Left Atrial Size and the Risk of Ischemic Stroke in an Ethnically Mixed Population

Marco R. Di Tullio, MD; Ralph L. Sacco, MD; Robert R. Sciacca, EngScD; Shunichi Homma, MD

Background and Purpose—The association between left atrial size and ischemic stroke is controversial and has been suggested to exist only in men and to be mediated by left ventricular mass. Data are available almost exclusively for white patients. The purpose of this study was to evaluate the association between left atrial size and ischemic stroke in a multiethnic population.

Methods—A population-based case-control study was conducted in 352 patients aged >39 years with first ischemic stroke and in 369 age-, gender-, and race-ethnicity–matched community controls. Left atrial diameter was measured by 2-dimensional transthoracic echocardiography and indexed by body surface area. Conditional logistic regression analysis was performed to assess the risk of stroke associated with left atrial index in the overall group and in the age, gender, and race-ethnic strata after adjustment for the presence of other stroke risk factors.

Results—Left atrial index was associated with ischemic stroke in the overall group (adjusted OR 1.47 per 10 mm/1.7 m² of body surface area; 95% CI 1.03 to 2.11). The association was present in men (adjusted OR 2.81, 95% CI 1.42 to 5.57) but not in women (adjusted OR 1.08, 95% CI 0.70 to 1.66), and in patients aged <60 years (adjusted OR 3.78, 95% CI 1.36 to 10.54) but not >60 years (adjusted OR 1.23, 95% CI 0.84 to 1.81). Subgroup analyses showed the risk to be present in men across all age subgroups. In women, the lack of association between left atrial index and stroke was most strongly influenced by left ventricular hypertrophy. A trend toward an association between left atrial index and stroke was observed in whites (adjusted OR 1.81, 95% CI 0.81 to 4.09) and Hispanics (adjusted OR 1.61, 95% CI 0.98 to 2.65) but was less evident in blacks (adjusted OR 1.25, 95% CI 0.74 to 2.14).

Conclusions—Left atrial enlargement is associated with an increased risk of ischemic stroke after adjustment for other stroke risk factors, including left ventricular hypertrophy. The association is observed in men of all ages, whereas in women it is attenuated by other factors, especially left ventricular hypertrophy. Interracial differences in the stroke risk may exist that need further investigation. (Stroke. 1999;30:2019-2024.)

Key Words: cerebrovascular disorders n cardioembolic stroke n echocardiography

Stroke is one of the leading causes of death and disability in the United States, with an incidence estimated at over 600,000 new cases per year. The identification and treatment of stroke risk factors is likely to have the biggest impact on stroke morbidity and mortality. Among the potential risk factors for ischemic stroke, the role of an increased atrial size has been controversial, having been supported by some studies and negated by others. Most of these studies, however, were conducted in patients with mitral valve disease or atrial fibrillation, so that the independent contribution of an increased atrial size to the risk of stroke in patients without those conditions was difficult to evaluate. Recently, prospective data from the Framingham study indicated that left atrial enlargement was a risk factor for ischemic stroke only in men and that the association appeared to be at least partially mediated by left ventricular mass. That study, however, was conducted in a white population over the age of 50; therefore, the risk of stroke associated with left atrial enlargement in younger patients and in different race-ethnic groups remained undefined.

The aim of the present community-based case-control study was to evaluate the role of left atrial enlargement as an independent risk factor for ischemic stroke in the multiethnic population enrolled in the Northern Manhattan Stroke Study (NOMASS).

Subjects and Methods

Study Population
The patient population of the present study was drawn from the Northern Manhattan Stroke Study (NOMASS), a community-based epidemiological study aimed at assessing stroke incidence, risk factors, and prognosis in the multiethnic population of Northern Manhattan. In 1990, nearly 260,000 people lived in the region, with 40% over the age of 39. The race-ethnic distribution in this...
Prospective case surveillance consisted of daily screening of all admissions, discharges, and head CT scan logs at the Presbyterian Hospital in the city of New York, the only hospital in the community, where approximately 80% of all patients in Northern Manhattan with cerebral infarction are hospitalized.

Community controls were eligible if they (1) had never been diagnosed with a stroke, (2) were aged $\geq 39$ years, and (3) had resided in Northern Manhattan for at least 3 months in a household with a telephone. Stroke-free subjects were identified by random-digit dialing, which used dual frame sampling to identify both published and unpublished telephone numbers. Control subjects were individually matched to stroke patients by age (within 5 years), gender, and race-ethnicity.

Data were collected through interview of the cases and controls by trained research assistants, review of the medical records, and neurological examination by the study physicians, in-person measurements, and fasting blood specimens for lipid and glucose metabolism. Data were obtained directly from study subjects with the standardized data collection instruments. If the subject was unable to answer questions because of death, aphasia, coma, demencia, or other conditions, a proxy who was knowledgeable about the patient’s history was interviewed. Stroke-free controls were interviewed in person and evaluated in the same manner as cases. Cases were interviewed as soon as possible after their stroke, within a median time of 4 days from stroke onset.

As a part of NOMASS, 384 patients with first ischemic stroke who were aged $\geq 39$ years and 405 stroke-free control subjects underwent 2-dimensional transthoracic echocardiography from June 1993 through December 1996. Written informed consent to participate in the study was obtained from all subjects. The study was approved by the Institutional Review Board of Columbia–Presbyterian Medical Center.

Diagnostic Evaluation
Stroke risk factors were collected by direct interview or medical record review in all case patients and control subjects. Routine laboratory tests included complete blood counts, coagulation studies, serum electrolytes, liver function tests, and glucose and cholesterol determination. Arterial hypertension was defined as the presence of a positive history or antihypertensive treatment, or blood pressure values $\geq 160$ mm Hg (systolic) or $\geq 95$ mm Hg (diastolic) during the interview. Hypercholesterolemia was defined as a total serum cholesterol $\geq 200$ mg/dL or the presence of appropriate drug treatment. Diabetes mellitus was defined on the basis of abnormal fasting blood sugar, positive history, or the presence of oral or insulin treatment. Coronary artery disease included history of myocardial infarction or typical angina, the presence of a positive diagnostic test (stress test or coronary angiography), or drug treatment. The presence of atrial fibrillation had to be documented on a current or past ECG or Holter monitoring. A diagnosis of congestive heart failure was made on the basis of clinical signs, symptoms, and/or anti-failure treatment. The diagnosis of ischemic stroke was confirmed in all cases by means of head CT or MRI. The cardiac evaluation included 12-lead ECG and 2-dimensional color-Doppler transthoracic echocardiography.

Echocardiographic Evaluation
Transthoracic echocardiography was performed in all study subjects with Hewlett-Packard Sonos 1000 and 2500 ultrasound equipment (Hewlett-Packard Imaging Systems Division). Studies were performed and measurements taken according to the guidelines of the American Society of Echocardiography. In particular, left atrial anteroposterior diameter was measured at the level of the aortic valve according to a leading edge-to-leading edge convention. The diameter was then normalized by the subject’s body surface area. The left atrial index thus obtained was used in the data analysis. Left ventricular hypertrophy was considered to be present when the interventricular septum or posterior wall thickness was $\geq 12$ mm (75th percentile of the control group). The interpretation of the echocardiographic studies was blinded to case-control status and other clinical characteristics.

Statistical Analysis
Data were reported as mean $\pm$SD for continuous variables and as frequency for categorical variables. Differences between proportions were assessed by the $\chi^2$ test, replaced by the Fisher exact test when the expected cell count was $<5$. Differences between mean values were assessed by unpaired Student’s $t$ test. A 2-tailed $P$ value of $0.05$ was considered significant.

Univariate and multivariate conditional logistic regression analysis (PROC PHREG, SAS statistical package, version 6.12; SAS Inc) was used to test the association between left atrial index (independent variable) and ischemic stroke (dependent variable). Unadjusted ORs for the association between left atrial index and ischemic stroke were calculated for the entire study group and for age, gender and race-ethnic subgroups.

Multivariate analysis was used to determine the adjusted OR for left atrial index after other established stroke risk factors were entered as potential confounding factors in the model. Variables significantly associated with ischemic stroke by univariate analysis (arterial hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure, and left ventricular hypertrophy) were entered as independent variables in the model. Mitral regurgitation was also added to the model because of its relevance to the size of the left atrium. Cigarette smoking was entered into the model even though not significantly associated with ischemic stroke in the entire group because of its biological relevance and because of a statistically significant association with stroke in some race-ethnic subgroups.

To assess the effect of age (40 to 59 years, $\geq 60$ years), gender, and race-ethnicity on the association between left atrial index and stroke, separate variables were fit in the model to quantify the effect of left atrial index independently for each strata. Differences between strata were tested with Wald’s $\chi^2$. An additional analysis was performed to test the age-gender interaction. Adjusted ORs and 95% CIs were calculated from the beta coefficients and the standard errors.

Results
The present report is based on 352 stroke patients (92% of the total) and 369 control subjects (91%) in whom all morphological and echocardiographic variables required for the study could be obtained. Demographics of the study population are shown in Table 1. Nineteen percent of subjects were white (64 cases, 68 controls), 29% black (99 cases, 111 controls), and 52% Hispanic (184 cases, 185 controls). Stroke risk factors in the entire study group and in the various race-ethnic subgroups are listed in Table 2. Arterial hypertension and cardiac risk factors (atrial fibrillation, coronary artery disease, congestive heart failure, echocardiographically determined left ventricular hypertrophy) were significantly associated with ischemic stroke in all race-ethnic subgroups, while interracial differences existed for diabetes mellitus and ciga-

### TABLE 1. Demographics of the Study Group

<table>
<thead>
<tr>
<th></th>
<th>Stroke Patients (n=352)</th>
<th>Control Subjects (n=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Men/Women</strong></td>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Overall group</td>
<td>68.8±11.6</td>
<td>167/185</td>
</tr>
<tr>
<td>Whites</td>
<td>75.8±12.0</td>
<td>34/30</td>
</tr>
<tr>
<td>Blacks</td>
<td>70.1±10.4</td>
<td>33/66</td>
</tr>
<tr>
<td>Hispanics</td>
<td>65.8±11.1</td>
<td>95/89</td>
</tr>
</tbody>
</table>

*Values are mean $\pm$SD years.
nette smoking. Elevated serum cholesterol was not found to be significantly associated with stroke. Among the variables possibly associated with left atrial size, the presence of mitral regurgitation of any degree was significantly more frequent in stroke patients than in control subjects (36.4% versus 29.2%; \( P \leq 0.04 \)); moderate or severe mitral regurgitation was also significantly more frequent in stroke patients (8% versus 3%; \( P \leq 0.003 \)).

Sixteen percent of strokes were considered to be atherosclerotic or atheroembolic in origin, 19% were considered cardioembolic, 23% small vessel lacunar, and 5% from other causes. The remaining 37% of strokes were considered cryptogenic.

**Left Atrial Dimension and Risk of Ischemic Stroke**

Mean left atrial anteroposterior diameter was 40.5±6.3 mm in stroke patients and 38.4±4.9 mm in control subjects \( (P<0.001) \). Mean left atrial index (left atrial diameter/body surface area) was 23.1±4.0 and 21.8±3.3 mm/m\(^2\) \( (P<0.001) \), respectively.

An increased left atrial index was found to be associated with ischemic stroke in the entire study group, both at univariate analysis and after adjusting for other stroke risk factors (Table 3). The unadjusted odds ratio was 1.97 (95% CI 1.48 to 2.62) per each 10-mm increase in left atrial index.

**Effect of Age, Gender, and Race-Ethnicity**

Table 3 also summarizes the stroke risk associated with an increased left atrial index in gender, age, and race-ethnic subgroups. A significant association was observed in men and in patients between the ages of 40 and 59, but not in women or in the older age subgroup. The difference in effect between age groups was statistically significant \( (P<0.05) \), as was the difference between genders \( (P<0.05) \). Among different race-ethnic subgroups, a trend toward an association between left atrial index and stroke was observed in whites and Hispanics, although it did not achieve independent statistical significance in the multivariate analysis, possibly due to the smaller number of subjects in each subgroup. No definite association was found between left atrial index and stroke risk factor distribution in the entire study group and by race-ethnicity.

**TABLE 2. Stroke Risk Factor Distribution in the Entire Study Group and by Race-Ethnicity**

<table>
<thead>
<tr>
<th></th>
<th>Entire Group, %</th>
<th>Whites, %</th>
<th>Blacks, %</th>
<th>Hispanics, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>( P )</td>
<td>Cases</td>
</tr>
<tr>
<td>Hypertension</td>
<td>69</td>
<td>56</td>
<td>0.001</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32</td>
<td>15</td>
<td>0.001</td>
<td>16</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>21</td>
<td>16</td>
<td>0.1</td>
<td>3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11</td>
<td>3</td>
<td>0.001</td>
<td>22</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>60</td>
<td>36</td>
<td>0.001</td>
<td>65</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>37</td>
<td>20</td>
<td>0.001</td>
<td>55</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>15</td>
<td>5</td>
<td>0.001</td>
<td>19</td>
</tr>
</tbody>
</table>

**TABLE 3. Association Between Left Atrial Index and Ischemic Stroke in the Entire Study Group and by Gender, Age, and Race-Ethnicity**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR* (95% CI)</th>
<th>Adjusted OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire group</td>
<td>1.97 (1.48–2.62)</td>
<td>1.47 (1.03–2.11)</td>
</tr>
<tr>
<td>Men</td>
<td>2.91 (1.77–4.79)</td>
<td>2.81 (1.42–5.57)</td>
</tr>
<tr>
<td>Women</td>
<td>1.56 (1.10–2.22)</td>
<td>1.08 (0.70–1.66)</td>
</tr>
<tr>
<td>Aged 40–59 y</td>
<td>2.83 (1.39–5.76)</td>
<td>3.78 (1.36–10.54)</td>
</tr>
<tr>
<td>Aged ≥60 y</td>
<td>1.81 (1.32–2.47)</td>
<td>1.23 (0.84–1.81)</td>
</tr>
<tr>
<td>White</td>
<td>2.56 (1.29–5.06)</td>
<td>1.81 (0.81–4.09)</td>
</tr>
<tr>
<td>Black</td>
<td>1.56 (0.96–2.53)</td>
<td>1.25 (0.74–2.14)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.13 (1.39–3.29)</td>
<td>1.61 (0.98–2.65)</td>
</tr>
</tbody>
</table>

*Odds ratios are per each 10 mm/1.7 m\(^2\) of body surface area.
†Adjusted for arterial hypertension, diabetes mellitus, cigarette smoking, atrial fibrillation, coronary artery disease, congestive heart failure, left ventricular hypertrophy, and presence of mitral regurgitation.

Association between left atrial (LA) index and ischemic stroke. ORs for the second, third, and fourth quartiles of left atrial index are relative to the first quartile. Quartile cutoffs were 20.5 (first), 22.4 (second), 24.8 (third), and >24.8 (fourth).
Discussion

The present study demonstrates that an increased left atrial diameter is associated with an increased risk of ischemic stroke, even after adjustment for the presence of other established stroke risk factors. A significant association was observed after adjustment for the presence of atrial fibrillation and congestive heart failure, 2 other potential confounders of the association between left atrial size and stroke. Although the mechanism of the increased risk is unclear, some potential explanations can be suggested. Left atrial enlargement has been shown to be a strong risk factor for the development of atrial fibrillation, and a more frequent occurrence of undetected episodes of paroxysmal atrial fibrillation might contribute to the increased stroke risk. Another possible explanation could be that blood stasis and thrombus formation might occur more often as the size of the left atrium increases. An increased atrial size may be the result of an elevated intraatrial pressure, which has been shown to decrease the flow velocity in the left atrial appendage and therefore increase the likelihood of thrombus formation and hence the embolic risk. Another potential hemodynamic determinant of left atrial enlargement, the presence of mitral regurgitation, was included as an independent variable in the multivariate analysis, and its effect was therefore factored in the risk estimates. Because the study did not include transesophageal echocardiography, we could not investigate the relationship between atrial size and atrial appendage flow velocity and thrombus frequency. The analysis of this relationship and its possible contribution to explaining the association between left atrial size and stroke deserves further investigation.

Effect of Gender, Age, and Race-Ethnicity

Considerable gender differences in the association between left atrial size and stroke risk were observed in our study, with a significant risk excess observed in men but not in women. This confirms the observations of the Framingham Study, which detected an increased risk of stroke associated with left atrial enlargement in men only. In that study, the association with ischemic stroke was largely mediated by left ventricular mass. In our study, the association between left atrial size and stroke did not appear to be mediated by the presence of left ventricular hypertrophy in the overall group, because it persisted after adjustment for the presence of echocardiographically determined hypertrophy. However, a separate analysis in women revealed that left ventricular hypertrophy was the most important variable in explaining the attenuation of the stroke risk observed in the multivariate analysis, whereas its effect on risk estimates was modest in men. This observation suggests that the stroke risk associated with left atrial enlargement may be mediated by left ventricular mass to a greater extent in women than in men. Gender differences in the role of left ventricular hypertrophy as a cardiovascular risk factor have been reported in the past, with a greater impact on total and cardiac death observed in women than in men.

Age differences in the stroke risk associated with an increased left atrial size were also observed in our study, with the younger group being at higher risk than the older group. The weaker role played by left atrial enlargement in the older subgroup may be a reflection of the relatively greater contribution of other conventional stroke risk factors. This appeared to be especially true for left ventricular hypertrophy in women, the effect of which erased any association between left atrial size and stroke risk in the older subgroup.

Left atrial enlargement tended to be associated with ischemic stroke in whites and Hispanics, although the relatively small number of subjects in each subgroup did not allow for the achievement of independent statistical significance. The weaker association observed in blacks may be explained at least in part by the greater proportion of women in that race-ethnic subgroup. The consistency of the OR observed in
whites and Hispanics despite differences in the distribution of stroke risk factors appears to further support the existence of an independent effect of left atrial size on the risk of stroke.

Comparison With Previous Studies
The results of the present study are related to similar observations from the Framingham study,19 which described a significant association between left atrial size and the risk of stroke in men and the risk of death in both genders. Such association was attenuated by adjustment for ECG-derived left ventricular mass/height. Although differences in the study design (case-control versus prospective) and subject characteristics prevent a direct comparison of the results, the present study suggests a stronger independent effect of left atrial size on the stroke risk even after adjustment for echocardiographically derived left ventricular hypertrophy. This is possibly due the presence in our study group of a larger number of younger subjects (the lower age limit was 40 years instead of 50), in whom the stroke risk associated with left atrial enlargement was found to be greater. Also, the adjustment for echocardiographically determined left ventricular hypertrophy in our study, with its higher sensitivity,27 may have allowed for a better assessment of the effect of left ventricular hypertrophy on the risk estimates. Our study included subjects from 3 different race-ethnic groups, which provided an opportunity for insight into possible race-ethnic differences in the stroke risk that was not obtainable from the exclusively white population of the Framingham study. Finally, echocardiographic variables were obtained from 2-dimensional instead of M-mode echocardiography, with potential differences in the measurement of left atrial size and in the determination of left ventricular hypertrophy.

Strengths and Limitations
The present study is the first to address the possible independent effect of left atrial size on the risk of ischemic stroke in a community-based multiethnic population. The sociodemographic distribution allowed for the assessment of the risk in age, gender, and race-ethnic subgroups after adjustment for other stroke risk factors.

Case-control design has some limitations, including potential bias in the selection of subjects. This was minimized in our study by the recruitment of cases and controls from the same community (to reduce the possibility of differences in socioeconomic variables, including access to medical care); the randomized procedure for control selection; and the individual matching of cases and controls by age, gender, and race-ethnicity. The possibility that differences between cases and controls may have existed in variables that were not measured cannot be excluded. Moreover, the study did not have the power to address the association between left atrial size and different stroke subtypes, and its power for detecting interracial differences in the stroke risk was also suboptimal.

The application of left atrial size measurement for assessing stroke risk in individual patients must be done with caution, because its accuracy is affected by measurement variability. In our study, the average left atrial index in controls was 21.8 mm/m². Given our quartiles distribution (Figure[fgc+]), a measurement variability of 10% (or 2.18 mm/m²) would correspond to half the difference between the top of the first quartile and the bottom of the fourth quartile. This suggests that, assuming a measurement variability of 10%, our data can be used in individual patients only to discriminate between subjects at high and low risk.

Clinical Implications
The demonstration of a significant association between left atrial size and stroke has potential preventive implications. Left atrial enlargement is a known potential consequence of arterial hypertension. Recently, different antihypertensive treatments have been shown to have differential effects in decreasing the left atrial size, partially independent of their effects on left ventricular hypertrophy.28 Our data seem to indicate that the size of the left atrium should be taken into consideration in the global assessment of the individual stroke risk, and possibly in the decision of the type of preventive treatment. The use of drugs that more effectively decrease left atrial size might be considered for the treatment of patients with arterial hypertension and left atrial enlargement, similar to the way in which antihypertensive drugs that promote reduction in left ventricular mass are chosen in patients with hypertension and left ventricular hypertrophy.

All other factors being equal, an increased atrial size could be an additional factor to consider when deciding on the need for prophylactic anticoagulation. Also, different stroke-prevention strategies could be envisioned for men and women, given the different impact of left atrial size and left ventricular hypertrophy on their respective risks. Additional studies are needed to evaluate the efficacy of decreasing the size of the left atrium in reducing the risk of stroke.

Acknowledgments
This project was supported in part by grants from the National Institute of Neurological Disorders and Stroke (R01 NS 29993 and NS 33248, T32 NS 07153). The authors gratefully acknowledge the support of J.P. Mohr, MD, Director of Cerebrovascular Research. They also wish to thank Bernadette Boden-Albala, MS, for her assistance in the data collection, and Lynette M. Mendoza, BS, and Inna Titova, BS, for their assistance in the preparation of the manuscript.

References


Left Atrial Size and the Risk of Ischemic Stroke in an Ethnically Mixed Population
Marco R. Di Tullio, Ralph L. Sacco, Robert R. Sciacca and Shunichi Homma

doi: 10.1161/01.STR.30.10.2019
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/30/10/2019

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/