Left Atrial Enlargement and Stroke Recurrence

The Northern Manhattan Stroke Study

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Background and Purpose—Although left atrial enlargement (LAE) increases incident stroke risk, the association with recurrent stroke is less clear. Our aim was to determine the association of LAE with recurrent stroke most likely related to embolism (cryptogenic and cardioembolic) and all ischemic stroke recurrences.

Methods—We followed 655 first ischemic stroke patients in the Northern Manhattan Stroke Study for ≤5 years. LA size from 2D echocardiography was categorized as normal LAE (52.7%), mild LAE (31.6%), and moderate–severe LAE (15.7%). We used Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for the association of LA size and LAE with recurrent cryptogenic/cardioembolic and total recurrent ischemic stroke.

Results—LA size was available in 529 (81%) patients. Mean age at enrollment was 69±13 years; 45.8% were male, 54.0% Hispanic, and 18.5% had atrial fibrillation. Over a median of 4 years, there were 65 recurrent ischemic strokes (29 were cardioembolic or cryptogenic). In multivariable models adjusted for confounders, including atrial fibrillation and heart failure, moderate–severe LAE compared with normal LA size was associated with greater risk of recurrent cardioembolic/cryptogenic stroke (adjusted hazard ratio 2.83, 95% confidence interval 1.03–7.81), but not total ischemic stroke (adjusted hazard ratio 1.06, 95% confidence interval, 0.48–2.30). Mild LAE was not associated with recurrent stroke.

Conclusion—Moderate to severe LAE was an independent marker of recurrent cardioembolic or cryptogenic stroke in a multiethnic cohort of ischemic stroke patients. Further research is needed to determine whether anticoagulant use may reduce risk of recurrence in ischemic stroke patients with moderate to severe LAE. (Stroke. 2015;46:1488-1493. DOI: 10.1161/STROKEAHA.115.008711.)

Key Word: embolism

Left atrial enlargement (LAE) is associated with the risk of first ischemic stroke,1,2 subclinical cerebrovascular disease,3 paroxysmal atrial fibrillation (AF) in the general population,4,5 and detection of AF in patients with cryptogenic stroke.6-9 These associations suggest that LAE, AF, and stroke could share a common disease pathway. Several gaps in knowledge persist, however. Evidence from large population-based studies suggests that LAE is associated with incident stroke independently of diagnosed AF.1,2 Prior studies have been limited by the lack of consideration of stroke subtypes; as a result, less is known whether LAE is associated with incident cryptogenic stroke, which is thought to often arise from embolism.10,11 Finally, though LAE is associated with detection of AF, it is less clear whether LAE increases the risk of stroke recurrence. A better understanding of the relationship between LAE and stroke risk may target prolonged monitoring strategies for AF and potentially improve secondary stroke prevention strategies. We hypothesized that LAE on echocardiography in ischemic stroke patients is associated with a higher risk of stroke recurrence, particularly of the subtypes likely related to embolism (cryptogenic and cardioembolic stroke).

Methods

Study Population

The Northern Manhattan Stroke Study (NOMASS) was designed to determine predictors of stroke recurrence and prognosis in a multiethnic, urban population. The methods of patient identification and
enrollment of this cohort (n=655) have been described previously. Patients were enrolled in NOMASS if (1) age was >40 years; (2) they had a diagnosis of first stroke; and (3) they lived in Northern Manhattan for ≥3 months in a household with a telephone. Only patients with ischemic strokes were included in our study. Patient evaluation was conducted at Columbia University Medical Center (CUMC). The cohort for this study represents a community-based cohort of stroke patients, and therefore, stroke patients were evaluated according to the practice of their local treating neurologists. Although systematic screening for paroxysmal AF was not performed, hospitalized patients underwent electrocardiogram and cardiac telemetry. Participants who were either not hospitalized (5%) or hospitalized elsewhere were evaluated in the outpatient research clinic or by their primary physician or community health clinic. Patients were interviewed at 6 months and then annually for ≤5 years, and new diagnoses, such as AF, were ascertained through interviews of patients and caregivers, physicians, and other providers, review of medical records, and discharge reports of interval hospitalizations. Patients unable or unwilling to come to the medical center were visited by a member of the research staff, and the evaluation was conducted at home or in an alternative place of residence (e.g., nursing home). An ongoing surveillance system of admissions to CUMC was used to identify study participants who were admitted for any reason. The surveillance included other local hospitals to identify study participants who experienced recurrent stroke, myocardial infarction, hospitalization, or death, and when available, their medical records were reviewed for all outcome events, including death.

The study was approved by the Institutional Review Board at CUMC. All participants gave consent directly or through a surrogate when appropriate.

**Echocardiographic Measurements**

Transesophageal echocardiography was performed as part of routine clinical care within 3 months from stroke onset. Studies were performed and measurements taken according to the guidelines of the American Society of Echocardiography. In particular, left atrial anteroposterior diameter was measured in parasternal long-axis view at the level of the aortic valve according to a leading edge–to–leading edge convention. The measurement was replaced by qualitative assessment of LA size when an accurate measurement was not possible; the agreement between measurement and qualitative assessment in patients who had both was excellent (Cronbach alpha =0.92) using the LA categorization that follows. Left atrial size was categorized into 4 groups according to left atrial diameter and sex: normal left atrial size in mm (women, ≤38; men, ≤40), mild LAE (women, 39–42; men, 41–46), moderate LAE (women, 43–46; men, 47–51), and severe LAE (women, ≥47; men, ≥52). We combined moderate and severe LAE into one category because of the expected small numbers of patients with severe LAE.

The interpretation of the echocardiographic studies was blinded to stroke recurrence.

**Covariates**

We adjusted for the following potential confounders in the association between LAE and stroke recurrence: baseline demographics (age, sex, and race-ethnicity) and risk factors at the time of the incident stroke evaluation (hypertension, diabetes mellitus, hyperlipidemia, smoking, AF, and congestive heart failure).

**Recurrent Stroke**

Annual follow-up for 5 years after index stroke assessed vital status, as well as interval hospitalization or illness, and specifically symptoms indicative of ischemic stroke. A suspected ischemic stroke was followed up by record review to confirm whether an outcome had occurred. We also prospectively screened all discharges from CUMC to detect hospitalizations and outcomes that may not have been captured by interview. Stroke was defined as the first symptomatic occurrence of fatal and nonfatal ischemic stroke according to the World Health Organization criteria. Ischemic stroke subtype was classified by a consensus of 2 neurologists, with a third neurologist adjudicating if needed, based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.

**Statistical Analysis**

Distributions of baseline characteristics were summarized and compared by LAE categories using chi-square tests for categorical and Kruskal–Wallis tests for continuous variables. The primary outcome was total recurrent ischemic stroke, and the secondary outcome was the combined recurrent cryptogenic or cardioembolic stroke subtypes. The primary predictor was LAE categories and the secondary predictor was LA size as a continuous variable. Cox proportional hazard models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association between left atrial size and the risk of recurrent stroke, unadjusted and adjusted for demographic characteristics (age, sex, race-ethnicity) and risk factors (hypertension, diabetes mellitus, hyperlipidemia, history of AF, and congestive heart failure). We tested for violations of the proportional-hazards assumption. Sensitivity analyses were performed by additionally adjusting for body mass index, systolic blood pressure, diastolic blood pressure, and stroke prevention strategies, such as antihypertensive and anticoagulant medications on discharge. We tested whether the associations between LA size and recurrent stroke were modified by baseline AF with an interaction term, and further sensitivity analyses were performed by excluding those with AF at baseline. Statistical analyses were conducted using SAS software (Version 8.2, SAS Institute, Cary, NC); P<0.05 was considered statistically significant.

**Results**

Among 655 patients with a first ischemic stroke, LA size data were available in 529 (80.7%). Patients without echocardiography were less likely to be Hispanic (P for difference =0.05) and more likely to have cryptogenic stroke (P for difference =0.01), but there were no other significant differences in characteristics, including follow-up time and recurrent stroke incidence rate between the 2 groups (Table 1). The mean LA diameter was 40.6 mm (SD 6.3). Mean age at the time of stroke was 69 years; 45.8% were male, 18.2% non-Hispanic white, 25.5% non-Hispanic black, 54.0% Hispanic, and 18.5% had history of AF and 13.1% had congestive heart failure (Table 1). There were 279 (52.7%) with normal LA size, 167 (31.6%) with mild LAE, and 83 (15.7%) with moderate to severe LAE.

Over a median of 4 years (interquartile range 1.3–5.0 years) of follow-up, recurrent stroke occurred in 80 patients (15%), of which 65 were confirmed to be ischemic in origin and were included in the primary analysis; 13 were cardioembolic (16.3%), 16 cryptogenic (20.0%), 12 large artery atherosclerosis (15.0%), and 15 lacunar (18.8%). None of the patients with cryptogenic stroke at baseline and recurrent stroke were found to have AF during annual follow-up. Baseline demographics based on left atrial size category are listed in Table 2.

**Association With Total Recurrent Ischemic Stroke**

In univariate and adjusted models, LA diameter was not associated with the risk of total recurrent ischemic stroke (Table 3). There was also no association between moderate to severe LAE and total recurrent ischemic stroke (unadjusted HR 1.24, 95% CI 0.61–2.52; adjusted HR 1.06, 95% CI 0.48–2.30). Kaplan–Meier survival analysis is displayed in Figure 1. Furthermore, there was no interaction between LAE and AF (P=0.97), suggesting that the effect of LAE on recurrent ischemic stroke was not modified by AF. The results remained unchanged after excluding those with AF (data not shown).
In an unadjusted model, compared with those with normal LA size, those with moderate to severe LAE had greater risk of recurrent combined cardioembolic or cryptogenic stroke (unadjusted HR 4.35, 95% CI 1.81–10.48). After adjusting for baseline demographics and risk factors, including AF and congestive heart failure, the associations persisted (adjusted HR 3.17, 95% CI 1.36–7.36).

Association With Combined Recurrent Cardioembolic or Cryptogenic Stroke Subtype

In an unadjusted model, compared with those with normal LA size, those with moderate to severe LAE had greater risk of recurrent combined cardioembolic or cryptogenic stroke (unadjusted HR 4.35, 95% CI 1.81–10.48). After adjusting for baseline demographics and risk factors, including AF and congestive heart failure, the associations persisted (adjusted HR 3.17, 95% CI 1.36–7.36).

Table 2. Baseline Demographics Based on the Left Atrial Size Categories

<table>
<thead>
<tr>
<th>Overall (n=529)</th>
<th>Normal n=279 (52.7%)</th>
<th>Mild LAE n=167 (31.6%)</th>
<th>Moderate–Severe LAE, N=83 (15.7%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>69±13</td>
<td>68±12</td>
<td>69±13</td>
<td>75±13</td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>45.8</td>
<td>39.8</td>
<td>54.5</td>
<td>48.2</td>
</tr>
<tr>
<td>Race-ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>18.2</td>
<td>12.9</td>
<td>22.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Black, %</td>
<td>25.5</td>
<td>28.3</td>
<td>24.0</td>
<td>19.3</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>54.1</td>
<td>57.4</td>
<td>49.1</td>
<td>53.0</td>
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<tr>
<td>Diabetes, %</td>
<td>44.8</td>
<td>41.6</td>
<td>52.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>83.6</td>
<td>82.4</td>
<td>82.6</td>
<td>89.2</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>13.1</td>
<td>7.9</td>
<td>16.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>50.1</td>
<td>51.3</td>
<td>54.5</td>
<td>37.4</td>
</tr>
<tr>
<td>Body mass index (median)</td>
<td>25.9</td>
<td>25.6</td>
<td>26.5</td>
<td>26.2</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>46.0</td>
<td>43.8</td>
<td>42.7</td>
<td>59.8</td>
</tr>
<tr>
<td>Past</td>
<td>33.3</td>
<td>31.9</td>
<td>37.8</td>
<td>29.3</td>
</tr>
<tr>
<td>Current</td>
<td>20.7</td>
<td>24.3</td>
<td>19.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Kruskal–Wallis test for continuous variables and χ² with 2 DF test for categorical variables were used. Ref indicates reference.
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2.83, 95% CI 1.03–7.81; Table 3). Mild LAE was not associated with combined recurrent cryptogenic or cardioembolic stroke subtypes (adjusted HR 1.32, 95% CI 0.51–3.39). The Kaplan–Meier survival analysis is displayed in Figure 2.

LA diameter as a continuous variable was also associated with greater risk of combined recurrent cardioembolic or cryptogenic stroke (unadjusted HR 1.76 per SD change in LA diameter, 95% CI 1.25–2.48; adjusted HR 1.55 per SD change in LA diameter, 95% CI 1.01–2.37).

There was no interaction between LAE and AF (P = 0.31), suggesting that the effect of LAE on combined recurrent cryptogenic or cardioembolic stroke subtypes was not modified by AF. After excluding patients with a history of AF in sensitivity analyses, those with moderate to severe LAE (versus normal LA size) had a trend toward greater risk of recurrent cardioembolic or cryptogenic stroke (adjusted HR 2.77, 95% CI 0.74–10.35), and the association of continuous LA size with recurrent cardioembolic or cryptogenic stroke remained significant (adjusted HR 1.85, 95% CI 1.03–3.33). None of the patients with moderate to severe atrial enlargement and noncardioembolic stroke at baseline were found to have AF at the time of the second stroke.

### Sensitivity Analyses

Sensitivity analyses were performed adjusting for body mass index, systolic blood pressure, diastolic blood pressure, and antihypertensive medications, and we found similar results (Table I in the online-only Data Supplement). In addition, in a sensitivity analysis adjusting for anticoagulant use on discharge, the association between moderate to severe LAE and recurrent cryptogenic/cardioembolic stroke remained significant (adjusted HR 3.44, 95% CI 1.14–10.31; Table I in the online-only Data Supplement).

**Figure 1.** Probability of survival free of total recurrent ischemic stroke for normal left atrial (LA) size, mild left atrial enlargement (LAE), and moderate to severe left atrial enlargement.

**Table 3.** Association of Left Atrial Size and Recurrent Ischemic Stroke and Recurrent Cryptogenic or Cardioembolic Stroke

<table>
<thead>
<tr>
<th>Left Atrial Size</th>
<th>Model 1, Unadjusted, Hazard Ratio (95% Confidence Interval)</th>
<th>Model 2,* Hazard Ratio (95% Confidence Interval)</th>
<th>Model 3,† Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ischemic stroke of any subtype</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Normal left atrial size</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild left atrial enlargement</td>
<td>1.15 (0.67–1.97)</td>
<td>1.10 (0.63–1.90)</td>
<td>1.06 (0.60–1.87)</td>
</tr>
<tr>
<td>Moderate to severe left atrial enlargement</td>
<td>1.24 (0.61–2.52)</td>
<td>1.06 (0.51–2.19)</td>
<td>1.06 (0.48–2.30)</td>
</tr>
<tr>
<td>Recurrent cardioembolic or cryptogenic stroke</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Normal left atrial size</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild left atrial enlargement</td>
<td>1.09 (0.84–1.41)</td>
<td>1.03 (0.79–1.34)</td>
<td>1.03 (0.76–1.38)</td>
</tr>
<tr>
<td>Moderate to severe left atrial enlargement</td>
<td>1.56 (0.64–3.84)</td>
<td>1.53 (0.61–3.80)</td>
<td>1.32 (0.51–3.39)</td>
</tr>
<tr>
<td>Left atrial size (per SD increase)</td>
<td>4.35 (1.81–10.48)</td>
<td>3.83 (1.54–9.54)</td>
<td>2.83 (1.03–7.81)</td>
</tr>
<tr>
<td>Left atrial size (per SD increase)</td>
<td>1.76 (1.25–2.48)</td>
<td>1.73 (1.21–2.49)</td>
<td>1.55 (1.01–2.37)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and race-ethnicity.
†Adjusted for age, sex, race-ethnicity, hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, and congestive heart failure.

283, 95% CI 1.03–7.81; Table 3). Mild LAE was not associated with combined recurrent cryptogenic or cardioembolic stroke subtypes (adjusted HR 1.32, 95% CI 0.51–3.39). The Kaplan–Meier survival analysis is displayed in Figure 2.

LA diameter as a continuous variable was also associated with greater risk of combined recurrent cardioembolic or cryptogenic stroke (unadjusted HR 1.76 per SD change in LA diameter, 95% CI 1.25–2.48; adjusted HR 1.55 per SD change in LA diameter, 95% CI 1.01–2.37).

There was no interaction between LAE and AF (P = 0.31), suggesting that the effect of LAE on combined recurrent cryptogenic or cardioembolic stroke subtypes was not modified by AF. After excluding patients with a history of AF in sensitivity analyses, those with moderate to severe LAE (versus normal LA size) had a trend toward greater risk of recurrent cardioembolic or cryptogenic stroke (adjusted HR 2.77, 95% CI 0.74–10.35), and the association of continuous LA size with recurrent cardioembolic or cryptogenic stroke remained significant (adjusted HR 1.85, 95% CI 1.03–3.33). None of the patients with moderate to severe atrial enlargement and noncardioembolic stroke at baseline were found to have AF at the time of the second stroke.

**Sensitivity Analyses**

Sensitivity analyses were performed adjusting for body mass index, systolic blood pressure, diastolic blood pressure, and antihypertensive medications, and we found similar results (Table I in the online-only Data Supplement). In addition, in a sensitivity analysis adjusting for anticoagulant use on discharge, the association between moderate to severe LAE and recurrent cryptogenic/cardioembolic stroke remained significant (adjusted HR 3.44, 95% CI 1.14–10.31; Table I in the online-only Data Supplement).

**Discussion**

In a multiethnic population, we found that those with moderate to severe LAE identified on echocardiography performed for clinical purposes was associated with greater risk of recurrent cryptogenic or cardioembolic stroke than those with normal LA size. This association persisted even after adjusting for baseline demographics and established stroke risk factors, including the 2 most likely potential confounders, history of AF, and congestive heart failure. In sensitivity analyses excluding the 97 participants with AF at baseline, we found a similar effect size, though the association did not reach statistical significance, probably because of reduced power.

We focused our analysis on the combined outcome of recurrent cryptogenic or cardioembolic stroke because of the expectation that these 2 subtypes may share a common embolic mechanism. It is increasingly recognized that among patients with unexplained superficial hemispheric infarcts and no significant arterial stenosis or definite cardiac source, lower risk or unrecognized cardiac sources of embolism are likely explanations for the stroke.10,11,18

The explanation of the association of LAE with recurrent cryptogenic/cardioembolic stroke could be as a result of several reasons. The mechanism of stroke recurrence in patients with moderate to severe LAE could be at least partially explained by concomitant AF. In our study, however, the association between recurrent stroke risk and left atrial dilatation remained even after adjusting for history of AF. We acknowledge, however, that our
LAE may serve as one of the markers of atrial cardiopathy dysfunction may have therapeutic implications. Similarly, natriuretic peptide levels, suggesting that biomarkers of atrial onset, with the most highly elevated N-terminal pro-brain among the 5% of stroke patients, none of whom had AF at 27 was superior to aspirin in reducing risk of stroke and death Study study, moreover, showed that treatment with warfarin been associated with increased stroke risk independent of AF. Post hoc analysis of the Warfarin-Aspirin Recurrent Stroke could also explain our outcome. For example, recent research suggests that prolonged AF monitoring can increase the detection of paroxysmal AF,2 but it was not routinely performed in our cohort, so we may have underestimated the prevalence of AF. However, none of the patients who had cryptogenic stroke at baseline and subsequent recurrent stroke were found to have AF during follow-up. Another proposed mechanism is that an increase in left atrial volume produces reduced flow velocity in the left atrial appendage,23 therefore contributing to stasis and predisposing to clot formation. This is supported by transesophageal echocardiographic data suggesting an association between left atrial dilatation and spontaneous echocardiographic contrast and embolic events.1 However, transesophageal echocardiography was not routinely performed in our study cohort to confirm this hypothesis. Another potential explanation is that because LAE is a manifestation of organ damage secondary to chronic hypertension, the increased stroke risk is instead a reflection of the well-established association of hypertension with recurrent stroke. Within our study, however, the association between LAE and stroke risk was independent of hypertension, arguing against this being an explanation for our findings. We cannot exclude residual confounding as an explanation, however.

Although AF is the most robust marker of left atrial dysfunction associated with ischemic stroke, other markers of left atrial dysfunction, such as elevated N-terminal pro-brain natriuretic peptide, p-wave terminal force in lead V1 of a 12-lead ECG,24,25 and paroxysmal supraventricular tachycardia,26 have been associated with increased stroke risk independent of AF. Post hoc analysis of the Warfarin-Aspirin Recurrent Stroke Study study, moreover, showed that treatment with warfarin was superior to aspirin in reducing risk of stroke and death among the 5% of stroke patients, none of whom had AF at onset, with the most highly elevated N-terminal pro-brain natriuretic peptide levels,27 suggesting that biomarkers of atrial dysfunction may have therapeutic implications. Similarly, LAE may serve as one of the markers of atrial cardiopathy that is also associated with increased risk of embolic strokes.24 These results may thus spur future research to determine whether anticoagulant use reduces risk of recurrence in ischemic stroke patients with moderate to severe LAE.

Limitations and Strengths
Our study has several limitations. First, we were missing LA size values on 19% of patients; however, baseline characteristics, as well as follow-up time and incidence rate of recurrent stroke, were more or less similar between the groups with and without LA size available, which suggests that no selection bias was introduced. Second, we did not routinely monitor our cohort for AF on follow-up visits and thus paroxysmal AF may have been undetected. Third, the categorization of left atrial size measurements was based on clinical readings and not standardized measurements from a core laboratory; however, the simple linear measurement of LA diameter used has good reproducibility and generalizability in the echocardiographic evaluation of stroke patients whose left atrial size measurements is also based on clinical readings. In addition, our study lacked data on LA volume, which is a more accurate way to assess LA size, and is more strongly associated with cardiovascular events. Having found an effect for LA diameter, however, it is likely that such effects would have been even stronger had we used LA volume.

Strengths of our study include the fact that it is a prospective multiethnic study with a relatively long follow-up, making the results robust and generalizable. Furthermore, we collected data on a wide range of potentially confounding risk factors, allowing us to estimate the independent effect of LAE. Our study also included data about stroke subtype using TOAST criteria and studied the association between left atrial size and recurrent stroke subtype.

Conclusions
Moderate to severe LAE is an independent marker of recurrent stroke of embolic subtypes in patients with ischemic stroke. Future studies are needed to improve stroke secondary prevention strategies in patients with moderate to severe LAE to reduce their risk of embolic stroke.

Disclosures
Dr Yaghi received funding from National Institute of Neurological Disorders and Stroke (NINDS) StrokeNet. Dr M.S.V. Elkind receives compensation for providing consultative services for Biotelemetry/ Cardionet, BMS-Pfizer Partnership, Biogen Idec, Boehringer-Ingelheim, Daiichi-Sankyo, and Janssen Pharmaceuticals; serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association; and receives royalties from UpToDate for a chapter related to cryptogenic stroke. Dr Willey received funding from the NIH and is a consultant for heartware incorporated. Dr Homma is a consultant for St Jules Medical, BMS/ Pfizer, and Daiichi Sankyo. Dr Sacco received funding from NINDS.

References


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**SUPPLEMENTAL MATERIAL**

| Supplemental table I: Association of left atrial size and recurrent ischemic stroke and recurrent cryptogenic or cardioembolic stroke |
|---|---|---|
| **Recurrence of ischemic stroke of any subtype** | **Left atrial size** | **Model 1** | **Model 2** |
| | Normal Left atrial size | Hazard ratio (95% confidence interval) | Hazard ratio (95% confidence interval) |
| | | reference | reference |
| | Mild left atrial enlargement | $1.07 (0.59-1.95)$ | $1.21 (0.67-2.21)$ |
| | Moderate to severe left atrial enlargement | $1.12 (0.50-2.48)$ | $1.15 (0.50-2.64)$ |
| | Left atrial size (per SD increase) | $1.07 (0.78-1.46)$ | $1.13 (0.82-1.55)$ |
| **Recurrence of cryptogenic or cardioembolic stroke** | **Normal left atrial size** | reference | reference |
| | Mild left atrial enlargement | $1.26 (0.48-3.32)$ | $1.77 (0.65-4.81)$ |
| | Moderate to severe left atrial enlargement | $2.70 (0.97-7.54)$ | $3.44 (1.14-10.31)$ |
| | Left atrial size (per SD increase) | $1.54 (1.00-2.38)$ | $1.68 (1.07-2.64)$ |

*model 1: adjusted for age, sex, race-ethnicity, diabetes, hypercholesterolemia, smoking, atrial fibrillation, congestive heart failure, systolic blood pressure, diastolic blood pressure, body mass index and antihypertensive medications on discharge

**model 2: adjusted for age, sex, race-ethnicity, hypertension, diabetes, hypercholesterolemia, smoking, atrial fibrillation, congestive heart failure, and anticoagulant use on discharge. For this model, the analytic cohort included 465 patients with information on anticoagulant use at discharge available.*
左房拡大と脳卒中再発
Northern Manhattan Stroke Study (NOMASS)
Left Atrial Enlargement and Stroke Recurrence
The Northern Manhattan Stroke Study
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背景および目的：左房拡大（LAE）のある患者では脳卒中再発症リスクが増加するが、LAEと脳卒中再発との関連についてはあまり明確になっていない。本研究では、塞栓症（原因不明および心原性）と最も強く関連すると考えられている脳卒中再発および全虚血性脳卒中再発とLAEとの関連を明確にすることを目的とした。

方法：本研究では、Northern Manhattan Stroke Study (NOMASS)の被験者のうち655例の初発虚血性脳卒中患者を最大5年にわたって追跡した。2Dエコー検査で左心房（LA）のサイズを調べ、正常LA（52.7%）、軽度LAE（31.6%）、中等度〜重度LAE（15.7%）に分類した。

Cox比例ハザードモデルを用いてハザード比（HR）と95%信頼限界（CI）を計算し、LAのサイズ、およびLAEと原因不明・心原性塞栓症および全虚血性脳卒中再発の関連について検討した。

結果：529例（81%）のLAサイズが得られた。被験者の登録時の平均年齢は69±13歳、男性が45.8%、ヒスパニック系が54.0%で、心房細動が18.5%に認められた。4年間（中位値）に虚血性脳卒中が再発した患者は65例であった（そのうち29例は心原性もしくは原因不明）。心房細動や心不全などの交絡因子で調整した多変量モデルでは、正常なLAサイズと比較して、中等度〜重度のLAEは心原性・原因不明の脳卒中再発リスクの増加と関連していた（調整HR = 2.83、95%CI：1.03～7.81）。全虚血性脳卒中の再発増加との関連は示されなかった（調整HR = 1.06、95%CI：0.48～2.30）。軽度LAEは脳卒中再発に関連しなかった。

結論：多民族から成る虚血性脳卒中患者コホートでは、中等度〜重度のLAEは心原性もしくは原因不明の脳卒中再発の独立したマーカーであった。抗凝固薬の使用が中等度〜重度のLAEを有する虚血性脳卒中患者の再発リスクを低下させるか否かについて、今後さらに調査する必要がある。

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허혈뇌졸중 재발과 연관이 높은 재발성 뇌졸중과의 연관을 조사

연구의 목적은 LAE와 색전증(원인불명과 심장성색전증)과 모든 허혈뇌졸중 재발과의 연관성은 불분명하다.

본원에서, 금성뇌졸중 환자 655명의 연관성을 분석하였다. 재발성 뇌졸중의 진단은 5년 이내의 재발 성격과 연관성을 조사하였다.

Figure. Relationship of percentage of patients achieving thrombolysis in cerebral infarction grade 2b or 3 (TICI2b3) flow and patients achieving modified Rankin Scale (mRS) of 0 to 2 in intervention (intra-arterial thrombectomy [IAT]) and control (CTL) groups (y axis) vs minutes from last seen normal to groin puncture for each of the 5 studies (x axis). The exact time to achieving maximal reperfusion is not available from published data for all studies, but where available is proportionate to time to groin puncture. Note the following: (1) the percentage of patients achieving good outcome is strikingly proportionate to the percentage of patients achieving TICI2b3 flow. (2) There is a consistent difference between the IAT and CTL groups in the percent achieving mRS 0 to 2 across all studies with the difference diminishing with increased time from last seen normal to groin puncture. (3) The percentage of patients achieving good outcome is roughly proportionate to the time from last seen normal to groin puncture (earlier groin puncture=higher proportion good outcome) with the exception being the EXTEND IA study, which was the only study to use advanced imaging for patient selection suggesting its use to identify responsive patients at delayed time intervals. ESCAPE indicates Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times; EXTEND IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment Trial; and REVASCAT, Randomized Trial of Revascularization With the Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset.

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허혈뇌졸중 재발

左側심방 비대와 뇌졸중 재발

左側심방 비대와 뇌졸중 재발

Left Atrial Enlargement and Stroke Recurrence

The Northern Manhattan Stroke Study

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Key Word: embolism

배경과 목적

우측 심방 비대(left atrial enlargement, LAE)가 뇌졸중 발생에

의연관성의 수준이 높다는 연구결과가 있다. 본 연구의 목적은 LAE와

색전증(원인불명과 심장성색전증)과 모든

허혈뇌졸중 재발과 연관이 높은 재발성 뇌졸중과의 연관을 조사

하는 것이다.

방법

Northern Manhattan Stroke Study에 등록된 655명의 첫

허혈뇌졸중 환자를 5년 이하의 기간 동안 추적 조사하였다. 2D
Table 3. Association of Left Atrial Size and Recurrent Ischemic Stroke and Recurrent Cryptogenic or Cardioembolic Stroke

<table>
<thead>
<tr>
<th>Left Atrial Size</th>
<th>Model 1, Unadjusted, Hazard Ratio (95% Confidence Interval)</th>
<th>Model 2, * Hazard Ratio (95% Confidence Interval)</th>
<th>Model 3, † Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ischemic stroke of any subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal left atrial size</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild left atrial enlargement</td>
<td>1.15 (0.67–1.97)</td>
<td>1.10 (0.63–1.90)</td>
<td>1.06 (0.60–1.87)</td>
</tr>
<tr>
<td>Moderate to severe left atrial enlargement</td>
<td>1.24 (0.61–2.52)</td>
<td>1.06 (0.51–2.19)</td>
<td>1.06 (0.48–2.30)</td>
</tr>
<tr>
<td>Recurrent cardioembolic or cryptogenic stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial size (per SD increase)</td>
<td>1.09 (0.84–1.41)</td>
<td>1.03 (0.79–1.34)</td>
<td>1.03 (0.76–1.38)</td>
</tr>
<tr>
<td>Normal left atrial size</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Mild left atrial enlargement</td>
<td>1.56 (0.64–3.84)</td>
<td>1.53 (0.61–3.80)</td>
<td>1.32 (0.51–3.39)</td>
</tr>
<tr>
<td>Moderate to severe left atrial enlargement</td>
<td>4.35 (1.81–10.48)</td>
<td>3.83 (1.54–9.54)</td>
<td>2.83 (1.03–7.81)</td>
</tr>
<tr>
<td>Left atrial size (per SD increase)</td>
<td>1.76 (1.25–2.48)</td>
<td>1.73 (1.21–2.49)</td>
<td>1.55 (1.01–2.37)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and race-ethnicity.
†Adjusted for age, sex, race-ethnicity, hypertension, diabetes mellitus, hypercholesterolemia, smoking, atrial fibrillation, and congestive heart failure.

Figure 1. Probability of survival free of total recurrent ischemic stroke for normal left atrial (LA) size, mild left atrial enlargement (LAE), and moderate to severe left atrial enlargement.

Figure 2. Probability of survival free of recurrent cryptogenic/cardioembolic stroke for normal left atrial (LA) size, mild left atrial enlargement (LAE), and moderate to severe left atrial enlargement.