Racial differences in sudden cardiac death among hypertensive patients during antihypertensive therapy: The LIFE study

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BACKGROUND In the general population, blacks appear to have a higher risk of sudden cardiac death (SCD).

OBJECTIVES To determine whether black hypertensive patients have a higher SCD incidence.

METHODS The incidence of SCD was examined in 533 black and 8660 nonblack hypertensive patients with electrocardiographic left ventricular hypertrophy randomly assigned to losartan- or atenolol-based treatment.

RESULTS During a mean follow-up of 4.8 ± 0.9 years, SCD occurred in 178 patients (1.9%); 5-year SCD incidence was significantly higher in black than in nonblack patients (3.9% vs 1.9%; $P = .007$). In univariate Cox analyses, black patients had a 97% higher risk of SCD (hazard ratio 1.97; 95% confidence interval 1.19–3.25; $P = .015$). In multivariate Cox analyses adjusting for randomized treatment, age, sex, body mass index, diabetes, history of heart failure, atrial fibrillation, myocardial infarction, ischemic heart disease, stroke, peripheral vascular disease, smoking, serum total and high-density lipoprotein cholesterol level, creatinine level, glucose level, and urine albumin/creatinine ratio and for incident myocardial infarction, in-treatment heart rate, QRS duration, diastolic and systolic pressure, Cornell voltage–duration product, and Sokolow–Lyon voltage left ventricular hypertrophy treated as time-varying covariates, black race remained associated with a 98% increased risk of SCD (hazard ratio 1.98; 95% confidence interval 1.12–3.59; $P = .020$).

CONCLUSIONS Black hypertensive patients are at increased risk of SCD. The higher risk of SCD in black patients persists after adjusting for the higher prevalence of risk factors in black patients, in-treatment blood pressure, and the established predictive value of in-treatment electrocardiographic left ventricular hypertrophy and heart rate for SCD in this population.

KEYWORDS Death; Sudden; Race and ethnicity; Hypertension

ABBREVIATIONS **CI** = confidence interval; **ECG** = electrocardiographic; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **LVH** = left ventricular hypertrophy; **SCD** = sudden cardiac death

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Introduction

Sudden cardiac death (SCD) is a significant public health issue, claiming 250,000–300,000 lives annually in the United States,[1,2] accounting for 5.6% of the overall mortality in a prospective population-based evaluation.[3] The vast majority of sudden cardiac arrests occur in the community and are associated with a <10% survival rate.[1] In addition, a high proportion of SCD cases present without prior warning or evidence of heart disease,[4,5] making identification of specific populations at increased risk for SCD a priority.[2,6] However, there is a paucity of data on risk of SCD in nonwhite ethnic and racial groups.[2,4]

In the general population, blacks appear to have a higher risk of sudden cardiac arrest and SCD[4,7–10] and black patients with in-hospital cardiac arrest are significantly less likely to survive to discharge.[11] Although the higher incidence of SCD in blacks has been potentially attributed to their greater burden of hypertension, heart failure, and left ventricular hypertrophy (LVH),[10,12–14] whether differences in SCD risk factors account for the higher rate of SCD in

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blacks has not been adequately assessed.[4,7–10] More recent work has suggested that the increased SCD rate in blacks may be in part attributable to an increased prevalence of mutations in the cardiac sodium channel gene *SCN5A* that may further predispose them to the development of fatal and nonfatal ventricular arrhythmias.[15–18]

In hypertensive patients with electrocardiographic (ECG) LVH, the serial assessment of ECG LVH, QRS duration, and heart rate has been demonstrated to stratify the risk of SCD beyond the information provided by standard risk factors.[19–21] However, whether black hypertensive patients have an increased risk of SCD independent of risk factors for SCD has not been examined. Therefore, the present study examined the relationship of SCD to race to determine whether black ethnicity was associated with a higher risk of SCD in hypertensive patients after adjusting for racial differences in the prevalence of SCD risk factors, treatment effects, and in-treatment blood pressure and for the previously demonstrated relationship of in-treatment ECG LVH, QRS duration, and heart rate for SCD.[19–21]

Methods

The LIFE study enrolled 9193 hypertensive patients with ECG LVH by Cornell voltage–duration product and/or Sokolow–Lyon voltage criteria on a screening ECG in a prospective, double-blind randomized study that compared cardiovascular morbidity and mortality with use of losartan- as opposed to atenolol-based treatment, as previously described in detail.[14,22] Blinded treatment was begun with losartan 50 mg or atenolol 50 mg daily and matching placebo of the other agent, with the up-titration of study medication and addition of additional nonstudy medications to achieve a target pressure of 140/90 mm Hg or lower as previously reported in detail.[22,23]

Study ECGs were obtained at baseline, at 6 months, and at yearly follow-up until study termination or patient death and were interpreted as previously reported.[14,19–23] Cornell product >2440 mm $\cdot$ ms or Sokolow–Lyon voltage >38 mm was used to identify LVH.[24,25] The heart rate was measured to the nearest beats per minute on each protocol-mandated study ECG.[21] ECG strain as a dichotomous variable was visually assessed on 8246 baseline ECGs available for this analysis as previously described.[26] Repolarization abnormalities in leads V_5 and/or V_6 were considered consistent with the presence of typical strain when there was a downsloping convex ST segment with an inverted asymmetrical T wave with polarity opposite to the main QRS deflection.[26]

SCD was a prespecified secondary end point in LIFE and was defined as death that was sudden and unexpected, including observed arrhythmic deaths and those not attributable to myocardial infarction, intractable heart failure, or other identifiable cause, and that occurred within 24 hours of symptom onset or when the subject was last seen alive if an unwitnessed SCD.[19,22] If an autopsy was performed in a patient who died suddenly and evidence of a recent myocardial infarction was found, the death was classified as secondary to myocardial infarction and not an SCD.[19] Each case was reviewed and verified by the Endpoint Committee who was blinded to study ECG LVH findings when classifying possible morbid events.[19,22]

Data management and analysis were performed with the software SPSS, version 12.0(SPSS Inc, Chicago, IL). Data are presented as mean $\pm$ SD for continuous variables and proportions for categorical variables. Differences in prevalences were compared by using χ^2 analyses, and differences in mean values were compared by using unpaired t test. Event rates were calculated and plotted according to the Kaplan–Meier product limit method, and statistical significance was tested by using the log-rank statistic. The relationship of SCD to black race was assessed by using Cox proportional hazards models. Partial residuals were plotted against survival times and visually examined to verify the proportional hazards assumption. The independence of the relationship of SCD to black race was evaluated in a multivariable Cox model that included randomized treatment, age, sex, body mass index, diabetes, prevalent atrial fibrillation by history or ECG, history of heart failure, myocardial infarction, ischemic heart disease, stroke, peripheral vascular disease, smoking status, baseline serum total and high-density lipoprotein cholesterol level, creatinine level, glucose level, and urine albumin/creatinine ratio as standard covariates and incident myocardial infarction, in-treatment heart rate, QRS duration, diastolic and systolic pressure, Cornell product, and Sokolow–Lyon voltage as time-varying covariates. Analyses were repeated stratifying the population by median in-treatment systolic blood pressure, by median decrease in ECG LVH by Cornell product and Sokolow–Lyon voltage, and by the presence or absence of the strain pattern on the baseline ECG. An interaction between race and these variables was formally tested by adding cross-product terms of race and these variables into the models of the total population. For all tests, 2-tailed $P < .05$ was required for statistical significance.

Role of the funding source

Merck & Co provided the authors with free access to all the data; the authors were free to interpret data and write the paper. The sponsor agreed to support performance of the study, at which time it was agreed that the findings would be published by the investigators regardless of the results. The decision to publish the paper, the choice of analyses to include, and drafting of the manuscript were wholly controlled by all authors.

Results

Clinical and demographic characteristics of patients in relationship to race are shown in Table 1. Compared with nonblacks, black hypertensive patients were younger, more likely to be male; smoke; have diabetes, prior ischemic heart disease, stroke, and heart failure; have higher body mass indexes, serum glucose level, creatinine level, lower total cholesterol levels, greater albuminuria; and more likely to have ECG strain on their baseline ECG, but were similar