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Plasma Lipid Profile and Incident Ischemic Stroke
The Atherosclerosis Risk in Communities (ARIC) Study
Eyal Shahar, MD, MPH; Lloyd E. Chambless, PhD; Wayne D. Rosamond, PhD; Lori L. Boland, MPH; Christie M. Ballantyne, MD; Paul G. McGovern, PhD†; A. Richey Sharrett, MD, DrPH

Background and Purpose—The role of circulating lipids and lipoproteins in the pathogenesis of ischemic stroke remains uncertain despite 3 decades of research. We examined this issue in a large population-based cohort.

Methods—Between 1987 and 1989, 14 175 middle-aged men and women, free of clinical cardiovascular disease, took part in the first examination of the Atherosclerosis Risk in Communities (ARIC) study cohort. Baseline measurements included plasma levels of LDL cholesterol, HDL cholesterol, apolipoprotein B, apolipoprotein A-1, and triglycerides and myriad risk factors for cardiovascular disease. The cohort was followed for cardiovascular disease end points.

Results—Over an average follow-up of 10 years (142 704 person-years at risk), we documented clinical ischemic stroke in 305 participants (161 men and 144 women). After multivariable adjustment for stroke risk factors, categorical and spline regression analyses of the entire sample, as well as the sample of men alone, revealed weak and inconsistent associations between ischemic stroke and each of the 5 lipid factors. Among women, the most consistent findings were decreasing risk of ischemic stroke within the top half of the distribution of HDL cholesterol and increasing risk within the lower range of the triglyceride distribution.

Conclusions—The relation of circulating cholesterol to ischemic stroke does not resemble its well-known relation to coronary heart disease. Either the pathogenesis of a substantial proportion of ischemic strokes does not involve classic atherosclerotic mechanisms, or the effect of plasma lipids on atherogenesis is substantially different in the intracranial vascular bed. (Stroke. 2003;34:623-631.)

Key Words: cholesterol $$\bullet$$ lipids $$\bullet$$ stroke, ischemic

Atherosclerosis afflicts multiple vascular beds, accounting for nearly all of coronary heart disease and some proportion of ischemic strokes. Although the role of cholesterol subfractions in acute coronary syndromes is well documented, it is still unclear whether the lipid profile plays an important etiologic role in ischemic stroke.

Three decades of research of this topic have yielded inconsistent results$^{1-19}$ and have led to sharply opposing viewpoints about the importance of circulating cholesterol in ischemic stroke.$^{10,20-24}$ At least part of the controversy can be attributed to methodological shortcomings of previous work. Many studies have not examined the end point of interest, namely, incident ischemic stroke, but rather have examined end points such as fatal stroke or a combination of ischemic stroke and hemorrhagic stroke, 2 distinctly different pathophysiological entities. Some studies lacked data on cholesterol subfractions or relied on poststroke measurements of the lipid profile. Few studies were large enough to examine the dose-response pattern within each sex group.

In the present study, we report results from a large prospective cohort study of incident ischemic stroke in relation to several components of the plasma lipid profile, measured at the time of recruitment.

Subjects and Methods
The Atherosclerosis Risk in Communities (ARIC) Study is a cohort study of atherosclerosis and cardiovascular disease in 4 US communities: Forsyth County, NC; the city of Jackson, Miss; 8 northwestern suburbs of Minneapolis, Minn; and Washington County, Md. The study design is described in detail elsewhere.$^{25}$ In brief, between 1987 and 1989, each field center recruited and examined $\sim$4000 subjects aged 45 to 64 years. African American residents were exclusively recruited in Jackson and oversampled in Forsyth County, whereas participants from the other 2 communities were predominantly white. Approximately 46% of sampled and eligible subjects in Jackson and 65% to 67% in the other sites agreed to take part in the baseline examination. The cohort reasonably represented its source communities with respect to numerous variables.$^{26,27}$

The study protocol was approved by the institutional review boards of the collaborating institutions. Informed written consent was obtained from each participant.
Baseline Plasma Measurements
Methods for blood collection and processing in ARIC have been described in detail. Participants were asked to fast for 12 hours before their morning clinic appointments, and blood was drawn from an antecubital vein with minimal trauma. The plasma was separated by centrifugation at 4°C and divided into tubes containing EDTA. Aliquots were stored locally at ~70°C until shipping on dry ice to a central lipid laboratory, where they were stored again at ~70°C until analysis. Most of the samples were analyzed within 6 weeks of receipt.

Plasma total cholesterol and triglycerides were measured by enzymatic methods, with the use of reagents supplied by Boehringer-Mannheim Biochemical, and were adapted for analysis in the Cobas-Bioanalyzer (Roche). The HDL cholesterol (HDL-C) level was measured by the method of Warnick et al., and the HDL-C cholesterol level was determined after reprecipitation of the total HDL-C supernatant. The level of HDL-C was calculated by subtracting HDL from total HDL-C. The concentration of LDL cholesterol (LDL-C) was calculated from the concentrations of total cholesterol, HDL-C, and triglycerides by the Friedewald formula. Apolipoprotein (apo) B was not assessed. To provide insight into variability due to intraindividual variability study demonstrated excellent short-term repeatability of most lipoprotein measurements in ARIC, with reliability coefficient ($R = 0.85$ for LDL-C, HDL-C, and triglycerides. The repeatability of apoA-I was not as good ($R = 0.60$). ApoB was not assessed. To provide insight into variability due to storage, shipping, and processing of samples, duplicate aliquots from ~5% of the samples were shipped to the central laboratory a week after the original shipping. The coefficients of variation for these replicates of total cholesterol, LDL-C, HDL-C, apoB, apoA-I, and triglycerides were 5%, 10%, 5%, 16%, 14%, and 7%, respectively.

Plasma fibrinogen and von Willebrand factor antigen were measured by the thrombin time titration method and ELISA, respectively. Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method.

Other Baseline Measurements and Definitions
Trained interviewers obtained information on demographic variables, educational attainment, smoking habits, and medical history. Education level was classified into 3 categories: less than high school, high school graduate, and education beyond high school. Smoking status (current, former, or never) and pack-years of smoking were derived from relevant questions. Prevalent cardiovascular disease was defined as self-report of physician-diagnosed myocardial infarction or stroke, ECG evidence of a previous myocardial infarction, or having undergone a revascularization procedure. Prevalent diabetes mellitus was defined as nonfasting glucose level $>11.1$ mmol/L (200 mg/dL), fasting glucose $>7.0$ mmol/L (126 mg/dL), a history of diabetes, or pharmacological treatment for diabetes. Three successive measurements of systolic and diastolic blood pressure were taken after a 5-minute rest with the use of a random-zero sphygmomanometer; the average of the last 2 measurements was used in this analysis. A 12-lead ECG tracing was obtained, and left ventricular hypertrophy was determined by Cornell voltage criteria. Participants were asked to bring all medications they had been taking during the 2-week period before the examination. Medication names were transcribed from the labels, and cholesterol-lowering agents and antihypertensive drugs were subsequently identified.

Ascertainment of Hospitalized Stroke
ARIC end-point ascertainment and classification of stroke are described in detail elsewhere. Participants (or next of kin in the case of death) were contacted annually by phone and asked about all hospitalizations in the previous year. In addition, lists of discharges from community hospitals were examined to identify unreported hospitalizations of cohort members. A hospitalization was reviewed for evidence of acute stroke 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 magnetic resonance (MR) report. A few out-of-hospital deaths with stroke listed as the underlying cause ($n = 4$) were not validated and, therefore, are not included in this analysis.

Relevant sections of the medical record were copied and abstracted by a single trained nurse. The abstraction form included items about the type, timing, and duration of neurological symptoms and signs, medical history, and results of relevant diagnostic procedures, including CT and MR of the brain.

Classification of Hospitalized Stroke
ARIC adopted the National Survey of Stroke criteria for clinical stroke. An event was classified as a probable or definite new stroke if all of the following criteria were met: (1) evidence of sudden or rapid onset of neurological symptoms that lasted $>24$ hours or led to death within 24 hours; (2) no evidence of pathology that could have mimicked stroke, such as brain tumor and subdural hemorrhage; and (3) presence of 1 “major” neurological deficit (eg, aphasia or hemiparesis) or 2 “minor” deficits (eg, diplopia and dysarthria). Qualifying clinical strokes were further classified into subtypes on the basis of neuroimaging studies and autopsy, when available. A stroke was classified as ischemic if a brain CT or MR revealed acute infarction or showed no evidence of hemorrhage.

The stroke criteria were translated into a computer algorithm. In addition, a physician reviewer classified each potential event by using the hospital discharge summary and reports of neurology consultation and diagnostic procedures. The reviewer was also provided with a summary of abstracted chart data but was otherwise blinded to the computer classification of the event. Disagreements between the computer classification and the reviewer classification were adjudicated by a second physician reviewer. Although the reviewers followed the ARIC algorithm, they used their own discretion whenever the algorithm classification clearly failed to match the clinical picture.

Analysis
A total of 15,792 subjects took part in the baseline ARIC study examination. Of these, 1392 observations were excluded for the following hierarchical reasons: history of cardiovascular disease (n=988), unknown stroke status at baseline (n=41), and use of a cholesterol-lowering medication (n=363). Because of missing data, the available sample size for various models ranged from 13,110 to 14,175 observations.

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, 1998.

Initial analyses were conducted on the entire sample, categorizing each of the 5 main analytes (LDL-C, HDL-C, apoB, apoA-1, and triglycerides) into quartiles, as well as dichotomizing each upper quartile at its median value. We computed the person-years at risk for each category and category-specific rates of ischemic stroke. Unadjusted (marginal) associations were estimated by crude rate ratios, contrasting the upper 3 quartiles and the 2 categories of the top quartile with the bottom quartile. Multivariable-adjusted hazard rate ratios and 95% CIs were estimated by Cox regression. We included an extensive list of determinants of ischemic stroke in the final models but also examined several models with fewer covariates. The results were not materially different.

Our analyses consistently indicated sex differences in the associations of ischemic stroke with some of the analytes, which were evident in either formal statistical tests for a multiplicative interaction or graphical display of dose-response functions. Therefore, we stratified the sample on sex and replicated the original analysis, using the sex-specific distribution of each analyte to group the observations.
Results

Of the 5 analytes (LDL-C, apoB, HDL-C, apoA-1, and triglycerides), 2 pairs were strongly correlated, as previously reported; LDL-C with apoB (Pearson correlation coefficient 0.73) and HDL-C with apoA-1 (Pearson correlation coefficient 0.78). All other pairwise correlations were weak to moderate, ranging from −0.41 to 0.32. Overall and sex-specific distributions were bell-shaped and fairly symmetrical except for the distribution of triglycerides, which was skewed to the right for both sexes. Median values (interquartile range) among men were as follows: LDL-C, 3.54 (2.93 to 4.18) mmol/L; apoB, 0.92 (0.75 to 1.11) g/L; HDL-C, 1.10 (0.92 to 1.32) mmol/L; apoA-1 1.20 (1.04 to 1.37) g/L; and triglycerides, 1.31 (0.93 to 1.86) mmol/L. The corresponding values among women were as follows: LDL-C, 3.40 (2.78 to 4.11) mmol/L; apoB, 0.87 (0.70 to 1.07) g/L; HDL-C, 1.44 (1.17 to 1.74) mmol/L; apoA-1, 1.40 (1.21 to 1.61) g/L; and triglycerides, 1.15 (0.84 to 1.63) mmol/L.

Over an average follow-up of 10 years, the cohort contributed 142 704 person-years at risk (61 136 men-years and 81 568 women-years). We documented 305 incident ischemic strokes: 161 among men and 144 among women.

Table 1 shows multivariable-adjusted associations of incident ischemic stroke with various risk factors, all of which were subsequently included as covariates in regression models. The results are largely consistent with previous findings from previous studies, including previous analyses of ARIC data.

The results of categorical analysis of the entire sample are shown in Table 2. Unadjusted hazard rate ratios are in accordance with expectation (>1.0 for LDL-C, apoB, and triglycerides; <1.0 for HDL-C and apoA-1), but multivariable-adjusted estimates are much closer to the null value. Furthermore, adjusted associations are weak, sometimes inconsistent in direction, and generally lack monotonicity of the risk function across ascending categories. Most adjusted hazard rate ratios are close to 1 and relatively precise (upper to lower 95% confidence limit ratios of ≈2).

Tables 3 and 4 show the results of sex-specific categorical analysis. Among women (Table 3), there is some suggestion of modest incremental risk within the top quartile of LDL-C and apoB (contrasting levels above and below the median) but an inconsistent pattern in lower quartiles. Similarly, there is some suggestion of a lower risk with increasing HDL-C within the top quartile, especially above its median (1.99 mmol/L, 77 mg/dL), but again, the pattern is inconsistent in quartiles I through III. The risk of ischemic stroke is relatively stable across quartiles of apoA-1 and modestly increases across quartiles of triglycerides.

With 1 questionable exception (top quartile of LDL-C), none of the 5 analytes was associated with incident ischemic stroke among men (Table 4). Any possible association, if at all, is weak and inconsistent across categories. Some of the estimates (eg, the second and third quartiles of apoB) do not even corroborate the hypothesized effect.

Categorical analysis imposes a fairly strict dose-response pattern on the data, namely, homogeneous risk within each category, and the results are sometimes sensitive to the choice of categories. Figures 1 and 2 depict, for women and
men, respectively, a less restrictive semiparametric dose-response analysis. The y-axis is a measure of stroke risk, with greater values indicating greater risk. (The baseline risk, log[hazard] = 0, was arbitrarily defined in the present study as the log hazard at the 25th percentile of each analyte and the mean value of each covariate.) To put the y-axis scale in the perspective of hazard ratios, one might keep in mind that increments of 0.25, 0.5, 0.75, and 1.0 on a log scale correspond to hazard ratios of 1.28, 1.65, 2.12, and 2.72, respectively. (For decrements, take the inverse value.) The stroke risk function for each analyte is displayed in a solid line along with 95% CIs (dashed lines).

The dose-response patterns in these graphs corroborate and extend the results of the categorical analysis. Among women (Figure 1), we note again some suggestion of increasing risk of ischemic stroke at the upper tail of the distributions of LDL-C and apoB, yet there is no solid evidence for important or consistent effects at lower values. Through most of the distributions of LDL-C and apoB, the risk function is fairly flat, varying within a vertical distance of 0.25 (hazard ratios of 0.78 to 1.28). Of course, some extreme contrasts, if true, are substantially larger. For example, the estimated hazard ratio for the 95th percentile of apoB (1.45 g/L) versus the 5th percentile (0.52 g/L) is 2.1. The HDL-C graph suggests that the risk of ischemic stroke among women starts to decline around the median value (1.44 mmol/L, 56 mg/dL) rather than the 75th percentile (1.74 mmol/L, 67 mg/dL) as computed from quartile analysis (Table 3). The estimated hazard ratio for HDL-C of 2.32 mmol/L (95th percentile) versus any value below the median is 0.5. A similar pattern was observed for HDL-2 and HDL-3 (not shown). The risk function for the concentration of triglycerides suggests rap-

### TABLE 2. Hazard Ratios (HR) of Ischemic Stroke According to Quartile of Plasma Lipids

<table>
<thead>
<tr>
<th>Variable</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>IVa</th>
<th>IVb</th>
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<tr>
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<td>56</td>
<td>67</td>
<td>102</td>
<td>49</td>
<td>53</td>
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<tr>
<td>Person years</td>
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<td>34 856</td>
<td>34 838</td>
<td>17 469</td>
<td>17 369</td>
</tr>
<tr>
<td>Crude HR</td>
<td>Ref.</td>
<td>0.89</td>
<td>1.07</td>
<td>1.62</td>
<td>1.56</td>
<td>1.69</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>...</td>
<td>0.83</td>
<td>0.91</td>
<td>1.26</td>
<td>1.32</td>
<td>1.22</td>
</tr>
<tr>
<td>95% CI*</td>
<td>...</td>
<td>0.57–1.20</td>
<td>0.64–1.30</td>
<td>0.91–1.76</td>
<td>0.89–1.95</td>
<td>0.83–1.79</td>
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<td>Apolipoprotein B</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
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<td>59</td>
<td>64</td>
<td>111</td>
<td>46</td>
<td>65</td>
</tr>
<tr>
<td>Person years</td>
<td>35 228</td>
<td>34 469</td>
<td>36 715</td>
<td>34 076</td>
<td>17 523</td>
<td>16 554</td>
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<tr>
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<td>Ref.</td>
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<td>1.89</td>
<td>1.52</td>
<td>2.28</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>...</td>
<td>0.97</td>
<td>0.84</td>
<td>1.31</td>
<td>1.12</td>
<td>1.47</td>
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<td>95% CI*</td>
<td>...</td>
<td>0.67–1.41</td>
<td>0.59–1.22</td>
<td>0.94–1.82</td>
<td>0.75–1.69</td>
<td>1.01–2.12</td>
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<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
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<td>77</td>
<td>81</td>
<td>44</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Person years</td>
<td>34 389</td>
<td>36 003</td>
<td>35 476</td>
<td>34 671</td>
<td>18 150</td>
<td>16 520</td>
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<tr>
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<td>Ref.</td>
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<td>0.84</td>
<td>0.47</td>
<td>0.47</td>
<td>0.47</td>
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<tr>
<td>Adjusted HR*</td>
<td>...</td>
<td>0.86</td>
<td>1.03</td>
<td>0.81</td>
<td>0.79</td>
<td>0.83</td>
</tr>
<tr>
<td>95% CI*</td>
<td>...</td>
<td>0.62–1.18</td>
<td>0.74–1.43</td>
<td>0.54–1.20</td>
<td>0.48–1.28</td>
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<td>Apolipoprotein A-1</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of events</td>
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<td>65</td>
<td>83</td>
<td>60</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Person years</td>
<td>35 531</td>
<td>34 020</td>
<td>35 352</td>
<td>35 646</td>
<td>18 187</td>
<td>17 459</td>
</tr>
<tr>
<td>Crude HR</td>
<td>Ref.</td>
<td>0.78</td>
<td>0.96</td>
<td>0.69</td>
<td>0.72</td>
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</tr>
<tr>
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<td>...</td>
<td>0.83</td>
<td>1.07</td>
<td>0.91</td>
<td>0.94</td>
<td>0.89</td>
</tr>
<tr>
<td>95% CI*</td>
<td>...</td>
<td>0.59–1.16</td>
<td>0.77–1.47</td>
<td>0.64–1.31</td>
<td>0.61–1.45</td>
<td>0.56–1.41</td>
</tr>
<tr>
<td>Triglycerides</td>
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<td></td>
</tr>
<tr>
<td>No. of events</td>
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<td>61</td>
<td>64</td>
<td>92</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Person years</td>
<td>34 367</td>
<td>33 885</td>
<td>33 971</td>
<td>33 906</td>
<td>17 180</td>
<td>16 726</td>
</tr>
<tr>
<td>Crude HR</td>
<td>Ref.</td>
<td>1.32</td>
<td>1.38</td>
<td>1.99</td>
<td>1.84</td>
<td>2.15</td>
</tr>
<tr>
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<td>...</td>
<td>1.18</td>
<td>1.06</td>
<td>1.21</td>
<td>1.24</td>
<td>1.18</td>
</tr>
<tr>
<td>95% CI*</td>
<td>...</td>
<td>0.80–1.75</td>
<td>0.72–1.58</td>
<td>0.83–1.77</td>
<td>0.80–1.91</td>
<td>0.76–1.83</td>
</tr>
</tbody>
</table>

*From a Cox regression model that included the following covariates: age, sex, race-field center, systolic blood pressure, use of antihypertensive medications, smoking status, pack-years of smoking, diabetes status, left ventricular hypertrophy by ECG, plasma levels of fibrinogen and von Willebrand factor, and education level.
TABLE 3. Hazard Ratios (HR) of Ischemic Stroke According to Sex-Specific Quartile of Plasma Lipids: Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>I (≤25th)</th>
<th>II (25th–49th)</th>
<th>III (50th–74th)</th>
<th>IV (≥75th)</th>
<th>IVa (75th–87th)</th>
<th>IVb (≥87th)</th>
</tr>
</thead>
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<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No. of events</td>
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<td>26</td>
<td>29</td>
<td>54</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
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<td>Ref.</td>
<td>0.90</td>
<td>0.86</td>
<td>1.33</td>
<td>1.13</td>
<td>1.51</td>
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<tr>
<td>95% CI</td>
<td>...</td>
<td>0.51–1.59</td>
<td>0.50–1.49</td>
<td>0.81–2.20</td>
<td>0.61–2.09</td>
<td>0.67–2.61</td>
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<tr>
<td>Apolipoprotein B</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
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<td>30</td>
<td>25</td>
<td>60</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>Ref.</td>
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<td>0.82</td>
<td>1.61</td>
<td>1.41</td>
<td>1.79</td>
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<tr>
<td>95% CI</td>
<td>...</td>
<td>0.78–2.39</td>
<td>0.45–1.47</td>
<td>0.96–2.69</td>
<td>0.77–2.58</td>
<td>1.02–3.15</td>
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<td>HDL cholesterol</td>
<td></td>
<td></td>
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<td>No. of events</td>
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<td>32</td>
<td>15</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Adjusted HR*</td>
<td>Ref.</td>
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<td>1.06</td>
<td>0.68</td>
<td>0.87</td>
<td>0.48</td>
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<td>95% CI</td>
<td>...</td>
<td>0.83–1.99</td>
<td>0.65–1.72</td>
<td>0.36–1.27</td>
<td>0.42–1.83</td>
<td>0.18–1.23</td>
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<td>Apolipoprotein A-1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>37</td>
<td>45</td>
<td>30</td>
<td>26</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>Ref.</td>
<td>1.31</td>
<td>1.01</td>
<td>1.04</td>
<td>1.22</td>
<td>0.82</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>0.83–2.07</td>
<td>0.61–1.67</td>
<td>0.62–1.76</td>
<td>0.67–2.22</td>
<td>0.39–1.73</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>16</td>
<td>23</td>
<td>37</td>
<td>45</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>Ref.</td>
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<td>1.43</td>
<td>1.48</td>
<td>1.00</td>
<td>1.97</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>0.59–2.15</td>
<td>0.78–2.62</td>
<td>0.80–2.73</td>
<td>0.47–2.15</td>
<td>1.01–3.84</td>
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</table>

*From a Cox regression model that included the following covariates: age, race-field center, systolic blood pressure, use of antihypertensive medications, smoking status, pack-years of smoking, diabetes status, left ventricular hypertrophy by ECG, plasma levels of fibrinogen and von Willebrand factor, and education level.

Discussed

Ischemic stroke is a heterogeneous pathophysiological entity in which vastly different pathways might lead to indistinguishable clinical presentations. Well-recognized mechanisms of ischemic stroke include cardiac or artery-to-artery embolism, atherothrombosis of an extracranial carotid or intracranial artery, and nonatherosclerotic disease of small-diameter penetrating arteries. However, it is generally accepted that atherosclerosis of extracranial or intracranial arteries accounts for a substantial proportion of clinical ischemic strokes via artery-to-artery embolization of plaque-associated thrombi or in situ (distal) atherothrombotic occlusion. Accordingly, known contributors to atherogenesis, often studied in the context of coronary disease, are assumed to be determinants of ischemic stroke. In particular, it has been hypothesized that the concentrations of cholesterol subtraction in the circulation play an important etiologic role, much like their role in acute and chronic coronary syndromes. Clearly documented benefits of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in ischemic stroke prevention have lent support to this hypothesis.

Surprisingly, neither the present study nor most previous research solidly corroborates the above-mentioned chain of reasoning. In the present study, the associations of LDL-C and HDL-C with ischemic stroke, if any, were strikingly different from their well-described associations with coronary heart disease. There was little evidence for any important association in the entire sample or in the sample of men. The risk functions of ischemic stroke did not exhibit a log-linear relation or monotonicity, and with few exceptions, effect estimates were not particularly large. Possible explanations for these results are discussed below.

Error in the measurements of predictors or end points, or some hidden bias, is a possible explanation of the results of...
any study, including ours. Several counterpoints should be considered, however. ARIC baseline measurements of cholesterol subfractions and triglycerides proved to have had excellent short-term repeatability comparable to, or better than, reported repeatability from other studies. The lipid profile at baseline was a strong predictor of incident coronary heart disease in the ARIC cohort, and incident ischemic stroke was associated with known nonlipid risk factors in the expected direction and magnitude (Table 1). Although subsequent use of cholesterol-lowering agents could have altered

![Figure 1. Multivariable-adjusted risk functions of incident ischemic stroke among women in relation to LDL-C, HDL-C, apoB, and triglycerides (TG) (see Subjects and Methods). The stroke risk function for each analyte is displayed in a solid line along with 95% CIs (dashed lines). The values of the 5 knots correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the analyte distribution.](http://stroke.ahajournals.org/)
lipid levels in some participants, it is quite unlikely that measurement error has uniquely affected the present analysis, completely distorting a true strong effect of the lipid profile on ischemic stroke. Moreover, one would also have to assume that measurement error has somehow produced spurious heterogeneity of associations by sex.

It is possible that the study end point was too heterogeneous, perhaps predominantly composed of strokes that were caused by nonatherosclerotic mechanisms. Indeed, if this were the case, we ought to conclude that the lipid profile was not an important determinant of ischemic stroke in the ARIC cohort and possibly in many similar populations. In particular, the vast majority of lacunar infarcts presumably results from occlusion of small-diameter arteries by nonatherosclerotic vasculopathy50–52 or by distinctive “miniature plaques.”53 In ARIC, approximately one quarter of ischemic strokes (45 of 144 among women and 41 of 161 among men) were classified as lacunar stroke on the basis of anatomic location and size. Although some of those cases might have been labeled erroneously as lacunar, there are likely unidentified lacunar strokes among the remainder. Overall, small-vessel occlusion due to nonatherosclerotic processes might have accounted for a considerable proportion of ischemic strokes in the ARIC cohort.54

Previous studies of stroke risk in relation to lipids and the lipid profile varied widely in design, sample size, end-point definition, analytical method, and results. Much of the early research examined the relation of all-stroke mortality to total cholesterol; more recent studies have measured cholesterol subfractions and ascertained incident ischemic stroke. Many research groups have concluded that total cholesterol was not associated positively with ischemic stroke or other stroke end points,1,2,4,5,7,9,11,14,16–19 whereas others have reached the opposite conclusion.3,6,8,10,12,13,15 In 2 large cohorts, any elevated risk was confined to the upper tail of the cholesterol distribution.55,56 Because total cholesterol and LDL-C are strongly correlated, one should expect similar disagreements about the role of LDL-C in ischemic stroke, as indeed was the case when both variables were studied.6,7,13,19 The relation of apoB to stroke was rarely examined,6,57 and no clear conclusion could be drawn.

Most previous studies reported an inverse association of HDL-C with ischemic stroke6,7,16,19,55,58–61 or unclassified stroke.56 However, methodological limitations of some of these studies should be borne in mind, particularly small sample size6,58,60 and poststroke measurements of HDL-C.6,7,19,58,60 Whether the concentration of HDL-C after stroke reasonably estimates habitual levels is debatable.62–65 Several cohort studies reported an inverse association between HDL-C and incident ischemic stroke,16,55,59 fatal ischemic stroke,61 or unclassified stroke.56 However, 2 cohorts did not enroll women,56,61 2 studies reported no statistical evidence for multiplicative interaction with sex,16,55 and only 1 group reported sex-specific analyses, with ≥30 ischemic strokes for each sex.59 In some of these studies, the investigators only reported a log-linear fit of HDL-C to the data, which is not the optimal method to investigate the dose-response relation. In a cohort of men, an inverse association of HDL-C with nonfatal unclassified stroke was confined to the upper fifth of the HDL-C distribution after the exclusion of those with a history of coronary disease or stroke at recruitment.56 A report from the Framingham study described the inverse relation between HDL-C and stroke incidence as “weak and not statistically significant.”59

Studies of triglyceride level in relation to stroke or ischemic stroke either reported a positive association13,55,66 or reported no association at all.8,16,56,67 Again, substantial heterogeneity of the study population, design, end-point definition, and analytical approach preclude a meaningful synthesis of these data. A positive association of ischemic stroke with triglycerides and an inverse association with HDL-C, as reported in the present study among women, might signal a connection between ischemic stroke and the insulin resistance syndrome (syndrome X). However, fasting

Figure 2. Multivariable-adjusted risk functions of incident ischemic stroke among men in relation to LDL-C, HDL-C, apoB, and triglycerides (TG) (see Subjects and Methods). The stroke risk function for each analyte is displayed in a solid line along with 95% CIs (dashed lines). The values of the 5 knots correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the analyte distribution.
insulin was not an important determinant of ischemic stroke in the ARIC cohort.43

How might one reconcile the puzzling results of the present study and others with the known role of carotid atherosclerosis in ischemic stroke,68,69 the strong associations of the lipid profile with carotid intimal-medial thickening42 and plaques,68 and the well-documented benefit of statins in stroke prevention?36–48 We offer several speculative explanations. First, despite gross morphological similarity of atherosclerotic plaques in different vascular beds, atherosgenensis in intracranial arteries, particularly the smaller arteries and arterioles, might be different from atherosgenensis in the coronary arteries.53,70 Hemodynamic conditions, which seem to have a role in atherosgenensis, might modify the effects of circulating agents in different vascular beds. Second, the contribution of carotid atherosclerosis to ischemic stroke may have been overestimated.71,72 In some stroke cases, a documented carotid plaque might have not been the culprit lesion. Third, ischemic stroke in the ARIC cohort has been linked to retinal microvascular abnormalities,54 pathology that was unrelated to plasma cholesterol and appeared to be distinct from atherosclerosis.73 Finally, it is not at all clear that the benefits of statins in coronary heart disease or stroke are exclusively explained by their known effects on the lipid profile.74

The lipid profile might have a more important role in those ischemic strokes that are the consequence of atherosgenesis of larger arteries, but at present, event classification according to the size of the occluded vessel is a challenging task.75 This is especially true for epidemiological research, which relies on retrospective review of medical records of varying quality. Although ARIC subclassified ischemic strokes,39 analysis of subtypes awaits longer follow-up of the cohort.

In summary, there is a sharp contrast between the effect of the plasma lipid profile on coronary heart disease and ischemic stroke. Either the pathogenesis of a substantial proportion of ischemic strokes does not involve classical atherosclerotic mechanisms, or the effect of plasma lipids on atherosgenesis is substantially different in the intracranial vascular bed. Future studies of this topic should take into account possible heterogeneous associations by sex and stroke subtype and carefully examine the dose-response functions.

Acknowledgments

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