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The Predictive Value of Left Atrial Size for Incident Ischemic Stroke and All-Cause Mortality in African Americans:

The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background and Purpose—The association between left atrial (LA) size, ischemic stroke, and death has not been well established in African Americans despite their disproportionately higher rates of stroke and cardiovascular mortality compared to non-Hispanic whites.

Methods—For the analysis, participants in the Jackson cohort of the Atherosclerosis Risk in Communities Study were followed from the date of the echocardiogram in cycle three to the date of the first ischemic stroke event (or death) or to December 31, 2004 if no ischemic stroke event (or death) was detected.

Results—There were 1886 participants in the study population (mean age 58.9 years, 65% women). Participants in the top quintile of LA diameter indexed to height (LA diameter/height; 2.57 to 3.55 cm/m) were more likely women, hypertensive, diabetic, and obese compared to those not in the top quintile. Over a median follow-up of 9.8 years for ischemic stroke and 9.9 years for all-cause mortality, there were 106 strokes and 242 deaths. In a multivariable model adjusting for traditional clinical risk factors, the top quintile of LA diameter/height was significantly related to ischemic stroke (HR 1.7; 95% CI: 1.1, 2.7) and all-cause mortality (HR 2.0; 95% CI: 1.5, 2.7). After further adjustment for left ventricular (LV) hypertrophy and low LV ejection fraction, the top quintile remained significantly related to all-cause mortality (HR 1.8; 95% CI: 1.3, 2.5).

Conclusions—In this population-based cohort of African Americans, LA size was a predictor of all-cause mortality after adjusting for traditional cardiovascular risk factors, LV hypertrophy, and low LV ejection fraction.

Keywords

echocardiography; hypertension; risk factors

Stroke is the third leading cause of death and disability in the United States, and African Americans have an approximately 2-fold higher stroke incidence and mortality compared to non-Hispanic whites.[1–3] It has been noted that the identification and treatment of stroke risk factors has the largest impact on stroke morbidity and mortality.[4,5]

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Disclosures
None.

Echocardiography has proven to be a potentially useful noninvasive tool in identifying additional risk factors for stroke and all-cause mortality. Echocardiographic left ventricular (LV) mass and cardiac calcification have both been demonstrated to be risk factors for stroke.[6,7] The role of echocardiographic left atrial (LA) size has been more controversial, having been supported by some studies and negated by others.[8–11] Most of the studies investigating the prognostic value of echocardiographic LA size have been conducted in predominantly white populations; therefore, the risk associated with LA size in the African American population remains undefined despite this group's greater burden of disease. The aim of the current investigation is to evaluate the role of LA size as an independent risk factor for ischemic stroke and all-cause mortality in a large population-based cohort of African Americans. For this investigation, we hypothesized that echocardiographic LA size would be independently associated with ischemic stroke and all-cause mortality in African Americans after adjusting for both clinical and echocardiographic risk factors.

Methods

Study Population and Design

The study population for this investigation consisted of participants from the Jackson, MS cohort of the Atherosclerosis Risk in Communities (ARIC) study. 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. The design and procedures for the ARIC study have been reported previously.[12] Briefly, the ARIC Study is a prospective study begun in 1987 designed to investigate the cause and natural history of cardiovascular disease in 4 U.S. communities. At the Jackson, Mississippi, field center, only African Americans were recruited. During the third ARIC examination (visit 3 from 1993 to 1995), echocardiograms were performed only in the Jackson cohort (mostly because of funding constraints). A total of 2445 middle-aged and elderly African American men and women aged 51 to 70 years were examined.[12] For the analysis participants were excluded if they had: missing echo data, prevalent stroke, greater than mild mitral regurgitation, any aortic stenosis, any mitral stenosis, LV aneurysm, or missing covariate data.

Echocardiography Measurements

The quality control measures for echocardiography during the third examination have been previously described.[13] Briefly, 2-dimensional guided M-mode echocardiograms were performed with participants in the left lateral decubitus position. An Acuson XP128/10c echocardiography machine (Siemens Medical) was used for image acquisition using 2.5, 3.5, and 5.0 MHz transducers. Two-dimensional directed M-mode and pulsed Doppler echocardiographic examination followed a standardized protocol.

M-mode measurements were made from paper strip charts by use of the American Society of Echocardiography leading-edge-to-leading-edge convention at the time of the index examinations. LA diameter was measured at end systole and indexed to height (LA diameter/height).[14] LV mass was calculated according to the ASE simplified cubed equation.[15] LV mass was indexed by height^{2,7} to normalize heart size to body size.[16] LV hypertrophy was defined as a LV mass index of ≥51 g/m^{2,7} in males and females.[17]

LV systolic function was described in terms of the LV ejection fraction. The LV ejection fraction was derived semiquantitatively by the primary cardiologist using a modified Quinones technique and visual assessment of the LV apex. Low ejection fraction was defined as an ejection fraction <50%

Clinical Parameters

All clinical measurements were made at the time of the echocardiographic examination. Three blood pressure (BP) measurements were taken using a random-zero sphygmomanometer, and the average of the last 2 values was computed. Hypertension was defined based on JNC VII guidelines (systolic blood pressure [BP] of 140 mm Hg, or a diastolic BP of 90 mm Hg, or the reported use of antihypertensive medications within 2 weeks before the visit).[18] Diabetes was defined based on the American Diabetes Association guidelines: fasting serum glucose of ≥126 mg/dL (7 mmol/L) or nonfasting glucose of ≥200 mg/dL (11.1 mmol/L), or use of diabetic medications within 2 weeks of the clinic visit, or a history of physician-diagnosed diabetes.[19] Fasting serum total to high density lipoprotein (HDL) cholesterol concentrations were assessed with Roche enzymatic methods using a Cobras centrifuge analyzer (Hoffman-La Roche), with the laboratory certified by the CDC-NHLBI Lipid Standardization Program. Body mass index (BMI) was calculated as weight (kg)/height (m).[2] Smoking status, defined by self-report, was categorized into 2 levels (current, former/never).

End Points

Details on quality assurance for identification and classification of ischemic stroke are described elsewhere.[20] Potential ischemic stroke events were identified from self-reported hospitalizations obtained during the annual follow-up and from ongoing community-wide hospital surveillance.[21] A certified abstractor recorded from hospital records signs and symptoms if the list of discharge diagnoses included a cerebrovascular disease code, if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular condition or procedure was noted on a CT or MRI report.[21] Cases were classified by computer algorithm and by physician reviewer according to criteria adapted from the National Survey of Stoke.[22] Disagreements between the algorithm and reviewer were adjudicated by a second physician reviewer.

Death certificates were obtained for all death events. Causes of death had been coded using the rules of International Classification of Diseases 9th or 10th revision, wherever applicable. For out-of-hospital deaths, next of kin and other informants, certifying and family physicians, and coroners or medical examiners were contacted for information describing the circumstances of the death, timing of events, prior symptoms, and medical history. All-cause deaths were defined as deaths from any cause.

The follow-up period was defined as the time elapsed from the date of the echocardiographic examination to the date of the first ischemic stroke event (or the date of death for deaths) or to December 31, 2004 if no ischemic stroke event (or death) was detected. Those lost to follow-up were censored.

Statistical Analysis

Data are presented as mean±SD for continuous variables (median and 25th/75th percentile for triglycerides because of its skewed distribution) and percentages for categorical variables. A 2-sided probability value <0.05 was used as the cut point to assess statistical significance. In the absence of any established ranges or cut points for LA diameter/height, clinical and demographic characteristics were initially examined by quintile of LA diameter/height; thereafter, the bottom 4 quintiles (range: 1.29 to 2.56 cm/m), were grouped into one category and compared to the top quintile (range: 2.57 to 3.55 cm/m) and the results presented in Table 1. Clinical and demographic characteristics are also presented by incident stroke status (Table 2) and mortality status (Table 3). Crude stroke incidence and all-cause mortality rates by group of LA diameter/height were calculated using Poisson regression and are expressed as events per deaths per 1000 person-years at risk; age- and sex-adjusted rate

ratios were also calculated. Cox proportional hazards regression was used to adjust the relation of the top quintile of LA diameter/height to incidence/survival for baseline differences in the distribution of covariates. The proportional hazards assumption was evaluated graphically; there was no evidence of violation. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). Covariates considered for inclusion in the regression models included age, sex, systolic BP, smoking status, diabetes, total serum cholesterol:HDL ratio, triglycerides, BMI, LVH, and low LV ejection fraction. Interaction between LA diameter and sex and LA diameter and age were examined but the interaction terms were not statistically significant. All statistical analyses were performed using SAS version 9 (SAS Institute).

Results

Of the 2445 participants who obtained echocardiograms during the third examination of the ARIC study, 559 were excluded (481 with missing echo data, 70 with prevalent stroke, 20 with mitral regurgitation, 9 with aortic stenosis, 4 with mitral stenosis, 2 with LV aneurysm, and 1 with missing height). Therefore, the study population consisted of 1886 participants (mean age=58.9±5.7 years, 65% females). The study population had a lower mean age (58.9 years. versus 60.2 years, $P<0.0001$) and a lower percentage of participants with diabetes (22.8% versus 29.9%, $P=0.001$) but was otherwise very similar to the group of excluded persons. Table 1 shows the clinical and demographic characteristics of the study population by LA diameter/height. The participants in the top quintile of LA diameter/height (2.57 to 3.55 cm/m) were more likely women, hypertensive, diabetic, and had a higher mean body mass index (BMI) and systolic BP.

Over a median follow-up period of 9.8 years for ischemic stroke and 9.9 years for all-cause mortality, there were 106 incident ischemic strokes and 242 deaths. Tables 2 and 3 show the clinical and demographic characteristics related to incident ischemic stroke and to all-cause mortality, respectively. Participants with ischemic stroke were less likely women, were more likely hypertensive, diabetic, had a higher mean systolic BP, a higher total cholesterol:HDL ratio, and a higher triglycerides level compared to participants without ischemic stroke. Participants who died had a similar risk factor profile as those with ischemic stroke and in addition, were more likely current smokers compared to those who survived.

Table 4 shows the crude incidence rates and the age- and sex-adjusted rate ratios for ischemic stroke and all-cause mortality by group of LA diameter/height. Over the follow-up period for ischemic stroke, the crude stroke incidence rate was 6.1 per 1000 person-years. The incidence rate of ischemic stroke in participants in the top quintile of LA diameter/height was twice that, on average, of those participants in the lower 4 quintiles (incidence rate ratio [IRR] 2.1; 95% CI: 1.6, 2.9). Over the follow-up period for all-cause mortality, the crude incidence death rate was 13.2 per 1000 person-years. Similar to the results with incident ischemic stroke, the incidence rate for all-cause mortality in participants in the top quintile of LA diameter/height was twice the rate, on average, as those in the lower 4 quintiles (IRR 2.0; 95% CI: 1.4, 2.9).

Table 5 displays the hazard ratio estimates for ischemic stroke and all-cause mortality by group of LA diameter/height with and without adjustment for clinical and echocardiographic covariates. LA diameter was associated with ischemic stroke in the age- and sex-adjusted model (HR 2.1; 95% CI 1.4, 3.2) and in the multivariable model adjusting for age, sex, systolic BP, smoking, diabetes, total cholesterol:HDL ratio, triglycerides, and BMI (HR 1.7; 95% CI 1.1, 2.7). This relation was attenuated after further adjusting for echocardiographic LV hypertrophy and low LV ejection fraction and did not reach statistical significance ($P=0.09$).

LA diameter/height was associated with all-cause mortality in both the multivariable model after adjustment for clinical risk factors (HR 2.0; 95% CI 1.5, 2.7) and in the expanded multivariable model with further adjustment for LV hypertrophy and low LV ejection fraction (HR 1.8; 95% CI 1.3, 2.5).

In a secondary analysis, using LA diameter/height as a continuous variable, similar results were obtained for all-cause mortality using both the multivariable model adjusting for clinical risk factors only (HR 1.7; 95% CI 1.14, 2.66) and in the expanded model (HR 1.6; 95% CI 1.02, 2.43).

Discussion

Principal Findings

In this large population-based cohort of African Americans, over a follow-up period of almost 10 years, LA diameter/height was significantly associated with incident ischemic stroke and all-cause mortality after adjusting for clinical risk factors. Further adjustments for echocardiographic LV hypertrophy and low LV ejection fraction attenuated the relation of LA diameter to both ischemic stroke and all-cause mortality; however, the relation to all-cause mortality remained significant.

Relation of LA Size to Stroke and Mortality in Other Population-Based Cohorts

Despite extensive study, it remains unclear whether LA enlargement is an independent risk factor for stroke.[8,11,23–26] Few investigators have looked at this relation prospectively in a large population-based cohort of African Americans.[5,27,28] Our findings in the ARIC study were somewhat similar to those in the predominant non-Hispanic white cohort of the Framingham Heart Study (FHS) and in the multi-ethnic population of the Northern Manhattan Stroke Study (NOMASS).[5,27] FHS investigators found that LA size remained a significant predictor of stroke in men and death in both sexes after adjusting for age, hypertension, diabetes, smoking, ECG LV hypertrophy, prevalent atrial fibrillation, and prevalent congestive heart failure or myocardial infarction. Similar to our study, in FHS investigators found that LV mass partially attenuated the attributable risk of stroke and death attributable to LA size.[27] In NOMASS (a population-based case-control design), investigators also found that LA size was associated with an increased risk of ischemic stroke. In NOMASS the relation between LA size and stroke remained high despite adjusting for the echocardiographic LV hypertrophy. In the subgroup analysis assessing the effect of ethnicity on the relation of LA size and stroke, investigators showed that after adding echocardiographic LV hypertrophy to the multivariable model in any of the three racial subsets (African American, white, or Hispanic) the relation was no longer significant.[5] This may have been a result of a smaller sample size; however, in our study of a large cohort of African Americans the relation of LA size to stroke was similarly attenuated after the addition of echocardiographic LV hypertrophy and low LV ejection fraction to the model. It is unclear in our cohort, however, to what degree the smaller number of stroke events may have impacted the change in the results with the addition of LV hypertrophy into the model. Notably, the attenuation attributable to adding echocardiographic covariates into the model did not have as strong an impact on the relation of LA size to all-cause mortality where the number of events was substantially higher than that of stroke.

Mechanism Relating LA Size to Stroke and All-Cause Mortality

Several theories have been proposed in an attempt to explain the mechanism underlying the relation between LA size and subsequent morbidity.[7,27] One potential explanation is that blood stasis and thrombus formation might occur more often as the size of the LA increases.[27] Supporting this theory, increases in LA size occur as a result of elevated

intraatrial pressure. It has been shown that with elevated pressures, flow velocity in the LA appendage decreases resulting in an increased risk for thrombus formation and potential for embolic stroke.[5,27,29,30]

Other theories are that LA size may serve as a strong risk factor for the development of atrial fibrillation, which is a well-established risk factor in the literature for both embolic stroke and mortality.[5,27] Additionally, LA enlargement may serve as a marker for structural heart disease, hypertension, or increased LV mass and thereby be related to increased risk for stroke and mortality. Supporting the latter theory, in our analysis we showed that after adjusting for LV hypertrophy and low LV ejection fraction in the multivariable model, the relation between LA size and both incident stroke and mortality is attenuated. Even if LA size is merely a biological marker for hypertensive heart disease, LA size may serve as a useful clinical predictor given the greater difficulty in measuring LV mass. Finally, LA enlargement may serve as a surrogate for other unidentified risk factors for incident stroke and death.[27]

Limitations

The major limitation of this study is that atrial fibrillation was not adequately coded in the ARIC cohort to analyze in this study. Therefore, we were unable to assess the impact of this arrhythmia on the association between LA size and incident stroke and mortality in this high-risk group. Additionally, because of the low number of known cardiovascular deaths, there was insufficient power to assess the relation of LA size to cardiovascular mortality.

LA volume is a more accurate measurement of LA size, however this measure was not used in the current analysis because needed images for volume measures were not obtained at the time the echocardiogram was acquired. It is unclear how our results would have been affected by an analysis on LA volume. Also, the generalizability of our results to other ethnic populations is unclear.

Conclusions

This is the first study of a large prospective population-based cohort of African Americans analyzing the association between LA size, stroke, and all-cause mortality. We found that LA size was associated with many cardiovascular risk factors for stroke and death; and after adjusting for age, sex, systolic BP, smoking, diabetes, total cholesterol:HDL ratio, and BMI, LA size remained a significant predictor of both ischemic stroke and all-cause mortality. LA size remained predictive of all-cause mortality after adjusting for echocardiographic LV hypertrophy and low LV ejection fraction. Our findings support the concept that LA size may serve as a significant and useful clinical predictor.

Though strategies for prevention of stroke and death in the setting of LA enlargement remain to be determined, echocardiographic LA enlargement commonly found in hypertensive patients with electrocardiographic LV hypertrophy is known to be reversed by antihypertensive therapy.[31] It remains to be seen whether the drugs that are effective for reduction of LA size confer benefit over and above that associated with reduction of blood pressure and LV mass in reducing the risk of stroke and all-cause mortality in patients with LA enlargement.

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Table 1

Characteristics of Study Population by LA Diameter/Height

Characteristic	Bottom Four Quintiles LA Diameter/Height (1.29–2.56 cm/m) (n = 1509)	Top Quintile LA Diameter/Height (2.57–3.55 cm/m) (n = 377)	*P* Value†
Mean age, y (SD)	58.8 (5.7)	59.3 (5.7)	0.16
Female, %	62.7	74.3	<0.0001
Current cigarette smoking, %	20.3	17.1	0.35
Diabetes, %	21.3	29.1	0.001
Hypertension, %	57.5	74.3	<0.0001
Mean SBP, mm Hg (SD)	130 (20)	138 (22)	<0.0001
Mean DBP, mm Hg (SD)	77 (11)	78 (11)	0.09
Mean BMI (SD)	29.4 (5.7)	34.6 (6.7)	<0.0001
Mean total chol:HDL ratio (SD)	4.00 (1.47)	4.05 (1.23)	0.47
Median triglycerides, mg/dL (Q1, Q3)	99.4 (73.9, 136.9)	101.9 (75.9, 129.9)	0.15
Mean LA diameter/height, cm/m (SD)	2.19 (0.24)	2.78 (0.18)	<0.0001
LV hypertrophy %	26.5	61.1	<0.0001
Low LV ejection fraction (<50%)	0.9	4.5	<0.0001

† χ^2 test or *t* test, as appropriate.

Values are percentages or means (SD); for triglycerides the median (1st and 3rd quartiles) is given because of skewness of its distribution.

LA diameter/height indicates left atrial diameter indexed to height; SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; LV, left ventricular.

Table 2

Characteristics of Participants With and Without Ischemic Stroke

Characteristic	No Ischemic Stroke (n = 1780)	Ischemic Stroke (n = 106)	*P* Value[†]
Mean age, y (SD)	58.8 (5.7)	60.5 (5.9)	0.004
Female, %	65.7	52.8	0.007
Current cigarette smoking, %	19.5	21.7	0.18
Diabetes, %	21.4	46.7	<0.0001
Hypertension, %	59.4	85.7	<0.0001
Mean SBP, mm Hg (SD)	131 (20)	144 (23)	<0.0001
Mean DBP, mm Hg (SD)	77 (11)	81 (13)	0.001
Mean BMI (SD)	30.3 (6.2)	31.5 (6.5)	0.07
Mean total chol:HDL ratio (SD)	3.98 (1.42)	4.47 (1.51)	0.001
Median triglycerides, mg/dL (Q1, Q3)	98.9 (73.9, 134.9)	115.9 (93.9, 168.9)	0.002
Mean LA diameter/height, cm/m (SD)	2.30 (0.32)	2.38 (0.36)	0.02
LV hypertrophy %	32.3	51.9	<0.0001
Low LV ejection fraction (<50%)	1.4	5.7	0.001

[†] χ^2 test or *t* test, as appropriate.

Values are percentages or means (SD); for triglycerides the median (1st and 3rd quartiles–Q1, Q3) is given because of skewness of its distribution.

LA diameter/height indicates left atrial diameter indexed to height; SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; LV, left ventricular.

Table 3

Characteristics of Participants by Survival Status

Characteristic	Survived (n = 1644)	Died (n = 242)	*P* Value†
Mean age, y (SD)	58.6 (5.6)	61.1 (5.8)	<0.0001
Female, %	66.8	52.9	<0.0001
Current cigarette smoking, %	17.7	32.9	<0.0001
Diabetes, %	20.7	37.7	<0.0001
Hypertension, %	58.9	74.2	<0.0001
Mean SBP, mm Hg (SD)	131 (20)	138 (25)	<0.0001
Mean DBP, mm Hg (SD)	77 (11)	77 (12)	0.35
Mean BMI (SD)	30.4 (6.1)	30.3 (7.3)	0.75
Mean total chol:HDL ratio (SD)	3.96 (1.36)	4.35 (1.80)	0.001
Median triglycerides, mg/dL (Q1, Q3)	98.9 (73.9, 132.9)	108.9 (78.9, 158.9)	0.005
Mean LA diameter/height, cm/m (SD)	2.30 (0.32)	2.36 (0.39)	0.03
LV hypertrophy, %	32.0	43.0	0.001
Low LV ejection fraction (<50%)	0.7	7.9	<0.0001

† χ^2 test or *t* test, as appropriate.

Values are percentages or means (SD); for triglycerides the median (1st and 3rd quartiles) is given because of skewness of its distribution.

LA diameter/height indicates left atrial diameter indexed to height; SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; LVH, left ventricular.

Table 4

Incidence of Ischemic Stroke and All-Cause Mortality by LA Diameter/Height

LA Diameter/Height (cm/m)	No. of Events	*Crude Event Rate	Age- and Sex-Adjusted Rate Ratio (95% CI)	Rate Ratio *P* Value†
Stroke				
Bottom four quintiles (1.29–2.56 cm/m)	73	5.1	…(ref.)	
Top quintile (2.57–3.55 cm/m)	33	10.1	2.1 (1.6, 2.9)	<0.0001
Total	106	6.1		
Death				
Bottom four quintiles (1.29–2.56 cm/m)	167	11.4	…(ref.)	
Top quintile (2.57–3.55 cm/m)	75	21.3	2.0 (1.4, 2.9)	0.0003
Total	242	13.2		

*Crude event rates describe No. of events per 1000 person-years.

†In a Poisson regression model.

LA diameter/height indicates left atrial diameter indexed to height.

Table 5

Relation of LA Diameter/Height to Ischemic Stroke and All-Cause Mortality

Events	Hazard Ratio (95% CI) Associated With Top Quintile of LA Diameter/Height (2.57–3.55 cm/m) [Reference Group–Bottom Four Quintiles]	Hazard Ratio *P* Value
Stroke		
Age and sex adjusted	2.1 (1.4, 3.2)	0.001
Multivariable adjusted (1)†	1.7 (1.1, 2.7)	0.02
Multivariable adjusted (2)¶	1.5 (0.9, 2.4)	0.09
Deaths		
Age and sex adjusted	2.1 (1.6, 2.7)	<0.0001
Multivariable adjusted (1)†	2.0 (1.5, 2.7)	<0.0001
Multivariable adjusted (2)¶	1.8 (1.3, 2.5)	0.0001

†Multivariable model (1): adjusts for age, sex, and the following clinical covariates: systolic BP, smoking, diabetes, total cholesterol:HDL ratio, triglycerides, and BMI.

¶Multivariable model (2): model (1)+LV hypertrophy+low LV ejection fraction.

LA diameter/height indicates left atrial diameter indexed to height.