Cholesterol Predicts Stroke Mortality in the Women’s Pooling Project

Richard B. Horenstein, MD; Dean E. Smith, PhD; Lori Mosca, MD, PhD; for the Women’s Pooling Project Investigators

Background and Purpose—Cholesterol is emerging as a risk factor for stroke; however, few data are available regarding the relation of cholesterol and stroke mortality in women and ethnic minorities.

Methods—We evaluated the risk of death caused by total stroke, nonhemorrhagic stroke, and hemorrhagic stroke by race, age, and cholesterol quintile in 24,343 women with no previous cardiovascular disease who were participating in 8 US longitudinal, prospective, cohort studies included in the Women’s Pooling Project.

Results—We observed 568 stroke deaths (461 nonhemorrhagic, 83 hemorrhagic) for women ≥30 years of age without previous cardiovascular disease during 339,215 person-years of follow-up. In multivariate models, black women <55 years of age had a 76% increased risk of death caused by stroke compared with white women [relative risk (RR), 1.76; 95% confidence interval (CI), 1.10 to 2.81]. For black women <55 years of age, the top compared with the lowest cholesterol quintile (Q5 versus Q1) remained an independent predictor of stroke mortality (RR, 2.58; 95% CI, 1.05 to 6.32) in multivariate models. For white women <55 years of age, Q5 versus Q1 cholesterol did not predict stroke mortality with significance (RR, 1.47; 95% CI, 0.57 to 3.76). In analogous multivariate models, we found a positive relation between continuous cholesterol and nonhemorrhagic stroke death in women <55 years of age (RR, 1.23; 95% CI, 1.02 to 1.49).

Conclusions—Our results show that cholesterol is a risk factor for nonhemorrhagic stroke death in women <55 years of age and is more strongly associated with mortality in black women <55 years of age than in white women. These data document the importance of cholesterol in addition to established risk factors for predicting stroke mortality in young women and may guide prevention strategies. (Stroke. 2002;33:1863-1868.)

Key Words: cholesterol ■ stroke prevention ■ women

Materials and Methods

The Women’s Pooling Project is a prospective cohort study that combines data from 9 long-term epidemiological studies based in the United States. Data from 24,343 women participating in the Atherosclerosis Risk in Communities Study (ARIC), Charleston Heart Study, Evans County Study, Framingham Heart Study, National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (NHEFS), Rancho Bernardo Study, San Antonio Heart Study, and Tecumseh Community Health Study were combined for this analysis. Details of sampling procedures, study designs, and methods for these 8 cohorts are given elsewhere. Women ≥30 years of age with no previous CVD were included. CVD was defined as a history of angina, myocardial infarction, or stroke based on cohort-specific definitions.

Stoke mortality determinations were cohort specific. Cohort studies with baseline evaluations in the 1960s (Charleston, Evans County, and Framingham) provided mortality data based on codes from revision 8 of the International Classification of Diseases (ICD), and the remaining cohorts provided deaths classified according to ICD revision 9.20,21 Strokes (ICD codes 430 through 438) were categorized as hemorrhagic (ICD-9 codes 431 and 432, ICD-8 code 431) or nonhemorrhagic (ICD-9 codes 433 through 438, ICD-8 codes 433 through 438, ICD-8...
The adjusted RR of stroke death for each 10 mm Hg increase in systolic blood pressure was 1.22 for black women <55 years of age (95% CI, 1.13 to 1.32) and 1.17 for white women <55 years of age (95% CI, 1.10 to 1.29). The adjusted RR of stroke death for each quintile of cholesterol increased with increased cholesterol: Q1 (4.2 mmol/L; range, <4.8 mmol/L), Q2 (5.1 mmol/L; range, 4.8 to 5.4 mmol/L), Q3 (5.6 mmol/L; range, 5.4 to 5.9 mmol/L), Q4 (6.3 mmol/L; range, 5.9 to 6.7 mmol/L), and Q5 (7.6 mmol/L; range, >6.7 mmol/L).

The mortality experience of the black and white participants is shown in Table 2. Approximately 10% of the deaths in the study population were due to stroke (10.6%, n = 568). Of the stroke deaths, 81% were categorized as nonhemorrhagic (81.2%, n = 465) and 14% as hemorrhagic (14.6%, n = 83). Of the 14 035 women whose baseline ages were 30 to 54 years with a mean age at entry of 44.3 years, stroke death occurred in 111 participants (0.8%), and the mean age of stroke death was 62.7 years. Of the 10 038 women with baseline ages of ≥55 years who had a mean age at entry of 62.7 years, 457 (4.6%) died of stroke, and the mean age of stroke death was 80.2 years. The age-adjusted death rates for all causes of mortality and for specific causes, including stroke, were higher for black women than white women. There were only 3 stroke deaths among Hispanic women, so they were not analyzed separately.

In multivariate models adjusted for age, time period, blood pressure, diabetes, smoking level, cholesterol quintile, education level, and body mass index, black women with baseline ages of <55 years had a 76% increased risk for death caused by stroke compared with white women (RR, 1.76; 95% CI, 1.10 to 2.81) (Table 3). Excess stroke mortality was less marked, although still substantial, for older black women compared with older white women (RR, 1.48; 95% CI, 1.14 to 1.92). For black women <55 years of age, the top (Q5) compared with the lowest (Q1) quintile of cholesterol re-

### TABLE 1. Description of Cohorts and Cholesterol Methods

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Baseline Year</th>
<th>Mean Follow-Up, y</th>
<th>Ethnicity</th>
<th>Age, y</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>Black</td>
<td>Hispanic</td>
</tr>
<tr>
<td>ARIC</td>
<td>1986–1990</td>
<td>6.2</td>
<td>5470</td>
<td>70</td>
<td>2340</td>
</tr>
<tr>
<td>Charleston</td>
<td>1960–1961</td>
<td>22.8</td>
<td>696</td>
<td>62</td>
<td>427</td>
</tr>
<tr>
<td>Evans County</td>
<td>1960–1962</td>
<td>22.1</td>
<td>771</td>
<td>61</td>
<td>483</td>
</tr>
<tr>
<td>Framingham</td>
<td>1958–1963</td>
<td>21.8</td>
<td>1695</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>NHFS</td>
<td>1971–1975</td>
<td>17.0</td>
<td>5406</td>
<td>84</td>
<td>992</td>
</tr>
<tr>
<td>Rancho Bernardo</td>
<td>1972–1974</td>
<td>16.5</td>
<td>2631</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>San Antonio</td>
<td>1979–1986</td>
<td>7.6</td>
<td>507</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Tecumseh</td>
<td>1962–1965</td>
<td>20.4</td>
<td>1736</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Total women</td>
<td>1958–1990</td>
<td>13.9</td>
<td>18912</td>
<td>78</td>
<td>4244</td>
</tr>
</tbody>
</table>

LRC indicates Lipid Research Clinics.

Codes 432 through 438). There were 24 stroke deaths resulting from subarachnoid hemorrhage (ICD code 430); these were not analyzed separately but were included in the stroke death totals.

Total blood cholesterol was measured at baseline with cohort-specific methods (Table 1). Prevalent diabetes was defined by glucose parameters or treatment in all cohorts except NHFS and the Charleston Study, which used self-reported physician diagnosis, and ARIC, which used a combination of these criteria. For the multivariate analysis, education was defined as less than high school education or high school graduation. Ethnicity was categorized as white (includes non-Hispanic whites), black, or Hispanic. Blood pressure measurements were based on the average of 2 blood pressure readings unless only 1 reading was available, in which case the single reading was used. Smoking was a derived variable categorized as current (based on individual study definition) or noncurrent (former smokers and those who had never smoked). Current smokers were divided into 2 groups based on whether they smoked >20 or <21 cigarettes per day.

### Statistical Methods

Cholesterol was analyzed as a continuous measurement, and quintiles were created. The multivariate models were adjusted for age to account for age-related changes in cholesterol. We calculated age-adjusted death rates per 1000 person-years by ethnic group and/or baseline age stratum. Rates were standardized according to the age distribution for the entire number of person-years of follow-up. The whole study population in each age group served as the standard.

Relative risks (RRs) and 95% confidence intervals (CIs) were obtained by fitting Cox proportional-hazards models. Separate models were created to assess the relation of blood cholesterol to total stroke, hemorrhagic stroke, and nonhemorrhagic stroke death in all women, white women, and black women, as well as among women <55 and those ≥55 years of age. Multivariate analysis was used to evaluate the effect of cholesterol on stroke mortality while simulta-

### Results

Baseline characteristics of the cohorts and participants are listed in Table 1. Our study included 24 343 women (77.7% white, 17.4% black, 4.9% Hispanic) with a mean age of 52.0 ± 11.2 years (range, 30 to 97 years) and a total of 339 215 person-years of follow-up. Mean blood total cholesterol for the study population was 5.8 mmol/L. Mean and range of cholesterol levels within quintiles were as follows: Q1 (4.2 mmol/L; range, <4.8 mmol/L), Q2 (5.1 mmol/L; range, 4.8 to 5.4 mmol/L), Q3 (5.6 mmol/L; range, 5.4 to 5.9 mmol/L), Q4 (6.3 mmol/L; range, 5.9 to 6.7 mmol/L), and Q5 (7.6 mmol/L; range, >6.7 mmol/L).

The mortality experience of the black and white participants is shown in Table 2. Approximately 10% of the deaths in the study population were due to stroke (10.6%, n = 568). Of the stroke deaths, 81% were categorized as nonhemorrhagic (81.2%, n = 465) and 14% as hemorrhagic (14.6%, n = 83). Of the 14 035 women whose baseline ages were 30 to 54 years with a mean age at entry of 44.3 years, stroke death occurred in 111 participants (0.8%), and the mean age of stroke death was 62.7 years. Of the 10 038 women with baseline ages of ≥55 years who had a mean age at entry of 62.7 years, 457 (4.6%) died of stroke, and the mean age of stroke death was 80.2 years. The age-adjusted death rates for all causes of mortality and for specific causes, including stroke, were higher for black women than white women. There were only 3 stroke deaths among Hispanic women, so they were not analyzed separately.

In multivariate models adjusted for age, time period, blood pressure, diabetes, smoking level, cholesterol quintile, education level, and body mass index, black women with baseline ages of <55 years had a 76% increased risk for death caused by stroke compared with white women (RR, 1.76; 95% CI, 1.10 to 2.81) (Table 3). Excess stroke mortality was less marked, although still substantial, for older black women compared with older white women (RR, 1.48; 95% CI, 1.14 to 1.92). For black women <55 years of age, the top (Q5) compared with the lowest (Q1) quintile of cholesterol re-

### References

1. Cholesterol levels within quintiles were as follows: Q1 (4.2 mmol/L; range, <4.8 mmol/L), Q2 (5.1 mmol/L; range, 4.8 to 5.4 mmol/L), Q3 (5.6 mmol/L; range, 5.4 to 5.9 mmol/L), Q4 (6.3 mmol/L; range, 5.9 to 6.7 mmol/L), and Q5 (7.6 mmol/L; range, >6.7 mmol/L).

The adjusted RR of stroke death for each 10 mm Hg increase in systolic blood pressure was 1.22 for black women <55 years of age (95% CI, 1.13 to 1.32) and 1.17 for white women <55 years of age (95% CI, 1.10 to 1.29). The adjusted RR of stroke death for each quintile of cholesterol increased with increased cholesterol: Q1 (4.2 mmol/L; range, <4.8 mmol/L), Q2 (5.1 mmol/L; range, 4.8 to 5.4 mmol/L), Q3 (5.6 mmol/L; range, 5.4 to 5.9 mmol/L), Q4 (6.3 mmol/L; range, 5.9 to 6.7 mmol/L), and Q5 (7.6 mmol/L; range, >6.7 mmol/L).
women <55 years of age (95% CI, 1.05 to 1.31). The RR estimates for stroke mortality per 10-mm Hg increase in blood pressure are larger in women <55 than in women ≥55 years of age, although the differences are without statistical significance. Diabetes predicted stroke mortality in all women ≥55 years of age (RR, 2.18; 95% CI, 1.62 to 2.95) but not in younger women. Diabetes was a stronger risk factor for older black women than for older white women (RR, 2.72; 95% CI, 1.52 to 4.85, and RR, 2.06; 95% CI, 1.44 to 2.96, respectively), although the differences in RR are again without statistical significance. Smoking was associated with an increased risk for stroke mortality across all ages and races except black women ≥55 years of age. RRs for women who smoked ≥21 cigarettes a day were higher than those for women who smoked <21 cigarettes per day. Smoking was a stronger risk factor in younger women than older women, but none of these RRs was statistically significant. Finally, attaining less than a high school education compared with graduating high school predicted stroke mortality in all women <55 years of age (RR, 1.79; 95% CI, 1.14 to 2.81) and in white women <55 years of age (RR, 1.99; 95% CI, 1.20 to 3.31). The corresponding RR in younger black women was weaker and not statistically significant (RR, 1.18; 95% CI, 0.47 to 2.98).

Using analogous Cox models to examine the relation of cholesterol to stroke type, we found that the effect of cholesterol in women with baseline ages of 30 to 54 years differs from that in women ≥55 years of age (Table 4). For younger women, the relation of cholesterol level to nonhemorrhagic stroke death and all-cause stroke mortality is positive (trend test, P = 0.03 for each). In particular, women with baseline ages of <55 years have a 23% increased risk of nonhemorrhagic stroke death for each 1-mmol/L increase in cholesterol (RR, 1.23; 95% CI, 1.02 to 1.49). For hemorrhagic stroke death in younger women, there is a relative paucity of events (n = 26), and the test for trend is not

### TABLE 3. RRs for All-Cause Stroke Mortality by Ethnicity in Multivariate Models* for Women 30 to 54 and ≥55 Years of Age

<table>
<thead>
<tr>
<th>Risk Comparison</th>
<th>All Women</th>
<th>White Women</th>
<th>Black Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30–54 y</td>
<td>≥55 y</td>
<td>30–54 y</td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Black vs white</td>
<td>1.76</td>
<td>1.10–2.81</td>
<td>1.48</td>
</tr>
<tr>
<td>Q5 vs Q1 cholesterol</td>
<td>1.69</td>
<td>0.91–3.13</td>
<td>0.64</td>
</tr>
<tr>
<td>1–20 cigs/d vs no current smoking</td>
<td>1.26</td>
<td>0.82–1.92</td>
<td>1.04</td>
</tr>
<tr>
<td>≥21 cigs/d vs no current smoking</td>
<td>2.14</td>
<td>0.96–4.76</td>
<td>1.58</td>
</tr>
<tr>
<td>Less than high school vs high school</td>
<td>1.79</td>
<td>1.14–2.81</td>
<td>1.12</td>
</tr>
<tr>
<td>graduation or higher</td>
<td>1.34</td>
<td>0.61–2.94</td>
<td>2.18</td>
</tr>
<tr>
<td>Diabetes (yes vs no)</td>
<td>1.20</td>
<td>1.13–1.28</td>
<td>1.14</td>
</tr>
<tr>
<td>Systolic blood pressure (10 mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cigs indicates cigarettes.

*All models are adjusted for age, time period, body mass index, smoking level, education, diabetes, cholesterol quintile, and systolic blood pressure. In addition, the models for All Women are adjusted for ethnicity.
significant. For the older women, the RRs were highest for the lowest cholesterol quintile, and there is a significant adjusted quadratic relation of cholesterol level and all-cause, nonhemorrhagic, and hemorrhagic mortality.

**Discussion**

Using this large data set of ethnically diverse women, we were able to show a significant relation between cholesterol and nonhemorrhagic stroke death in women <55 years of age. We also demonstrated that age modifies the black/white differences in stroke mortality in women. Finally, we revealed the continuing significance of traditional risk factors for stroke mortality, especially systolic blood pressure.

Our study found a positive relation between cholesterol and stroke mortality in younger women that persisted for up to 30 years of follow-up. Although hypercholesterolemia is a well-established, modifiable risk factor for coronary artery disease, it has not consistently been considered a risk factor for stroke.22–25 Three large prospective studies conducted in the 1980s and 1990s to look in part at this relationship reported a positive association between cholesterol level and nonhemorrhagic stroke,26–28 but other studies did not observe a significant association.22–24 Prior efforts to link cholesterol to stroke may have been limited because of small sample size, inadequate follow-up, possible confounding, and a failure to distinguish between the differing causes of nonhemorrhagic and hemorrhagic stroke. Total cholesterol itself may not be the most sensitive predictor of stroke mortality because it combines the atherogenic properties of high-density lipoprotein with the atherogenic properties of low-density lipoprotein (LDL). Studies relating serum cholesterol and stroke incidence in blacks have been particularly scarce.3

Elevated blood cholesterol may contribute to stroke risk through several mechanisms, including heart disease and a consequent increase in atrial fibrillation and left ventricular dysfunction that promote mural thrombi that can cause embolic strokes. Cholesterol also contributes to atherosclerosis of the carotid arteries and cerebral vessels that may promote atheroembolic and atherothrombotic events. Results from various HMG-CoA reductase inhibitor trials suggest that lowering cholesterol levels reduces cardiac and cerebrovascular events, although statins may work through other mechanisms in addition to cholesterol lowering, such as improved endothelial function, a reduction in inflammation, increased plaque stability, and a reduction in thrombus formation.29–31

Our results are consistent with 2 previous studies showing that cholesterol is a risk factor for stroke in young women. A study of 2873 women from the Framingham data set used adjusted models to find a positive relationship between cholesterol level and stroke mortality in women <55 years of age followed up for at least 9 years.32 In a review of 45 international observational cohort studies, the Prospective Studies Collaboration found a significant, positive relationship of stroke (incidence and/or mortality) over cholesterol categories for men and women <45 years of age but not for older ages.24 By documenting differences by age group for both white and black women, our results extend these previous findings.

We also document the effect of cholesterol on stroke subtype. The results from Table 4 show a positive relation between cholesterol and both nonhemorrhagic and all-cause stroke mortality in women with baseline age of 30 to 54 years. These findings agree in part with a report from the Multiple Risk Factor Intervention Trial (MRFIT) that studied 350 977 men with baseline ages of 35 to 57 years.32 Adjusted models in that study showed a positive relation between cholesterol and nonhemorrhagic stroke mortality and a negative association between cholesterol and hemorrhagic stroke death, whereas the overall results find no relation between cholesterol level and all-cause stroke death. The inconsistent results between our study and MRFIT may be due to differences in the populations studied, secular trends, and varying lengths of follow-up. In addition, differences in the mix of nonhemorrhagic to hemorrhagic stroke deaths may explain in part the disparate association of cholesterol and all-stroke mortality between men and women. Several studies have suggested a positive association between cholesterol and nonhemorrhagic stroke death and a negative association between cholesterol and hemorrhagic stroke death.34,27,28,33–36 These opposing effects on stroke subtypes may yield an overall neutral outcome on total stroke mortality.

The RRs in Tables 3 and 4 show that the relation of cholesterol to stroke mortality in women <55 years of age differs from that in women ≥55 years of age. This interaction may be related to confounding in the elderly. For example,
low cholesterol may be a marker of poor health in older women rather than a causal factor for stroke. This possibility has been explored in other contexts. In a study of coronary heart disease mortality in an older population, a U-shaped relation between cholesterol and death became positive after adjustments were made for markers of frailty and after deaths in the first year of follow-up were excluded.97 A study analyzing the relationship of low cholesterol to all-cause mortality in a national cohort found that factors relating to underlying health status, such as a low level of physical activity, likely account for the increased risk of death.98 We were unable to evaluate how poor health may increase stroke mortality in women ≥55 years of age with low cholesterol because we had no similar variables for frailty, such as serum albumin and iron, to analyze. Finally, reports from the coronary heart disease literature have shown that absolute mortality rather than RR measures better estimate the effect of high total cholesterol on advancing age.99,100 Elevations in cholesterol may still be a risk factor in the elderly, but such effects may be masked both by comorbid conditions that favor stroke in the low-cholesterol frail and by multiple risk factors that increase in prevalence in the elderly and exert a more powerful effect on stroke mortality, making RR estimates an ineffective standard.

Univariate predictors of stroke in our study, including blood pressure, diabetes, smoking, and education, are consistent with previous reports. These traditional risk factors for stroke death remained vigorous in our analysis. Increases in systolic blood pressure produced similar increases in risk of stroke mortality among white and black women, as well as among older and younger women. In contrast to cholesterol, the impact of blood pressure was not limited to younger women in this study. Although our risk estimates for systolic blood pressure and cholesterol are similar in women <55 years of age, blood pressure is a stronger predictor of stroke death when one accounts for the distribution of blood pressure and cholesterol readings in the population and the intervals used for the analysis (per 10 mm Hg and per 1 mmol/L, respectively). Our results also support that diabetics are more strongly related to stroke mortality in women ≥55 than in younger women.

Although tobacco use is a leading modifiable risk factor contributing to all types of strokes in whites, few data are available for blacks.3 We show large increases in adjusted RR for stroke mortality in white and black women <55 years of age who smoke ≥21 cigarettes per day. Our results are consistent with an analysis from MRFIT showing no interaction of race with smoking for stroke mortality among men.41 Low socioeconomic status in the United States has been related to increased hypertension and stroke mortality in both whites and blacks.42,43 In our multivariate models, attaining the extremes of age and is more strongly associated with mortality in black women <55 years of age than in white women. The study supports the emerging consensus regarding cholesterol as a risk factor for stroke and quantifies this relation in younger women. This study also documents the continuing importance of traditional risk factors for stroke mortality such as high blood pressure. Strategies for stroke prevention should consider the long-term consequences of risk factors, including elevated cholesterol in relatively young women.

Acknowledgments
This study was funded by the American Heart Association (9750703N) and the National Heart, Lung and Blood Institute (K0803681). Women’s Pooling Project Investigators included the following: Ralph D’Agostino, Boston University; Elizabeth Barrett-Conner, University of California San Diego; Victor Hawthorne, University of Michigan; Millicent Higgins, University of Michigan; William Kannel, Framingham Heart Study; Julian Keil, Medical University of South Carolina; Braxton D. Mitchell, University of Maryland School of Medicine; Lori Mosca, Columbia University; Michael P. Stern, University of Texas Health Science Center; Susan Sutherland, Research Institute at Mission St Joseph’s; Moyes Szko, Johns Hopkins University; and H. Al Tyrode, University of North Carolina.

References


Cholesterol Predicts Stroke Mortality in the Women's Pooling Project
Richard B. Horenstein, Dean E. Smith and Lori Mosca
for the Womens Pooling Project Investigators

Stroke. 2002;33:1863-1868
doi: 10.1161/01.STR.0000020093.67593.0B
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/33/7/1863

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/