Echocardiographic Left Ventricular Mass Index Predicts Incident Stroke in African Americans
Atherosclerosis Risk in Communities (ARIC) Study
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Background and Purpose—Despite theories that link stroke to left ventricular mass, few large, population-based studies have examined the predictive value of echocardiographically derived left ventricular mass index (LVMI) to incident stroke in African Americans.

Methods—Participants in the Jackson cohort of the Atherosclerotic Risk in Communities study have had extensive baseline evaluations, have undergone echocardiography during the third examination (1993–1995), and have been followed up for incident cardiovascular disease including ischemic stroke.

Results—The study population consisted of 1792 participants, of whom 639 (35.7%) were men and the mean±SD age was 58.8±5.7 years. Compared with those without ischemic stroke, those with ischemic stroke had a higher frequency of hypertension (85.6% vs 58.7%) and diabetes (46.9% vs 21.0%). Left ventricular hypertrophy was more prevalent in those with stroke (62.2% vs 38.6%). During a median follow-up of 8.8 years, 98 incident strokes occurred (6.5 per 1000 person-years). LVMI was independently associated with stroke after adjusting for age, sex, hypertension, systolic blood pressure, smoking, diabetes, total to HDL cholesterol ratio, body mass index, and low left ventricular ejection fraction (adjusted hazard ratio per 10 g/m² increment of LVMI = 1.15; 95% CI, 1.02 to 1.28). The relation remained statistically significant after adding left atrial size and mitral annular calcification to the multivariable model.

Conclusions—In this large, population-based African American cohort, we found that echocardiographic LVMI was an independent predictor of incident ischemic stroke even after taking into account traditional clinical risk factors. (Stroke. 2007;38:2686-2691.)

Key Words: African American ■ echocardiography ■ left ventricular mass ■ stroke

Cerebrovascular disease is the third leading cause of death in the United States and the most important single cause of severe disability in people living at home. African Americans experience a disproportionate burden from cerebrovascular disease, with an ~2-fold higher stroke incidence and mortality compared with whites. Racial disparities in stroke risk and mortality are even more pronounced in middle age. Echocardiographic left ventricular mass (LVM) is an independent predictor of cardiovascular morbidity and mortality and has been associated with stroke in non-Hispanic white populations. A recent large, prospective study has shown that regression of LVM with antihypertension medication predicts reduction of stroke risk independent of blood pressure (BP) reduction. Currently, the relation of LVM to incident ischemic stroke has not been well studied in African Americans. For this study, we hypothesized that LVM is an independent predictor of ischemic strokes in African Americans and that this association would remain after adjusting for both clinical and echocardiographic risk factors for LVM and stroke.

Methods

Study Design and Population
The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, population-based investigation of the predictors and outcomes of atherosclerosis in 4 US communities (Jackson, Miss; Forsyth County, NC; Washington County, Md; and the northwestern suburbs of Minneapolis, Minn) between 1987 and 1989. Detailed study procedures, including recruitment, study sampling, study design, and examination protocol for the ARIC study, have been reported previously. Echocardiograms were performed only in the Jackson cohort (mostly because of funding constraints) and were obtained during the third examination (visit 3) between 1993 and 1995.
Table 1. Characteristics of Participants by Quartile of LVMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile of LVMI, g/m²²</th>
<th>P Value for Trend Across Quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>16.2–38.9 (n=448)</td>
<td>16.2–38.9 (n=448)</td>
</tr>
<tr>
<td></td>
<td>57.8 (5.7)</td>
<td>58.8 (5.9)</td>
</tr>
<tr>
<td>Female, %</td>
<td>62.6</td>
<td>66.1</td>
</tr>
<tr>
<td>Current cigarette smoking, %</td>
<td>19.1</td>
<td>19.7</td>
</tr>
<tr>
<td>DM, %</td>
<td>13.2</td>
<td>19.0</td>
</tr>
<tr>
<td>Mean SBP, mm Hg (SD)</td>
<td>123 (16)</td>
<td>128 (17)</td>
</tr>
<tr>
<td>Mean DBP, mm Hg (SD)</td>
<td>74 (10)</td>
<td>76 (10)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>40.6</td>
<td>55.6</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>26.9 (4.6)</td>
<td>29.4 (5.2)</td>
</tr>
<tr>
<td>Mean total to HDL cholesterol ratio (SD)</td>
<td>3.8 (1.5)</td>
<td>4.0 (1.4)</td>
</tr>
<tr>
<td>Mean LDL cholesterol, mg/dL (SD)</td>
<td>123.4 (37.3)</td>
<td>128.8 (34.1)</td>
</tr>
<tr>
<td>Mean LA size, cm (SD)</td>
<td>36 (5)</td>
<td>38 (4)</td>
</tr>
<tr>
<td>Mitral annular calcification, %</td>
<td>3.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Low systolic ejection fraction, %</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Prevalent CHD/CHF, %</td>
<td>1.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Plaque/shadowing in any carotid site, %</td>
<td>30.6</td>
<td>26.4</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CHF, congestive heart failure.

*Low ejection fraction includes those participants with an ejection fraction <50%.

This study was approved by the institutional review board of the University of Mississippi Medical Center, and the subjects gave written, informed consent. The procedures followed were in accordance with institutional guidelines.

Echocardiography

Participants were examined by 2-dimensional and Doppler echocardiography on an Acuson 128XP/10c with 2.5-, 3.5-, and 5.0-MHz transducers. The quality control measures for echocardiography during the third examination have been previously described. In brief, echocardiograms were read by 1 cardiologist reader (T.N.S.). Intrasonographer and intersonographer and intrareader variabilities were assessed throughout the examination period. Intrasonographer and intersonographer and intrareader variabilities during the third examination have been previously described. In the current study, intrareader correlation for M-mode LVM was 0.98. Left ventricular internal diastolic diameter, left ventricular posterior wall thickness, and interventricular septal thickness were assessed in diastole on 2-dimensional echocardiograms according to the American Society of Echocardiography criteria. LVM was calculated according to the American Society of Echocardiography simplified cubed equation. LVM was indexed (LVMI) by height¹¹ to normalize heart size to body size.¹² Left ventricular hypertrophy (LVH) was defined as an LVMI of ≥51 g/m²² in both males and females.¹³

Clinical Covariates

Clinical covariates considered in this study included those that have been shown in previous investigations to potentially confound the relation between LVMI and ischemic stroke.¹⁷,¹⁸ Obesity was defined as a body mass index (BMI) ≥30 kg/m². Hypertension was defined on the basis of Joint National Committee VII guidelines (systolic blood pressure [SBP] of ≥140 mm Hg, a diastolic blood pressure [DBP] of ≥90 mm Hg, or the reported use of antihypertensive medications within 2 weeks before the visit). Diabetes mellitus (DM) was defined on the basis of American Diabetes Association guidelines: a fasting serum glucose value ≥126 mg/dL (7 mmol/L), use of diabetic medications within 2 weeks of the clinic visit, or a history of physician-diagnosed DM. The ratio of fasting serum total to HDL cholesterol concentrations was assessed with Roche enzymatic methods on a Cobas centrifuge analyzer (Hoffman–La Roche), with the laboratory certified by the Centers for Disease Control and Prevention—National Heart, Lung, and Blood Institute Lipid Standardization Program.

End Point

Data on stroke events occurring between the time of echocardiography (at ARIC visit 3) and December 31, 2003 were collected.¹² Details on quality assurance for identification and classification of ischemic stroke have been described elsewhere.¹ Potential ischemic stroke events were identified from self-reported hospitalizations obtained during the annual follow-up and from ongoing community-wide hospital surveillance.¹ A certified abstractor recorded, from hospital records signs and symptoms, whether the list of discharge diagnoses included a cerebrovascular disease code, whether a cerebrovascular condition or procedure was mentioned in the discharge summary, or whether a cerebrovascular condition or procedure was noted on a computed tomography or magnetic resonance imaging report. Cases were classified by computer algorithm and by a physician reviewer, according to criteria adapted from the National Survey of Stroke.¹² Disagreements between the algorithm and reviewer were adjudicated by a second physician reviewer.

Statistical Analysis

Patient characteristics by quartiles of LVMI and stroke event status are presented as mean±SD for continuous variables and percentages for categorical variables. To test for trend across LVMI quartiles, they were coded as an ordinal variable and the probability value for the parameter estimate for the ordinal variable examined in a linear model. For each LVMI quartile, crude stroke incidence rates were age adjusted by the direct method to the age distribution of the entire study sample; both crude and age-adjusted rates are expressed as events per 1000 person-years at risk. Age-adjusted rate ratios (with the lowest LVMI quartile as the reference group) were assessed for statistical significance in a Poisson regression model. Preliminary examination of the frequency of incident ischemic strokes by decile of LVMI showed that the frequency of incident strokes changed little from 0.47 g/m²² and then increased, suggesting a possible threshold in the relation between LVMI and stroke incidence. Therefore, in a secondary analysis, the relation between...
LVMI and incident ischemic stroke (taking follow-up time into account) was explored with several smoothing parametric and semiparametric methods. With each method, there was no evidence to support a nonlinear relation and no appearance of a threshold of LVMI above which the risk of stroke increased.

Cox proportional-hazards regression was used to adjust the relation of LVMI (as a continuous variable in 10-unit increments) to stroke incidence risk for baseline differences in the distribution of covariates. Results are expressed as hazard ratios (HRs) and 95% CIs. Covariates considered for inclusion in the regression models included age, sex, smoking status, DM, hypertension, SBP, DBP, BMI, total to HDL cholesterol ratio, serum LDL, prevalent coronary heart disease or congestive heart failure, low left ventricular ejection fraction, left atrial (LA) diameter, mitral annular calcification, and plaque/shadowing at any site on carotid ultrasound. The proportional-hazards assumption was evaluated graphically; no evidence was found that the proportional-hazards assumption had been violated. All statistical analyses were performed with SAS version 9.1 (SAS Institute).

Results

A total of 1792 participants had echocardiograms with technically adequate imaging to allow for accurate estimation of LVM. There were 639 (35.7%) men and 1153 (64.3%) women. The mean ± SD age was 58.8 ± 5.7 years. Compared with the group with echocardiographic measurements, the group with missing left ventricular measurements was slightly older and less healthy, with a higher mean BMI, total to HDL cholesterol ratio, and LDL cholesterol and a higher frequency of smoking, DM, hypertension, and prevalent coronary heart disease/congestive heart failure. Most of the group differences were not large, and we believe that the differences were not large, and we believe that the

Table 2. Characteristics of Participants With and Without Stroke Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke Event (n=1694)</th>
<th>Stroke Event (n=98)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>58.7 (5.7)</td>
<td>61.1 (6.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, %</td>
<td>65.0</td>
<td>53.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Current cigarette smoking, %</td>
<td>19.2</td>
<td>21.4</td>
<td>0.11</td>
</tr>
<tr>
<td>DM, %</td>
<td>21.0</td>
<td>46.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean SBP, mm Hg (SD)</td>
<td>131 (20)</td>
<td>143 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean DBP, mm Hg (SD)</td>
<td>77 (10)</td>
<td>80 (14)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>58.7</td>
<td>85.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>30.2 (6.1)</td>
<td>31.5 (6.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean total to HDL cholesterol ratio</td>
<td>3.97 (1.40)</td>
<td>4.41 (1.53)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean LDL cholesterol, mg/dL (SD)</td>
<td>125.8 (36.4)</td>
<td>131.5 (37.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean LA size, cm (SD)</td>
<td>3.86 (0.53)</td>
<td>4.05 (0.66)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral annular calcification, %</td>
<td>4.3</td>
<td>7.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Prevalent CHD/CHF, %</td>
<td>3.7</td>
<td>13.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plaque/shadowing in any carotid site, %</td>
<td>31.4</td>
<td>36.5</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean mean LA thickness, mm</td>
<td>12 (0.23)</td>
<td>13 (0.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean posterior wall thickness, mm</td>
<td>12 (0.20)</td>
<td>13 (0.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean left ventricular internal diameter, mm</td>
<td>46 (0.58)</td>
<td>48 (0.69)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean relative wall thickness, ratio</td>
<td>0.50 (0.12)</td>
<td>0.56 (0.18)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mean LVM, g/m²m (SD)</td>
<td>49.3 (15.1)</td>
<td>59.6 (21.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVH, %</td>
<td>38.6</td>
<td>62.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low ejection fraction, %</td>
<td>1.5</td>
<td>7.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CHF, congestive heart failure.

*Low ejection fraction include those participants with an ejection fraction of <50%.
†χ² test or t test, as appropriate.

Table 3. Crude and Age-Adjusted Incidence of Stroke by Quartiles of LVM

<table>
<thead>
<tr>
<th>Quartile of LVM</th>
<th>No. of Stroke Events</th>
<th>Crude Incidence of Stroke†</th>
<th>Age-Adjusted Incidence of Stroke†</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (16.2–38.9)</td>
<td>14</td>
<td>3.6</td>
<td>4.3</td>
<td>Reference</td>
</tr>
<tr>
<td>2 (38.9–47.5)</td>
<td>13</td>
<td>3.3</td>
<td>3.3</td>
<td>0.80</td>
</tr>
<tr>
<td>3 (47.5–58.2)</td>
<td>27</td>
<td>7.2</td>
<td>7.2</td>
<td>0.17</td>
</tr>
<tr>
<td>4 (58.2–140.7)</td>
<td>44</td>
<td>12.6</td>
<td>12.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P values comparing incidence rates by quartile of LVM with the first quartile as a reference.
†Crude and age-adjusted incidence rates for stroke are in units of 1000 person-years.
In the study population, LVH was highly prevalent (n=714; 39.8%). Table 1 shows the distribution of participants’ characteristics by quartiles of LVMI. LVMI was significantly associated with age, DM, SBP, DBP, hypertension, BMI, total to HDL cholesterol ratio, LA diameter, low left ventricular ejection fraction, and prevalent coronary heart disease and congestive heart failure.

There were a total of 98 incident ischemic strokes during a median follow-up period of 8.8 years. Table 2 displays the characteristics of participants with and without stroke. Compared with those without incident stroke, participants with incident stroke were more likely to be older (58.7 versus 61.1 years), male (35.0% versus 44.9%), hypertensive (58.7% versus 85.6%), diabetic (21.0% versus 46.9%), have a higher BMI (30.2 versus 31.5 kg/m2), have LVH (38.6% versus 62.2%), and have a low left ventricular ejection fraction (1.5% versus 7.1%) on echocardiograms.

During the follow-up period, the total incidence rate for ischemic stroke was 6.5 per 1000 person-years. Table 3 illustrates the crude and age-adjusted incidence rates by quartiles of LVMI. With the first quartile of LVMI as a reference, the age-adjusted incidence of stroke was increased in both the third and fourth quartiles, although only the fourth quartile rate was statistically significantly different from that of the first quartile. Table 4 displays the HR estimates for each 10 g/m2 increment in LVMI without and with adjustment for covariates. In the multivariable-adjusted hazard model, after adjusting for age, sex, hypertension, SBP, smoking, DM, total to HDL cholesterol ratio, BMI, prevalent coronary heart disease/congestive heart failure, and low left ventricular ejection fraction, LVMI was predictive of ischemic stroke events independent of significant clinical risk factors (HR per increment of LVMI=1.15; 95% CI, 1.03 to 1.28). LVMI remained significant after further adjustment for LA diameter, mitral annular calcification, and carotid artery plaque/shadowing (HR=1.17; 95% CI, 1.03 to 1.32).

Discussion
This investigation is the first multivariable analysis performed on a large African American population showing that LVMI on the echocardiogram is an independent predictor of ischemic stroke. LVMI remains significantly associated with incident ischemic stroke after adjusting for both clinical and echocardiographic risk factors.

Clinical Correlates of LVMI in African Americans
In our cohort, we found that age, DM, SBP, DBP, hypertension, BMI, total to HDL cholesterol ratio, LA diameter, and low left ventricular ejection fraction were significantly associated with LVMI. Echocardiographic LVMI in African Americans has previously been shown to be significantly associated with hypertension, BMI, and DM in earlier investigations. In the non-Hispanic white cohort of the Framingham Heart Study, investigators found similar associations between these clinical markers and echocardiographic LVMI.23,24 In the Coronary Artery Risk Development in Young Adults study, wherein the participants were much younger than our cohort (age 23 to 35 years), LVM was highly correlated with body weight, subscapular skinfold thickness, height, and SBP across race and sex subgroups. There was no significant association between LVMI and age, however.25

Association of Echocardiographic LVM With Stroke
In this longitudinal study of a African American cohort, the risk of stroke was associated with echocardiographic LVMI, even after adjusting for age, sex, hypertension, DM, current smoking, and total to HDL cholesterol ratio. These findings are similar to those for the non-Hispanic white cohort of the Framingham Heart Study and the elderly, predominantly non-Hispanic white cohort of the Cardiovascular Health Study.17,18 Recently, in the Hispanic cohort of the Northern Manhattan Study, LVMI was shown to be independently predictive of cardiovascular events according to a combined end point of myocardial infarction, stroke, or vascular death (adjusted HR=1.34 per SD change in LVMI; 95% CI, 1.10 to 1.63). However, this association was not statistically significant with stroke alone.26 The association between LVMI and incident stroke remained statically significant after adjusting for 2 other known echocardiographic correlates of stroke (LA size and mitral annular calcification). These findings are similar to those seen in the Framingham Heart Study.

The mechanism linking LVM to incident ischemic stroke is unclear. It has been suggested that individuals with LVH may be predisposed to ischemic stroke owing to the association of LVMI with LA enlargement. LA enlargement increases the risk of ischemic stroke by potentiating the formation of a clot in the atrial chamber that can result in thromboembolism. LA enlargement also predisposes to atrial arrhythmias, such as atrial fibrillation, that can result in ischemic stroke by increasing the risk of thromboembolism.18,27 Framingham Heart Study investigators found that LVM-height remained significantly associated with stroke even after excluding...
participants with atrial fibrillation and after adjusting for LA size in a multivariate model.\textsuperscript{18}

LVMI may be related to ischemic stroke through shared risk factors, including longitudinal exposure to elevated BP and obesity.\textsuperscript{18} The most important of these appears to be arterial hypertension. Both the brain and heart are potential end organs at risk for injury from longstanding hypertension.\textsuperscript{11,18,28,29} Risk factors other than hypertension, such as age, obesity, and prevalent coronary heart disease, have been shown in population-based studies to be associated with echocardiographic LVM and stroke.\textsuperscript{11,24,30–32} In the current study, the significance of the relation between LVMI and ischemic stroke was substantially attenuated by clinical and echocardiographic risk factors for stroke.

Increased LVM may reflect the presence of atherosclerosis and a predisposition for vascular events. LVMI has been found to be correlated with the severity of aortic atherosclerosis and wall thickness.\textsuperscript{37} Indeed, carotid disease has been found to parallel LVM after adjusting for conventionally measured BP.\textsuperscript{11,35}

Finally, it is postulated that the relation between LVM and atherosclerosis may derive from the impact of atherosclerotic disease on vascular stiffness.\textsuperscript{11,36,37} Increased vascular stiffness is thought to cause an increase in LVM when poorly compliant vessels reflect pressure waves back toward the central circulation, resulting in a late systolic rise in central arterial pressure. This increase in central arterial pressure is thought to occur without necessarily increasing peripheral (measured) SBP.

\textbf{Limitations}

In the current study, \textasciitilde27\% of participants with echocardiograms were excluded because of inadequate assessment of LVM. Adequate estimation of echocardiographic LVM may be hampered by several factors unique to the participant, including poor acoustic windows, obesity, and lung disease.

Another limitation is that atrial fibrillation was not adequately coded in the ARIC cohort to analyze for this study. Therefore, we were unable to assess the impact of this arrhythmia on the association between LVMI and incident stroke. Finally, the generalizability of results from this study to other ethnic populations is unclear.

\textbf{Conclusions}

In this first large, population-based cohort study of African Americans assessing the relation between echocardiographic LVMI and incident stroke, we found that echocardiographic LVMI is a strong and independent predictor of incident stroke, even after adjusting for established clinical risk factors, low ejection fraction, LA size, and mitral annular calcification. Further studies in the African American population are warranted to evaluate the efficacy of echocardiography and other noninvasive tools, such as cardiac magnetic resonance imaging, in the management and treatment of stroke through assessing changes in LVMI over time.

\textbf{Acknowledgments}

The authors thank the staff and participants of the ARIC study for their important contributions.

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\textbf{Disclosures}

None.

\textbf{References}


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