Carotid Artery Wall Thickness and Risk of Stroke Subtypes
The Atherosclerosis Risk in Communities Study

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Background and Purpose—Understanding associations of carotid atherosclerosis with stroke subtypes may contribute to more effective prevention of stroke.

Methods—Between 1987 and 1989, 13 560 men and women aged 45 to 64 years and free of clinical stroke took part in the first examination of the Atherosclerosis Risk in Communities (ARIC) study. Incident strokes were ascertained by hospital surveillance.

Results—During an average follow-up of 15.7 years, 82 incident hemorrhagic and 621 incident ischemic strokes (131 lacunar, 358 nonlacunar, and 132 cardioembolic strokes) occurred. The incidence rates of hemorrhagic and ischemic strokes were greater across higher carotid intima-media thickness levels. Although this positive association was observed for all stroke subtypes, the age-, gender-, and race-adjusted risk ratios were higher for cardioembolic and nonlacunar strokes than for hemorrhagic and lacunar strokes. Compared with participants in the lowest quintile (<0.61 mm), the adjusted risk ratios for those in the highest quintile (≥0.85 mm) of intima-media thickness were 2.55 (95% CI, 1.09–5.94) for hemorrhagic, 2.89 (95% CI, 1.50–5.54) for lacunar, 3.61 (95% CI, 2.33–5.99) for nonlacunar, and 6.12 (95% CI, 2.71–13.9) for cardioembolic stroke. The risk ratios were attenuated by additional adjustment for covariates but remained statistically significant for nonlacunar and cardioembolic strokes (P for trend <0.001, respectively). The association between carotid intima-media thickness and lacunar stroke was somewhat stronger in blacks than in whites (P for interaction =0.07).

Conclusions—Carotid atherosclerosis was associated with increased risk of all stroke subtypes, but the association of carotid atherosclerosis with stroke may vary by subtypes. (Stroke. 2011;42:00-00.)

Key Words: brain infarction | carotid artery | epidemiology | intima-media thickness | stroke subtypes

Carotid artery intima-media thickness (IMT) and carotid plaques are markers of subclinical atherosclerosis and help in the early identification of individuals at risk for clinical cardiovascular events. Previous epidemiological studies have documented that carotid IMT predicts future stroke events, but few studies have demonstrated associations of IMT with subtypes of stroke, and these results are inconsistent. Although the associations of carotid IMT with atherothrombotic (nonlacunar) stroke were observed in all 3 previous studies, an association with lacunar stroke was observed in 2 of 3 studies and an association with embolic stroke was shown in only 1 study. Further, there has been no study to examine the association between carotid IMT and hemorrhagic stroke in a population-based study. Because previous studies were cross-sectional, the association of carotid IMT and plaques with risk of stroke subtypes should be confirmed prospectively. The pathogenesis, prognosis, and treatment differ among subtypes; therefore, evaluating the predictive value of IMT for individual subtypes may contribute to more effective primary prevention of stroke.

Previously, the Atherosclerosis Risk in Communities (ARIC) study reported that blacks had a 2.4-fold higher age-adjusted relative risk of stroke incidence compared with whites, which could be partially explained by higher prevalence of stroke risk factors such as hypertension, diabetes, and current smoking among blacks than among whites. In addition, ARIC showed that although blacks had a 3-fold multivariable-adjusted risk ratio of lacunar stroke compared with whites, there was no racial difference for nonlacunar and cardioembolic strokes after adjustment for traditional and nontraditional cardiovascular risk factors. Mean common carotid artery-IMT was higher among blacks than among whites, and moderate carotid stenosis may have an important role in the development of lacunar stroke and nonlacunar stroke.
Therefore, the association of carotid IMT with the incidence of lacunar stroke may be stronger among blacks than whites. To examine the relationships of carotid IMT with the incidence of stroke subtypes, we used data from follow-up of men and women in the ARIC study.

**Subjects and Methods**

**Study Population**
The ARIC cohort comprised 15,792 men and women aged 45 to 64 years between 1987 and 1989 in 4 U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; 8 northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. We excluded participants in Forsyth County who were not white or black (n = 21) and participants in Minneapolis and Washington County who were not white (n = 82), because these participants were scarcely represented in their field centers. We then excluded participants with a history of stroke or transient ischemic attack at baseline (n = 282) and participants with missing data for carotid ultrasound measurements (n = 318) or cardiovascular risk factors (n = 199) at baseline. The remaining 13,560 participants (2027 black women, 1266 black men, 5481 white women, and 4786 white men) were used in the present analyses of stroke. The study protocol was approved by the Institutional Review Boards of the collaborating institutions and informed written consent was obtained from each participant.

**Baseline Measurements**
Methods for blood processing in the ARIC study have been described. Participants were asked to fast for 12 hours before their morning clinic appointments. Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Lipoprotein(a) was measured as total protein component [apolipoprotein(a) plus apolipoprotein B] with a double-antibody enzyme-linked immunosorbent assay technique for apolipoprotein(a) detection. Plasma fibrinogen and von Willebrand factor antigen were measured by immunosorbent assay technique for apolipoprotein(a) detection. Plasma fibrinogen and von Willebrand factor antigen were measured by an enzyme-linked immunosorbent assay, respectively. Sitting blood pressures were measured using a random-zero sphygmomanometer after 5 minutes of rest. The average of the second and third of 3 consecutive measurements was used to calculate systolic and diastolic blood pressure levels. Body mass index was calculated as weight (kg)/height (m)². The ratio of waist (umbilical level) and hip (maximum buttocks) circumferences (waist-to-hip ratio [WHR]) was calculated as a measure of fat distribution. A 12-lead ECG tracing was obtained, and left ventricular hypertrophy was determined by Cornell voltage criteria. Carotid IMT was measured by high-resolution B-mode ultrasound, based on the technique validated by Pignoli et al, using a Biosound 2000II-SA ultrasound system (Biosound). Sonographers who were trained to use standardized procedures in all study centers read the ultrasound measurements. Far-wall IMT was estimated for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries (right and left) were estimated as the mean of as many 1-mm-apart IMT distances as were available. Detailed descriptions of the ultrasound scanning and reading techniques are described elsewhere.

The mean IMT values at the 6 carotid sites were calculated to many 1-mm-apart IMT distances as were available. Detailed descriptions of the ultrasound scanning and reading techniques are described elsewhere. Mean IMT values at the 6 carotid sites were combined to produce an overall mean IMT. Further, sonographers recorded the presence of a plaque if 2 of the following 3 characteristics were met: (1) wall shape (protrusion into the lumen, loss of alignment with adjacent arterial boundary, roughness of the arterial boundary); (2) wall texture (brighter echoes than adjacent boundaries); and (3) wall thickness (IMT ≥ 1.5 mm).

We defined prevalent coronary heart disease and stroke at baseline, as a self-reported history of a physician-diagnosed heart attack, previous myocardial infarction diagnosed by ECG, previous cardiovascular surgery, previous coronary angioplasty, or previous stroke or TIA identified by a standardized interview.

**End Point Determination**
For the present study, we included stroke events occurring between ARIC visit 1 (1987–1989) and December 31, 2005. TIA were not ascertained. ARIC participants were contacted annually by telephone, and reported hospitalizations and deaths related to possible strokes in the previous year were identified. The annual follow-up retention rate was 93% through 2005, and the rates did not differ appreciably between races. Some additional strokes in those who quit participating in follow-up calls were found through ARIC hospital surveillance. We also surveyed lists of discharges from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events. Abstractors recorded signs and symptoms and photocopied neuroimaging (CT or MRI) and other diagnostic reports if the list of discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, 9th Revision, code 430–438), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or MRI report. Of the stroke-eligible hospitalizations, 92% had at least 1 CT scan, 49% had an MRI of the head, 4% had a cerebral angiography, and 3% had a lumbar puncture. Each eligible case was classified by computer algorithm and by a physician reviewer, according to criteria adapted from the National Survey of Stroke. Disagreements were adjudicated by another reviewer. Details on quality-assurance for ascertainment and classification of stroke are described elsewhere. Qualifying strokes were further classified into definite or probable hospitalized ischemic (cardioembolic or thrombotic) or hemorrhagic stroke on the basis of neuroimaging studies and autopsy, when available.

A stroke was classified as ischemic if a brain CT or MRI revealed acute infarction or showed no evidence of hemorrhage. All definite ischemic strokes were further classified as either lacunar or nonlacunar on the basis of the recorded neuroimaging results. A stroke was classified as lacunar if 2 criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤ 2 cm or unstated size. Definite or probable cardioembolic stroke required the same criteria as ischemic infarction plus either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus, such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus.

**Statistical Analysis**
Differences among the quintiles of carotid IMT in age-, gender-, and race-adjusted mean values or prevalence of potential confounding factors at baseline were calculated using ANOVA or logistic regression models, and their trends were tested using linear regression for continuous variables and logistic regression for dichotomous variables. Median values of the carotid IMT categories were used in these analyses.

Time at risk (time to event or time to censoring) was calculated from the date of the baseline examination to the earliest of the following: date of hospital admission for incident stroke, date of death, date of last follow-up contact, or December 31, 2005. The rate ratios (RR) of incidence of ischemic stroke and its subtypes and 95% CI relative to the lowest quintile of carotid IMT were calculated with adjustment for age and other potential confounding factors using the Cox proportional hazards model. We selected covariates based on previous prospective findings for ischemic stroke in ARIC. Covariates included age (years), gender, race–field center, systolic blood pressure (mm Hg), antihypertensive medication use (yes or no), diabetes status (yes or no), smoking status (never, former, or current smokers), heavy drinking (≥ 252 g/wk of ethanol), WHR, low-density lipoprotein cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), history of coronary heart diseases (yes or no), education level (more than high school, high school or less), left ventricular hypertrophy (yes or no), white blood cell count (cells/mm³), lipoprotein(a) (ug/mL), fibrinogen (mg/dL), and von Willebrand factor (%).
Results

As Table 1 shows, age-, gender-, and race-adjusted mean levels of systolic and diastolic blood pressure, WHR, body mass index, low-density lipoprotein cholesterol, lipoprotein(a), fibrinogen, and white blood cells were positively associated with carotid IMT levels, and high-density lipoprotein cholesterol levels were negatively associated. Higher prevalence of current smoking, diabetes mellitus, heavy drinking, and left ventricular hypertrophy were also associated with greater carotid IMT levels. The von Willebrand factor was not associated with carotid IMT levels.

Among 13,560 men and women followed-up for an average of 15.7 years, 82 hemorrhagic and 621 ischemic stroke cases occurred, including 131 lacunar, 358 nonlacunar, and 132 cardioembolic strokes. As shown in Table 2, the incidence rates of hemorrhagic and ischemic strokes were greater across successive carotid IMT levels. Compared with the participants in the lowest quintile (IMT <0.61 mm), the age-, gender-, and race-adjusted RR of ischemic stroke for those in the other groups were 1.46 (95% CI, 1.02–2.10) for the second quintile (0.61 mm ≤ IMT <0.67 mm), 1.70 (95% CI, 1.20–2.42) for the third quintile (0.67 mm ≤ IMT <0.74 mm), 2.52 (95% CI, 1.80–3.52) for the fourth quintile (0.74 mm ≤ IMT <0.85 mm), and 3.80 (95% CI, 2.73–5.28) for the highest quintile (IMT ≥0.85 mm; P for trend <0.001). The RR were attenuated by additional adjustment for systolic blood pressure, use of antihypertensive medication, diabetes mellitus, smoking status, heavy drinking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, history of coronary heart diseases, education level, WHR, left ventricular hypertrophy, white blood cell, fibrinogen, and von Willebrand factor but remained statistically significant (P for trend <0.001). The age-, gender-, and race-adjusted RR of hemorrhagic stroke was significantly elevated for those in the highest vs lowest quintile of IMT elevated (RR, 2.55; 95% CI, 1.09–5.94) but was attenuated after adjustment for the covariates (RR, 2.34; 95% CI, 0.99–5.58).

Carotid IMT levels were significantly positively associated with risk of each ischemic stroke subtype: lacunar, nonlacunar, and cardioembolic strokes (Table 3). Compared with participants in the lowest quintiles, the age-, gender-, and race-adjusted RR for those in the highest quintile groups were 2.89 (95% CI, 1.50–5.54) for lacunar, 3.61 (95% CI, 2.33–5.59) for nonlacunar, and 6.12 (95% CI, 2.70–13.9) for cardioembolic stroke. The RR were attenuated by additional adjustment for covariates but remained statistically signifi-
cant for nonlacunar and cardioembolic strokes (\(P\) for trend <0.001, respectively). The presence of carotid plaques was also associated with the incidence of each ischemic stroke subtype. Compared with the participants without plaques (n=8,970), the age-, gender-, and race-adjusted RR for those with plaques (n=4,950) were 1.59 (95% CI, 1.11–2.26) for lacunar, 2.00 (95% CI, 1.61–2.47) for nonlacunar, and 2.01 (95% CI, 1.46–2.94) for cardioembolic stroke. The RR were attenuated by additional adjustment for covariates but remained statistically significant for nonlacunar and cardioembolic strokes; the multivariate-adjusted RR for those with plaques were 1.21 (95% CI, 0.87–1.71) for lacunar, 1.66 (95% CI, 1.37–2.02) for nonlacunar, and 1.75 (95% CI, 1.22–2.51) for cardioembolic stroke compared with participants without plaques.

As shown in Table 4, the association between carotid IMT and lacunar stroke was somewhat stronger in blacks than in whites (\(P\) for trend=0.07), whereas there were no racial differences in the associations of carotid IMT with nonlacunar and cardioembolic strokes (\(P\) for interaction >0.15). Compared with the lowest quintile, the age- and gender-adjusted RR of lacunar stroke for the highest quartile of IMT were 5.81 (95% CI, 1.99–17.0; \(P\) for trend <0.001) for blacks and 1.43 (95% CI, 0.58–3.48; \(P\) for trend=0.29) for whites.

### Discussion

Although previous epidemiological studies have documented that carotid IMT predicts future stroke events,1–4 no prospective study has reported whether the association between carotid IMT and incidence of stroke varies by subtype.5–8 Our study found that although carotid IMT levels were associated with the incidence of all stroke subtypes, the estimated risk ratios of carotid intima-media thickening for stroke subtypes were higher for cardioembolic and nonlacunar strokes than for hemorrhagic and lacunar strokes. Further, the associations of carotid IMT with stroke subtypes were also observed for analyses using the presence of plaque.

Previously, a few studies have reported associations between carotid IMT and ischemic stroke subtypes.5–7 Results were inconsistent and limited because these studies were performed in a clinical setting and used a case-control design. A cross-sectional case-control study of 470 cases and 463 controls in France showed that an increased common carotid artery-IMT was associated with all ischemic stroke subtypes, namely atherothrombotic, lacunar, and cardioembolic strokes, even after adjustment for cardiovascular risk factors; the association between common carotid artery-IMT and ischemic stroke was stronger for the atherothrombotic stroke than for other subtypes.5 Another cross-sectional case-control study of 311 cases and 792 controls in Japan observed that...
common carotid artery-IMT and plaque score were significantly associated with atherothrombotic and lacunar strokes but not cardioembolic stroke. Further, a cross-sectional Italian case-control study of 292 cases and 129 controls reported that common carotid artery-IMT values were significantly higher in subjects with nonlacunar stroke vs those with lacunar stroke and control subjects. In the present study, carotid IMT levels were significantly associated with nonlacunar stroke.

### Table 3. Rate Ratios and 95% CI of Ischemic Stroke Subtypes According to Carotid Intima-Media Thickness Levels: ARIC 1987–2005

<table>
<thead>
<tr>
<th>Quintiles of Carotid Intima-Media Thickness (mm)</th>
<th>Q1 (Low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (High)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of cases</td>
<td>13</td>
<td>17</td>
<td>25</td>
<td>32</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-, race-adjusted RR Reference</td>
<td>1.11</td>
<td>1.55</td>
<td>1.97</td>
<td>2.89</td>
<td>&lt;0.001</td>
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<tr>
<td>95% CI</td>
<td>0.54–2.30</td>
<td>0.79–3.05</td>
<td>1.02–3.82</td>
<td>1.50–5.54</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Multivariate-adjusted* RR</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
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<td>. .</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.97</td>
<td>1.14</td>
<td>1.36</td>
<td>1.57</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Nonlacunar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of cases</td>
<td>26</td>
<td>51</td>
<td>50</td>
<td>87</td>
<td>144</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-, race-adjusted RR Reference</td>
<td>1.64</td>
<td>1.45</td>
<td>2.30</td>
<td>3.61</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>95% CI</td>
<td>1.02–2.63</td>
<td>0.90–2.34</td>
<td>1.47–3.60</td>
<td>2.33–5.59</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted* RR</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.91–2.36</td>
<td>0.73–1.92</td>
<td>1.09–2.71</td>
<td>1.44–3.52</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of cases</td>
<td>7</td>
<td>11</td>
<td>25</td>
<td>38</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-, race-adjusted RR Reference</td>
<td>1.39</td>
<td>2.97</td>
<td>4.39</td>
<td>6.12</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.54–3.58</td>
<td>1.28–6.90</td>
<td>1.93–9.98</td>
<td>2.70–13.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted* RR</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
<td>. .</td>
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<td>. .</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.32</td>
<td>2.50</td>
<td>3.49</td>
<td>4.24</td>
<td>&lt;0.001</td>
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</tr>
</tbody>
</table>

ARIC indicate Atherosclerosis Risk in Communities Study; RR, rate ratio.

*Adjusted for age, race–field center, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, smoking status, heavy drinking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, history of coronary heart diseases, education level, waist-to-hip ratio, left ventricular hypertrophy, white blood cell count, lipoprotein(a), fibrinogen, and von Willebrand factor.

### Table 4. Rate Ratios and 95% CI of Ischemic Stroke Subtypes According to Carotid Intima-Media Thickness Levels Stratified by Race: ARIC 1987–2005

<table>
<thead>
<tr>
<th>Quintiles of Carotid Intima-Media Thickness (mm)</th>
<th>Q1 (Low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (High)</th>
<th>P for Trend</th>
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<tbody>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N at risk</td>
<td>548</td>
<td>703</td>
<td>713</td>
<td>693</td>
<td>636</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lacunar, n of cases</td>
<td>4</td>
<td>7</td>
<td>18</td>
<td>20</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>1.32 (0.39–4.52)</td>
<td>3.24 (1.09–9.62)</td>
<td>3.66 (1.24–10.9)</td>
<td>5.81 (1.99–17.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Nonlacunar, n of cases</td>
<td>9</td>
<td>23</td>
<td>17</td>
<td>34</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>1.93 (0.89–4.17)</td>
<td>1.32 (0.59–2.98)</td>
<td>2.59 (1.23–5.48)</td>
<td>3.57 (1.70–7.51)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic, n of cases</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>16</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>0.94 (0.25–3.52)</td>
<td>1.66 (0.51–5.42)</td>
<td>3.02 (0.99–9.23)</td>
<td>3.54 (1.14–11.0)</td>
<td>0.002</td>
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<td>Whites</td>
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<tr>
<td>N at risk</td>
<td>2154</td>
<td>2013</td>
<td>2009</td>
<td>2012</td>
<td>2079</td>
<td>&lt;0.001</td>
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<tr>
<td>Lacunar, n of cases</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>12</td>
<td>16</td>
<td>0.29</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>1.06 (0.43–2.64)</td>
<td>0.68 (0.25–1.87)</td>
<td>1.10 (0.45–2.73)</td>
<td>1.43 (0.58–3.48)</td>
<td>0.29</td>
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<tr>
<td>Nonlacunar, n of cases</td>
<td>17</td>
<td>28</td>
<td>33</td>
<td>53</td>
<td>101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>1.44 (0.78–2.63)</td>
<td>1.50 (0.83–2.71)</td>
<td>2.14 (1.22–3.75)</td>
<td>3.56 (2.07–6.12)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Cardioembolic, n of cases</td>
<td>3</td>
<td>6</td>
<td>16</td>
<td>22</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-, gender-adjusted RR Reference</td>
<td>1.88 (0.47–7.54)</td>
<td>4.66 (1.34–16.1)</td>
<td>5.99 (1.76–20.4)</td>
<td>9.08 (2.69–30.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

ARIC indicates Atherosclerosis Risk in Communities Study; RR, rate ratio.
cunar and cardioembolic strokes, but not hemorrhagic and lacunar strokes, after adjustment for cardiovascular risk factors. This may support the hypothesis, in part, that lacunar and hemorrhagic strokes are different from the other type of ischemic strokes pathophysiologically.

In ARIC, traditional risk factors, such as hypertension, diabetes mellitus, and smoking, were major risk factors for the incidence of ischemic stroke regardless of its subtypes. These traditional risk factors were also important factors for progression of carotid artery atherosclerosis. Therefore, carotid intima-media thickening is most certainly associated with the incidence of all stroke subtypes via chronic atherosclerotic change attributable to hypertension, diabetes, and smoking. However, in addition to the differences in traditional risk factors between hemorrhagic and ischemic strokes, the estimated impacts of several nontraditional risk factors, such as WHR, lipoprotein(a), high-density lipoprotein cholesterol, and von Willebrand factor, on the incidence of ischemic stroke likewise varied according to subtype in ARIC. Left ventricular hypertrophy and von Willebrand factor were independent risk factors for both nonlacunar and cardioembolic stroke; WHR, history of coronary heart disease, and lipoprotein(a) were independent risk factors for nonlacunar stroke only; white blood cell count for both lacunar and cardioembolic stroke; and education level and high-density lipoprotein cholesterol were independent risk factors for lacunar stroke only. This suggests that the etiologic relation of risk factors with ischemic stroke varies by subtype. The present results provide further evidence that carotid intima-media thickening could be related to ischemic stroke not only as a marker of generalized atherosclerosis but also as a source of thromboemboli. A recent study, conducted with 180 patients with ischemic stroke or TIA of undetermined origin, showed that greater carotid IMT was associated with greater cardiovascular sources of emboli identified on transesophageal echocardiography. This may support our results.

In the present study, the association between carotid IMT and lacunar stroke was confined to blacks but not whites. Although we have no clear explanation for this ethnic difference, a greater impact of carotid IMT on incidence of lacunar stroke among blacks may contribute to the difference in the incidence rates of lacunar stroke between blacks and whites. Previously, we showed that blacks had a 5.7-fold higher age- and gender-adjusted RR of lacunar stroke compared with whites, and the excess risk for blacks remained after adjustment for traditional and nontraditional risk factors; the multivariate-adjusted RR was 3.0 (95% CI, 1.9–4.8). In the present study, however, when we further adjusted for carotid IMT levels, the multivariate-adjusted RR remained statistically significant; the RR was 2.96 (95% CI, 1.95–4.49). Therefore, further research is needed to determine factors explaining the difference in the incidence ratio of lacunar stroke between blacks and whites.

This study had some limitations. First, we had only a single assessment of IMT at baseline, and measurement error may have led to misclassification of carotid IMT in some individuals. Second, to evaluate carotid IMT, we used mean far-wall IMT estimated for 1-cm lengths of the carotid bifurcation and the internal and common carotid arteries, whereas previous case-control studies used only the common carotid artery. This difference may have contributed to different results between the present study and previous studies of the association of carotid IMT with the incidence of stroke subtypes. Third, ischemic stroke subtypes may have been misclassified for some participants, even though neuroimaging reports and clinical features were used to classify ischemic stroke cases into subtypes. For example, some embolic strokes attributable to cryptogenic sources of emboli, such as aortic arch atheroma, might be classified into nonlacunar but not cardioembolic stroke. Further, the nonlacunar stroke group could have included some missed lacunar strokes. These may have led to an overestimate or underestimate of the impact of carotid IMT on ischemic stroke subtypes. Fourth, although the associations of carotid IMT with nonlacunar and embolic strokes were found to be independent of cardiovascular risk factors, other residual confounders such as duration of hypertension and other coagulation factors may have affected the associations. Fifth, the lack of assessment of TIA may have biased the observed association between stroke subtypes and carotid IMT, because the association between TIA and incidence of stroke may vary by its subtypes. Sixth, the associations between carotid plaques and the incidence of stroke subtypes may vary by sonographic characteristics of the plaques, such as surface irregularity, ulceration, or dysmorphic echogenicity, which were not measured in this study. Finally, the number of incident strokes differed among stroke subtypes, potentially decreasing precision of RR for hemorrhagic, lacunar, and cardioembolic strokes.

Conclusion
In conclusion, carotid atherosclerosis was associated with all stroke subtypes, but the impact of carotid atherosclerosis on the incidence of stroke may vary by subtypes. Further study is needed to confirm the association of carotid IMT with stroke subtypes in additional large, multi-ethnic, prospective studies.

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

Sources of Funding
The ARIC Study was funded by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

Disclosures
None.

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Carotid Artery Wall Thickness and Risk of Stroke Subtypes: The Atherosclerosis Risk in Communities Study
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Stroke. published online December 16, 2010;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 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/early/2010/12/16/STROKEAHA.110.592261

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