# Ventricular Conduction and Long-Term Heart Failure Outcomes and Mortality in African Americans

## Insights From the Jackson Heart Study

Robert J. Mentz, MD; Melissa A. Greiner, MS; Adam D. DeVore, MD; Shannon M. Dunlay, MD, MS; Gaurav Choudhary, MD; Tariq Ahmad, MD, MPH; Prateeti Khazanie, MD, MPH; Tiffany C. Randolph, MD; Michael E. Griswold, PhD; Zubin J. Eapen, MD, MHS; Emily C. O'Brien, PhD; Kevin L. Thomas, MD; Lesley H. Curtis, PhD; Adrian F. Hernandez, MD, MHS

***Background***—QRS prolongation is associated with adverse outcomes in mostly white populations, but its clinical significance is not well established for other groups. We investigated the association between QRS duration and mortality in African Americans.

***Methods and Results***—We analyzed data from 5146 African Americans in the Jackson Heart Study stratified by QRS duration on baseline 12-lead ECG. We defined QRS prolongation as QRS≥100 ms. We assessed the association between QRS duration and all-cause mortality using Cox proportional hazards models and reported the cumulative incidence of heart failure hospitalization. We identified factors associated with the development of QRS prolongation in patients with normal baseline QRS. At baseline, 30% (n=1528) of participants had QRS prolongation. The cumulative incidences of mortality and heart failure hospitalization were greater with versus without baseline QRS prolongation: 12.6% (95% confidence interval [CI], 11.0–14.4) versus 7.1% (95% CI, 6.3–8.0) and 8.2% (95% CI, 6.9–9.7) versus 4.4% (95% CI, 3.7–5.1), respectively. After risk adjustment, QRS prolongation was associated with increased mortality (hazard ratio, 1.27; 95% CI, 1.03–1.56; *P*=0.02). There was a linear relationship between QRS duration and mortality (hazard ratio per 10 ms increase, 1.06; 95% CI, 1.01–1.12). Older age, male sex, prior myocardial infarction, lower ejection fraction, left ventricular hypertrophy, and left ventricular dilatation were associated with the development of QRS prolongation.

***Conclusions***—QRS prolongation in African Americans was associated with increased mortality and heart failure hospitalization. Factors associated with developing QRS prolongation included age, male sex, prior myocardial infarction, and left ventricular structural abnormalities. **(*Circ Heart Fail*. 2015;8:243-251. DOI: 10.1161/CIRCHEARTFAILURE.114.001729.)**

**Key Words:** African American ■ heart failure ■ mortality ■ ventricular conduction

Prolonged duration of the QRS complex on a 12-lead ECG is associated with adverse events, including heart failure, sudden cardiac death, and all-cause mortality.[1–3] Previous studies of QRS interval have focused on patients with known cardiac disease[4–7] and were conducted in primarily white populations.[3,8] Racial differences in ventricular conduction have been identified in the general population and among patients with cardiac disease.[9,10] However, associations between QRS duration and clinical outcomes in African Americans have not been well characterized. The availability of ECG information on >5000 African American participants in the Jackson Heart Study allows a comprehensive investigation of the relationship between QRS duration and mortality in this population.[11] Therefore, we investigated associations between QRS duration and long-term outcomes of African Americans in the Jackson Heart Study. In addition, we sought to identify clinical factors associated with the development of QRS prolongation in this cohort.

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## Methods

### Data Sources

The Jackson Heart Study is a prospective community-based observational study initiated in 2000 to investigate risk factors for cardiovascular disease in African Americans.[11] All participants provided written informed consent, and study protocols were approved by

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From the Department of Medicine, Division of Cardiology, Duke University School of Medicine (R.J.M., A.D.D., T.A., P.K., T.C.R., Z.J.E., E.C.O'B., K.L.T., A.F.H.), and Duke Clinical Research Institute (R.J.M., M.A.G., A.D.D., T.C.R., Z.J.E., E.C.O'B., K.L.T., L.H.C., A.F.H.), Durham, NC; Department of Medicine, Mayo Clinic, Rochester, MN (S.M.D.); Vascular Research Laboratory, Providence VA Medical Center and Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI (G.C.); and Center of Biostatistics and Bioinformatics, University of Mississippi Medical Center, Jackson, MS (M.E.G.).

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Correspondence to Robert J. Mentz, MD, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27715. E-mail robert.mentz@duke.edu

local institutional review boards. The study recruited participants from the Jackson, Mississippi, cohort of the Atherosclerosis Risk in Communities study and from the overall tricounty population, as described previously.[12] Participants completed 3 study visits: exam 1 between September 2000 and March 2004, exam 2 between October 2005 and December 2008, and exam 3 between February 2009 and January 2013. Data collected include demographic characteristics, comorbid conditions, medications, laboratory test results, and cardiac test results, including ECG (exams 1 and 3 only) and echocardiogram (exam 1 only).[13] The details of visit procedures, including supine 12-lead digital electrocardiography, have been described previously.[13] The definitions of comorbid conditions and the details of electrocardiography measurements and medication collection and coding have also been reported.[14,15] The Jackson Heart Study cohort surveillance system collects follow-up data on all participants, including deaths, study terminations (from 2000 through 2010), and heart failure hospitalizations (from 2005 through 2010).[16]

## Study Population

For the primary analysis of mortality, we included participants who completed exam 1 with documentation of QRS duration and intraventricular conduction on an ECG. We excluded participants who had a ventricular pacemaker as noted by the presence of an ECG atrioventricular Minnesota Code of 6 to 8.[13] For the analysis assessing clinical factors associated with the development of QRS prolongation, we included participants from the primary analysis cohort who completed exam 3 with documentation of QRS duration. Participants with delayed ventricular conduction at exam 1 (ie, QRS duration of ≥100 ms) were excluded from this part of the analysis (Figure 1).

## QRS Prolongation

The study variable of interest was QRS duration on ECG at clinical exams 1 and 3. Previous studies defined QRS prolongation as ≥110 ms or ≥120 ms,[3,5] but we were also interested in more modest degrees of QRS prolongation (ie, 100–119 ms) as assessed in other recent analyses.[9] We defined normal ventricular conduction as QRS duration of <100 ms, and we defined QRS prolongation as ≥100 ms. We categorized the severity of QRS prolongation as mild (100–119 ms), moderate (120–149 ms), or severe (150 ms or greater) conduction delay. We determined these groups on the basis of previous research[5] and thresholds that are used to determine eligibility and expected response from implantable cardiac resynchronization therapy in the context of reduced ejection fraction.[17] Intraventricular conduction defects were recorded using Minnesota 7- codes. Complete LBBB was defined as Minnesota code 7–11 and complete RBBB was defined as Minnesota code 7–21.[13]

## Outcomes

The primary outcome was all-cause mortality within 8 years after the exam 1 visit date. Methods for identification of all-cause mortality and determination of cause of death in the Jackson Heart Study cohort have been described previously.[16] Annual follow-up included interviews with participants and next of kin to ascertain health events, such as hospitalization or death. These data and questionnaires completed by physicians and medical examiners or coroners were obtained and reviewed by the medical record abstraction unit to generate diagnosis information. These diagnoses were reviewed and adjudicated by trained medical personnel. For the present analysis, we classified mode of death on the basis of the cause of death recorded in the Jackson Heart Study long-term follow-up file.[16] We also assessed the cumulative incidence of heart failure hospitalization between 2005 and 2010 among study participants who survived to January 1, 2005, when heart failure hospitalization surveillance began. Potential heart failure hospitalizations in the Jackson Heart Failure cohort were identified and adjudicated as described previously.[16] Hospitalization data were obtained from the hospital discharge index from all catchment area hospitals and annual follow-up data. Hospitalization data from noncatchment area hospitals were obtained after patient consent. The self-reported data from annual follow-up were reconciled with the hospital discharge index data. The primary diagnoses based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were reviewed and adjudicated by trained medical personnel.

The secondary outcome for the present analysis was the development of QRS prolongation from baseline to follow-up. Because ECG data were not collected at exam 2, the development of QRS prolongation was defined as a QRS duration of ≥100 ms at exam 3 among participants who had normal conduction (QRS duration of <100 ms) at exam 1.

## Covariates

Variables from the baseline clinical exam included demographic characteristics, medical history, physical examination measurements, medications, laboratory test results, and cardiac test results. Medical history was based on either direct clinical examination (hypertension, diabetes mellitus, and atrial fibrillation) or self-reported disease history (myocardial infarction, stroke, chronic lung disease, and smoking). Because heart failure history was not collected, we used both

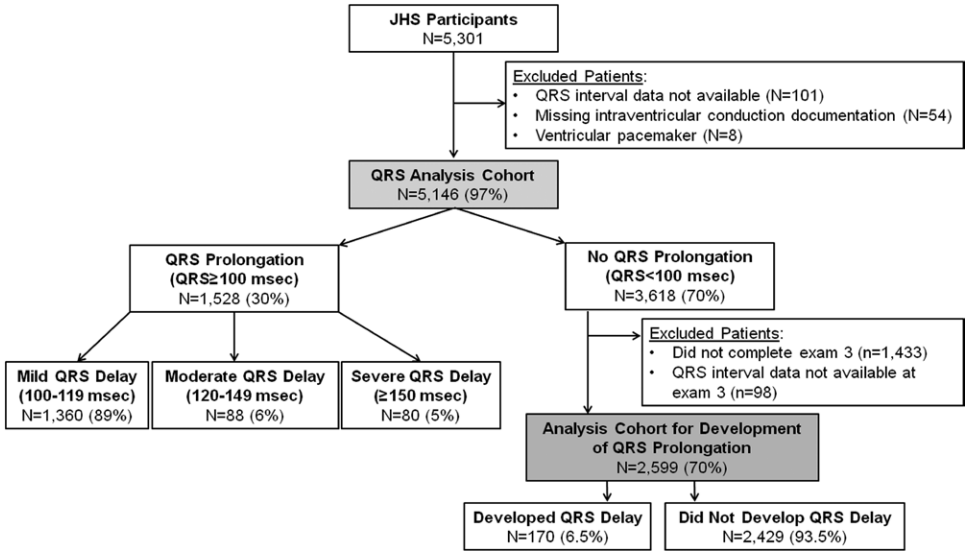


**Figure 1.** Derivation of the study cohort. JHS indicates Jackson Heart Study.

self-reported disease and clinical measurements at exam 1 to derive baseline heart failure using the modified Gothenburg criteria developed and validated in the Atherosclerosis Risk in Communities data set (Table I in the Data Supplement).[18] To ascertain left ventricular hypertrophy, we used quantitative left ventricular mass measurement from M-mode echocardiography when available (missing for 35% of participants); otherwise, left ventricular hypertrophy was based on a qualitative assessment of mild, moderate, or severe hypertrophy, as described previously.[13] We derived medication variables by searching for therapeutic classification codes that were recorded based on medications taken within 2 weeks of exam 1. Most variables had very low rates of missingness (ie, <5%). For variables with <5% missingness, we imputed continuous variables to the overall median value, dichotomous variables to no, and multichotomous variables to the most frequent categorical value. For variables with >5% missingness (medication variables), we treated the missing values as a separate category.

## Statistical Analysis

We describe exam 1 baseline characteristics of the study population by QRS duration category using frequencies with percentages for categorical variables and medians with interquartile range or means with SDs for continuous variables. We tested for differences between groups using $\chi^2$ tests for categorical variables and Kruskal–Wallis tests for continuous variables.

We calculated the cumulative incidence of all-cause mortality and heart failure hospitalization by QRS duration category (normal conduction versus any prolonged conduction stratified by normal, mild, moderate, and severe delay) using Kaplan–Meier estimates, and we tested for differences between groups using log-rank tests. For all survival analyses, we censored data for participants at the time of study participation refusal or the end of study follow-up (December 31, 2010). For heart failure hospitalization, we also censored data for participants at the time of death. For mode of death, we used frequencies with percentages, calculated exact confidence interval (CI)s for binomial proportions, and tested for differences between groups using Fisher exact tests.

We assessed the unadjusted and adjusted associations between QRS duration category and mortality using Cox proportional hazards models. We also investigated the association between QRS duration as a continuous variable and all-cause mortality. We explored both linear and nonlinear functional forms, including polynomials and restricted cubic splines. We selected the adjustment variables on the basis of previous studies[3] and clinical judgment. Covariates included age, sex, prior myocardial infarction, heart failure, hypertension, prior stroke, diabetes mellitus, chronic lung disease, current or prior smoking, body mass index, systolic blood pressure, heart rate, sodium, estimated glomerular filtration rate, hemoglobin level, ejection fraction, left ventricular hypertrophy, left ventricular end-diastolic dimension, β-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, statin, antiplatelet therapy, and a variable for missing medication data. We tested for interactions between QRS (yes/no, categorical and continuous) and sex, as well as intraventricular conduction category (none, complete LBBB, complete RBBB, and other intraventricular conduction defect), in our multivariable mortality models. We did not use multivariable modeling to assess the association between QRS duration and heart failure hospitalization because of discontinuity between baseline evaluation and the start of heart failure hospitalization surveillance.

To determine factors associated with the development of QRS prolongation, we used a modified Poisson model with an offset parameter to adjust for the log of participant time between exam 1 and exam 3 (range, 6–12 years).[19,20] We determined the allowable number of variables based on 10 events per variable using a blinded review of the event rate. We chose the variable list on the basis of previous research[9] and clinical judgment. Covariates included age, sex, prior myocardial infarction, heart failure, hypertension, prior stroke, diabetes mellitus, chronic lung disease, current smoking, body mass index, systolic blood pressure, heart rate, sodium, estimated glomerular filtration rate, hemoglobin level, ejection fraction, left ventricular hypertrophy, left ventricular dimension, and baseline QRS duration.

We used a 2-tailed $\alpha$=0.05 to establish statistical significance, and we report 95% CIs. We used SAS version 9.3 (SAS Institute Inc, Cary, NC) for all analyses. The institutional review board of the Duke University Health System approved the study.

# Results

Of 5301 participants who completed exam 1, participants for whom QRS duration data (n=101 [1.9%]) or intraventricular conduction documentation (n=54 [1.0%]) was missing and participants with a ventricular pacemaker (n=8 [0.2%]) were excluded from all analyses (Figure 1). For the assessment of predictors, we excluded participants who had QRS prolongation at exam 1 (n=1528), those who did not complete exam 3 (n=1433), and those without QRS documentation at exam 3 (n = 98). After all exclusions, the analysis sample consisted of 5146 participants eligible for the mortality assessment and 2599 eligible for the assessment of predictors of the development of QRS prolongation.

Of the 5146 individuals in the analysis, 1528 (30%) had a baseline QRS duration of ≥100 ms (Table 1). Conduction delay was mild in 89% (n=1360), moderate in 6% (n=88), and severe in 5% (n=80). Participants with QRS prolongation at baseline were more often men, were older, and had a greater prevalence of comorbid conditions, including hypertension, prior myocardial infarction, and heart failure, compared with those without QRS prolongation. With increasing severity of conduction delay (Table II in the Data Supplement), systolic blood pressure was higher and estimated glomerular filtration rate was lower. Patients with conduction delay were more likely to have an ejection fraction <40%, compared with patients with a normal QRS duration. However, on average, ejection fraction was preserved in all groups. Use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and calcium channel blockers was higher among patients with QRS prolongation.

Median follow-up was 8.3 years (interquartile range, 7.5–9.0 years) and was similar in all groups. Table 2 shows the cumulative incidence of death within 8 years after exam 1. The cumulative incidence of death among participants with normal conduction was 7.1% (95% CI, 6.3–8.0) compared with 12.6% (95% CI, 11.0–14.4) among those with any QRS prolongation at baseline ($P$<0.001). With increasing severity of conduction delay, there was an increase in mortality associated with mild delay (11.2%; 95% CI, 9.6–13.1), moderate delay (14.9%; 95% CI, 9.0–24.6), and severe delay (33.7%; 95% CI, 24.5–46.3; Table III in the Data Supplement). Figure 2 shows the curves for the cumulative incidence of death by baseline QRS interval. Table 2 and Table III in the Data Supplement also show associations between QRS prolongation and mode of death and heart failure hospitalization. The number of events was low among participants with severe conduction delay, but there was a marked increase in the proportions of sudden cardiac death and heart failure death compared with participants with normal conduction.

Table 3 shows the association between baseline QRS duration and 8-year all-cause mortality. After risk adjustment, any conduction delay was associated with a 27% increase in mortality. Mild and severe delays were associated with a 26% and 57% increase in adjusted mortality, respectively.

**Table 1. Baseline Characteristics of the Study Population Stratified by Normal Conduction Versus Any Conduction Delay**

| Characteristic | Normal Conduction (QRS<100 ms) | Any Delay (QRS≥100 ms) | *P* Value |
|---|---|---|---|
| No. of participants | 3618 | 1528 | |
| Age, median (IQR), y | 54.1 (44.4–63.8) | 59.3 (48.5–67.3) | <0.001 |
| Male sex, No. (%) | 1114 (30.8) | 752 (49.2) | <0.001 |
| Medical history, No. (%) | | | |
| Atrial fibrillation | 7 (0.2) | 11 (0.7) | 0.003 |
| Chronic lung disease | 250 (6.9) | 121 (7.9) | 0.20 |
| Diabetes mellitus | 735 (20.3) | 375 (24.5) | <0.001 |
| Heart failure | 222 (6.1) | 153 (10.0) | <0.001 |
| Hypertension | 2091 (57.8) | 1054 (69.0) | <0.001 |
| Myocardial infarction | 153 (4.2) | 117 (7.7) | <0.001 |
| Smoker currently | 461 (12.7) | 205 (13.4) | 0.51 |
| Smoker previously | 634 (17.5) | 353 (23.1) | <0.001 |
| Stroke | 152 (4.2) | 71 (4.6) | 0.47 |
| Physical examination, median (IQR) | | | |
| Body mass index, kg/m$^2$ | 30.2 (26.5–35.1) | 31.3 (27.7–36.4) | <0.001 |
| Pulse, beats/min | 64.0 (58.0–71.0) | 62.0 (56.0–70.0) | <0.001 |
| Systolic blood pressure, mm Hg | 124.0 (114.0–136.0) | 126.0 (116.0–139.0) | <0.001 |
| Laboratory test results, median (IQR) | | | |
| eGFR, mL/min/1.73 m$^2$ | 85.9 (75.9–97.1) | 85.5 (75.1–95.4) | 0.006 |
| Glucose, mg/dL | 91.0 (85.0–100.0) | 93.0 (87.0–104.0) | <0.001 |
| Hemoglobin, g/dL | 13.0 (12.1–13.9) | 13.2 (12.4–14.3) | <0.001 |
| Low-density lipoprotein, mg/dL | 124.0 (101.0–147.0) | 124.0 (102.0–147.0) | 0.86 |
| Serum potassium, mEq/L | 4.3 (4.0–4.5) | 4.3 (4.0–4.5) | 0.08 |
| Serum sodium, mEq/L | 141.0 (139.0–142.0) | 141.0 (139.0–142.0) | <0.001 |
| Cardiac test results | | | |
| Complete LBBB, No. (%) | 0 | 52 (3.4) | <0.001 |
| Complete RBBB, No. (%) | 0 | 64 (4.2) | <0.001 |
| Other IV conduction Defect, No. (%) | 94 (2.6) | 132 (8.6) | <0.001 |
| Ejection fraction, mean (SD), % | 62.5 (6.7) | 60.7 (8.8) | <0.001 |
| Ejection fraction < 40%, No. (%) | 9 (0.2) | 35 (2.3) | <0.001 |
| Left ventricular dimension, median (IQR), cm | 48.1 (45.2–50.3) | 49.3 (47.0–52.5) | <0.001 |
| Left ventricular hypertrophy, No. (%) | 222 (6.1) | 166 (10.9) | <0.001 |
| Medications, No. (%) | | | |
| ACE inhibitor/ARB | 548 (15.1) | 302 (19.8) | <0.001 |
| Anti-arrhythmic agent | 6 (0.2) | 12 (0.8) | <0.001 |
| Antiplatelet agent | 44 (1.2) | 34 (2.2) | 0.007 |
| β-Blocker | 319 (8.8) | 189 (12.4) | <0.001 |
| Calcium channel blocker | 597 (16.5) | 357 (23.4) | <0.001 |
| Digoxin | 28 (0.8) | 46 (3.0) | <0.001 |
| Diuretic | 742 (20.5) | 430 (28.1) | <0.001 |
| Insulin | 197 (5.4) | 121 (7.9) | <0.001 |
| Oral diabetic agent | 380 (10.5) | 172 (11.3) | 0.42 |
| Statin | 377 (10.4) | 207 (13.5) | 0.001 |

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; and IQR, interquartile range.

In contrast, moderate conduction delay was not associated with a statistically significant increase in mortality after risk adjustment. To investigate this lack of association between moderate conduction delay and mortality, we assessed how the sequential addition of adjustment variables attenuated the association. After adjustment for age alone, the hazard ratio decreased from 2.36 to 1.25 and was no longer significant ($P$=0.43). After including sex and prior myocardial

**Table 2. Outcomes Stratified by Normal Conduction Versus Any Conduction Delay**

| Outcome | Normal Conduction (<100 ms) | Any Delay (≥100 ms) | *P* Value |
|---|---|---|---|
| Mortality, No. (cumulative incidence*) | 241 (7.1) | 186 (12.6) | <0.001 |
| 95% CI | (6.3–8.0) | (11.0–14.4) | |
| Mode of death, No. (%) | | | |
| Cardiac mortality | 101 (41.9) | 97 (52.2) | 0.04 |
| 95% CI | 35.6–48.4 | 44.7–59.5 | |
| Sudden cardiac death | 8 (3.3) | 15 (8.1) | 0.05 |
| 95% CI | 1.4–6.4 | 4.6–13.0 | |
| Heart failure or cardiomyopathy | 6 (2.5) | 10 (5.4) | 0.13 |
| 95% CI | 0.9–5.3 | 2.6–9.7 | |
| Noncardiovascular mortality | 140 (58.1) | 89 (47.8) | 0.04 |
| 95% CI | 51.6–64.4 | 40.5–55.3 | |
| Heart failure hospitalization, No. (cumulative incidence)† | 153 (4.4) | 118 (8.2) | <0.001 |
| 95% CI | 3.7–5.1 | 6.9–9.7 | |

CI indicates confidence interval.

*Cumulative incidence of death within 8 y after exam 1.

†Calculated among the 5065 participants who survived to January 1, 2005, when heart failure hospitalization surveillance began.

infarction in the model, the hazard ratio decreased to 1.16 (*P*=0.60) and 1.09 (*P*=0.77), respectively. The QRS×sex and QRS×intraventricular conduction delay category interactions were insignificant, indicating that the effect of QRS duration on mortality does not differ between males and females or based on the type of conduction delay (eg, complete LBBB, complete RBBB, other intraventricular conduction defect).

When we assessed the association between QRS duration as a continuous variable and mortality, we found no statistically significant evidence of a nonlinear association (*P*=0.57). When we assessed the multivariable-adjusted linear association, the hazard ratio per 10 ms increase in QRS duration was 1.06 (95% CI, 1.01–1.12; *P*=0.02). Figure 3 shows the association between the continuous QRS variable and mortality (using QRS duration of 70 ms as the reference). Participants with QRS duration of 125 ms had a 50% higher hazard of death compared with participants with a QRS duration of 70 ms. The hazard of death was twice as high for those with a QRS duration of 185 ms compared with a QRS duration of 70 ms.

Table IV in the Data Supplement shows the baseline characteristics of the 2599 participants who completed exam 3 and had normal conduction at baseline. The median age of the population at baseline was 53 years and 69% were women. Hypertension and diabetes mellitus were present in 55% and 17%, respectively. The median body mass index was 30 kg/m$^2$, systolic blood pressure was 123 mm Hg, and estimated glomerular filtration rate was 87 mL/min/1.73 m$^2$. Of these participants, 170 (6.5%) developed QRS prolongation during the follow-up period. Table 4 shows the factors associated with the development of QRS prolongation. Greater age, male sex, prior myocardial infarction, lower ejection fraction, left ventricular hypertrophy, and larger left ventricular end-diastolic dimension were associated with QRS prolongation (*P*<0.05

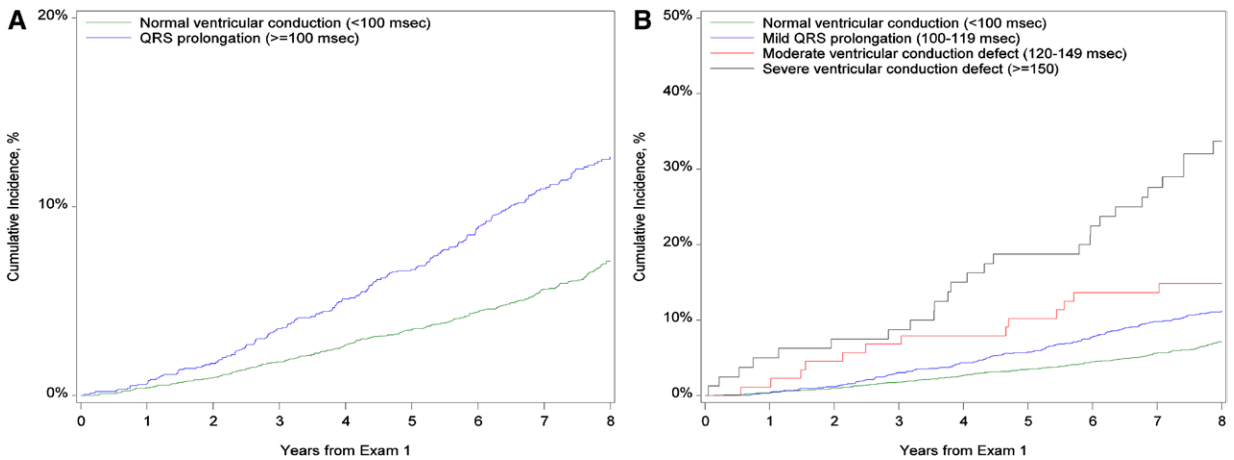


**Figure 2.** Cumulative incidence of death by baseline QRS duration. **A**, The comparison between no conduction delay and any QRS delay. **B**, The comparison between normal conduction, mild conduction delay, moderate conduction delay, and severe conduction delay.

**Table 3. Associations Between QRS Duration and 8-Year All-Cause Mortality**

| | Unadjusted Analysis | | Adjusted Analysis* | |
|---|---|---|---|---|
| Variable | Hazard Ratio (95% CI) | *P* Value | Hazard Ratio (95% CI) | *P* Value |
| Normal conduction | 1.00 [Reference] | | 1.00 [Reference] | |
| Any QRS delay | 1.89 (1.56–2.29) | <0.001 | 1.27 (1.03–1.56) | 0.02 |
| Mild conduction delay | 1.67 (1.36–2.05) | <0.001 | 1.26 (1.01–1.56) | 0.04 |
| Moderate conduction delay | 2.36 (1.35–4.12) | 0.003 | 1.09 (0.61–1.93) | 0.77 |
| Severe conduction delay | 5.63 (3.76–8.44) | <0.001 | 1.57 (1.01–2.45) | 0.047 |

CI indicates confidence interval.

*Adjusted for age, sex, prior myocardial infarction, heart failure, hypertension, stroke, diabetes mellitus, chronic lung disease, current smoking, prior smoking, body mass index, systolic blood pressure, heart rate, sodium, estimated glomerular filtration rate, hemoglobin level, ejection fraction, left ventricular hypertrophy, left ventricular dimension, β-blocker, angiotensin-converting enzyme inhibitor, statin, and antiplatelet agent.

for all comparisons). For example, each 5-year increase in age was associated with a 15% greater risk for developing QRS prolongation, and male sex was associated with a 58% greater risk. Prior myocardial infarction and left ventricular hypertrophy on echocardiogram were associated with a 72% and 64% increased risk of developing QRS prolongation, respectively.

## Discussion

We found that 30% of African Americans in this community-based cohort had QRS prolongation at baseline. The participants with QRS prolongation tended to be older, were more likely to be men, and had greater comorbidity. After risk adjustment, QRS prolongation was associated with a 27% increase in all-cause mortality compared with no prolongation. Severe prolongation of ≥150 ms was associated with a 57% increase in all-cause mortality. All-cause mortality increased 6% per 10 ms increase in QRS duration. Relatively few baseline factors were associated with the development of QRS prolongation, but these included increasing age, male sex, prior myocardial infarction, and left ventricular structural abnormalities. These results extend previous findings regarding the prognostic utility of QRS duration to African Americans. In addition, clinicians may be able to use the identified clinical variables associated with the development of QRS prolongation to assist with prognostication in African American populations.

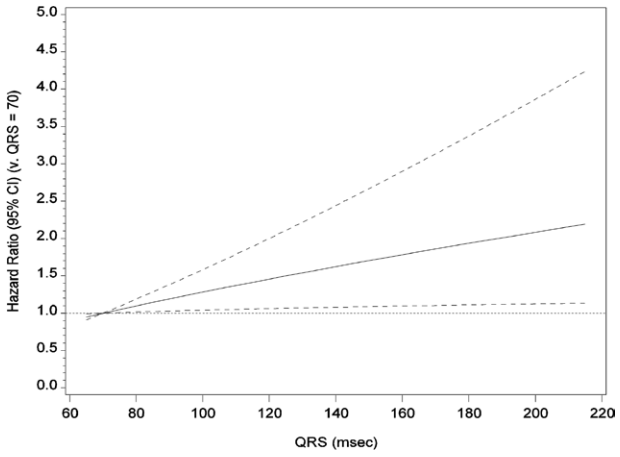


**Figure 3.** Adjusted hazard of mortality by QRS duration as a continuous variable. The reference category is QRS duration of 70 ms. The solid black line represents the hazard ratio and the dotted lines represent the 95% confidence intervals (CIs). The analysis is adjusted for age, sex, prior myocardial infarction, heart failure, hypertension, stroke, diabetes mellitus, chronic lung disease, current smoking, prior smoking, body mass index, systolic blood pressure, heart rate, serum sodium level, estimated glomerular filtration rate, hemoglobin level, ejection fraction, left ventricular hypertrophy, left ventricular dimension, β-blocker, angiotensin-converting enzyme inhibitor, statin, and antiplatelet therapy.

A major finding of this analysis was the high prevalence of QRS prolongation in a community cohort of mostly middle-aged African Americans. Thirty percent had a baseline QRS duration of ≥100 ms. In comparison, in a large middle-aged Finnish cohort, 1.3% had a QRS duration of ≥110 ms.[3] In the National Health and Nutrition Examination Survey (NHANES) data set of mostly white participants, the top quartile (ie, 25%) had a QRS duration of ≥106 ms.[8] Contrary to these findings, a previous analysis of patients with heart failure found that a QRS duration >120 ms was less prevalent among black patients than white patients (15.8% versus 26.0%).[21] We found that the vast majority of Jackson Heart Study participants with QRS prolongation had a QRS duration of 100 to 119 ms (ie, 89% of prolongation cases). These findings support previous research suggesting important differences in ventricular conduction by race[10,22,23] and highlight the high prevalence of mild QRS prolongation in African Americans. Genetic differences may explain, in part, these racial differences in QRS duration. For example, a previous analysis from the Jackson Heart Study found that polymorphisms in the *SCN5A* gene encoding a cardiac voltage-gated sodium channel were associated with QRS duration.[24]

To our knowledge, ours is the first report of an association between QRS prolongation and increased mortality in a community cohort of African Americans. The cumulative incidence of 8-year mortality was nearly twice as high with any QRS prolongation compared with no prolongation (12.6% versus 7.1%). The cumulative incidence of mortality was >30% in participants with QRS duration of ≥150 ms. In addition, when QRS duration was assessed as a continuous variable, there was a linear association with increased mortality. These observations suggest that the ambulatory African American population with delayed ventricular conduction is at substantial risk for mortality. Conduction disease was an independent risk factor even after adjustment for other markers of cardiac disease, such as hypertension, left ventricular

**Table 4. Associations Between Clinical Factors and the Development of QRS Prolongation**

| Variable | Unadjusted RR (95% CI) | *P* Value | Adjusted RR (95% CI) | *P* Value |
|---|---|---|---|---|
| Age, per 5-year increase | 1.17 (1.10–1.25) | <0.001 | 1.15 (1.06–1.25) | <0.001 |
| Male sex | 2.21 (1.66–2.95) | <0.001 | 1.58 (1.10–2.26) | 0.01 |
| Medical history | | | | |
| Myocardial infarction | 2.57 (1.56–4.24) | <0.001 | 1.72 (1.01–2.92) | 0.04 |
| Heart failure | 1.05 (0.55–2.00) | 0.89 | 0.99 (0.51–1.91) | 0.98 |
| Hypertension | 2.15 (1.55–2.99) | <0.001 | 1.45 (0.98–2.14) | 0.06 |
| Stroke | 2.11 (1.15–3.84) | 0.02 | 1.36 (0.70–2.65) | 0.37 |
| Diabetes mellitus | 1.26 (0.89–1.80) | 0.20 | 0.95 (0.65–1.37) | 0.78 |
| Chronic lung disease | 0.54 (0.24–1.20) | 0.13 | 0.54 (0.24–1.21) | 0.13 |
| Current smoker | 1.00 (0.63–1.58) | >0.99 | 0.90 (0.57–1.40) | 0.63 |
| Physical examination results | | | | |
| BMI, kg/m$^2$ | 1.00 (0.98–1.02) | 0.96 | 1.00 (0.97–1.02) | 0.76 |
| Systolic blood pressure, mm Hg | 1.09 (1.05–1.13) | <0.001 | 1.02 (0.97–1.07) | 0.43 |
| Pulse, beats/min | 0.97 (0.90–1.05) | 0.45 | 1.02 (0.95–1.09) | 0.61 |
| Laboratory test results | | | | |
| Serum sodium, mEq/L | 1.03 (0.97–1.10) | 0.35 | 0.99 (0.93–1.05) | 0.72 |
| eGFR, mL/min/1.73 m$^2$ | 0.97 (0.94–1.02) | 0.22 | 1.01 (0.97–1.06) | 0.60 |
| Hemoglobin, g/dL | 1.12 (1.00–1.25) | 0.05 | 0.99 (0.88–1.12) | 0.92 |
| Baseline cardiac test results | | | | |
| Ejection fraction, % | 1.24 (1.12–1.38) | <0.001 | 1.17 (1.06–1.28) | 0.001 |
| Left ventricular hypertrophy | 2.35 (1.52–3.63) | <0.001 | 1.64 (1.03–2.62) | 0.04 |
| Left ventricular end diastolic dimension, cm | 1.11 (1.07–1.15) | <0.001 | 1.05 (1.02–1.09) | 0.002 |
| QRS duration, ms | 1.11 (1.09–1.13) | <0.001 | 1.09 (1.07–1.12) | <0.001 |

BMI indicates body mass index; eGFR, estimate glomerular filtration rate; and RR, risk ratio.

hypertrophy, and left ventricular dimension. There was no evidence of a differential association between QRS duration and mortality based on sex or QRS morphology. Thus, our results support other recent data, suggesting that RBBB (in addition to LBBB) may be an important negative prognostic variable[25] in both men and women. These findings are in contrast to earlier reports of RBBB representing a benign finding.[26]

The specific reasons for the increased risk associated with even mild conduction delay is unclear. It has been hypothesized that QRS duration may represent a marker of underlying structural heart disease or that it may be linked to other adverse genetic features.[27] Abnormal electric activation of the ventricles may be related to mechanical dyssynchrony and reduced cardiac efficiency. We found that QRS prolongation was associated with an increased incidence of heart failure hospitalization. The increased prevalence of symptomatic heart failure may represent an important link with increased mortality. In addition, disrupted electric conduction may lead to the development of ventricular arrhythmias.[3] In the present analysis, patients with QRS delay died from a cardiac cause 52.2% of the time compared with 41.9% cardiac death in those without delay. In particular, there was an increased incidence of sudden cardiac death and heart failure death in patients with any QRS prolongation. Thus, QRS delay in the Jackson Heart Study population was associated with increased mortality because of arrhythmic and pump failure death.

Our finding that moderate conduction delay in the range of 120 to 149 ms was not associated with risk-adjusted mortality was unexpected. These results are likely related to the overall modest sample size of the moderate delay group (n=88) or statistical chance. The analysis of QRS duration as a continuous variable did not demonstrate any statistically significant nonlinear associations and overall had greater statistical power compared with the analysis of QRS duration as a categorical variable.

We found that increasing age, male sex, prior myocardial infarction, lower ejection fraction, left ventricular hypertrophy, and larger left ventricular dimension were associated with developing QRS prolongation. Previous studies have also identified male sex and markers of ventricular mass as predictors of the development of QRS prolongation.[9] Our study extends these data by demonstrating the prognostic utility of prior myocardial infarction and echocardiographic features, such as left ventricular dimension and left ventricular hypertrophy. These characteristics can be used to identify African American patients at higher risk of developing QRS prolongation. If these findings are validated in additional studies, it may be reasonable to perform an echocardiogram to evaluate left ventricular dimension and assess left ventricular hypertrophy in African American patients with other risk factors for the development of QRS prolongation. Earlier identification of the constellation of these factors may allow for targeted

use of medications with ventricular remodeling effects. These findings may be particularly relevant given the increased incidence of heart failure hospitalization in patients who demonstrate QRS prolongation. Future studies are needed to determine whether the addition of medications, such as angiotensin-converting enzyme inhibitors or β-blockers, in patients with features, such as left ventricular hypertrophy or increased left ventricular dimension, can reduce conduction delays.

Our study has limitations. This was a retrospective analysis from a community cohort of African Americans in the southern United States. Other measured and unmeasured variables may have influenced the results. The sample size in the groups with a greater degree of QRS prolongation was modest. Limited data are available in this cohort regarding implantation of biventricular pacing therapy, which would be expected to influence outcomes. Future studies should further investigate the association between QRS prolongation and mode-specific mortality, including heart failure death. The unexpectedly higher rate of QRS prolongation at baseline (30%) resulted in a smaller than expected cohort available for analysis of predictors of new QRS prolongation and, subsequently, a lower event count (n=170 with QRS delay by exam 3). Therefore, the number of variables was restricted, and we could not explore the effect of medications on development of QRS prolongation.

In conclusion, QRS prolongation on a standard 12-lead ECG in African Americans seems to be associated with increased mortality. Factors associated with developing QRS prolongation in African Americans include prior myocardial infarction, left ventricular hypertrophy, ejection fraction, and left ventricular dimension. QRS prolongation should be considered an important risk factor for long-term morbidity and mortality in African American populations and a potential therapeutic target for interventions.

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## CLINICAL PERSPECTIVE

We analyzed data from 5146 African Americans in the Jackson Heart Study stratified by QRS duration on baseline 12-lead ECG. We defined QRS prolongation as QRS≥100 ms. We found that 30% of African Americans in this community-based cohort had QRS prolongation at baseline. The participants with QRS prolongation tended to be older, were more likely to be men, and had greater comorbidity. The cumulative incidence of HF hospitalization was greater with versus without baseline QRS prolongation: 8.2% (95% confidence interval, 6.9–9.7) versus 4.4% (95% confidence interval, 3.7–5.1). After risk adjustment, QRS prolongation was associated with a 27% increase in all-cause mortality compared with no prolongation. All-cause mortality increased 6% per 10 ms increase in QRS duration. We also identified factors associated with the development of QRS prolongation in patients with normal baseline QRS. Older age, male sex, prior myocardial infarction, lower ejection fraction, left ventricular hypertrophy, and left ventricular dilatation were associated with the development of QRS prolongation. These results extend previous findings regarding the prognostic utility of QRS duration related to mortality and HF hospitalization to the African American population. In addition, clinicians may be able to use the identified clinical variables associated with the development of QRS prolongation to assist with prognostication in African American populations.

## SUPPLEMENTAL MATERIAL

**Supplemental Table 1**. Heart Failure Classification[a]

| Cardiac Score | ARIC Questions | JHS Variables |
|---|---|---|
| Prior coronary heart disease (1 point) | Positive response to "Has a doctor ever said you had a heart attack?" | Positive history or response to any of the questions (Note: Verified that the JHS derived variable CHDhx=1 can be substituted for items a-e below):<br>PFHA4A: Has doctor said you had heart attack (missing at exam 2)?<br>MHXA16/17: Saw a doctor because of chest pain? What did the doctor say it was? (H=Heart Attack)<br>MHXA30/31: Saw a doctor because of this pain? What did the doctor say it was? (H=Heart Attack)<br>MHXA32: Hospitalized for heart attack a week+?<br>MI from ECG (missing at exam 2)<br>MHXA52A: Have a coronary bypass?<br>MHXA54A: Ever had angioplasty of coronary arteries? |
| Prior angina pectoris (1 point) | Positive response to all:<br>• "Have you ever had any pain or discomfort in your chest?"<br>• "Do you get it when you walk uphill or hurry?" or "Do you get it when you walk at an ordinary pace on the level?"<br>Response of "stop or slow down" to "What do you do if you get it while you are walking?"<br>Response of "relieved" to "If you stand still, what happens?"<br>Response of "10 minutes or less" to "How soon?" | Positive response to either series of questions:<br>1) MHXA16:/17 Saw a doctor because of chest pain? What did the doctor say it was? (A=Angina)<br>*or*<br>2) Positive response to <u>ALL</u> of the questions:<br>MHXA8: Ever had any pain/discomfort in chest?<br>MHXA9: 'Chest pain walking up hill?' *or*<br>MHXA10: 'Chest pain walking at ordinary pace on level?'<br>MHXA11: What do you do if you get chest pain while you are walking? Response=S (Stop or slow down)<br>MHXA12: If you stand still, what happens? Response=R (Relieved)<br>MHXA13: Time required for relief of chest pain. Response=L (10 min or less) |
| Swollen legs at end of day (1 point) | Positive response to both:<br>• "Have you ever had swelling of your feet or ankles (excluding pregnancy)?"<br>• "Did it tend to come on during the day and go down overnight?" | Positive response to both questions:<br>MHXA49: Ever have swelling of the feet or ankles?<br>MHXA50: Swelling come during day, go down overnight? |

| Cardiac Score | ARIC Questions | JHS Variables |
|---|---|---|
| Nocturnal dyspnea (1 point) | Positive response to "Have you ever been awakened at night by trouble breathing?" | Positive response to:<br>MHXA48: Ever awakened by trouble breathing? |
| Pulmonary rales at physical exam | Not applicable | Not applicable |
| Atrial fibrillation on ECG (1 point) | Not applicable | JHS analysis variable afib=1 (Derived from ECGA15: Arrhythmia Minnesota code 8-3-1 [value=1]). |
| Pulmonary disease score | | |
| History of chronic bronchitis (1 point) | Positive response "Have you ever had chronic bronchitis?" | Positive response to:<br>PFHA9A: Doctor said you have chronic lung disease? |
| History of asthma (1 point) | Positive response to "Have you even had chronic asthma?" | Positive response to any series of questions:<br>PFHA10A: Has the doctor said you have asthma?<br>RPAA13: Have you ever had asthma? and<br>RPAA14: Was it confirmed by a doctor? |
| History of coughing, phlegm, or wheezing (1 point) | Positive response to any:<br>• "Do you usually have a cough?"<br>• "Do you usually bring up phlegm from your chest?"<br>• "Does your chest ever sound wheezy or whistling apart from colds?" | Positive response to any:<br>RPAA1: Do you usually have a cough?<br>RPAA6: Bring up phlegm, 3+ months?<br>RPAA8: Chest ever sound wheezy w/out cold?<br>RPAA9: Chest sound wheezy most days? |
| Presence of rhonchi at physical exam | Not applicable | Not applicable |
| Therapy score | | |
| History of digitalis administration (1 point) | Medication codes (312xxx) | Search medications for digitalis drug code = cardiac glycosides (TC 312xxx) |
| History of diuretic administration (1 point) | Medication codes (37xxxx) | Search medications for drug class: Diuretics (Loop diuretics, mercurial diuretics, osmotic diuretics, potassium sparing diuretics; TC 37xxxx) |

[a] Gothenburg is a point system that assigns heart failure grades based on cardiac, pulmonary, and drug therapy component scores. The following grades are assigned: 0 (heart failure absent) if all 3 scores are 0; 1 (latent) if cardiac score greater than 0 and pulmonary and therapy scores equal 0; 2 (manifest heart failure) if cardiac score greater than 0 and either pulmonary or therapy score greater than 0; 3 if cardiac score greater than 0 and both pulmonary and therapy scores greater than 0; and 4 if the patient died in heart failure. For the current study, we ascertained heart failure based on grade 3.

**Supplemental Table 2**. Baseline Characteristics of the Study Population Stratified by Severity of Conduction Delay

| Characteristic | Severity of Conduction Delay | | | *P* Value |
|---|---|---|---|---|
| | Mild (QRS 100-119 msec) | Moderate (QRS 120-149 msec) | Severe (QRS ≥ 150 msec) | |
| No. of participants | 1360 | 88 | 80 | |
| Age, median (IQR), y | 58.1 (47.6-66.3) | 66.5 (59.6-73.0) | 68.9 (63.0-73.4) | < .001 |
| Male sex, No. (%) | 669 (49.2) | 42 (47.7) | 41 (51.3) | < .001 |
| Medical history, No. (%) | | | | |
| Atrial fibrillation | 10 (0.7) | 1 (1.1) | 0 (0.0) | .02 |
| Chronic lung disease | 102 (7.5) | 11 (12.5) | 8 (10.0) | .15 |
| Diabetes mellitus | 312 (22.9) | 33 (37.5) | 30 (37.5) | < .001 |
| Heart failure | 126 (9.3) | 11 (12.5) | 16 (20.0) | < .001 |
| Hypertension | 919 (67.6) | 69 (78.4) | 66 (82.5) | < .001 |
| Myocardial infarction | 88 (6.5) | 12 (13.6) | 17 (21.3) | < .001 |
| Smoker currently | 185 (13.6) | 9 (10.2) | 11 (13.8) | .73 |
| Smoker previously | 312 (22.9) | 22 (25.0) | 19 (23.8) | < .001 |
| Stroke | 56 (4.1) | 6 (6.8) | 9 (11.3) | .01 |
| Physical examination, median (IQR) | | | | |
| Body mass index, $kg/m^2$ | 31.4 (27.7-36.5) | 30.6 (27.6-34.7) | 31.1 (27.8-35.4) | < .001 |
| Pulse, beats/min | 62.0 (56.0-70.0) | 64.0 (56.5-71.0) | 64.5 (55.0-70.5) | < .001 |
| Systolic blood pressure, mm Hg | 125.0 (115.0-138.0) | 132.0 (123.0-141.5) | 135.0 (123.5-148.5) | < .001 |
| Laboratory test results, median (IQR) | | | | |
| eGFR, mL/min/1.73 $m^2$ | 85.9 (76.0-96.0) | 82.5 (69.5-91.5) | 76.4 (59.6-85.9) | < .001 |
| Glucose, mg/dL | 93.0 (87.0-104.0) | 94.5 (88.0-104.0) | 98.0 (90.0-115.5) | < .001 |
| Hemoglobin, g/dL | 13.2 (12.4-14.3) | 13.0 (12.0-14.4) | 12.8 (11.9-13.5) | < .001 |
| Low-density lipoprotein, mg/dL | 124.0 (102.0-147.0) | 121.0 (94.5-143.5) | 123.5 (103.0-147.0) | .67 |
| Serum potassium, mEq/L | 4.3 (4.0-4.5) | 4.3 (4.0-4.6) | 4.3 (4.0-4.5) | .32 |
| Serum sodium, mEq/L | 141.0 (139.0-142.0) | 141.0 (140.0-142.5) | 141.0 (139.0-143.0) | .001 |
| Cardiac test results | | | | |
| Complete LBBB, No. (%) | 0 | 19 (21.6) | 33 (41.3) | < .001 |
| Complete RBBB, No. (%) | 1 (0.1) | 30 (34.1) | 33 (41.3) | < .001 |
| Other IV conduction Defect, No. (%) | 79 (5.8) | 39 (44.3) | 14 (17.5) | < .001 |
| Ejection fraction, mean (SD), % | 61.0 (8.3) | 59.8 (11.1) | 57.7 (13.5) | < .001 |
| Ejection fraction < 40%, No. (%) | 24 (1.8) | 3 (3.4) | 8 (10.0) | < .001 |
| Left ventricular dimension, median (IQR), cm | 49.3 (46.9-52.3) | 50.6 (46.5-53.7) | 49.0 (47.9-53.4) | < .001 |
| Left ventricular hypertrophy, No. (%) | 141 (10.4) | 14 (15.9) | 11 (13.8) | < .001 |
| Medications, No. (%) | | | | |

| Characteristic | Severity of Conduction Delay | | | *P* Value |
|---|---|---|---|---|
| | Mild (QRS 100-119 msec) | Moderate (QRS 120-149 msec) | Severe (QRS ≥ 150 msec) | |
| ACE inhibitor/ARB | 251 (18.5) | 21 (23.9) | 30 (37.5) | < .001 |
| Anti-arrhythmic agent | 8 (0.6) | 3 (3.4) | 1 (1.3) | < .001 |
| Antiplatelet agent | 30 (2.2) | 2 (2.3) | 2 (2.5) | .06 |
| β-Blocker | 160 (11.8) | 13 (14.8) | 16 (20.0) | < .001 |
| Calcium channel blocker | 313 (23.0) | 21 (23.9) | 23 (28.8) | < .001 |
| Digoxin | 32 (2.4) | 7 (8.0) | 7 (8.8) | < .001 |
| Diuretic | 358 (26.3) | 37 (42.0) | 35 (43.8) | < .001 |
| Insulin | 95 (7.0) | 11 (12.5) | 15 (18.8) | < .001 |
| Oral diabetic agent | 138 (10.1) | 22 (25.0) | 12 (15.0) | < .001 |
| Statin | 169 (12.4) | 19 (21.6) | 19 (23.8) | < .001 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

**Supplemental Table 3**. Outcomes Stratified by Severity of Conduction Delay

| Outcome | Severity of Conduction Delay | | | |
|---|---|---|---|---|
| | Mild (100-119 msec) | Moderate (120-149 msec) | Severe (≥ 150 msec) | *P* Value |
| Mortality, No. (cumulative incidence[a]) | 147 (11.2) | 13 (14.9) | 26 (33.7) | < .001 |
| 95% CI | 9.6-13.1 | 9.0-24.6 | 24.5-46.3 | |
| Mode of death, No. (%) | | | | |
| Cardiac mortality | 75 (51.0) | 6 (46.2) | 16 (61.5) | .13 |
| 95% CI | 42.7-59.3 | 19.2-74.9 | 40.6-79.8 | |
| Sudden cardiac death | 12 (8.2) | 0 (0.0) | 3 (11.5) | .07 |
| 95% CI | 4.3-13.8 | — | 6.6-39.4 | |
| Heart failure or cardiomyopathy | 4 (2.7) | 1 (7.7) | 5 (19.2) | .004 |
| 95% CI | 0.7-6.8 | 0.2-36.0 | 6.6-39.4 | |
| Noncardiovascular mortality | 72 (49.0) | 7 (53.8) | 10 (38.5) | .13 |
| 95% CI | 40.7-57.3 | 25.1-80.8 | 20.2-59.4 | |
| Heart failure hospitalization, No. (cumulative incidence)[b] | 86 (6.7) | 9 (11.2) | 23 (33.4) | < .001 |
| 95% CI | 5.4-8.2 | 6.0-20.8 | 23.8-47.0 | |

a Cumulative incidence of death within 8 years after exam 1.

b Calculated among the 5065 participants who survived to January 1, 2005, when heart failure hospitalization surveillance began.

**Supplemental Table 4**. Baseline Characteristics of Participants Who Completed Exam 3 and Had Normal Conduction at Baseline

| Characteristic | Participants (n = 2599) |
|---|---|
| Age, median (IQR), y | 53.0 (44.2-62.2) |
| Male sex, No. (%) | 799 (30.7) |
| Medical history, No. (%) | |
| Atrial fibrillation | 4 (0.2) |
| Chronic lung disease | 168 (6.5) |
| Diabetes mellitus | 452 (17.4) |
| Heart failure | 130 (5.0) |
| Hypertension | 1,432 (55.1) |
| Myocardial infarction | 86 (3.3) |
| Smoking status | |
| Current smoker | 287 (11.0) |
| Prior smoker | 429 (16.5) |
| Stroke | 74 (2.8) |
| Physical examination results, median (IQR) | |
| Body mass index, $kg/m^2$ | 30.2 (26.6-35.1) |
| Pulse, beats/min | 63.0 (57.0-71.0) |
| Systolic blood pressure, mm Hg | 123.0 (113.0-134.0) |
| Laboratory test results, median (IQR) | |
| eGFR, mL/min/1.73 m2 | 86.7 (76.8-97.3) |
| Glucose, mg/dL | 91.0 (85.0-99.0) |
| Hemoglobin, g/dL | 13.0 (12.1-13.8) |
| Low-density lipoprotein, mg/dL | 124.0 (102.0-147.0) |
| Potassium, mEq/L | 4.3 (4.0-4.5) |
| Sodium, mEq/L | 140.0 (139.0-142.0) |
| Uric acid, mg/dL | 5.2 (4.2-6.2) |
| Cardiac test results | |
| Ejection fraction, % | |
| Mean (SD) | 62.5 (6.5) |
| Median (IQR) | 65.0 (55.0-65.0) |

| Characteristic | Participants (n = 2599) |
|---|---|
| Ejection fraction < 40%, No. (%) | 3 (0.1) |
| Left ventricular dimension, median (IQR), cm | 48.1 (45.3-50.3) |
| Left ventricular hypertrophy, No. (%) | 138 (5.3) |
| Medications, No. (%) | |
| ACE inhibitor/ARB | 349 (13.4) |
| Anti-arrhythmic agent | 2 (0.1) |
| Antiplatelet agent | 24 (0.9) |
| β-Blocker | 211 (8.1) |
| Calcium channel blocker | 405 (15.6) |
| Digoxin | 11 (0.4) |
| Diuretic | 492 (18.9) |
| Insulin | 99 (3.8) |
| Oral diabetic agent | 242 (9.3) |
| Statin | 257 (9.9) |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

# Ventricular Conduction and Long-Term Heart Failure Outcomes and Mortality in African Americans: Insights From the Jackson Heart Study

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