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# Cholesterol and the Risk of Ischemic Stroke

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**Background and Purpose**—Large epidemiological studies have not established cholesterol levels as a risk factor for ischemic stroke, but recent clinical trials have demonstrated a reduction in the ischemic stroke rate for patients taking HMG-CoA reductase inhibitors (“statins”). The goal of this study was to evaluate whether total cholesterol (TC), high-density lipoprotein (HDL), triglycerides, and the TC:HDL ratio are risk factors for ischemic stroke in apparently healthy men enrolled in the Physicians’ Health Study.

**Methods**—We used a nested case-control study design and matched 296 ischemic stroke cases with an equal number of controls on age, tobacco use, and follow-up time. At baseline, TC, HDL, and triglyceride levels were measured. We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) using conditional logistic regression, adjusting for major risk factors for ischemic stroke.

**Results**—Compared with the reference lowest quartile, the highest quartile for TC had an adjusted OR of 1.56 (95% CI, 0.84 to 2.92), the highest quartile of HDL had an adjusted OR of 0.75 (95% CI, 0.43 to 1.30), and the highest quartile of triglycerides had an adjusted OR of 1.07 (95% CI, 0.63 to 1.82). Although the highest quartile of the TC:HDL ratio had an adjusted OR of 1.62 (95% CI, 0.93 to 2.82), the risk of ischemic stroke was not a linear relationship.

**Conclusions**—After adjustment, TC, HDL, and triglycerides were not significantly associated with ischemic stroke risk, and for the TC:HDL ratio, a suggestion of increased risk of ischemic stroke was limited to those with the highest levels. (*Stroke*. 2003;34:2930-2934.)

**Key Words:** cerebrovascular disorders ■ epidemiology ■ lipids ■ risk factors ■ stroke

There are >700 000 incident strokes in the United States annually, and stroke is the third-leading cause of death.<sup>1</sup> In addition, survivors of stroke are often disabled, leading to an estimated annual cost of care exceeding \$50 billion.<sup>1</sup> Eighty percent of total strokes in the United States are due to an ischemic event, with the remainder due to hemorrhagic or unknown causes.<sup>2</sup> Although elevated total cholesterol (TC) and low high-density lipoprotein (HDL) are clearly established risk factors for coronary heart disease,<sup>3</sup> observational studies have yielded mixed results for lipid levels and cerebrovascular disease risk.<sup>4-7</sup>

In a meta-analysis, early lipid-lowering clinical trials found no benefit of cholesterol lowering on the risk of stroke (relative risk [RR], 1.0; 95% confidence interval [CI], 0.8 to 1.2),<sup>8</sup> but results from statin intervention trials demonstrate a consistent reduction in the ischemic stroke rate.<sup>9-14</sup> The beneficial effect of statins on ischemic stroke may be mediated by changes in cholesterol levels.

The association of cholesterol levels with ischemic stroke in prior epidemiological studies may have been attenuated

because of the inability to differentiate between cholesterol components and stroke subtype.<sup>15</sup> Therefore, we evaluated whether TC, HDL, triglycerides, and the TC:HDL ratio are risk factors for ischemic stroke in a nested case-control study consisting of men free of cardiovascular disease at baseline and followed up prospectively for a median of 11.5 years.

## Methods

### Study Population

Study subjects were participants in the Physicians’ Health Study (PHS), a completed randomized trial of low-dose aspirin and beta-carotene in the primary prevention of cardiovascular disease and cancer. The design and methods of the PHS have been described in detail previously.<sup>16-18</sup> Briefly, the PHS consisted of 22 071 apparently healthy male physicians without prior history of cardiovascular disease, cancer (except nonmelanoma skin cancer), current liver disease, kidney dysfunction (defined as kidney failure or insufficiency), or other major illnesses. Baseline information was self-reported and collected by mailed questionnaire on demographic, medical history, and lifestyle characteristics, including information about alcohol consumption, age, height, weight, systolic and diastolic blood pressures, history of angina pectoris, diabetes mellitus,

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TABLE 1. Baseline Characteristics of Cases and Controls

Characteristic	Cases (n=296)	Controls (n=296)
Age,* y	61.0±8.3	60.5±8.1
Tobacco use,* %		
Never	40.1	40.2
Past	41.8	41.5
Current <20/d	5.8	6.1
Current ≥20/d	12.2	12.2
BMI, kg/m <sup>2</sup>	25.7±3.48	25.0±2.90
History of HTN, %	51.4	29.4
Diabetes, %	12.8	3.4
Alcohol use, %		
Daily	29.2	31.3
Weekly	38.0	43.9
Monthly	12.5	9.9
Rare/never	20.3	15.0
Exercise, %		
≥2 Times per week	46.8	55.1
<2 Times per week	35.6	32.4
Rarely/never	17.6	12.5
History of hyperlipidemia, %	21.7	15.7

BMI indicates body mass index; HTN, hypertension.

\*Matching variables were age and tobacco use.

history of hypertension, history of hyperlipidemia, medication use, exercise, and cigarette smoking. Every 6 months for the first year and annually thereafter, the participants were mailed follow-up questionnaires requesting information about newly diagnosed conditions, including stroke and transient ischemic attack. Morbidity and mortality data were available for >99% of the study participants through March 2001. Deaths were usually reported by family members or by the postal authorities and were verified by a review of all available medical records, death certificates, and eyewitness accounts if relevant.

### Baseline Blood Collection

At baseline, all participants were asked to voluntarily provide blood samples. Blood collection kits, including EDTA Vacutainer tubes, were sent to participants. Participants were instructed to have their blood drawn into the EDTA tubes and to return the plasma (accompanied by a cold pack) by overnight courier. The paired, blinded plasma samples were shipped on dry ice to the Core Laboratory of the Children's Hospital (a Centers for Disease Control and Prevention–certified laboratory for lipid testing) for analysis of triglycerides, TC, and HDL cholesterol using reagents from Roche Diagnostics and Genzyme. Of the 22 071 participants, 14 916 (68%) provided random baseline plasma samples.

TABLE 3. Randomization-Status Adjusted and Multivariable ORs for Quartiles of Exposure

	TC Quartile, mg/dL				HDL Quartile, mg/dL			
	1, 193.5	2, 193.5–227	3, 227–258.5	4, ≥258.5	1, <41.15	2, 41.15–49.8	3, 49.8–59.05	4, ≥59.05
Adjusted*	1.00	1.53 (0.95–2.45)	1.04 (0.62–1.75)	1.26 (0.73–2.17)	1.00	0.82 (0.52–1.28)	0.56 (0.35–0.90)	0.58 (0.36–0.94)
MV adjusted†	1.00	1.44 (0.85–2.46)	1.16 (0.65–2.06)	1.56 (0.84–2.92)	1.00	0.83 (0.50–1.37)	0.69 (0.40–1.18)	0.75 (0.43–1.30)

MV indicates multivariable.

\*Matched on age and smoking status and adjusted for randomization status (aspirin, beta-carotene, both, or neither).

†Further adjusted for body mass index, history of hypertension and diabetes, exercise level, and alcohol use.

TABLE 2. Exposure Variables for Cases and Controls

Exposure	Cases (n=296)	Controls (n=296)	P
TC, mg/dL	231.7±51.1	228.6±46.5	0.44
HDL, mg/dL	49.0±15.9	52.4±16.0	<0.01
Triglycerides, mg/dL	192.3±155.9	157.0±93.0	<0.01
TC:HCL ratio	5.11±1.70	4.66±1.42	<0.01

### Evaluation of Stroke

All participants who reported an incident stroke on a questionnaire were asked permission to review their medical records. The End Points Committee confirmed a diagnosis of stroke only after review of medical records and results of diagnostic tests. Stroke was defined as a focal neurological deficit of sudden onset and vascular mechanism that lasted >24 hours. Documentation of stroke required evidence of a cerebrovascular mechanism obtained from all available sources, including death certificates and hospital records. Stroke was classified according to the criteria established by the National Survey of Stroke<sup>19</sup> into ischemic, hemorrhagic, and unknown subtype. Stroke classification was performed on the basis of medical records, reports of brain imaging, and the judgment of the neurologist on the End Points Committee. Only first cases of stroke were considered for these analyses. We did not attempt to distinguish embolic from thrombotic stroke. There was a high level of interobserver agreement in the diagnosis of hemorrhagic and ischemic stroke throughout the study.<sup>20,21</sup>

### Selection of Ischemic Stroke Cases and Controls

Cases were defined as confirmed ischemic strokes through March 2001. Seventy percent of the ischemic stroke cases initially provided baseline blood samples, and this analysis included 296 cases of fatal and nonfatal ischemic stroke with baseline blood samples. For each case, 1 control subject was selected. Potential controls included all participants free of stroke through the time of the stroke case and for whom baseline blood samples were available. Controls were selected randomly from study participants who met the matching criteria of age (±1 year), smoking status (never, former, current), and follow-up time (6 months for the first year and annually thereafter). Those who reported taking medication for hyperlipidemia at baseline were not included in this prospective, nested case-control study.

### Laboratory Analyses

TC, HDL, and triglycerides were assayed in the Lipid Research Laboratory of Brigham and Women's Hospital (Boston, Mass).<sup>22,23</sup> This laboratory participates in the standardization program for TC and HDL cholesterol of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute. At least 1 blinded pair from a pooled plasma sample was included in each batch of 40 specimens. Pooled plasma specimens were stored under the same conditions as those from participating physicians. The coefficients of variation from these blinded samples were as follows: TC, 1.2%; HDL, 2.7%; and triglycerides, 4.8%. Laboratory personnel were blinded to subjects' status (case versus control).

### Statistical Analysis

Means for baseline characteristics were compared for cases and controls through the use of Student's *t* test. We calculated randomization-assignment (aspirin, beta-carotene, both, or neither) adjusted and multivariable-adjusted odds ratios (ORs) and their 95% CIs by using conditional logistic regression models that accounted for the matching variables (age, tobacco use, and follow-up time). The multivariable models controlled for random treatment assignment (aspirin, beta-carotene, both, or neither), body mass index (continuous), history of hypertension (defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic pressure  $\geq 90$  mm Hg, or treatment of hypertension), history of diabetes, alcohol use (daily, weekly, monthly, rarely/never), and exercise ( $\geq 2$  times per week,  $< 2$  times per week, and rarely/never). All probability values were 2 tailed, and 95% CIs were calculated. We categorized the exposure groups into quartiles based on the distribution of TC, HDL, triglycerides, and TC:HDL ratio found in the control population. Using these cutoffs, we were able to compare increasing quartiles of exposure with the reference first quartile. When we substituted blood pressure measures in place of our dichotomous hypertension variable in the multivariable models, the results were not materially changed. All statistical analyses were performed with SAS version 8.1.

### Results

Table 1 shows the baseline characteristics of the 296 ischemic stroke cases and matched controls. As expected, cases of ischemic stroke were more likely to have a history of hypertension, a history of diabetes, and a higher body mass index. Exercise and alcohol use were similar in the 2 groups. Cases were more likely to have a history of hyperlipidemia. Because of our matching criteria, cases and controls were similar in age and tobacco use.

Baseline TC, HDL, triglyceride level, and the TC:HDL ratio were compared in cases and controls (Table 2). Mean TC was similar ( $P=0.44$ ), but the mean HDL level was significantly lower in cases than in controls (49.0 versus 52.4 mg/dL;  $P<0.01$ ). In these nonfasting blood samples, the mean triglyceride level was higher in cases than in controls ( $P<0.01$ ). The mean TC:HDL ratio was also significantly higher in cases than in controls ( $P<0.01$ ).

Table 3 presents the RRs and 95% CI levels for ischemic stroke according to increasing quartiles of TC, HDL, triglyceride level, and TC:HDL ratio. For TC, there was no significant relationship with risk of ischemic stroke across quartiles, although in the highest quartile in the multivariable model there was the suggestion of excess risk compared with the lowest quartile (OR, 1.56; 95% CI, 0.84 to 2.92). In the multivariable model, the highest quartile of HDL was not statistically associated with a lower stroke risk (OR, 0.75; 95% CI, 0.43 to 1.30), and nonfasting triglyceride levels in the highest quartile were not associated with a higher ischemic stroke risk (OR, 1.07; 95% CI, 0.63 to 1.82). Increasing

levels of TC:HDL ratio did not demonstrate a linear relation; however, the highest quartile had the suggestion of an increased risk of ischemic stroke, which did not reach statistical significance (multivariable OR, 1.62; 95% CI, 0.93 to 2.82). In an analysis of the 15 cases of ischemic stroke in the 95th percentile of TC:HDL ratio ( $>7.81$ ), the treatment-adjusted OR was 5.84 (95% CI, 1.59 to 21.4) while the multivariable adjusted OR was 3.41 (95% CI, 0.86 to 13.58), consistent with a threshold above which the TC:HDL ratio has an increased risk of ischemic stroke.

### Discussion

In our study of apparently healthy men without prior evidence of coronary or cerebrovascular disease, TC, HDL, and triglyceride level were not risk factors for ischemic stroke. The highest quartile of the TC:HDL ratio had a suggestion of increased risk, but there was not a linear trend across quartiles. Mean HDL, triglycerides, and TC:HDL ratio were significantly different in the cases compared with controls, and several ORs that were significant in the simple matched analysis lost significance in the multivariable models.

Prior observational studies have been inconclusive in identifying a relationship between cholesterol components and stroke risk. The Multiple Risk Factor Intervention Trial (MRFIT) found an association between high serum cholesterol levels and nonhemorrhagic fatal stroke.<sup>24</sup> A meta-analysis found no association between TC and stroke, but that study was unable to distinguish between ischemic and hemorrhagic stroke.<sup>15</sup> Another study found an association only between the highest 5% of TC levels ( $>269$  mg/dL) and subsequent ischemic stroke in smokers.<sup>25</sup> In an observational study of subjects with coronary heart disease, TC levels were associated with risk of ischemic stroke (RR, 1.43; 95% CI, 1.20 to 1.70),<sup>26</sup> whereas another study in subjects without known coronary heart disease did not show an association with plasma lipids.<sup>7</sup> Because of the inconsistent observational data, lipids have not been recognized as a risk factor for stroke.<sup>1,26-28</sup>

HDL may be protective against stroke, particularly nonfatal stroke<sup>28</sup> and ischemic stroke in the elderly.<sup>29</sup> In patients with coronary heart disease, risk of ischemic stroke has been inversely related to the highest tertile of HDL level (RR, 0.84; 95% CI, 0.70 to 1.00),<sup>26</sup> but although a low HDL level is clearly a risk factor for CHD, the relationship with ischemic stroke is still unclear. Although the TC:HDL ratio is a predictor of cardiovascular disease, which contains both an atherogenic and an antiatherogenic lipid component,<sup>23,30,31</sup> the TC:HDL ratio has not been as widely studied in association with ischemic stroke.

TABLE 3. Continued

Triglycerides Quartile, mg/dL				TC:HDL Ratio Quartile			
1, $<91$	2, 91-129	3, 129-198	4, $\geq 198$	1, $<3.60$	2, 3.60-4.49	3, 4.49-5.56	4, $\geq 5.56$
1.00	0.77 (0.47-1.27)	1.21 (0.76-1.93)	1.34 (0.84-2.14)	1.00	0.97 (0.59-1.58)	1.06 (0.66-1.71)	1.90 (1.19-3.04)
1.00	0.68 (0.39-1.19)	0.97 (0.57-1.64)	1.07 (0.63-1.82)	1.00	0.74 (0.42-1.28)	0.78 (0.48-1.34)	1.62 (0.93-2.82)

Clinical trials with HMG-CoA reductase inhibitors have demonstrated reduced cardiovascular events and fewer ischemic strokes, possibly indicating a lipid mechanism common to both outcomes.<sup>3,32–36</sup> A meta-analysis of statin trials found a significant reduction in the stroke event rate (RR, 0.71; 95% CI, 0.59 to 0.86).<sup>10</sup> A subsequent meta-analysis compared the risk ratio for fatal or nonfatal stroke in the statin trials (RR, 0.76; 95% CI, 0.62 to 0.92) to the rate in the nonstatin trials (RR, 1.02; 95% CI, 0.91 to 1.15),<sup>11</sup> raising the possibility that statins had properties independent of their lipid-modifying effects that were responsible for the reduction in ischemic strokes.<sup>37,38</sup>

More recent clinical trials not included in the published meta-analyses continue to demonstrate lower ischemic stroke rates in groups randomized to statin treatment. The Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) trial<sup>13</sup> found that statin use reduced the absolute rate of nonhemorrhagic stroke from 4.4% to 3.4%, with no effect on the rate of hemorrhagic stroke. The Prospective Pravastatin Pooling (PPP) Project<sup>12</sup> found a reduced total stroke rate that was due entirely to fewer ischemic strokes (RR, 0.77; 95% CI, 0.63 to 0.94). In the Heart Protection Study, simvastatin reduced the ischemic stroke rate (4.0% versus 2.8%), with no change in the hemorrhagic stroke rate (0.5% in both groups).

Gemfibrozil, a fibrate that raises HDL levels, reduced the risk of ischemic stroke by 31% (95% CI, 2 to 52) in men with coronary heart disease,<sup>39</sup> supporting the idea that HDL levels may be important in the pathogenesis of ischemic stroke. The TC:HDL ratio is an important risk factor for coronary heart disease,<sup>30</sup> and it incorporates both atherogenic and antiatherogenic lipid components. Because the pathophysiology of ischemic stroke may be similar to that of CHD, a high TC:HDL ratio may be an unrecognized risk factor for ischemic stroke. Our observational results are consistent with the possibility of increased risk in those with the highest levels of TC:HDL ratio.

A poor lipid profile has been clearly established as a risk factor for coronary heart disease,<sup>3</sup> a physiological process of plaque accumulation and rupture.<sup>40</sup> The classification of stroke subtypes in our study is important because only ischemic strokes are likely to be related to an atherosclerotic process. However, only some subtypes of ischemic stroke (eg, atherothrombotic stroke) may be related to lipids, and further classification of ischemic stroke subtypes is difficult, with low interobserver agreement.<sup>20,41</sup>

Our study has several strengths, including its prospective design, high interrater agreement in the classification of strokes that were confirmed by medical review, and complete follow-up. The study subjects are a relatively homogeneous population, which reduces potential confounding by variability in access to medical care, race-ethnicity, or socioeconomic status.

Our study has several limitations. The PHS consists entirely of apparently healthy, mostly white, middle-aged men and this may affect the generalizability of the findings to other populations. However, we have no reason to believe that the biological mechanism by which cholesterol and its subtypes may be associated with ischemic stroke is unique to

our study population. In our multivariable model, we adjusted for major confounders, but as with all observational studies, the possibility of residual confounding might affect the results. The plasma blood samples were collected only at baseline in 1982, before widespread statin use, a treatment that would change cholesterol exposure variables. Although we do not have initial bloods collected for 30% of our baseline population, we do not expect this to be subject to selection bias, nor should it affect the interpretation of our results. We do not have direct measurements of low-density lipoprotein cholesterol and could not calculate low-density lipoprotein cholesterol for these samples because many were nonfasting. Triglyceride levels can be elevated after a meal, but previous analysis in this cohort found that adjustment for time since last meal had no material impact on the overall results.<sup>22</sup> Whether these blood samples provide an accurate assessment of a long-term exposure variable (eg, TC) is not known.

In conclusion, TC, HDL, and triglyceride level were not independent risk factors for ischemic stroke after multivariable adjustment. The TC:HDL ratio did not have a linear association with the risk of ischemic stroke; however, there was a suggestion of increased risk for those with a TC:HDL ratio in the highest quartile. Further research, including the results of an ongoing clinical trial of statin therapy for the secondary prevention of ischemic stroke,<sup>42</sup> is needed to elucidate the relationship between cholesterol components and the risk of ischemic stroke.

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### References

- Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke*. 2001;32:280–299.
- Wolf PA, Kannel WB, Verter J. Current status of risk factors for stroke. *Neurol Clin*. 1983;1:317–343.
- NCEP. Summary of third report of NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults III. *JAMA*. 2001;286–2497.
- Qizilbash N. Are risk factors for stroke and coronary disease the same? *Curr Opin Lipidol*. 1998;9:325–328.
- Taylor WC, Landau WM. Atherosclerosis and stroke. *Ann Neurol*. 1990;28:109–110.
- Demchuk AM, Hess DC, Brass LM, et al. Is cholesterol a risk factor for stroke? *Arch Neurol*. 1999;56:1518–1520.
- Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke. *Stroke*. 2003;34:623–631.
- Hebert PR, Gaziano JM, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Arch Intern Med*. 1995;155:50–55.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
- Hebert PR, Gaziano JM, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. *JAMA*. 1997;278:313–321.
- Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 1998;128:89–95.
- Byington RP, Davis BR, Plehn JF, et al. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation*. 2001;387–392.

13. White HD, Simes RJ, Anderson NE, et al. Pravastatin therapy and the risk of stroke. *N Engl J Med*. 2000;343:317–326.
14. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol*. 1998;81:333–335.
15. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet*. 1995;346:1647–1653.
16. Steering Committee of the Physicians' Health Study Research Group. Final Report on the ASA component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321:129–135.
17. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta-carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145–1149.
18. Manson JE, Buring JE, Satterfield S, et al. Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians. *Am J Prev Med*. 1991;7:150–154.
19. Walker AE, Robins M, Weinfeld FD. The national survey of stroke: clinical findings. *Stroke*. 1981;12:113–144.
20. Berger K, Kase CS, Buring JE. Interobserver agreement in the classification of stroke in the Physicians' Health Study. *Stroke*. 1996;27:238–242.
21. Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. *Arch Intern Med*. 2002;162:2557–2562.
22. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276:882–888.
23. Stampfer MJ, Sacks FM, Salvini S, et al. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med*. 1991;325:373–381.
24. Iso H, Jacobs DR, Wentworth D, et al. Serum Cholesterol levels and six year mortality from stroke in 350977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904–909.
25. Leppala JM, Virtamo J, Fogelholm R, et al. Different risk factors for different stroke subtypes. *Stroke*. 1999;30:2535–2540.
26. Koren-Morag N, Tanne D, Graff E, et al. Low and high-density lipoprotein cholesterol and ischemic cerebrovascular disease. *Arch Intern Med*. 2002;162:993–999.
27. Hart CL, Hole DJ, Smith GD. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley study in Scotland. *Stroke*. 2000;31:1893–1896.
28. Wannamethee SG, Shaper AG, Ebrahim S. HDL-cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*. 2000;31:1882–1888.
29. Sacco RL, Benson RT, Kargman DE, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly. *JAMA*. 2001;285:2729–2735.
30. Kinoshita B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med*. 1994;121:641–647.
31. Criqui MH, Golomb BA. Epidemiologic aspects of lipid abnormalities. *Am J Med*. 1998;105:48S–57S.
32. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with Lovastatin in men and women with average cholesterol levels: the results of AFCAPS/TEXCAPS. *JAMA*. 1998;279:1615–1622.
33. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301–1307.
34. Sacks F, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001–1009.
35. Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
36. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the 4S study. *Lancet*. 1994;344:1383–1389.
37. Plutzky J, Ridker PM. Statins for stroke: the second story? *Circulation*. 2001;103:348–350.
38. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins. *JAMA*. 1998;279:1643–1650.
39. Rubins HB, Davenport J, Babikian V, et al. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation*. 2001;103:2828–2833.
40. Sulc T, Ceska R. Cholesterol lowering and the vessel wall: new insights and future perspectives. *Physiol Res*. 2001;50:461–471.
41. Atiya M, Kurth T, Berger K, et al. Interobserver agreement in the classification of stroke in the Women's Health Study. *Stroke*. 2003;34:565–567.
42. Callahan A. Cerebrovascular disease and statins: a potential addition to the therapeutic armamentarium for stroke prevention. *Am J Cardiol*. 2001;88:33J–37J.