Racial Differences in Incident Heart Failure During Antihypertensive Therapy

Peter M. Okin, MD; Sverre E. Kjeldsen, MD, PhD; Björn Dahlof, MD, PhD; Richard B. Devereux, MD

Background—Blacks have a higher prevalence of heart failure (HF) than nonblacks, possibly reflecting a greater burden of HF risk factors, including hypertension. Although HF incidence is significantly higher in blacks during long-term follow-up of young adults, the relationship of incident HF to race in hypertensive patients undergoing treatment is unclear.

Methods and Results—Incident HF was evaluated in 497 black and 8199 nonblack hypertensive patients with no history of HF randomly assigned to losartan- or atenolol-based treatment. During 4.7±1.1 years mean follow-up, HF hospitalization occurred in 265 patients (3.0%); 5-year HF incidence was significantly greater in black than nonblack patients (7.0 versus 3.1%, P<0.001). In Cox multivariate analyses adjusting for randomized treatment, age, sex, the presence of the strain pattern on the baseline ECG, and other HF risk factors treated as standard covariates, and for incident myocardial infarction, in-treatment QRS duration, diastolic and systolic pressure, Cornell product, and Sokolow-Lyon voltage criteria for left ventricular hypertrophy (LVH) treated as time-varying covariates, black race remained associated with a 130% increased risk of developing new HF (hazard ratio 2.30, 95% confidence interval 1.24 to 4.28).

Conclusions—Incident HF is substantially more common among black than nonblack hypertensive patients. The increased risk of developing new HF in blacks persists after adjusting for the higher prevalence of HF risk factors in blacks, for treatment effects and in-treatment blood pressure, and for the known predictive value of the ECG strain pattern and in-treatment ECG LVH and QRS duration for incident HF in this population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00338260.

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Key Words: ECG ■ hypertension ■ hypertrophy ■ race

Heart failure (HF) is a growing public health problem, with a 20% lifetime risk in both men and women.1 Because of the large clinical and societal impact of HF, current recommendations emphasize the importance of its prevention,2–4 necessitating better understanding of HF risk factors and of populations that may be at increased risk of HF. Some,5,6 but not all,7 previous studies have suggested that blacks have a higher prevalence of HF and a greater burden of HF risk factors than people of other races.8–12 These findings raise the question of whether HF incidence differs between racial/ethnic groups or if the generally higher prevalence of HF among blacks is more a manifestation of their higher HF risk factor profile.

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Examination of ethnic/racial differences in HF incidence in population-based studies12–18 has yielded variable results, with a minority finding no differences in HF incidence or risk between black and white subjects,17,18 but most finding a higher HF incidence in blacks.12–16 However, in most of these populations, black race was no longer a significant predictor of new HF after adjusting for potential risk factors12–14 or was only independently associated with increased HF risk in a subset of the population.15 Moreover, despite the markedly increased risk of HF associated with hypertension,1,19,20 little is known about racial differences in HF incidence among hypertensive patients.

Recent analysis of incident HF among young adults16 demonstrated a markedly increased HF incidence in black men and women compared with their white counterparts and that the risk of new HF among blacks was related to prevalent kidney disease, higher diastolic pressure and body mass index, lower high-density lipoprotein (HDL) cholesterol, and left ventricular (LV) systolic dysfunction. However, the small number of incident HF cases and the solitary case of new HF in white participants precluded meaningful analysis of racial differences in HF incidence after adjusting for possible racial differences in HF risk factors.16 Thus, whether apparent racial differences in HF incidence can be explained by racial differences in risk factors remains unclear. Therefore, the present study examined whether black race is associated with increased HF risk in hypertensive patients undergoing treatment, independent of other HF risk factors, treatment effects, blood pressure reduction, and the known effects of in-treatment QRS duration and...
WHAT IS KNOWN

• Understanding determinants of heart failure is a national priority.
• Blacks have a greater burden of heart failure and heart failure risk factors, including hypertension.
• Whether the risk of heart failure in blacks is greater than whites, after adjusting for blood pressure control, is unknown.

WHAT THE STUDY ADDS

• Among patients enrolled in a clinical trial of blood pressure treatment, incident heart failure developed significantly more often in black than nonblack patients with hypertension.
• This increased risk persisted after adjusting for the higher prevalence of heart failure risk factors in blacks, including in-treatment blood pressure.
• These findings suggest that new treatments may need to be developed to reduce heart failure incidence in black patients with hypertension, and that further work to define racial differences in the mechanisms of heart failure development, are needed.

Methods

Subjects

The LIFE study21–24 enrolled hypertensive patients with ECG LVH by Cornell product25 and/or Sokolow-Lyon voltage criteria26 on a screening ECG in a prospective, double-blind study large enough (n=9193) to demonstrate an appreciable reduction in mortality and morbidity events with use of losartan as opposed to atenolol.23 Eligible patients were men and women age 55 to 80 years with previously untreated or treated essential hypertension with a mean blood pressure of 120/75 mm Hg.21,22

Electrocardiography

Hard-copy ECGs were interpreted at a core laboratory by experienced readers blinded to clinical information as previously reported in detail.21,22,27 The product of QRS duration times the Cornell voltage combination (R aVL + S V5, with 6 mm [0.6 mV] added in women21,25,27) >2440 mm · ms or Sokolow-Lyon voltage (S V5 + RV5) >38 mm were used to identify ECG LVH. ECG strain was defined by the presence of a downsloping convex ST segment with an inverted asymmetrical T wave with polarity opposite to the main QRS deflection in leads V5 and/or V6.27

End Point Determination

Hospitalization for HF was a prespecified secondary end point in the LIFE study.21,22,24,27 The diagnosis of HF was based on clinical and diagnostic findings modified from the Framingham criteria28 (Table 1). Each case was reviewed and verified by the End Point Committee, which was blinded to study ECG strain and LVH results.23,24

Table 1. Criteria for Diagnosis of Heart Failure on Hospitalization

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical findings</td>
<td></td>
</tr>
<tr>
<td>1. Paroxysmal nocturnal dyspnea</td>
<td>1. Night cough</td>
</tr>
<tr>
<td>2. Jugular venous distention</td>
<td>2. Dyspnea on ordinary exertion</td>
</tr>
<tr>
<td>3. Pulmonary rales</td>
<td>3. Bilateral ankle edema</td>
</tr>
<tr>
<td>4. Ventricular S3 gallop</td>
<td>4. Hepatomegaly</td>
</tr>
<tr>
<td>5. Hepatomegaly</td>
<td></td>
</tr>
<tr>
<td>6. Diuresis of 10 lb or 5 kg in response to diuretic treatment with clinical improvement in congestive symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic findings

- Chest X-ray
  - 1. Acute pulmonary edema on chest X-ray
  - Chest x-ray
- Hemodynamic
  - 1. Pulmonary capillary wedge pressure 16–19 mm Hg
  - 2. Left ventricular ejection fraction 36-44%
- Autopsy
  - 1. Pulmonary edema, visceral congestion or cardiomegaly

Echocardiography

To examine whether racial differences in LV structure or systolic function could in part explain racial differences in HF incidence, baseline and year-2 echocardiograms were compared in 771 non-black and 126 black patients in the LIFE echocardiography substudy. Year-2 studies were selected based on previous analyses demonstrating that LV structural and functional remodeling in LIFE had maximized by year 2.29,30 These patients were not further subgrouped according to HF development because of the small number of black patients with incident HF (n=3).

Echocardiograms were performed and analyzed as previously reported in detail29–33 to determine LV internal dimensions, wall thicknesses, LV mass indexed for body surface area, and ejection fraction. Relative wall thickness was calculated as LV posterior wall thickness/internal radius. Myocardial contractile performance was assessed by measuring midwall shortening in relation to circumferential end-systolic stress (stress-corrected midwall shortening) and expressed as a percentage of the value predicted from an equation derived in apparently healthy adults.32 Stress-corrected midwall shortening <89.2% was considered low.32

Statistical Methods

Data management and analysis were performed with SPSS version 12.0 software. Data are presented as mean ± SD for continuous variables and proportions for categorical variables. Differences in prevalences were compared using χ² analyses, and differences of mean values were compared using 2-way ANOVA or unpaired t test for echocardiographic variables. Event rates were calculated and regression of ECG left ventricular hypertrophy (LVH) on HF incidence in this population.21,22
plotted according to the Kaplan-Meier product limit method, and statistical significance was tested using the log-rank statistic. The relation of incident HF to black race was assessed using Cox proportional hazards models. Partial residuals were plotted against the Kaplan-Meier product limit method, and the independence of the relationship of incident HF to black race was evaluated in a multivariable Cox model that included randomized treatment, age, sex, body mass index, prevalence, and history of atrial fibrillation, history of MI, ischemic heart disease, stroke, peripheral vascular disease, smoking status, baseline serum total and HDL cholesterol, creatinine, glucose, uric acid, urine albumin/creatinine ratio, and the presence of the strain pattern on the baseline ECG as standard covariates and incident myocardial infarction (MI), in-treatment QRS duration, diastolic and systolic pressure, Cornell product, and Sokolow-Lyon voltage as time-varying covariates. For all tests, a 2-tailed probability value of 0.05 was required for statistical significance.

### Results

During 4.7 ± 1.1 years mean follow-up, HF hospitalization occurred in 29 of 497 black patients (5.8%) and in 236 of 8199 nonblack patients (2.9%, P < 0.0001). The majority of black patients came from the United States (98.4%), with a minority from the United Kingdom (1.2%) and Denmark (0.4%). In contrast, country of origin of the nonblack patients was distributed similarly to the overall LIFE study population (United States 13.0%, United Kingdom 9.0%, Denmark 15.9%, Finland 17.6%, Norway 16.5%, Sweden 26.3%, and Iceland 16.6%, P < 0.001 versus blacks). Clinical and demographic characteristics of patients in relationship to race and the development of new HF are shown in Table 2. Black patients were younger; were more likely to be men, to have diabetes, to have a history of ischemic heart disease or stroke, be current smokers or have the ECG strain pattern; had higher body mass indexes, serum creatinine, and uric acid levels, greater albuminuria, and lower total cholesterol levels than nonblack patients. Patients who developed new HF were older; were more likely to have diabetes, a history of ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease, current or prior atrial fibrillation, be current smokers or have the ECG strain pattern; had lower HDL cholesterol levels, higher serum glucose and creatinine levels, and greater albuminuria than patients who did not develop HF.

Blood pressure, ECG LVH, and QRS duration measurements at baseline and changes in these measurements between baseline and last in-study determination in relation to race and the development of new HF are shown in Table 3. Black patients had lower mean baseline Cornell product and QRS duration, higher baseline Sokolow-Lyon voltage, but were similar to nonblack patients with respect to baseline pressures and changes in blood pressure and ECG variables between baseline and last in-study measurement. Patients who developed HF had lower baseline diastolic pressures, smaller reductions in systolic pressure and Cornell product, and greater increases in QRS duration between baseline and last in-study determination, whereas only nonblack patients with HF had higher baseline Cornell product LVH.

The relation of incident HF to race is shown in Table 4 and Figure. Five-year HF incidence was 7.0% in black patients and 3.1% in nonblack patients (P < 0.0001); in individual variable Cox analyses, black race was associated with a 132% higher risk of developing HF. The independent

### Table 2. Demographic and Clinical Characteristics in Relation to Race and Development of New Heart Failure*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonblack</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No HF (n = 7963)</td>
<td>HF (n = 236)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.8 ± 7.0</td>
<td>70.9 ± 6.2</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>54.6</td>
<td>50.4</td>
</tr>
<tr>
<td>Losartan treatment (%)</td>
<td>50.2</td>
<td>50.4</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>11.5</td>
<td>27.1</td>
</tr>
<tr>
<td>History of IHD (%)</td>
<td>14.2</td>
<td>37.3</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>5.2</td>
<td>19.9</td>
</tr>
<tr>
<td>History of Stroke (%)</td>
<td>3.8</td>
<td>8.9</td>
</tr>
<tr>
<td>History of PVD (%)</td>
<td>5.2</td>
<td>13.6</td>
</tr>
<tr>
<td>Current or prior AF (%)</td>
<td>3.4</td>
<td>14.0</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>15.5</td>
<td>28.0</td>
</tr>
<tr>
<td>ECG strain pattern (%)</td>
<td>9.2</td>
<td>23.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.9 ± 4.6</td>
<td>28.6 ± 5.7</td>
</tr>
<tr>
<td>Total cholesterol (mM)</td>
<td>6.08 ± 1.11</td>
<td>5.82 ± 1.18</td>
</tr>
<tr>
<td>HDL cholesterol (mM)</td>
<td>1.50 ± 0.44</td>
<td>1.37 ± 0.45</td>
</tr>
<tr>
<td>UACR (mg/mM)</td>
<td>6.5 ± 32.2</td>
<td>16.1 ± 35.0</td>
</tr>
<tr>
<td>Glucose (mM)</td>
<td>5.94 ± 2.07</td>
<td>6.85 ± 3.33</td>
</tr>
<tr>
<td>Creatinine (µM)</td>
<td>84.9 ± 18.7</td>
<td>90.4 ± 22.1</td>
</tr>
<tr>
<td>Uric acid (mg/mM)</td>
<td>327 ± 76</td>
<td>335 ± 78</td>
</tr>
</tbody>
</table>

* Differences in prevalences between groups were compared using ² analyses and mean values of continuous variables were compared using 2-way ANOVA. AF indicates atrial fibrillation; ECG, electrocardiogram; IHD, ischemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; and UACR, urine albumin/creatinine ratio.
relation of new HF to race was examined after adjusting for possible effects of treatment, age, sex, prevalent diabetes, history of ischemic heart disease, myocardial infarction, stroke, and peripheral vascular disease, current or prior atrial fibrillation and current smoking, baseline urine albumin/creatinine ratio, total and HDL cholesterol, glucose, creatinine, uric acid, body mass index, and prevalent ECG strain, and for incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Cornell product, Sokolow-Lyon voltage treated as time-varying covariates. In the multivariate model, in-treatment Cornell voltage-duration product entered as standard covariates, incident myocardial infarction, baseline and in-treatment systolic and diastolic blood pressure, QRS duration, Sokolow-Lyon voltage, and Cornell voltage-duration product entered as time-varying covariates.

Table 3. Baseline and Change from Baseline to Last In-Study Measurement of Blood Pressure and Electrocardiographic Left Ventricular Hypertrophy in Relation to Race and the Development of New Heart Failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Nonblack</th>
<th>Black</th>
<th>P Value Black vs Nonblack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>174.5±14.3</td>
<td>175.0±13.6</td>
<td>0.338</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>97.9±8.7</td>
<td>95.2±9.8</td>
<td>0.508</td>
</tr>
<tr>
<td>Cornell product (mm · ms)</td>
<td>2816±997</td>
<td>3243±1308</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage (mm)</td>
<td>29.6±10.1</td>
<td>32.8±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>100.8±17.7</td>
<td>109.0±22.4</td>
<td>0.010</td>
</tr>
<tr>
<td>Change from baseline to last measurement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>−29.6±19.3</td>
<td>−35.7±21.5</td>
<td>0.070</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>−17.3±10.1</td>
<td>−18.1±12.6</td>
<td>0.306</td>
</tr>
<tr>
<td>Cornell product (mm · ms)</td>
<td>−215±820</td>
<td>97±1410</td>
<td>0.827</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage (mm)</td>
<td>−3.8±7.1</td>
<td>−4.3±9.7</td>
<td>0.507</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>1.6±12.2</td>
<td>7.3±17.7</td>
<td>0.074</td>
</tr>
</tbody>
</table>

To explore whether racial differences in LV structure and function could in part explain racial differences in HF incidence, baseline and year-2 LV findings were examined in relation to race in the subset of the population who underwent echocardiography (Table 5). At baseline, there were no significant differences between black and nonblack patients in LV mass index, LV diastolic dimension, relative wall thickness, ejection fraction, midwall shortening, stress-corrected midwall shortening, or the prevalence of stress-corrected midwall shortening <89.2%. In contrast, after 2 years of treatment, black patients had significantly higher LV mass index and relative wall thickness, lower midwall shortening, and stress-corrected midwall shortening and were more likely to have stress-corrected midwall shortening <89.2%. Of note, the greater LV mass index and relative wall thickness and lower absolute and stress-corrected midwall shortening in black patients remained significant in analyses of covariance that adjusted for age, sex, baseline, and change from baseline to year-2 systolic and diastolic pressure and for baseline measures of each variable (all P<0.01). In addition, these findings remained statistically unchanged if patients with incident HF were excluded from the analyses.

Table 4. Individual Variable and Multivariable Cox Regression Analyses to Assess the Relation of New Heart Failure to Black Race

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate Cox model</td>
<td>2.32</td>
<td>1.58–3.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate Cox model*</td>
<td>2.30</td>
<td>1.24–4.28</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Adjusted for possible effects of treatment with losartan versus atenolol, age, sex, prevalent diabetes, history of ischemic heart disease, myocardial infarction, stroke, peripheral vascular disease, atrial fibrillation or smoking, baseline albumin/creatinine ratio, total and HDL cholesterol, glucose, creatinine, body mass index entered as standard covariates, incident myocardial infarction, baseline, in-treatment systolic and diastolic blood pressure, QRS duration, Sokolow-Lyon voltage, and Cornell voltage-duration product entered as time-varying covariates.

Discussion

These findings demonstrate that black hypertensive patients have a significantly increased, >2-fold higher risk of new hospitalization for HF than nonblack patients during nearly 5 years. The Kaplan-Meier curves comparing new-onset heart failure rates between patients according to race are shown in Figure.
years mean follow-up. The increased HF risk in black patients was independent of their greater burden of HF risk factors and remained significant after adjusting for incident myocardial infarction, in-treatment blood pressure, and the previously demonstrated predictive values of ECG strain and in-treatment QRS duration and ECG LVH for HF in this population.21,22,27 Echocardiographic findings in a subset of the population suggest that racial differences in LV structure and midwall performance during antihypertensive treatment may play a role in the increased HF risk in black patients with hypertension. These findings suggest that new treatment and serial evaluation plans may need to be developed to reduce HF incidence in this high-risk population.

In previous population-based studies,12–18 black participants had higher unadjusted incidence of HF in the majority of studies,12–16 but black race was not a significant predictor of new HF after adjusting for risk factors.12–15 In the Multi-Ethnic Study of Atherosclerosis,12 blacks had a 1.8-fold greater risk of developing HF than white participants. However, adding hypertension and/or diabetes to models including ethnicity eliminated this statistical difference in HF incidence.12 During 19 years mean follow-up in >13,000 men and women evaluated in the First National Health and Nutrition Examination Survey,13 black race was associated with a greater cumulative HF incidence by age 85 in women but was not an independent predictor of HF after adjusting for age, sex, and other HF risk factors.13 Similarly, in the Health Aging and Body Composition (Health ABC) study of well-functioning elderly individuals,14 blacks had a higher cumulative incidence of HF but race was not an independent predictor of HF in the final multivariate models. Among middle-aged subjects in the Atherosclerosis Risk in Communities Study,15 HF incidence was higher in black men and women, but the greater incidence was largely explained by a greater burden of atherosclerosis risk factors in blacks, with no significant increased risk of HF in black participants after adjusting for these risk factors. Among hypertensive patients in ALLHAT,20 there were no racial differences in treatment effects on HF incidence, but racial differences in HF incidence, per se, were not examined.

In a recent analysis of 2637 black and 2478 white participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study,16 new HF developed in 27 participants during 20 years follow-up, all but one of whom was black (P = 0.001). Among blacks, increased risk of new HF that occurred 15 years, on average, was related to higher baseline diastolic pressure and body mass index, lower HDL cholesterol, chronic kidney disease, and LV systolic dysfunction on echocardiography that was performed 5 years after baseline assessment. However, the small total number of incident HF cases and the solitary case of new HF in white participants precluded analysis of racial differences in HF incidence.16

In contrast, the current study demonstrates a significantly higher incidence of HF among black hypertensive patients, even after adjusting for the greater burden of many HF risk factors among black patients at baseline and, in particular, the ECG strain pattern (Table 2), a known strong predictor of new HF in this and other populations.27 In addition, the increased risk of HF among black patients was independent of baseline and inpatient systolic and diastolic pressure and persisted after adjusting for the previously demonstrated predictive value of in-treatment systolic pressure and ECG LVH in this population.21,22

Examination of echocardiographic findings at baseline and year-2 among the subset of patients who underwent echocardiography in the LIFE study (Table 5) suggests that the higher incidence of HF in black patients may be mediated via a differential response of LV structure and function to hypertension over time. Although baseline LV mass, size, wall thicknesses, and function were similar in black and nonblack patients, by year 2 black patients had greater LV mass and relative wall thickness, had lower LV midwall shortening, and were more likely to have depressed LV midwall shortening than nonblack patients, even after adjusting for age, sex, and both baseline and change in systolic and diastolic pressure between baseline and year 2 (Table 5). Previous findings in hypertensive patients further support this hypothesis.20,33–35 In the Hypertension Genetic Epidemiology Network (HyperGEN) Study, black race was an independent correlate of lower LV ejection fraction33 and was associated with a greater risk of echocardiographic LVH that was more likely to have a concentric geometry.34 In the Anglo-Scandinavian Cardiac Outcomes Trial,35 hypertensive patients of
African-Caribbean origin had greater diastolic dysfunction than white Europeans that persisted after adjusting for ethnic differences in age, sex, blood pressure, diabetes, and LV mass and function. Finally, the higher indexed LV mass and lower LV ejection fraction in black participants in CARDIA who went on to develop new HF further support the possibility that differences in LV structural and functional responses to blood pressure and other risk factors may play a role in the higher incidence of HF among blacks.

Several studies provide preliminary evidence of possible genetic differences that could in part mediate some of the observed ethnic differences in susceptibility to HF. Arnett et al found strong evidence for linkage of a region on the short arm of chromosome 11 that coincides with myosin-binding protein C in blacks but not whites and that this marker locus accounted for 72% of the variability in LV midwall shortening in blacks. Corin is a transmembrane serine protease that is highly expressed in cardiomyocytes and cleaves inactive proatrial and brain natriuretic peptide into biologically active molecules. The corin I555(P568) allele, defined by the presence of 2 single-nucleotide polymorphisms in near-complete linkage disequilibrium, is common in blacks and rare in whites; it is associated with higher blood pressure and an increased risk of hypertension and with increased LV mass at any given level of blood pressure and an increased risk of LVH in the presence of untreated hypertension. Moreover, in a retrospective analysis of 354 subjects with systolic HF in the African American Heart Failure Trial Genetic Risk Assessment in Heart Failure substudy, the corin I555(P568) allele was associated with increased risk for death or HF hospitalization in the subjects receiving standard neurohormonal blockade, but it was not associated with adverse outcome in those in the fixed-dose combination isosorbide-dinitrate/hydralazine arm that had been associated with increased survival in the overall study population. This difference was thought to possibly reflect an impaired processing of brain natriuretic peptide in carriers of the corin I555(P568) allele. However, all of these genetic associations are preliminary and require confirmation.

In addition to these possible genetic differences, racial differences in risk factors and access to care also have been proposed as possible factors in the higher prevalence of HF in blacks. In the current study, black patients had a greater prevalence and severity of baseline risk factors for HF (Table 2). However, the increased risk of new HF in black patients persisted after adjusting for the possible impact of these factors, with almost no change in the hazard ratio between univariate and multivariate Cox analyses. Moreover, it is unlikely that differences in access to care would be implicated in the higher incidence of HF among blacks in the current study because all patients received structured antihypertensive treatment in the LIFE study that achieved similar reductions in BP and ECG LVH in black and nonblack participants (Table 3).

**Study Limitations**

Several limitations of our study warrant review. First, use of Cornell product and Sokolow-Lyon voltage criteria to select patients for the LIFE study increased the baseline risk of the population and, as a consequence, our findings may not be representative of hypertensive populations with less severe disease or of other lower-risk populations. Second, use of hospitalization for HF to define new-onset HF almost certainly underestimates the true incidence of HF, potentially reducing the precision of the estimates. Third, there are potential biases involved in self-description of race and significant issues with using race/ethnicity as a surrogate for potential genetic and environmental factors that may more accurately reflect risk differences between subsets of populations. Fourth, there was a relatively small total number of black compared with nonblack patients, a small number of incident HF cases in blacks, and nonblack and black patients differed significantly with respect to a number of variables that may impact the development of HF. Although the relationship between race and incident HF persisted after adjustment for these potential confounders, multivariate analyses may not fully take into account the possible impact of these or other unmeasured confounders on this relationship, and the large number of variables relative to incident HF cases may limit the inferences that can be drawn from these findings. Finally, the small number of black patients in the LIFE echocardiography substudy who developed new HF precluded meaningful analysis of differences in LV structure and function between black and white patients who go on to develop HF. However, the greater LV mass and lower LV function as measured at the midwall among the overall subset of black patients with hypertension who underwent echocardiography at year 2 (Table 5) support the possibility that these differences may partly mediate the increased risk of HF among blacks with hypertension.

**Implications**

The findings demonstrate that black patients with hypertension with ECG LVH have a significantly higher incidence of hospitalization for HF than nonblack patients, independent of treatment allocation, HF risk factors, and the response of blood pressure and ECG LVH to treatment. Potential racial differences in LV structure and function over time demonstrated in the current and previous studies, taken together with possible genetic differences that correlate with the presence and severity of hypertension and LVH and with a measure of LV contractility, provide insights into a number of possible mechanisms that might in part account for these findings. However, the higher HF burden in blacks with hypertension emphasizes the importance of better understanding the impact of hypertension in this population and the need to develop better treatments to prevent or retard the development of HF. Further study is necessary to better define genetic, structural, and functional differences that lead to the increased incidence of HF in black patients with hypertension and to determine whether more accurately targeted therapies could decrease the risk of developing HF in black patients.
Disclosures
Dr Okin has no disclosures. Dr Kjeldsen has served as a consultant to Bayer, Boehringer-Ingelheim, and Takeda; received honoraria from Astra-Zeneca, Menarini, Sanofi-Aventis, Servier, and Takeda; and received grant support from the Norwegian government, Norwegian Council on Cardiovascular Diseases, European Society for Hypertension and Ulleval Hospital. Dr Dahlöf has served as a consultant to Novartis and Boehringer-Ingelheim; served on speakers' bureaus for Novartis, Boehringer-Ingelheim, Pfizer, Daiichi Sankyo, and MSD; and has an ownership interest in Mintage Scientific. Dr Devereux has served as a consultant to Merck & Co., Inc., Novartis, Sanofi-Aventis, Novo-Nordisk, and Clinsmart, and has received honoraria from Merck & Co., Inc.

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33. Devereux RB, Bella JN, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Morgan D, Paranicans M, Fishman D, Arnett DK. Left


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