HDL-Cholesterol, Total Cholesterol, and the Risk of Stroke in Middle-Aged British Men

S. Goya Wannamethee, PhD; A. Gerald Shaper, FRCP; S. Ebrahim, FRCP

Background and Purpose—The purpose of this study was to examine the relation between serum HDL cholesterol and total cholesterol and risk of stroke.

Methods—We carried out a prospective study in 7735 men, 40 to 59 years of age, drawn from 1 group practice in each of 24 British towns. Men with history of stroke were excluded (n=52).

Results—During the mean follow-up period of 16.8 years, there were 343 stroke cases (fatal and nonfatal) in the 7683 men with no history of stroke. Higher levels of HDL cholesterol were associated with a significant decrease in risk of stroke even after adjustment for potential confounders (top fifth versus lowest fifth: adjusted relative risk 0.68, 95% CI 0.46 to 0.99). The inverse relation was seen only for nonfatal strokes (adjusted relative risk 0.59, 95% CI 0.39 to 0.90; top fifth versus lowest fifth). Total cholesterol showed no graded association with fatal strokes, but men with levels ≥8.1 mmol/L (top 5% of the distribution) showed increased risk of nonfatal stroke, although this was not statistically significant after adjustment (adjusted RR 1.46, 95% CI 0.91 to 2.32). The beneficial effects of elevated HDL cholesterol on nonfatal stroke were seen in both smokers and nonsmokers and were more evident in men with hypertension than in normotensives. In hypertensive men, elevated HDL cholesterol (top fifth) was associated with a significant 50% reduction in risk of nonfatal strokes compared with men in the lowest fifth.

Conclusions—Higher levels of HDL cholesterol were associated with a significant decrease in risk of nonfatal stroke. In contrast, elevated total cholesterol showed a weak positive association with nonfatal strokes. The marked inverse association between HDL cholesterol and stroke seen in hypertensives emphasizes the importance of those modifiable risk factors for stroke known to lower the concentrations of HDL cholesterol. (Stroke. 2000;31:1882-1888.)

Key Words: cholesterol ■ lipoproteins, HDL cholesterol ■ stroke

There is a well-established inverse relation between serum concentrations of HDL cholesterol and the risk of coronary heart disease, but it is not a well-documented risk factor for stroke. Several case-control studies have noted an inverse relation between HDL cholesterol and risk of stroke or transient ischemic attack, but few prospective studies have addressed this issue. The Framingham Study, the Copenhagen Study, and the Israeli Heart Disease Study have all demonstrated a trend toward higher risk of stroke with lower HDL cholesterol levels in men. We have examined the relation between HDL cholesterol and stroke risk as well as the relation between total cholesterol and risk of stroke in a large prospective study of middle-aged men followed up for an average of 16.8 years.

Subjects and Methods
The British Regional Heart Study is a large, prospective study of cardiovascular disease comprising 7735 men, 40 to 59 years of age, selected from the age-sex registers of 1 group general practice in each of 24 towns in England, Wales, and Scotland (78% response rate). The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported. In 1978 to 1980, research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made, and blood samples (nonfasting) were taken throughout the day between 8:30 AM and 6:30 PM. Details of the measurement of serum lipid concentrations have been described. Serum concentrations of total cholesterol and HDL cholesterol were not available in 45 and 315 men, respectively, because of missing data. Serum triglyceride measurements were only available for men in 18 towns (7th to 24th; n=5675) because the decision to estimate triglycerides was not taken until 6 towns had been studied. Adjustments were made for the marked diurnal variation in triglyceride measurements. The London School of Hygiene sphygmononometer was used to measure blood pressure twice in succession, with the subjects seated and with the arm supported on a cushion. The mean of the 2 readings was used in the analysis, and all blood pressure readings were adjusted for observer variation within each town. Hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥90 mm Hg or receiving antihypertensive treatment. Details of classification methods for smoking status, alcohol consumption, social class (longest held occupation), and physical activity have been reported. The men were classified according to their current cigarette smoking status into 6 groups:

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From the Department of Primary Care and Population Sciences (S.G.W., A.G.S.), Royal Free and University College Medical School, and the Department of Social Medicine (S.E.), University of Bristol, Canynge Hall, Bristol, UK.
Correspondence to Dr S. Goya Wannamethee, Department of Primary Care and Population Sciences, Royal Free and University College Medical School, Rowland Hill St, London NW3 2PF, UK. E-mail goya@rfhsm.ac.uk
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those who had never smoked cigarettes, ex-cigarette smokers, and 4 groups of current cigarette smokers (1 to 19, 20, 21 to 39, and $\geq 40$ cigarettes/d). Heavy drinking is defined as drinking 6 units (1 UK unit = 8 to 10 g alcohol) daily or on most days in the week. A physical activity score was derived for each man on the basis of frequency and type of leisure activity, and the men were grouped into 6 broad categories on the basis of their total score: inactive, occasional, light, moderate, moderately vigorous, and vigorous.13 “Active men” were those graded “moderate or more active.”

Preexisting Disease
The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis), stroke, diabetes, and a number of other disorders. They were also asked for details of any regular medical treatment including antihypertensive treatment. The World Health Organization (Rose) chest pain questionnaire14 was administered to all men at the initial examination, and a 3-orthogonal-lead ECG was recorded at rest.

Previous Stroke
Evidence of a previous stroke was determined by the subject’s recall of such a diagnosis made by a physician (n = 52 men), and these men have been excluded from the analyses.

Coronary Heart Disease
Men with evidence of coronary heart disease (CHD) were defined as those with recall of a diagnosis of angina or heart attack made by a physician, those with angina or a possible myocardial infarction on World Health Organization (Rose) chest pain questionnaire,14 or with ECG evidence of possible or definite myocardial ischemia or myocardial infarction.

Diabetes
History of diabetes was based on recall of a physician’s diagnosis.

Lipid-Lowering Drugs
Only 35 men were taking lipid-lowering drugs at screening, and they are included in the overall analyses.

Follow-Up
All men irrespective of previous CHD or stroke events were followed up for all-cause mortality and for cardiovascular morbidity.16 All cardiovascular events occurring in the period up to December 1995 are included in the study, an average follow-up of 16.8 years (range 15.5 to 18.0 years), and follow-up has been achieved for 99% of the cohort. Information on death was collected through the established “tagging” procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Fatal stroke episodes were those coded on the death certificate to International Classification of Diseases codes 430 to 438.

### TABLE 1. Characteristics of Men With and Without Stroke

<table>
<thead>
<tr>
<th></th>
<th>No Stroke (7340)</th>
<th>Total Stroke (343)</th>
<th>Nonfatal (283)</th>
<th>Fatal (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>50.08</td>
<td>52.97*</td>
<td>52.97*</td>
<td>54.33*</td>
</tr>
<tr>
<td>Mean cholesterol, mmol/L</td>
<td>6.29</td>
<td>6.38</td>
<td>6.39</td>
<td>6.34</td>
</tr>
<tr>
<td>Mean HDL-cholesterol, mmol/L</td>
<td>1.15</td>
<td>1.11*</td>
<td>1.11*</td>
<td>1.15</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>144.5</td>
<td>157.3*</td>
<td>155.9*</td>
<td>163.7*</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>82.0</td>
<td>86.8</td>
<td>86.3*</td>
<td>89.6*</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>25.47</td>
<td>25.76</td>
<td>25.83</td>
<td>25.41</td>
</tr>
<tr>
<td>Mean FEV₁, L</td>
<td>1.73</td>
<td>1.81</td>
<td>1.82</td>
<td>1.80</td>
</tr>
<tr>
<td>% Current smokers</td>
<td>40.6</td>
<td>54.3*</td>
<td>54.5*</td>
<td>53.3*</td>
</tr>
<tr>
<td>% Heavy drinkers</td>
<td>10.7</td>
<td>11.7</td>
<td>11.0</td>
<td>15.0</td>
</tr>
<tr>
<td>% Active</td>
<td>37.7</td>
<td>27.9*</td>
<td>25.8*</td>
<td>21.1*</td>
</tr>
<tr>
<td>% Any preexisting CHD</td>
<td>24.4</td>
<td>35.9*</td>
<td>36.4*</td>
<td>33.3*</td>
</tr>
<tr>
<td>% Myocardial infarction</td>
<td>5.1</td>
<td>10.5*</td>
<td>11.0</td>
<td>8.3</td>
</tr>
<tr>
<td>% Diabetes</td>
<td>1.4</td>
<td>3.2*</td>
<td>3.2*</td>
<td>3.3</td>
</tr>
<tr>
<td>% Antihypertensive treatment</td>
<td>4.2</td>
<td>13.4*</td>
<td>11.3*</td>
<td>23.3*</td>
</tr>
</tbody>
</table>

*Comparisons with no stroke, P < 0.05.

### TABLE 2. Serum HDL-Cholesterol, Total Cholesterol, and Total Stroke Rates per 1000 Person-Years and Adjusted Relative Risks (95% CI) in Men With No History of Stroke

<table>
<thead>
<tr>
<th></th>
<th>No. of Men</th>
<th>No. of Cases</th>
<th>Rates/1000 Person-Years</th>
<th>Age-Adjusted RR</th>
<th>Adjusted* RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol, mmol/L†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.93</td>
<td>1503</td>
<td>80</td>
<td>3.6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.93-1.06</td>
<td>1566</td>
<td>79</td>
<td>3.4</td>
<td>0.89 (0.65, 1.22)</td>
<td>1.00 (0.73, 1.38)</td>
</tr>
<tr>
<td>1.06-1.18</td>
<td>1323</td>
<td>64</td>
<td>3.2</td>
<td>0.85 (0.61, 1.18)</td>
<td>1.02 (0.73, 1.43)</td>
</tr>
<tr>
<td>1.18-1.33</td>
<td>1478</td>
<td>54</td>
<td>2.4</td>
<td>0.63 (0.45, 0.89)</td>
<td>0.80 (0.56, 1.14)</td>
</tr>
<tr>
<td>1.33-</td>
<td>1499</td>
<td>52</td>
<td>2.3</td>
<td>0.59 (0.41, 0.83)</td>
<td>0.68 (0.46, 0.99)</td>
</tr>
<tr>
<td>Test for linear trend across groups</td>
<td></td>
<td></td>
<td></td>
<td>P = 0.005</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>1608</td>
<td>61</td>
<td>2.5</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5.5-5.9</td>
<td>1377</td>
<td>71</td>
<td>3.4</td>
<td>1.35 (0.96, 1.89)</td>
<td>1.42 (1.00, 2.01)</td>
</tr>
<tr>
<td>6.0-5.9</td>
<td>1478</td>
<td>64</td>
<td>2.8</td>
<td>1.08 (0.77, 1.53)</td>
<td>1.02 (0.72, 1.46)</td>
</tr>
<tr>
<td>6.5-6.9</td>
<td>1690</td>
<td>73</td>
<td>2.9</td>
<td>1.07 (0.77, 1.50)</td>
<td>1.02 (0.72, 1.44)</td>
</tr>
<tr>
<td>7.2-8.1</td>
<td>1087</td>
<td>45</td>
<td>2.7</td>
<td>1.05 (0.72, 1.54)</td>
<td>1.14 (0.81, 1.63)</td>
</tr>
<tr>
<td>8.1-</td>
<td>398</td>
<td>26</td>
<td>4.5</td>
<td>1.80 (1.14, 2.84)</td>
<td>1.46 (0.91, 2.32)</td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking, physical activity, alcohol intake, BMI, preexisting CHD, diabetes, antihypertensive treatment, and systolic blood pressure.
†Data on HDL-cholesterol not available in 314 men; ‡data on cholesterol not available in 45 men.
TABLE 3. Serum HDL-Cholesterol, Total Cholesterol, and Fatal and Nonfatal Stroke Rates per 1000 Person-Years and Adjusted Relative Risks in Men With No History of Stroke

<table>
<thead>
<tr>
<th>HDL-cholesterol, mmol/L*</th>
<th>Nonfatal Rates/1000 Person-Years, (n)</th>
<th>Adjusted RR</th>
<th>Fatal Rates/1000 Person-Years, (n)</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.93</td>
<td>3.2 (71)</td>
<td>1.00</td>
<td>0.4 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>0.93-</td>
<td>2.6 (61)</td>
<td>0.87 (0.61, 1.23)</td>
<td>0.8 (18)</td>
<td>2.09 (0.93, 4.72)</td>
</tr>
<tr>
<td>1.06-</td>
<td>2.7 (54)</td>
<td>0.97 (0.68, 1.40)</td>
<td>0.5 (10)</td>
<td>1.44 (0.57, 3.62)</td>
</tr>
<tr>
<td>1.18-</td>
<td>2.0 (46)</td>
<td>0.77 (0.53, 1.14)</td>
<td>0.4 (8)</td>
<td>1.01 (0.38, 2.69)</td>
</tr>
<tr>
<td>1.33-</td>
<td>1.7 (39)</td>
<td>0.59 (0.39, 0.90)</td>
<td>0.6 (13)</td>
<td>1.32 (0.52, 3.33)</td>
</tr>
<tr>
<td>Test for linear trend across groups</td>
<td>p = 0.03</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Total cholesterol, mmol/L† | Nonfatal Rates/1000 Person-Years, (n) | Adjusted RR | Fatal Rates/1000 Person-Years, (n) | Adjusted RR |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.5</td>
<td>2.1 (51)</td>
<td>1.00</td>
<td>0.4 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>5.5-</td>
<td>2.8 (58)</td>
<td>1.37 (0.93, 2.00)</td>
<td>0.6 (13)</td>
<td>1.77 (0.76, 4.15)</td>
</tr>
<tr>
<td>6.0-</td>
<td>2.3 (53)</td>
<td>1.00 (0.67, 1.48)</td>
<td>0.5 (11)</td>
<td>1.16 (0.49, 2.75)</td>
</tr>
<tr>
<td>6.5-</td>
<td>2.4 (62)</td>
<td>1.01 (0.69, 1.48)</td>
<td>0.4 (11)</td>
<td>1.06 (0.44, 2.50)</td>
</tr>
<tr>
<td>7.2-</td>
<td>2.1 (34)</td>
<td>0.91 (0.59, 1.41)</td>
<td>0.7 (11)</td>
<td>1.59 (0.68, 3.69)</td>
</tr>
<tr>
<td>8.1-</td>
<td>4.0 (23)</td>
<td>1.54 (0.93, 2.54)</td>
<td>0.5 (3)</td>
<td>1.09 (0.30, 3.96)</td>
</tr>
<tr>
<td>Test for linear trend across the groups</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data on HDL-cholesterol not available in 314 men; †data on cholesterol not available in 45 men.

Results

In the 7683 men with no history of stroke, there were 343 stroke events (283 nonfatal, 60 fatal) during the mean follow-up period of 16.8 years, a rate of 2.9 per 1000 person-years. Table 1 contrasts the characteristics of men who had a stroke event during the follow-up period with those who did not. On average, stroke subjects were significantly older, had higher systolic and diastolic blood pressures, lower HDL cholesterol concentrations, and lower FEV₁. They were significantly more likely to be smokers, to be less physically active, and to have evidence of preexisting CHD and treatment for hypertension.

Blood Lipids and Risk of Total Stroke

HDL Cholesterol

Risk of stroke decreased significantly with increasing levels of HDL cholesterol after adjustment for age (test for trend P=0.005) (Table 2). In this cohort, HDL cholesterol concentrations have been shown to be associated with wide range of cardiovascular risk factors.9,18 Further adjustment for potential confounders viz cigarette smoking, physical activity, alcohol intake, BMI, preexisting CHD, diabetes, antihypertensive treatment, and systolic blood pressure increased the RR and reduced the trend, but it remained significant (P=0.03). There was little difference among the lower 3 quintiles, but men in the highest fifth of HDL cholesterol concentration still showed significantly lower risk than those in the lowest fifth.

Total Cholesterol

Risk of stroke was only significantly increased among men in the top 5% of the distribution after adjustment for age (Table
Further adjustment for confounders considerably reduced the increased risk, which was no longer statistically significant.

**HDL Cholesterol/Total Cholesterol Ratio**
A weak inverse association was seen between the HDL cholesterol/total cholesterol ratio and risk of stroke after adjustment. The adjusted RRs for the 5 quintiles of the distribution were 1.00, 0.91 (0.66, 1.27), 1.02 (0.73, 1.43), 0.78 (0.54, 1.11), and 0.81 (0.56, 1.18).

**Serum Triglycerides**
No association was seen between triglycerides and risk of total stroke (data not shown).

**Fatal and Nonfatal Stroke**
Subjects with fatal stroke (Table 1) were older, had higher systolic and diastolic blood pressures, and were far more likely to be receiving treatment for hypertension than those with nonfatal stroke. They were more likely to be heavy drinkers and thus, not surprisingly, had higher HDL cholesterol concentrations than nonfatal stroke subjects. The relations between HDL cholesterol and stroke and serum total cholesterol and stroke were examined separately for fatal and nonfatal strokes (Table 3). An inverse association with HDL cholesterol was seen with nonfatal strokes after adjustment, with lower risk from the fourth quintile (test for trend \( P = 0.03 \)). Men in the highest fifth showed significantly lower risk of nonfatal stroke than men in the lowest fifth. No association was seen between serum triglycerides and nonfatal stroke.

**HDL Cholesterol and Stroke by Levels of Risk Factors**
Because of the strong relation between stroke and risk factors such as hypertension, cigarette smoking, and preexisting CHD,19 we have examined the effects of serum HDL cholesterol on nonfatal stroke by the degree of risk associated with these factors. The Figure shows the age-adjusted nonfatal rates per 1000 person-years and Table 4 shows the RRs adjusted for age, physical activity, alcohol intake, BMI, diabetes, smoking, systolic blood pressure, and preexisting CHD by levels of these factors. Because of the smaller number involved when stratifying, we are primarily concerned with whether the associations differ between the levels of these factors rather than the statistical significance within each subgroup. Higher levels of serum HDL cholesterol were associated with reduced risk of nonfatal stroke in both normotensives and hypertensives, although the reduction was more marked in hypertensives. A test for interaction to see
whether the relation between HDL cholesterol and nonfatal strokes differed by hypertension status was not statistically significant ($P = 0.09$). The inverse relation was seen in both smokers and nonsmokers and in men both with and without preexisting CHD, although the inverse trend was more apparent in those with CHD. However, tests for interaction showed no significant interaction between HDL cholesterol and smoking status or preexisting CHD ($P = 0.50$ and $P = 0.41$, respectively).

BMI, HDL Cholesterol, and Stroke

Because of the strong influence that BMI has on HDL cholesterol, we examined the relation between HDL cholesterol and risk of stroke in men with BMI levels $<25$ and those with levels $\geq 25$, generally regarded to be overweight (Figure 1 and Table 4). An inverse association was seen in both groups of men after adjustment for age, although the inverse relation was more marked in leaner men. After further adjustment for potential confounders, the inverse association was only seen in lean men, and a test for interaction was significant ($P = 0.04$). Further exploration of the findings in the $\geq 25$ kg/m$^2$ group indicate that men in the 25 to 27.9 kg/m$^2$ subgroup behaved similarly to the men in the $<25$ kg/m$^2$ group. Those with BMI $\geq 28$ kg/m$^2$ show an increased risk of stroke in men in the highest HDL cholesterol category. This group of obese men with high HDL cholesterol had a particularly high proportion of heavy drinkers (25%).

Discussion

In this study of middle-aged British men followed up for $>16$ years, an inverse association was seen between serum HDL cholesterol concentration and risk of nonfatal stroke, with risk decreasing from the fourth quintile to the fifth quintile. Men in the highest fifth of the distribution showed significantly reduced risk of nonfatal strokes compared with men in the lowest fifth, even after adjustment for risk factors for stroke. No association was seen with fatal strokes. Few prospective studies have examined the relation between HDL cholesterol and stroke. The Framingham Study noted an inverse trend that was not statistically significant, but the number of cases was small. Our findings are consistent with the Copenhagen and Israeli prospective studies, which noted an inverse relation between HDL cholesterol and ischemic strokes. Although we have no information on type of stroke, 85% of stroke cases in Great Britain are apparently caused by ischemia, and nonfatal strokes are likely to be predominantly ischemic. Although hemorrhagic strokes are less common, they are likely to make up a high proportion of fatal strokes, and the lack of relation with first-event fatal strokes in the present study suggests that HDL cholesterol is only related to ischemic strokes. The weak association between the HDL cholesterol/total cholesterol ratio and stroke risk suggests that it is the absolute level of HDL cholesterol that is of
importance in determining stroke risk. We observed no association between nonfasting serum triglyceride and risk of stroke even in the univariate analysis, in contrast to the Copenhagen study, which noted a positive association. The discrepancy in these findings is not clear because the Copenhagen Study also used nonfasting triglyceride measurements.

Blood Cholesterol and Stroke

The role of blood cholesterol in stroke prevention is unclear. Most prospective studies have failed to find a relation between total cholesterol and risk of total stroke. It has been proposed that this may be due to the differing association with subtypes of stroke. An inverse association has been observed with hemorrhagic strokes and a positive association with ischemic stroke. However, not all observational studies have found a positive association between total cholesterol and nonfatal strokes except at the extreme end of the distribution. Risk of stroke was increased only in men with levels ≥8.1 mmol/L (top 5%), although this was not statistically significant after adjustment. This finding is consistent with the findings from the Copenhagen Study. Despite the lack of association between serum total cholesterol and risk of stroke in observational epidemiological studies, the results of lipid-lowering trials with statin agents suggest benefit for stroke reduction.

Clinical Implications

HDL cholesterol is inversely associated with risk of nonfatal stroke (presumably ischemic), and this relation was observed in both smokers and smokers and was more apparent in lean men and in men with preexisting CHD and was particularly striking in hypertensive men. The lack of protective effect in the heavier men (≥25 kg/m²) may be explained by the high proportion of heavy drinkers with high HDL cholesterol and obesity, who are likely to have an increased risk of stroke. In hypertensives, elevated HDL cholesterol was associated with a 50% reduction in the risk of nonfatal strokes. Because these men are at very high absolute risk of stroke, the absolute benefits of high HDL cholesterol are large. Our findings also suggest that caution should be taken in using β-blockers in hypertensive men because these drugs tend to lower HDL cholesterol by up to 10% and to raise triglycerides by up to 30%. β-Blockers, unlike thiazides, did not show any significant effect on stroke risk in the MRC mild hypertension trial, and it may be that their lack of effect was due to their effect on HDL cholesterol.

HDL cholesterol is recognized as one of the factors adversely influencing prognosis in hypertensive subjects, although it is not currently used for risk stratification. Our findings confirm that HDL cholesterol is an independent risk factor for nonfatal stroke, and it remains to be determined whether its inclusion in overall stroke risk assessment is of any value. HDL cholesterol is lowered by many adverse lifestyle factors associated with cardiovascular disease, in particular smoking and overweight and or obesity. Our findings emphasize the importance of modifying these lifestyle factors in the management of hypertension.

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References

15. Deleted in proof.
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