Outcomes in African Americans undergoing cardioverter-defibrillator implantation for primary prevention of sudden cardiac death: Findings from the Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD)

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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 (AAs).

OBJECTIVE The purpose of this study was to determine the association between AA race and outcomes in a cohort of primary prevention 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 end-point was appropriate ICD shock defined as a shock for rapid ventricular tachyarrhythmias. The secondary end-point was all-cause mortality.

RESULTS There were 1189 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 ratio (95% confidence interval) comparing AAs vs non-AAs were 1.24 (0.96–1.59) 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%–69.5%), 18.7% (5.3%–58.0%), and 13.6% (3.8%–53.6%) of the excess risk of mortality in AAs, with a large proportion of the mortality difference remaining unexplained.

CONCLUSION 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; implantable cardioverter-defibrillator shock

ABBREVIATIONS **AA** = African American; **ACE-I** = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **ASA** = aspirin; **ATP** = antitachycardia pacing; **CI** = confidence interval; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **NYHA** = New York Heart Association; **PROSE-ICD** = Prospective Observational Study of Implantable Cardioverter-Defibrillators; **SCD** = sudden cardiac death

(Heart Rhythm 2014;11:1377–1383)

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 were derived from studies comprised predominantly of Caucasian subjects with

Drs. Zhang and Kennedy contributed equally to this work. The Donald W. Reynolds Foundation funded the initial design of the study and patient enrollment. Patient follow-up, data collection, and analyses were supported by Grants NIH R01 HL091062 to Dr. Tomaselli and NIH R01 HL103946 to Dr. Cheng. Dr. Eldadah reports receiving honoraria from St. Jude Medical. Dr. Ellenbogen reports research grant support and honoraria from Boston Scientific, Medtronic, and St. Jude Medical. Dr. Cheng reports receiving honoraria from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. **Address reprint requests and correspondence:** Dr. Alan Cheng, Division of Cardiology, Johns Hopkins University School of Medicine, 600 N. Wolfe St, Carnegie 568, Baltimore, MD 21287. E-mail address: alcheng@jhmi.edu.

limited representation of African Americans (AAs). 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 are limited data on whether outcomes after implantation of primary prevention ICDs in AA differ from those of 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 nonischemic 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 4 clinical centers in the United States from 2003 to 2013 (Johns Hopkins Hospital and Bayview Medical Center, Baltimore, MD; University of Maryland Hospital, Baltimore, MD; Washington Hospital Center, Washington, DC; Virginia Commonwealth University Hospital, Richmond, VA). Details of the study design and clinical end-points have been described previously.[18] Briefly, patients between 18 and 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 >40 days prior to implant) with an ejection fraction $\leq 30\%$ and stable New York Heart Association (NYHA) Class I–III heart failure symptoms on optimal pharmacotherapy; (2) ischemic or nonischemic cardiomyopathy with an ejection fraction $\leq 35\%$ and NYHA Class II or III heart failure; or (3) NYHA Class IV heart failure symptoms undergoing implantation of a cardiac resynchronization therapy 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 ECG, a 5-minute 3-lead ECG, an echocardiogram (if one was not previously available), and fasting blood collection. Race/ethnicity was identified 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 6 options available: Caucasian, African American (AA), Native American or Alaskan, Asian, Pacific Islander, and other. We then further categorized race into AA and non-AA (all other races/ethnicities). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. CKD was defined as estimated glomerular filtration rate <60 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 end-point 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 2 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 end-point started at the time of ICD implantation and continued until the occurrence of the first 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 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 analysis

Baseline differences between AAs and non-AAs were evaluated using 2-sided Student t test, Wilcoxon rank-sum test, or χ^2 test, as appropriate. Cox proportional hazards models were used to estimate multivariate adjusted hazard ratios (HRs) for end-points comparing AA vs non-AA. For each end-point, we used 2 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(survival)) vs log(survival time) and by using the Schoenfeld residuals.

To examine the mediation effect of each covariate on the association between race and end-points, we calculated the percent change in the β-coefficient of race comparing the base model (adjusted for age, sex, and enrollment center),