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Outcomes in African-Americans Undergoing Cardioverter Defibrillators Implantation for Primary Prevention of Sudden Cardiac Death: Findings from The Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD)

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Abstract

Background—Implantable cardioverter defibrillators (ICDs) reduce the risk of death in patients with left ventricular dysfunction. Little is known regarding the benefit of this therapy in African-Americans (AA).

Objective—To determine the association between African-American race and outcomes in a cohort of primary prevention cardioverter defibrillators (ICD) patients.

Methods—We conducted a prospective cohort study of patients with systolic heart failure who underwent ICD implantation for primary prevention of sudden cardiac death. The primary

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endpoint was appropriate ICD shock defined as a shock for rapid ventricular tachyarrhythmias. The secondary endpoint was all-cause mortality.

Results—There were 1,189 patients (447 AAs and 712 non-AAs) enrolled. Over a median follow-up of 5.1 years, a total of 137 patients experienced an appropriate ICD shock, and 343 died (294 of whom died without receiving an appropriate ICD shock). The multivariate adjusted hazard ratios (95% CI) comparing AAs vs. non-AAs were 1.24 (0.96 to 1.59) for all-cause mortality, 1.33 (1.02, 1.74) for all-cause mortality without receiving appropriate ICD shock, and 0.78 (0.51, 1.19) for appropriate ICD shock. Ejection fraction, diabetes, and hypertension appeared to explain 24.1% (10.1 to 69.5%), 18.7% (5.3 to 58.0%), and 13.6% (3.8 to 53.6%) of the excess risk of mortality in AAs, with a large proportion of the mortality difference remains unexplained.

Conclusions—In patients with primary prevention ICDs, AAs had an increased risk of dying without receiving an appropriate ICD shock compared to non-AAs.

Keywords

African-American; implantable cardioverter defibrillator; sudden cardiac death; all-cause mortality; ICD shock

INTRODUCTION

Large randomized trials have shown that implantable cardioverter defibrillators (ICDs) reduce the risk of sudden cardiac death (SCD) and all-cause mortality in patients with systolic heart failure.^{1–6} These findings have been derived from studies comprised predominantly of Caucasian subjects with limited representation of African Americans (AA). AA individuals, however, have a greater prevalence of heart failure and a higher risk for SCD compared with the general population^{7–11} and there is evidence of racial disparity in the utilization of primary prevention ICDs.^{12–14} Hence, there is limited data on whether outcomes after implantation of primary prevention ICDs in AA differ from other racial/ethnic groups.^{15–17} The main objective of this study was to compare the risk of ICD shock and mortality among AAs and non-AAs in the Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD), a large well-phenotyped cohort of patients with ischemic and non-ischemic cardiomyopathy undergoing ICD implantation for primary prevention of SCD.

METHODS

Study Population and Clinical Data Collection

PROSE-ICD is a multicenter prospective study of patients with systolic heart failure eligible for a primary prevention ICD conducted at four clinical centers in the United States from 2003 to 2013: the Johns Hopkins Hospital and Bayview Medical Center, Baltimore, MD; the University of Maryland Hospital, Baltimore, MD; the Washington Hospital Center, Washington, DC; and the Virginia Commonwealth University Hospital, Richmond, VA. Details of the study design and clinical endpoints have been described previously.¹⁸ Briefly, patients between 18–80 years of age referred for primary prevention ICD implantation were enrolled if they met any of the following criteria: (1) ischemic cardiomyopathy (myocardial

infarction greater than 40 days prior to implant) with an ejection fraction of $<30\%$ and stable New York Heart Association (NYHA) Class I–III heart failure symptoms on optimal pharmacotherapy; (2) ischemic or non-ischemic cardiomyopathy with an ejection fraction $<35\%$ and NYHA Class II or III heart failure; or (3) patients with NYHA Class IV heart failure symptoms undergoing implantation of a cardiac resynchronization therapy (CRT) device with an ICD. All centers obtained approval from their respective institutional review boards and all patients provided written informed consent.

At enrollment and prior to ICD implantation, all patients underwent a comprehensive review of medical history and cardiovascular examination along with a digitally-recorded resting 12-lead electrocardiogram (ECG), a 5-min three-lead ECG, an echocardiogram (if one was not previously available) and fasting blood collection. Race/ethnicity was identified exclusively on participants' self-report. During the enrollment visit, a standardized questionnaire was administered by a trained interviewer, and patients were asked how they would identify their racial/ethnic group, with six options available including Caucasian, African American, Native American or Alaskan, Asian, Pacific Islander, and other. We then further categorized race into AA (African American) and non-AA (all other racial/ethnicities). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CKD was defined as $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$.

Follow-up and Outcomes

Enrollment occurred from November 2003 to January 2013. Patients were evaluated every 6 months after ICD implantation either in person or by phone and soon after any ICD therapy recognized by the patient. For the current analysis, participants were followed for events through July 1, 2013. The minimum duration of follow-up was 5.6 months. The primary endpoint of the study was the occurrence of a first appropriate ICD shock for adjudicated ventricular tachyarrhythmia. Detailed information for all arrhythmic events resulting in ICD therapy was downloaded for adjudication by two clinical cardiac electrophysiologists blinded to patient demographic information. Disagreements were reconciled by a third electrophysiologist. Shocks were considered appropriate if the arrhythmia triggering ICD shock was secondary to rapid ventricular tachycardia or ventricular fibrillation. In cases where ventricular tachycardia or ventricular fibrillation occurred simultaneously with a supraventricular arrhythmia, the events were considered appropriate. Follow-up for the primary endpoint started at the time of ICD implantation and continued until the occurrence of the 1st appropriate ICD shock or the occurrence of the following censoring events: death, ICD deactivation or explantation, cardiac transplantation or implantation of a circulatory support device, or last follow-up visit. The secondary outcome was all-cause mortality. Deaths were ascertained by phone contact with the next of kin and by searches of the National Death Index. In addition, we also examined the association between race and all-cause mortality without receiving an appropriate shock (i.e., all-cause mortality censored at the first appropriate shock) as a measure of mortality in the absence of receiving definite benefit from the defibrillator component of the device.

Statistical Analyses

Baseline differences between AAs and non-AAs were evaluated using two-sided Student's *t* test, Wilcoxon's rank-sum test, or chi-square test, as appropriate. Cox proportional hazards models were used to estimate multivariate adjusted hazard ratios for endpoints comparing AA vs non-AA. For each endpoint, we used two models with progressive degrees of adjustment. The initial model was adjusted for age, sex, and enrollment center. The second model was further adjusted for education, smoking status, body mass index, ejection fraction, NYHA class, ischemic cardiomyopathy, atrial fibrillation, diabetes, hypertension, and chronic kidney disease. The proportional hazards assumption was checked by plotting the $\log(-\log(\text{survival}))$ versus $\log(\text{survival time})$ and by using the Schoenfeld Residuals.

To examine the mediation effect of each covariate on the association between race and endpoints, we calculated the percent change in the β -coefficient of race comparing the base model (adjusted for age, sex, and enrollment center) and the model further adjusted for the covariate of interest. The 95% CIs were calculated by using boot-strapping. In addition, we performed stratified analyses in pre-specified subgroups defined by the categorical variables of age (< 65, ≥ 65 years), sex, ejection fraction (< 20%, ≥ 20%), NYHA class (I/II, III/IV), cardiomyopathy etiology (ischemic, non-ischemic), atrial fibrillation, hypertension, diabetes, and chronic kidney disease. Interactions by subgroups were tested using the likelihood ratio tests comparing models with and without interaction terms of race and subgroups. We also performed sensitivity analysis further adjusting for device characteristics (device type, lowest cut-off rate, ATP zone used) and medication use (aspirin [ASA], angiotensin converting enzyme inhibitors [ACE-I] or angiotensin receptor blockers [ARBs], beta-blocker, diuretics, and aldosterone antagonist). In addition, we repeated all analysis using the endpoint of appropriate ICD therapy (which included both antitachycardia pacing [ATP] and shock) and found similar results (data not shown). All analyses were performed using STATA version 12 (StataCorp LP, College Station, Texas).

RESULTS

Among 1,189 participants enrolled, 477 (40.1%) were AA (Table 1) and the remaining 712 participants were non-AA (95.4% Caucasians). Compared to non-AAs, AAs were on average younger (56.8 vs. 63.2 years), more likely to be women (34.4% vs. 22.2%), current smokers (24.1% vs. 19.0%), to have a lower ejection fraction (20.8% vs. 23.2%), non-ischemic cardiomyopathy (60.0% vs. 36.7%), diabetes (41.7% vs. 30.2%), hypertension (72.5% vs. 56.3%), to use diuretics (80.9% vs. 66.2%), aldosterone antagonists (30.8% vs. 21.8%), and to have a single chamber device (64.2% vs. 49.0%) and ATP programmed on (63.3% vs. 55.1%) (all p-values comparing AA vs. non-AA were <0.01). The AA population, however, was less likely to complete high school (69.2% vs. 80.5%; p-value = 0.001), to have atrial fibrillation (21.2% vs. 29.6; p-value = 0.001), or to use ASA (61.4% vs. 68.5%; p-value = 0.01) and ACE-I/ARB (67.3% vs. 74.3%; p-value = 0.01).

During a median follow-up of 5.1 years, 137 subjects experienced an appropriate ICD shock (40 in AA and 97 in non-AA), and 343 participants died (133 AA and 210 non-AA; Table 2). Among those who died, 85.7% died without experiencing an appropriate ICD shock for ventricular arrhythmias. In multivariate models adjusted for age, sex, and enrollment center,

AA had an increased risk for all-cause death (HR = 1.42, 95% CI 1.12 to 1.80), death without receiving appropriate ICD shock (HR = 1.51, 95% CI 1.18 to 1.95), and a weak trend toward lower risk for appropriate ICD shocks (HR = 0.85, 95% CI 0.58 to 1.26) (Table 2). When the model was further adjusted for education, smoking status, body mass index, ejection fraction, NYHA class, ischemic cardiomyopathy, atrial fibrillation, diabetes, hypertension, and chronic kidney disease, the hazard ratios were 1.24 (0.96 to 1.59) for all-cause death, 1.33 (1.02 to 1.74) for death without receiving appropriate ICD shock, and 0.78 (0.51 to 1.19) for appropriate ICD shock, respectively. In an exploratory analysis, the increased mortality risk among AAs was most prominent during the first two years of follow-up (Table 3). Sensitivity analysis further adjusted for device characteristics (device type, lowest cut-off rate, ATP zone used) and medication use (ASA, ACE-I/ARB, beta-blocker, diuretics, and aldosterone antagonists) yielded nearly identical results (data not shown).

In mediation analysis, ejection fraction, diabetes, and hypertension appeared to explain 24.1% (10.1 to 69.5%), 18.7% (5.3 to 58.0%), and 13.6% (3.8 to 53.6%) of the excess risk of mortality in AAs, respectively, with a large proportion of the mortality difference left unexplained (Table 4). When stratified by pre-specified subgroups, the associations between race and mortality were similar across subgroups, except that the association between AA and mortality appeared to be stronger in younger patients and in patients without hypertension (Figure 1).

DISCUSSION

In a prospective cohort of patients undergoing ICD implantation for primary prevention of SCD, AA patients had an increased risk of dying without receiving an appropriate ICD shock compared to non-AA patients, particularly in the first two years after implantation. This racial difference was only explained in part by differences in ejection fraction and prevalence of diabetes and hypertension between AA and non-AA patients.

AA individuals are more likely to experience cardiac arrest or SCD, and less likely to survive an out-of-hospital cardiac arrest compared with non-AAs.^{7–11} While several studies have highlighted utilization disparities among ICD eligible AA patients,^{12–14} racial differences in outcomes have not been well examined in ICD recipients.^{15–17} In the SCD-HeFT study (425 AA and 1932 Caucasian), mortality risk was significantly higher in AA compared with Caucasians, but there was no significant difference in the rate of ICD shocks.¹⁶ In addition, the survival benefit from the ICD (i.e., reduction in the risk of mortality) compared to conventional therapy was similar in AA and Caucasian patients. This was consistent with another study of 5948 elderly cardiac arrest survivors (519 AAs and 5429 Caucasians) in which AA and Caucasian participants had a similar mortality benefit from ICDs.¹⁹ Results from the MADIT-II trial, however, showed that ICDs were associated with a reduction in SCD and all-cause mortality in Caucasians (n=1073) but not in AAs (n=102).¹⁵ The exact cause of the racial difference was unclear. It is possible that AAs were less likely to receive an appropriate ICD shock in the first place, or that ICD shocks were less effective at preventing SCD, although the small number of AA participants in MADIT-II may have limited the statistical power of the study to detect an effect in AA participants.

In our study, the mortality difference between AA and non-AA patients was most prominent in the first two years after initial ICD implantation despite a younger age and comparable severity of heart failure to non-AA individuals. AA patients, however, had a lower ejection fraction, more comorbidities, and a different pattern of medication use. Consistent evidence has shown that a greater burden of comorbidity was associated with all-cause mortality in heart failure patients.^{20–22} As the burden of comorbidity increased, the risk of non-SCD increased, whereas the risk of SCD decreased.²⁰ This may partly explain the increased risk of death without receiving an appropriate ICD shock among AA patients compared to non-AA patients. However, in our study, a large proportion of the difference in mortality risk between AA and non-AA patients remained unexplained even after accounting for comorbidities. The difference may be related to other important factors such as socioeconomic status, compliance with medications, or patient education resources for heart failure management that we did not take into account. Furthermore, recent changes in the way we program devices suggest that higher rate cut offs and longer detection duration times reduce shocks and possibly all-cause mortality.²³ As these programming paradigms are adopted, the likelihood of ICD shocks will likely decrease and may increase the probability of patients dying from nonarrhythmic mechanisms over time. It is important to point out that our findings do not justify a differential indication of ICD implantation by race. Rather, they call for a more thorough investigation of the mechanisms explaining the racial difference in mortality in primary prevention ICD patients.

A few limitations of this study need to be considered. Although we adjusted for multiple confounders including educational level and comorbidities in our analysis, unmeasured confounders, particularly socioeconomic status, may limit the inferences that can be drawn from our results. Also, the mode of death could not be firmly established in many patients due to the lack of reliable records when patients died out of hospital since autopsies and/or postmortem ICD interrogations were rarely performed. As a consequence, we could not examine differences in cause-specific mortality and could not investigate which disease processes may explain the difference in outcomes between AA and non-AA patients. Lastly, since our study is observational in nature, we did not have a comparison cohort with heart failure patients who did not undergo ICD implantation, and therefore, we were not able to evaluate the net survival benefit of ICDs comparing AAs and non-AAs. It is possible that although AAs had a higher mortality risk, they may still derive similar survival benefit from the ICDs.

The strengths of the study are that this is the largest cohort of AA patients with primary prevention ICDs that we are aware of, the stringent enrollment criteria and quality-control procedures in acquiring the data, and the careful adjudication of appropriate ICD shocks.

CONCLUSION

In this large prospective study of patients undergoing primary prevention ICD implantation, AA patients had an increased risk of dying without receiving an appropriate ICD shock compared to non-AA patients. Further research is needed to establish the reasons underlying this racial difference so that the potential benefits of primary prevention ICDs can be equally applied to AA and non-AA patients.

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Abbreviations list

AA	African American
ECG	Electrocardiogram
ICD	Implantable cardioverter defibrillators
CI	Confidence interval
CRT	Cardiac resynchronization therapy
NYHA	New York Heart Association
PROSE-ICD	Prospective Observational Study of Implantable Cardioverter-Defibrillators
SCD	Sudden cardiac death

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Figure 1. Multivariable adjusted hazard ratios (95% CI) for mortality comparing African-Americans (AA) with non-AA, by pre-specified subgroups

Hazard ratios were adjusted for age, sex, enrollment center, education, smoking status, body mass index, ejection fraction, NYHA class, ischemic cardiomyopathy, atrial fibrillation, diabetes, hypertension, and chronic kidney disease. Deviation to the right of 1 indicates higher mortality in AAs in the indicated subgroup.

Table 1

Baseline characteristics of patients at the time of ICD implantation.

Characteristic	Total (n = 1189)	Non-AA (n=712)	AA (n = 477)	p-value
Age (year)	60.6 (12.7)	63.2 (11.8)	56.8 (12.9)	<0.001
Sex				<0.001
Male	867 (72.9)	554 (77.8)	313 (65.6)	
Female	322 (27.1)	158 (22.2)	164 (34.4)	
Education				<0.001
<12 years	168 (14.1)	91 (12.8)	77 (16.1)	
12 years	903 (75.9)	573 (80.5)	330 (69.2)	
Unknown	118 (9.9)	48 (6.7)	70 (14.7)	
Smoking				<0.001
Never	398 (33.5)	219 (30.8)	179 (37.5)	
Former	541 (45.5)	358 (50.3)	183 (38.4)	
Current	250 (21.0)	135 (19.0)	115 (24.1)	
Body mass index (kg/m ²)	29.8 (6.5)	29.1 (5.9)	30.7 (7.3)	<0.001
Ejection fraction (%)	22.3 (7.4)	23.2 (7.4)	20.8 (7.1)	<0.001
NYHA class				0.32
Class I	196 (16.5)	123 (17.3)	73 (15.3)	
Class II	524 (44.1)	300 (42.1)	224 (47.0)	
Class III	464 (39.0)	285 (40.0)	179 (37.5)	
Class IV	5 (0.4)	4 (0.6)	1 (0.2)	
Cardiomyopathy				<0.001
Non-ischemic	547 (46.0)	261 (36.7)	286 (60.0)	
Ischemic	642 (54.0)	451 (63.3)	191 (40.0)	
Atrial fibrillation	312 (26.2)	211 (29.6)	101 (21.2)	0.001
Diabetes	414 (34.8)	215 (30.2)	199 (41.7)	<0.001
Hypertension	747 (62.8)	401 (56.3)	346 (72.5)	<0.001
Chronic kidney disease	360 (30.3)	224 (31.5)	136 (28.5)	0.54
Medications				
ASA	781 (65.7)	488 (68.5)	293 (61.4)	0.01
ACE-I/ARB	850 (71.5)	529 (74.3)	321 (67.3)	0.01
Beta blocker	1061 (89.2)	629 (88.3)	432 (90.6)	0.23
Diuretics	857 (72.1)	471 (66.2)	386 (80.9)	<0.001
Aldosterone antagonist	302 (25.4)	155 (21.8)	147 (30.8)	<0.001
Device type				<0.001
Single	655 (55.1)	349 (49.0)	306 (64.2)	
BiV (no atrial lead)	26 (2.2)	25 (3.5)	1 (0.2)	
Dual	211 (17.7)	133 (18.7)	78 (16.4)	
Dual/BiV	297 (25.0)	205 (28.8)	92 (19.3)	
Lowest rate of cutoff (beats/min)	185.2 (14.6)	184.7 (14.0)	186.0 (15.4)	0.15
ATP zone used	694 (58.4)	392 (55.1)	302 (63.3)	0.005

Values are number (%), or mean (SD).

Non-AA: non-African-American; AA: African-American.

Table 2

Hazard ratio (95%CI) for mortality and appropriate shock.

	All-cause mortality		All-cause mortality without appropriate shock		1st Appropriate shock	
	Non-AA	AA	Non-AA	AA	Non-AA	AA
Events/Person-years	210/3692	133/2236	172/3410	122/2104	97/2683	40/1597
Model 1 *	Reference	1.42 (1.12, 1.80)	Reference	1.51 (1.18, 1.95)	Reference	0.85 (0.58, 1.26)
Model 2 †	Reference	1.24 (0.96, 1.59)	Reference	1.33 (1.02, 1.74)	Reference	0.78 (0.51, 1.19)

* Model 1: Adjusted for age, sex, and enrollment center.

† Model 2: Further adjusted for education, smoking status, body mass index, ejection fraction, NYHA class, ischemic cardiomyopathy, atrial fibrillation, diabetes, hypertension, and chronic kidney disease.
Non-AA: non-African-American; AA: African-American.

Table 3

Hazard ratio (95%CI) for mortality by years of follow-up.

Year(s) of follow-up	All-cause mortality			All-cause mortality without appropriate shock		
	N of events (%)		HR (95% CI) *	N of events (%)		HR (95% CI) *
	Non-AA	AA	AA vs. non-AA	Non-AA	AA	AA vs. non-AA
First year	32 (4.5)	29 (6.1)	1.71 (0.98, 2.99)	29 (4.1)	29 (6.1)	1.91 (1.08, 3.40)
First 2 years	24 (3.4)	21 (4.4)	1.70 (1.12, 2.59)	21 (2.9)	21 (4.4)	1.83 (1.19, 2.83)
First 3 years	40 (5.6)	16 (3.4)	1.44 (1.02, 2.03)	33 (4.6)	16 (3.4)	1.57 (1.09, 2.25)
First 4 years	31 (4.4)	23 (4.8)	1.38 (1.02, 1.88)	21 (2.9)	19 (4.0)	1.57 (1.13, 2.18)
First 5 years	30 (4.2)	28 (5.9)	1.43 (1.09, 1.88)	24 (3.4)	24 (5.0)	1.58 (1.17, 2.11)
First 6 years	23 (3.2)	10 (2.1)	1.37 (1.06, 1.78)	21 (2.9)	8 (1.7)	1.48 (1.12, 1.95)
First 7 years	17 (2.4)	4 (0.8)	1.30 (1.01, 1.68)	12 (1.7)	4 (0.8)	1.43 (1.09, 1.88)
First 8 years	10 (1.4)	0 (0.0)	1.23 (0.96, 1.58)	8 (1.1)	0 (0.0)	1.35 (1.03, 1.76)
First 9 years	3 (0.4)	1 (0.2)	1.24 (0.96, 1.59)	3 (0.4)	0 (0.0)	1.33 (1.02, 1.74)

* Hazard ratios were calculated over the indicated years of follow-up. Models were adjusted for age, sex, enrollment center, education, smoking status, body mass index, ejection fraction, NYHA class, ischemic cardiomyopathy, atrial fibrillation, diabetes, hypertension, and chronic kidney disease.

Non-AA: non-African-American; AA: African-American.

Table 4

Mediation analysis of the association between AA status and mortality.

	% Change (95% CI) in the β -coefficient of race [*]	
	<u>All-cause mortality</u>	<u>All-cause mortality without appropriate shock</u>
High school education	8.5 (−4.4, 43.9)	7.1 (−4.7, 35.0)
Smoking	−0.2 (−9.5, 8.8)	−1.2 (−10.7, 4.2)
Body mass index	0.0 (−3.3, 3.0)	0.3 (−1.4, 7.0)
Ejection fraction	24.1 (10.1, 69.5)	20.7 (8.4, 57.1)
NHYA class	−2.3 (−30.0, 14.2)	−4.2 (−30.0, 10.6)
Ischemic cardiomyopathy	0.3 (−13.0, 14.2)	−0.7 (−11.6, 9.1)
Atrial fibrillation	−2.3 (−19.6, 1.5)	−1.7 (−15.4, 1.8)
Diabetes	18.7 (5.3, 58.0)	18.0 (6.9, 53.3)
Hypertension	13.6 (3.8, 53.6)	12.3 (3.2, 36.3)
Chronic kidney disease	−0.1 (−27.1, 22.4)	−0.6 (−24.7, 17.6)
Cumulative effect of all the above covariates	42.8 (8.3, 96.2)	35.2 (4.7, 94.4)

* Adjusted for age, sex, and enrollment center.