Background and Purpose—Numerous case-control and cross-sectional studies have reported higher median lipoprotein(a) [Lp(a)] levels among stroke patients than controls, but existing prospective studies have not consistently shown an association. We sought to examine the relationship between plasma Lp(a) levels and the incidence of ischemic stroke among blacks and whites.

Methods—Between 1987 and 1989, 14,221 men and women (3647 blacks and 10,574 whites) aged 45 to 64 years and free of clinical cardiovascular disease, took part in the first examination of the Atherosclerosis Risk in Communities (ARIC) study cohort. Lp(a) and other risk factors for cardiovascular disease were measured at baseline.

Results—During the 13.5-year follow-up, 496 ischemic strokes occurred. Participants with Lp(a) ≥300 µg/mL had a 79% higher age, sex, and race-adjusted rate ratio (RR) of ischemic stroke than did those with Lp(a) levels <100 µg/mL. Compared with Lp(a) <100 µg/mL, the multivariate adjusted RRs for Lp(a) ≥300 µg/mL were 1.84 (95% CI, 1.05 to 3.07) in black women, 1.72 (95% CI, 0.86 to 3.48) in black men, 2.42 (95% CI, 1.30 to 4.53) in white women, and 1.18 (95% CI, 0.47 to 2.90) in white men. There was no significant increment in the RRs for 100 to 199 µg/mL and 200 to 299 µg/mL groups.

Conclusions—A high Lp(a) concentration is associated with a higher incidence of ischemic stroke in blacks and white women, but not in white men. (Stroke. 2006;37:1407-1412.)

Key Words: brain infarction ■ epidemiology ■ lipoprotein ■ risk factors

Numerous case-control and cross-sectional studies have reported higher median lipoprotein(a) [Lp(a)] levels among stroke/transient ischemic attack (TIA) patients than controls among whites, blacks, and Asians, but existing prospective studies have not consistently shown an association. Specifically, 4 case-control studies nested within prospective studies failed to demonstrate an association of Lp(a) and the future risk of stroke, but 3 non-nested prospective studies reported that elevated levels of Lp(a) independently predicted an increased risk of stroke/TIA. Because instability of Lp(a) during prolonged storage has been reported, analysis of Lp(a) should be performed on the baseline samples within a year of collection. However, prospective studies that satisfied the above conditions are scarce. Furthermore, no prospective study has examined the relationship between Lp(a) and the incidence of stroke among blacks, despite blacks having approximately twice the median plasma Lp(a) level of whites.

A link between Lp(a) and ischemic stroke is biologically plausible. Apo(a), a unique apolipoprotein contained within Lp(a), has structural homology with plasminogen, so Lp(a) could have a thrombogenic effect by suppressing fibrinolysis. Lp(a) particles are susceptible to oxidative modification and avidly taken up by the scavenger receptor pathway, which leads to intracellular cholesterol accumulation and foam cell formation. Most prior prospective studies did not distinguish ischemic stroke from other types of stroke in their analyses.

To examine the relationship between plasma Lp(a) levels and the incidence of ischemic stroke among blacks and whites, we used data from a 13.5-year follow-up of men and women in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Study Population

The populations surveyed included 15,792 men and women aged 45 to 64 years who participated in the ARIC study between 1987 and 1989 in 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; 8 northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The study design is described in detail elsewhere.
We first 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). We then excluded participants with missing Lp(a) data (n=570) at baseline, participants with a history of coronary heart disease (n=713) at baseline, and participants with a history of stroke or TIA at baseline (n=185). The remaining 14,221 participants were included in the analyses. Subjects were followed to determine the incidence of stroke through 2002. The average (interquartile range) follow-up time was 13.5 (13.3 to 14.9) years. 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 collection and processing in the ARIC study have been described in detail. Participants were asked to fast for 12 hours before their morning clinic appointments. Most of the blood samples were analyzed within 6 weeks of receipt. Lp(a) was measured as total protein component (apolipoprotein(a) plus apolipoprotein B) with a double-antibody ELISA technique for apo(a) detection. This protein moiety represents approximately one-third of total Lp(a) lipoprotein mass. Therefore, a value of 100 µg/mL Lp(a) protein is comparable to a total Lp(a) value of 300 µg/mL. For this assay at Lp(a) protein levels in the range 10 to 100 µg/mL, the contribution from plasminogen at physiological concentrations (2000 µg/mL) was negligible. In a 40-person subsample, the assay reliability (between-person component of the variance divided by the total variance) was 0.90, with essentially no within-person variability (indicative of a largely genetic measurement), and 9% of the total variance was associated with the assay method itself. Total cholesterol and triglycerides were measured by enzymatic methods. High-density lipoprotein (HDL) cholesterol was assayed after dextran sulfate-magnesium precipitation, and low-density lipoprotein (LDL) cholesterol was estimated from the Friedewald equation.

### End Point Determination

For the present study, we included stroke events occurring between ARIC visit 1 and December 31, 2002. TIs were not ascertained. All participants were contacted annually by phone and asked about all hospitalizations and deaths in the previous year. We also surveyed lists of discharges from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events. A nurse abstractor recorded from hospital records 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 to 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. Each eligible case was classified by computer algorithm and by expert reviewer, according to criteria adapted from the National Survey of Stroke. 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. Cardioembolic stroke was defined as an ischemic stroke with establishment of a likely source of embolus, such as valvular heart disease, atrial fibrillation, cardiac or arterial procedure, and intracardiac thrombus. A small number of out-of-hospital fatal strokes (n=4) were not counted as end points.

### Statistical Analysis

Because the distribution of Lp(a) was highly right-skewed in both race groups and differed by race and gender, incidence rates were calculated according to categories of Lp(a) (<100 µg/mL, 100 to 199 µg/mL, 200 to 299 µg/mL, and ≥300 µg/mL) stratified by gender and race. Differences among the categories of Lp(a) in age-adjusted mean values or prevalences of potential confounding factors at baseline were calculated using ANOVA or logistic regression models.

We compared Kaplan-Meier survival plots according to Lp(a) levels stratified by gender and race. The rate ratios of stroke incidence and 95% CIs relative to Lp(a) levels <100 µg/mL were calculated with adjustment for age and other potential confounding factors using the Cox proportional hazards model. The proportional hazards assumption was confirmed. Covariates included age (years), race-field center, systolic blood pressure (mm Hg), antihypertensive medica-
tion (yes, no), smoking status (never, former, and current smokers), use of postmenopausal hormone therapy (yes, no), diabetes status (yes, no), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), fibrinogen (mg/dL), and von Willebrand factor (%).

**Results**

Mean (SD) and median values (interquartile range) of Lp(a) at baseline were 167 (128), 137 (74 to 228) μg/mL for black women, 146 (112), 119 (64 to 195) μg/mL for black men, 86 (97), 48 (20 to 118) μg/mL for white women, and 73 (86), 39 (17 to 97) μg/mL for white men. Age- and gender-adjusted geometric mean values of Lp(a) were higher in blacks than whites \((P<0.001)\), and age- and race-adjusted geometric mean values of Lp(a) were higher in women than men \((P<0.001)\).

Table 1 shows age-, gender-, and race-adjusted mean values or prevalences of risk characteristics at baseline according to Lp(a) levels. The proportions of black women, white women, black men, and white men who had Lp(a) levels \(\geqslant 300 \mu g/mL\) were 13.6%, 4.6%, 9.8%, and 2.8%. LDL cholesterol and fibrinogen levels were greater with increasing Lp(a) levels. Higher Lp(a) levels also tended to be associated with lower prevalence of taking estrogen or progesterone. BMI and smoking status were not associated with Lp(a) levels.

Among 14 221 men and women followed for an average 13.5 years, 83 incident hemorrhagic strokes and 496 incident ischemic strokes (103 lacunar, 302 nonlacunar, and 91 cardioembolic) occurred. Participants with Lp(a) \(\geqslant 300 \mu g/mL\) had a 79% higher age-, sex-, and race-adjusted rate ratio (RR) of ischemic stroke than did those with Lp(a) levels \(<100 \mu g/mL\); the RR was 1.79 (95% CI, 1.32 to 2.42). As the Figure shows, Kaplan-Meier plots for ischemic stroke were significantly different by Lp(a) level in black women (log-rank test, \(P=0.03\)) and white women \((P=0.0005)\), but not black men \((P=0.69)\) and white men \((P=0.90)\).

Compared with Lp(a) \(<100 \mu g/mL\), the multivariate-adjusted RRs for Lp(a) \(\geqslant 300 \mu g/mL\) were 1.84 (95% CI, 1.05 to 3.07) in black women, 1.72 (95% CI, 0.86 to 3.48) in black men, 2.42 (95% CI, 1.30 to 4.53) in white women, and 1.18 (95% CI, 0.47 to 2.90) in white men (Table 2). There was no significant increment in the RRs for the 100 to 199 μg/mL and 200 to 299 μg/mL groups. When we excluded cardioembolic strokes, the associations of Lp(a) levels with ischemic stroke incidence in men grew stronger. The respective multivariate-adjusted RRs for Lp(a) \(\geqslant 300 \mu g/mL\) versus Lp(a) \(<100 \mu g/mL\) were 1.78 (95% CI, 0.97 to 3.29) in black women, 2.08 (95% CI, 1.01 to 4.38) in black men, 2.25 (95% CI, 1.10 to 4.60) in white women, and 1.47 (95% CI, 0.59 to 3.65) in white men. There were no interactions between Lp(a) and race or gender \((P\) for interaction were \(>0.10\)) for ischemic stroke.
Discussion
This prospective study found that increased levels of Lp(a) were associated positively and independently with the incidence of ischemic stroke in black and white women. The association of Lp(a) with ischemic stroke incidence was also seen among black men after excluding cardioembolic strokes. The multivariate-adjusted RRs for ischemic stroke were not very different between black women and men, but Lp(a) was not associated with ischemic stroke among white men.

Three previous prospective studies of stroke incidence, in which Lp(a) was measured concurrent with a baseline examination, reported that elevated levels of Lp(a) independently predicted an increased risk of stroke/TIA. The Cardiovascular Health Study, conducted among 3972 elderly people, showed that higher Lp(a) levels were independently associated with increased risk of stroke in men but not in women. Another prospective study of 11,335 middle-aged whites reported significant positive associations between Lp(a) and stroke/TIA incidence in men but not in women. On the other hand, the Framingham Heart Study showed that elevated plasma Lp(a) was an independent predictor of stroke/TIA in 3103 middle-aged women. Although Lp(a) levels were positively associated with LDL cholesterol and fibrinogen levels, these previous prospective studies did not control the effect of these confounders. Further, these studies did not distinguish ischemic stroke from other types of strokes in their analyses. Because the pathogenesis is different between ischemic and hemorrhagic stroke, it is difficult to compare the results of these previous studies with our results. A previous ARIC study reported that plasma lipids, such as triglycerides and HDL cholesterol, were weakly associated with incidence of ischemic stroke in women but not men, which shows the possibility that effects of lipids on incidence of ischemic stroke may differ according to sex.

The present study showed no monotonic dose-response relationship between Lp(a) levels and ischemic stroke incidence, which suggests the existence of a threshold relationship. The Cardiovascular Health Study also reported that the

**TABLE 2. RR and 95% CI of Ischemic Stroke According to Lp(a) Levels Stratified by Gender and Race: ARIC 1987–2002**

<table>
<thead>
<tr>
<th>Lp(a) Range (μg/ml)</th>
<th>&lt;100</th>
<th>100–199</th>
<th>200–299</th>
<th>≥300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>828</td>
<td>745</td>
<td>397</td>
<td>311</td>
</tr>
<tr>
<td>No. of cases</td>
<td>33</td>
<td>42</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>10,935</td>
<td>9,757</td>
<td>5,297</td>
<td>3,931</td>
</tr>
<tr>
<td>Incidence rate/1000 person-years</td>
<td>3.0</td>
<td>4.3</td>
<td>3.6</td>
<td>6.4</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>Ref.</td>
<td>1.36 (0.86–2.15)</td>
<td>1.09 (0.62–1.92)</td>
<td>2.00 (1.19–3.37)</td>
</tr>
<tr>
<td>Multivariate-adjusted* RR (95% CI)</td>
<td>...</td>
<td>1.24 (0.78–1.98)</td>
<td>0.98 (0.54–1.81)</td>
<td>1.84 (1.05–3.20)</td>
</tr>
<tr>
<td>Black men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>559</td>
<td>475</td>
<td>198</td>
<td>134</td>
</tr>
<tr>
<td>No. of cases</td>
<td>35</td>
<td>30</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>70,39</td>
<td>59,34</td>
<td>2,497</td>
<td>1,650</td>
</tr>
<tr>
<td>Incidence rate/1000 person-years</td>
<td>5.0</td>
<td>5.1</td>
<td>5.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>Ref.</td>
<td>1.00 (0.62–1.63)</td>
<td>1.02 (0.54–1.93)</td>
<td>1.46 (0.76–2.81)</td>
</tr>
<tr>
<td>Multivariate-adjusted* RR (95% CI)</td>
<td>...</td>
<td>1.03 (0.62–1.71)</td>
<td>0.90 (0.46–1.77)</td>
<td>1.72 (0.86–3.48)</td>
</tr>
<tr>
<td>White women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>4088</td>
<td>9,38</td>
<td>460</td>
<td>263</td>
</tr>
<tr>
<td>No. of cases</td>
<td>80</td>
<td>15</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>56,847</td>
<td>12,901</td>
<td>6,282</td>
<td>3,559</td>
</tr>
<tr>
<td>Incidence rate/1000 person-years</td>
<td>1.4</td>
<td>1.2</td>
<td>1.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>Ref.</td>
<td>0.83 (0.48–1.44)</td>
<td>1.23 (0.65–2.31)</td>
<td>2.56 (1.42–4.60)</td>
</tr>
<tr>
<td>Multivariate-adjusted* RR (95% CI)</td>
<td>...</td>
<td>0.90 (0.52–1.56)</td>
<td>1.31 (0.69–2.47)</td>
<td>2.42 (1.30–4.53)</td>
</tr>
<tr>
<td>White men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. at risk</td>
<td>3648</td>
<td>756</td>
<td>287</td>
<td>134</td>
</tr>
<tr>
<td>No. of cases</td>
<td>123</td>
<td>30</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>49,095</td>
<td>10,246</td>
<td>3,807</td>
<td>1,777</td>
</tr>
<tr>
<td>Incidence rate/1000 person-years</td>
<td>2.5</td>
<td>2.9</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>Ref.</td>
<td>1.15 (0.77–1.72)</td>
<td>1.07 (0.56–2.03)</td>
<td>1.19 (0.49–2.92)</td>
</tr>
<tr>
<td>Multivariate-adjusted* RR (95% CI)</td>
<td>...</td>
<td>1.14 (0.76–1.71)</td>
<td>0.98 (0.50–1.95)</td>
<td>1.18 (0.47–2.90)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race-field center, systolic blood pressure, use of antihypertensive medication, smoking status, use of postmenopausal hormone therapy, diabetes status, LDL cholesterol, HDL cholesterol, fibrinogen, and von Willebrand factor.
association was not linear, with a multivariate-adjusted relative risk for the highest versus lowest quintile of Lp(a) in men being 2.92 (95% CI, 1.53 to 5.57). The other 2 prospective studies detected Lp(a) qualitatively as a sinking pre-β-lipoprotein band on electrophoresis, and could not assess a dose-response relationship between Lp(a) levels and stroke incidence. The first strength of the present study is that measurement of Lp(a) was performed on the baseline samples within 6 weeks of collection to avoid effects of prolonged storage. Kronenberg et al measured Lp(a) levels after 3 and 28 months of storage at −80°C and reported that Lp(a) decreased markedly, more in subjects with low-molecular-weight isoforms than with high-molecular-weight apo(a) isoforms. Because low-molecular-weight apo(a) isoforms are more frequent in patients with atherothrombotic disease compared with control subjects, long storage of blood samples may create biased associations between Lp(a) levels and stroke incidence. Simo et al measured Lp(a) levels in 65 survivors of myocardial infarction and 95 age-matched controls before and after storage for 5 years at −70°C. During storage, mean Lp(a) levels decreased significantly in samples from patients (−23%) but not in samples from controls (−9%), which also supports the above hypothesis. Four previous case-control studies nested within prospective studies measured Lp(a) after storage for 7 to 14 years. This prolonged storage may be one reason why these studies failed to demonstrate an association of Lp(a) and the future risk of stroke. On the other hand, 3 non-nested prospective studies, which measured Lp(a) within a year after storage, reported that elevated levels of Lp(a) independently predicted an increased risk of stroke.

A second strength was our study’s inclusion of both blacks and whites, with a relatively large number of events. Although the median plasma Lp(a) level in blacks is approximately twice as high as in whites, no prospective study has examined the relationship between Lp(a) and the incidence of stroke among blacks. The present study suggests that higher Lp(a) levels are associated with increased risk of ischemic stroke in women, with higher RRs in whites than blacks. However, it is not necessarily the case that Lp(a) confers less cardiovascular disease risk in blacks than whites. Because the frequency of high Lp(a) levels (≥300 μg/mL) was higher in blacks than whites, the population-attributable fractions of ischemic stroke for high Lp(a) levels are higher in blacks than in whites (6.2% versus 2.7% in women, 4.1% versus 0.4% in men).

Potential limitations of this study warrant consideration. First, we analyzed the associations between Lp(a) and ischemic stroke incidence using a single assessment of Lp(a) at baseline, which may lead to misclassification of the habitual Lp(a) levels of some individuals. However, Lp(a) is primarily genetically determined, and therefore is little influenced by age, diet and lifestyle. Second, many blacks with high plasma levels of Lp(a) have apo(a) isoforms of intermediate size, whereas most whites with high plasma levels of Lp(a) have a small apo(a) isoform. Because elevated levels of Lp(a) with small apo(a) isoforms independently predict risk of cardiovascular disease in blacks, it may be important to measure apo(a) isoforms in future studies.

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Lipoprotein(a) and Incident Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study
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