ACTION model + income, employment, marital status, and education covariates (n = 1496)	1.14 (0.98-1.33)	.09
All-cause mortality		
Unadjusted	1.10 (0.88-1.36)	.40
Adjusted for HF-ACTION model covariates† (n = 1954)	1.01 (0.80-1.29)	.91
Adjusted for HF-ACTION model + income, employment, marital status, and education covariates (n = 1670)	1.09 (0.84-1.43)	.51
Cardiovascular mortality or HF hospitalization		
Unadjusted	1.46 (1.25-1.70)	<.001
Adjusted for HF-ACTION model covariates* (n = 1705)	1.46 (1.20-1.77)	<.001
Adjusted for HF-ACTION model + income, employment, marital status, and education covariates (n = 1482)	1.41 (1.13-1.75)	.002

Sample size for the unadjusted analysis was n = 2296 for all end points, as 35 of the 2331 in HF-ACTION were not classified as black, white or other.

* Adjusted for variables listed in Figure 1 footnote.

† Adjusted for exercise duration on baseline CPX, serum creatinine level, BMI, sex, loop diuretic dose, left ventricular ejection fraction, CCS angina classification, and ventricular conduction before baseline CPX.

+11 m (95% CI, 0 to +21) in blacks. No other exercise or health status variable demonstrated a statistically significant interaction with race and exercise training.

Discussion

The high enrollment of blacks, robust data collection on socioeconomic status, and long-term follow-up in HF-ACTION make this a unique data set to investigate the

association between race, exercise training response, and outcomes. We demonstrated that black race was associated with more comorbidities, shorter 6-minute walk distance and lower peak VO₂ at baseline, and increased mortality/hospitalization and cardiovascular morbidity/mortality driven by increased HF hospitalization compared with white race. We did not observe increased mortality or a differential response to exercise training in black patients. These findings confirm and extend

Table IV. Interaction between race, exercise training, and outcomes

Outcome	P value for interaction between black vs white race and treatment assignment*
Clinical outcomes	
All-cause mortality or all-cause hospitalization	.66
All-cause mortality	.68
Cardiovascular mortality or HF hospitalization	.75
Change in exercise and health status variables from baseline to 3 mo	
Kansas City Cardiomyopathy Questionnaire Overall Score	.82
6-min walk distance	.02
CPX test duration	.10
Peak VO ₂	.53

KCCQ score: adjusted for baseline KCCQ overall summary score, Beck Depression score, and peak VO₂; 6-minute walk: adjusted for baseline 6-minute walk distance, blood urea nitrogen, CPX duration, and peak VO₂; CPX duration: adjusted for baseline CPX duration, number of hospitalizations in the previous 6 months, chronic obstruction pulmonary disease, blood urea nitrogen, peak respiratory exchange ratio, heart rate, and peak VO₂; peak VO₂: adjusted for baseline peak VO₂, age, sex, number of HF hospitalizations in the previous 6 months, ischemic etiology, pacemaker, blood urea nitrogen, and CPX duration.

* Clinical end points were adjusted as indicated in the footnote for Table III or in the legend for this table.

previous research by demonstrating the distinct characteristics of blacks with HF and by documenting the prognostic significance of race in contemporary patients with HF.

Black patients were more likely to be female and were significantly younger than white patients. Black patients also had an increased burden of hypertension and diabetes. These risk factors coupled with their higher BMI likely contributed to more frequent nonischemic etiology as the cause of HF among black patients. As others have shown, the high prevalence of cardiovascular risk factors among black patients^{1,11} suggests that efforts to reduce HF incidence,¹⁸ and subsequent morbidity and mortality should include control of obesity and the prevention and treatment of diabetes. Because the risk for adverse outcomes for patients with HF substantially increases with the number of chronic conditions,¹⁹ the diagnosis and management of comorbidities should be a priority in patients with HF irrespective of race.

!HF-ACTION is among the largest studies to characterize exercise capacity in black patients with HF. Functional limitation as quantified by 6-minute walk distance and CPX testing has been associated with poor quality of life and higher morbidity/mortality.²⁰⁻²³ However, racial differences in baseline functional capacity of patients with HF have not been well characterized. We demonstrated that compared with white patients, black patients had a median 6-minute walk distance 35 m shorter and a median peak VO₂ 1.8 mL kg⁻¹ min⁻¹ lower. These observed

differences in baseline exercise capacity should be considered when interpreting functional evaluations for clinical risk stratification and in the design/analysis of future trials.

Patients in the HF-ACTION study had high ACE inhibitor and β-blocker prescription rates regardless of race. This finding may have been related to the protocol, which encouraged the use of an optimal HF regimen for 6 weeks before enrollment. Based on the African American Heart Failure Trial study (A-HeFT),²⁴ guidelines give the adjunctive use of isosorbide dinitrate/hydralazine the highest-tier recommendation in black patients with NYHA class II to IV symptoms.²⁵ Only 15% of blacks in HF-ACTION were treated with isosorbide dinitrate/hydralazine. Notably, A-HeFT was published during the time of HF-ACTION patient enrollment. Although the use of hydralazine/nitrates was higher than in previous registries,¹⁰ the overall modest usage indicates that further opportunities remain to improve guideline-based care for black patients with HF. Similarly, despite recent evidence suggesting that racial disparities in ICD use have narrowed over time,²⁶ we observed a significantly lower use of ICDs in blacks. The lower prevalence of bundle-branch block in blacks likely influenced the lower use of CRT.

Previous studies have provided conflicting results with respect to outcomes in black patients.^{1,10,11} After adjustment for the HF-ACTION model covariates, black race was associated with increased mortality/hospitalization and cardiovascular morbidity/mortality. The secondary analysis adjusting for socioeconomic covariates attenuated the association between black race and the primary end point. The nonsignificant trend between race and mortality/hospitalization may have been related to the reduced sample size owing to exclusion of those with unavailable socioeconomic data. Another possible explanation is related to “overadjustment,” where variables in the causal pathway for poor prognosis in blacks are added to the model.

Adjustment for socioeconomic status did not markedly change the association between black race and ~40% higher cardiovascular morbidity/mortality. Previous studies have demonstrated racial disparities in hospitalization rates.⁵ Potential mechanisms for worse outcomes in black patients with HF include the more malignant pathophysiology of hypertension in blacks, the higher prevalence and severity of left ventricular hypertrophy, an impaired vasodilatory response, and genetic polymorphisms.^{3,4,27} Additional unrecognized differences in the pathophysiology of HF in blacks remain an alternative explanation. Disparities in health care access, along with a greater burden of socioeconomic stressors, may be associated with increased adverse events in black patients.

The lack of independent association between black race and mortality may be explained, in part, by the observation that factors such as BMI, gender, and renal dysfunction^{28,29} play a more prominent role than race on

fatal events. Alternatively, similar mortality between groups may be related to improved medical follow-up in the controlled setting of a trial of exercise training.

Despite lower exercise adherence and volume in blacks and recent data suggesting that exercise volume mediates the impact of exercise training on outcomes,¹⁷ there was insufficient evidence to suggest that exercise training had a differential association with outcomes based on race. The specific reason for these findings is unclear, but potential explanations include racial differences in the association between exercise volume and outcomes or insufficient power to detect a between-group difference.

There are several additional incongruencies in this study that warrant discussion. First, clinical characteristics seen in black patients, which have been associated with a reduction in HF hospitalizations (eg, aldosterone antagonist use, higher β -blocker dose), did not translate into comparatively lower risk. One potential explanation for these findings is the higher comorbidity burden and lower CRT use in blacks. Another explanation is that despite statistically significant differences for several characteristics, the between-group differences may have not been large enough to result in clinically apparent differences in outcome (eg, impact of 43% aldosterone antagonist use in blacks vs 49% in whites). Alternatively, in some circumstances, there may be a differential association between therapies and outcomes based on race. For instance, the Beta Blocker Evaluation of Survival Trial demonstrated a blunted effect of bucindolol in African Americans.³⁰ Future research is needed to explore racial differences in clinical risk predictors and responses to therapy in patients with HF. Furthermore, despite black patients having a higher risk for HF readmission, which has previously been associated with increased mortality, we did not observe increased mortality in black patients. Potential explanations for this finding include a differential mortality risk related to HF hospitalization depending on the severity of underlying disease³¹ or differences in outpatient follow-up.

Limitations

This was a retrospective analysis from a clinical trial of exercise training. The study population had strict inclusion and exclusion criteria, such that these findings may not apply to those with different baseline characteristics. The cohort was substantially younger, with higher baseline HF medication use than the general HF community, and the treatment group participated in exercise training such that these results may not be generalizable to other populations. Despite covariate adjustment, other measured and unmeasured factors may have influenced these findings. For instance, the adjustment variables for the present analysis are those that were initially developed for the HF-ACTION data set and include variables such as ventricular conduction, but not device use.

Conclusion

In patients with chronic systolic HF, black race was associated with younger age, increased prevalence of modifiable risk factors, and reduced peak VO_2 at baseline. Despite a similar use of evidence-based HF pharmacologic therapies, blacks experienced increased HF hospitalization, but not increased mortality or a differential response to exercise training. Given the findings of the primary HF-ACTION trial, that regular exercise confers a modest reduction in the adjusted risk for all-cause mortality or hospitalization, these data support efforts to improve conditioning through exercise training in patients with HF regardless of race. These results highlight strategies to improve outcomes in the black population including a proactive approach to diet, exercise, and weight management and increased use of therapies, including hydralazine/nitrates and ICDs.

Disclosures

None.

References

1. Dries DL, Exner DV, Gersh BJ, et al. Racial differences in the outcome of left ventricular dysfunction. *N Engl J Med* 1999;340(8):609-16.
2. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. *N Engl J Med* 2009; 360(12):1179-90.
3. Yancy CW. Heart failure in African Americans. *J Card Fail* 2000; 6(3):183-6.
4. Yancy CW, Strong M. The natural history, epidemiology, and prognosis of heart failure in African Americans. *Congest Heart Fail* 2004;10(1):15-8.
5. Joynt KE, Orav EJ, Jha AK. Thirty-day readmission rates for Medicare beneficiaries by race and site of care. *JAMA* 2011;305(7):675-81.
6. Deswal A, Petersen NJ, Souchek J, et al. Impact of race on health care utilization and outcomes in veterans with congestive heart failure. *J Am Coll Cardiol* 2004;43(5):778-84.
7. Jha AK, Shlipak MG, Hosmer W, et al. Racial differences in mortality among men hospitalized in the Veterans Affairs health care system. *JAMA* 2001;285(3):297-303.
8. Rathore SS, Foody JM, Wang Y, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. *JAMA* 2003;289(19):2517-24.
9. Kamath SA, Drazner MH, Wynne J, et al. Characteristics and outcomes in African American patients with decompensated heart failure. *Arch Intern Med* 2008;168(11):1152-8.
10. Yancy CW, Abraham WT, Albert NM, et al. Quality of care of and outcomes for African Americans hospitalized with heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry. *J Am Coll Cardiol* 2008;51(17):1675-84.
11. Thomas KL, Hernandez AF, Dai D, et al. Association of race/ethnicity with clinical risk factors, quality of care, and acute outcomes in patients hospitalized with heart failure. *Am Heart J* 2011;161(4):746-54.
12. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301(14):1439-50.

13. Whellan DJ, O'Connor CM, Lee KL, et al. Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION): design and rationale. *Am Heart J* 2007;153(2):201-11.
14. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301(14):1451-9.
15. Mentz RJ, Schulte PJ, Fleg JL, et al. Clinical characteristics, response to exercise training, and outcomes in patients with heart failure and chronic obstructive pulmonary disease: findings from Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION). *Am Heart J* 2013;165(2):193-9.
16. Fiscella K, Tancredi D. Socioeconomic status and coronary heart disease risk prediction. *JAMA* 2008;300(22):2666-8.
17. Keteyian SJ, Leifer ES, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol* 2012;60(19):1899-905.
18. Avery CL, Loehr LR, Baggett C, et al. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol* 2012;60(17):1640-6.
19. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003;42(7):1226-33.
20. Myers J, Arena R, Dewey F, et al. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J* 2008;156(6):1177-83.
21. Francis DP, Shamim W, Davies LC, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO₂ slope and peak VO₂. *Eur Heart J* 2000;21(2):154-61.
22. Curtis JP, Rathore SS, Wang Y, et al. The association of 6-minute walk performance and outcomes in stable outpatients with heart failure. *J Card Fail* 2004;10(1):9-14.
23. Arslan S, Erol MK, Gundogdu F, et al. Prognostic value of 6-minute walk test in stable outpatients with heart failure. *Tex Heart Inst J* 2007;34(2):166-9.
24. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351(20):2049-57.
25. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail* 2010;16(6):e1-e194.
26. Al-Khatib SM, Hellkamp AS, Hernandez AF, et al. Trends in use of implantable cardioverter-defibrillator therapy among patients hospitalized for heart failure: have the previously observed sex and racial disparities changed over time? *Circulation* 2012;125(9):1094-101.
27. McNamara DM, Tam SW, Sabolinski ML, 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(6):1277-82.
28. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;5(1):63-71.
29. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. *J Am Coll Cardiol* 2010;55(9):872-8.
30. Domanski MJ, Krause-Steinrauf H, Massie BM, et al. A comparative analysis of the results from 4 trials of beta-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *J Cardiac Fail* 2003;9(5):354-63.
31. Kommuri NV, Koelling TM, Hummel SL. The impact of prior heart failure hospitalizations on long-term mortality differs by baseline risk of death. *Am J Med* 2012;125(2):209e9-209e15.

Appendix. Supplementary Tables

Supplementary Table I. Adverse events (%) by race

Adverse event	Black (n = 749)	White (n = 1426)
Worsening HF	36	24
Myocardial infarction	3.7	3.4
Unstable angina	7.7	7.4
Serious adverse arrhythmia	14	14
Stroke	3.9	1.9
Transient ischemic attack	2.0	1.7
Any of the above events	45	36

Supplementary Table II. Mode-specific event rates for death and hospitalization by race

Event	Black (n = 749)	White (n = 1426)
All-cause mortality, no. (%)	134 (17.9)	225 (15.8)
Cardiovascular mortality, no. (%)	97 (13.0)	152 (10.7)
Noncardiovascular mortality or other, no. (%)	37 (4.9)	73 (5.1)
Total hospitalization, no. (%)	502 (67.0)	886 (62.1)
Cardiovascular hospitalization, no. (%)	422 (56.3)	717 (50.3)
HF hospitalization, no. (%)	243 (32.4)	300 (21.0)
Noncardiovascular hospitalization or other, no. (%)	80 (10.7)	169 (11.9)

Supplementary Table III. Association between black race and outcomes in chronic HF (reference = white race)

	HR (95% CI)	P
Cardiovascular mortality		
Unadjusted (n = 2296)	1.18 (0.91, 1.52)	.21
Adjusted for HF-ACTION model covariates* (n = 1705)	1.25 (0.90-1.74)	.18
Adjusted for HF-ACTION model + income, employment, marital status, and education covariates (n = 1482)	1.29 (0.90-1.86)	.17
HF hospitalization		
Unadjusted (n = 2296)	1.62 (1.37-1.92)	<.001
Adjusted for HF-ACTION model covariates* (n = 1705)	1.58 (1.27-1.96)	<.001
Adjusted for HF-ACTION model + income, employment, marital status, and education covariates (n = 1482)	1.55 (1.22-1.97)	<.001

*Adjusted for loop diuretic dose, left ventricular ejection fraction, mitral regurgitation grade, ventricular conduction before baseline CPX, KCCQ symptom stability score, blood urea nitrogen, sex, age, peak VO₂ characterized by Weber class, and V_E/VCO₂ on baseline CPX.