Serum Cholesterol and Hemorrhagic Stroke in the Honolulu Heart Program

Katsuhiko Yano, MD, Dwayne M. Reed, MD, PhD, and Charles J. MacLean, PhD

During an average 18 years of follow-up for 7,850 Japanese-American men in Hawaii who were free of stroke at entry, 116 developed hemorrhagic stroke (subarachnoid hemorrhage or intracerebral hemorrhage). There was a significant ($p=0.001$) inverse association between serum cholesterol and the risk of intracerebral hemorrhage but not of subarachnoid hemorrhage. This inverse association was nonlinear, with a higher incidence rate only for men with serum cholesterol in the lowest quintile (<189 mg/dl). The relative risk (lowest quintile/other four quintiles) was 2.55 (95% confidence interval 1.58–4.12) after controlling for age, blood pressure, serum uric acid, cigarette smoking, and alcohol consumption. There was no evidence for an interaction between blood pressure and serum cholesterol, although the inverse association was stronger for normotensive than for hypertensive men. Public health implications would differ in different countries depending on the relative frequency of intracerebral hemorrhage and on the distribution of serum cholesterol levels in the population. 

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A n inverse association between serum cholesterol and the risk of hemorrhagic stroke (subarachnoid hemorrhage and intracerebral hemorrhage) has been noted in epidemiologic studies of Japanese people in Japan\textsuperscript{1–4} and in Hawaii.\textsuperscript{5,6} In the United States this finding was first reported, only for women, in the Framingham Study.\textsuperscript{7} More recently, Iso et al\textsuperscript{8} have presented clear evidence of an inverse association between serum cholesterol and mortality from intracranial hemorrhage on the basis of 6-year follow-up data for 350,977 American men screened for the Multiple Risk Factor Intervention Trial (MRFIT). This association was observed at a very low serum cholesterol level (<160 mg/dl) and only for persons with hypertension (diastolic blood pressure of $\geq$90 mm Hg).

We present results of our investigation on the relation between serum cholesterol measured at the initial examination of the Honolulu Heart Program and the subsequent incidence of hemorrhagic stroke on the basis of long-term (average 18 years) follow-up data. We also examine the possible interaction between serum cholesterol and blood pressure for the risk of hemorrhagic stroke.

Subjects and Methods

The Honolulu Heart Program is a prospective epidemiologic investigation of coronary heart disease and stroke among men of Japanese ancestry who were born between 1900 and 1919 and were living on Oahu Island, Hawaii, in 1965. Details of recruitment, initial examination, follow-up procedures, and population characteristics at the initial examination are given elsewhere.\textsuperscript{9–12} Briefly, of 11,136 eligible men, 8,006 aged 45–68 years participated in the initial examination during 1965–1968. Repeat examinations were carried out 2 and 6 years following the initial examination, with response rates of 95% and 90%, respectively. Nonfasting serum total cholesterol was measured at the initial examination using the Auto-Analyzer N24A method\textsuperscript{13} at the laboratory of the United States Public Health Service Hospital in San Francisco, California. Blood pressure was determined three times on the left arm of seated subjects using a mercury sphygmomanometer, and the average of the three readings was used for the analysis. The fifth phase of the Korotkoff sounds was taken as diastolic blood pressure.

The prevalent cases of stroke ($n=112$) at the initial examination were identified by a neurologist on the basis of definite history or existing neurologic deficits with possible history of stroke. New stroke events developing among men free of stroke at the initial examination were ascertained through
continuous surveillance of hospital discharges, death certificates, and autopsy reports during the follow-up period (through December 1985). Medical practice in the study region is such that virtually all patients with suspected stroke are hospitalized. Also, follow-up is nearly perfect due to a very low emigration rate in the study population.

Definite stroke was diagnosed by a neurologist when a neurologic deficit occurred suddenly and lasted for at least 2 weeks or until death. Definite stroke could usually be determined as hemorrhagic or thromboembolic on the basis of clinical findings at hospitalization, surgery, or autopsy. Computed tomography (CT) has been available for stroke diagnosis in this study population since 1977.

Hemorrhagic stroke was identified on the basis of a focal neurologic deficit accompanied by headache, loss of consciousness, and bloody spinal fluid obtained from a nontraumatic lumbar puncture or on the basis of CT or surgical findings. Intracerebral hemorrhage was distinguished from subarachnoid hemorrhage by the presence of lateralizing signs, occasionally by evidence of an aneurysm or a space-occupying lesion detected through angiography, brain scan, or CT. A focal neurologic deficit in the absence of bloody spinal fluid or CT evidence of hemorrhagic lesions and usually without prolonged unconsciousness, nuchal rigidity, fever, or pronounced leukocytosis was considered to indicate a thromboembolic event. Further details of the diagnosis of stroke are given elsewhere.5

To examine the relation between serum cholesterol and the risk of stroke, age-adjusted incidence rates (per 1,000 person-years) of type-specific stroke by serum cholesterol level measured at the initial examination were estimated using Cox proportional hazards models with a person-years approach.14 Upon examination of the data, it was apparent that serum cholesterol was related to hemorrhagic stroke inversely and to thromboembolic stroke directly. Since we were mainly interested in the inverse association between serum cholesterol and hemorrhagic stroke, further analyses were restricted to hemorrhagic stroke. The relation between hemorrhagic stroke and serum cholesterol appeared to be nonlinear, with a strong discontinuity at a serum cholesterol somewhat below 200 mg/dl. Rather than search for the exact break point, which was of no special interest, we simply contrasted the relation among men with serum cholesterol in the lowest population quintile (<189 mg/dl) against the relation among men with serum cholesterol in the upper four quintiles taken together. Although this post hoc choice of break point weakens statistical tests slightly, the effect is minor. Thus, we used Cox proportional hazards models14 to test the statistical significance of the association between serum cholesterol and hemorrhagic stroke by comparing men with serum cholesterol in the lowest quintile with all other men, taking into account age as a covariate. Furthermore, the independent effect of serum cholesterol on the risk of stroke was evaluated by controlling for confounding variables chosen from known risk factors for hemorrhagic stroke found in previous studies of this cohort.5,6 These possible confounding variables that showed a significant association with serum cholesterol included age, blood pressure, serum uric acid, cigarette smoking, and alcohol consumption.

To evaluate the risk of hemorrhagic stroke by category of serum cholesterol, the relative risk and 95% confidence interval for men with serum cholesterol in the lowest quintile compared with all other men together were estimated, adjusting for age and other confounding risk factors on the basis of corresponding regression coefficients determined by Cox proportional hazards models.14 We examined the possible interaction between serum cholesterol and blood pressure for the risk of hemorrhagic stroke by comparing the age-adjusted incidence rates of hemorrhagic stroke by serum cholesterol quintile separately for hypertensive men (those with an average blood pressure of ≥140/90 mm Hg or on antihypertensive medication) and for normotensive men (those with an average blood pressure of <140/90 mm Hg and not on antihypertensive medication). Also, a formal statistical test for interaction was performed by including the product of serum cholesterol and hypertension status (0 and 1 degrees of freedom) as a covariate in a multivariate Cox regression analysis.14

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Serum cholesterol (mg/dl)</th>
<th>Subarachnoid hemorrhage</th>
<th>Intracerebral hemorrhage</th>
<th>Thromboembolic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean</td>
<td>n</td>
<td>No.</td>
</tr>
<tr>
<td>I</td>
<td>51–188</td>
<td>168</td>
<td>1,559</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>189–207</td>
<td>198</td>
<td>1,591</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>208–225</td>
<td>216</td>
<td>1,567</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>226–247</td>
<td>236</td>
<td>1,571</td>
<td>3</td>
</tr>
<tr>
<td>V</td>
<td>248–537</td>
<td>273</td>
<td>1,562</td>
<td>10</td>
</tr>
</tbody>
</table>

Test for association* $p=0.182$ $p=0.001$ $p=0.275$

*Lowest quintile vs. other four quintiles combined, using Cox regression with age as covariate.
Results

Of the 7,850 men who were free of stroke and who had their serum cholesterol determined at the initial examination, 490 developed new events of definite stroke during follow-up. These new events included 116 hemorrhagic strokes (39 subarachnoid hemorrhages, 77 intracerebral hemorrhages), 322 thromboembolic strokes, and 52 strokes of unspecified type. The diagnosis of stroke was confirmed by autopsy in 12% and by CT in an additional 24%. This diagnostic evidence was present in 63% of hemorrhagic strokes and 32% of thromboembolic strokes.

Table 1 presents age-adjusted incidence rates of type-specific stroke by serum cholesterol quintile. The incidence rates of subarachnoid hemorrhage and intracerebral hemorrhage were highest for men with serum cholesterol in the lowest quintile. On the other hand, the incidence rates of thromboembolic stroke were higher for men with serum cholesterol in the two highest quintiles than for men with serum cholesterol in the three lowest quintiles. The inverse association between serum cholesterol at the initial examination and the subsequent risk of intracerebral hemorrhage was significant ($p=0.001$). The incidence rate of subarachnoid hemorrhage decreased progressively from the lowest quintile to the second highest quintile but increased abruptly in the highest quintile, almost reaching the rate in the lowest quintile. There was no significant association between serum cholesterol and either subarachnoid hemorrhage or thromboembolic stroke. These findings indicate that the inverse relation between serum cholesterol and hemorrhagic stroke is restricted to intracerebral hemorrhage and that there appears to be a threshold effect in this relation. Since our purpose was to examine the relation between serum cholesterol and hemorrhagic stroke, thromboembolic stroke was excluded from further analysis.

The range of serum cholesterol in the lowest quintile was rather wide (51–188 mg/dl), which raises the question of whether there was a further gradient in the risk of hemorrhagic stroke within this group. Table 2 shows age-adjusted incidence rates of hemorrhagic stroke for men with serum cholesterol of $<200$ mg/dl, with breakdown by 20-mg/dl interval. As only 97 men had a serum cholesterol of $<140$ mg/dl, they were combined with men with serum cholesterol of 140–159 mg/dl. The highest incidence rate was noted for both subarachnoid hemorrhage and intracerebral hemorrhage among men with the lowest serum cholesterol (<160 mg/dl), which accounted for only 4.7% of all men at risk.

Table 3 presents the relative risks (and the 95% confidence intervals) of the categories of hemorrhagic stroke for men with serum cholesterol in the lowest quintile ($<189$ mg/dl) compared with all other men, estimated on the basis of Cox regression coefficients. When adjusted for age alone, the risk of all hemorrhagic stroke for men with serum cholesterol in the lowest quintile ($<189$ mg/dl) compared with all other men, estimated on the basis of Cox regression coefficients. When adjusted for age alone, the risk of all hemorrhagic stroke for men with serum cholesterol in the lowest quintile was nearly double that for men with higher serum cholesterol, and their relative risk of intracerebral hemorrhage was 2.2. As indicated by the 95% confidence intervals, these relative risks differ significantly from unity ($p=0.001$). Further adjustment for additional risk factors slightly increased the relative risk for all hemorrhagic stroke and intracerebral hemorrhage. Although the relative risk of subarachnoid hemorrhage was 1.6 after adjusting for age and 1.5 after further adjustment for additional risk factors, neither was significantly different from unity.

Table 4 presents age-adjusted incidence rates of

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**Table 2.** Age-Adjusted Incidence Rates (per 1,000 Person-Years) of Hemorrhagic Stroke for Men With Serum Cholesterol of $<200$ mg/dl at Initial Examination of Honolulu Heart Program

<table>
<thead>
<tr>
<th>Serum cholesterol (mg/dl)</th>
<th>Subarachnoid hemorrhage</th>
<th>Intracerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>Mean</td>
<td>$n$</td>
</tr>
<tr>
<td>51–159</td>
<td>144</td>
<td>366</td>
</tr>
<tr>
<td>160–179</td>
<td>171</td>
<td>723</td>
</tr>
<tr>
<td>180–199</td>
<td>190</td>
<td>1,366</td>
</tr>
</tbody>
</table>

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**Table 3.** Estimated Relative Risk and 95% Confidence Intervals of Hemorrhagic Stroke for Men According to Serum Cholesterol at Initial Examination of Honolulu Heart Program

<table>
<thead>
<tr>
<th>Age-adjusted</th>
<th>Risk factor-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk</td>
<td>95% Confidence interval</td>
</tr>
<tr>
<td>All hemorrhagic stroke</td>
<td>1.98</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>2.19</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Serum cholesterol, lowest quintile vs. other four quintiles combined. Risk factors included age, diastolic blood pressure, serum uric acid, cigarettes/day, and alcohol consumption. Relative risks estimated on basis of Cox regression coefficients.
subarachnoid hemorrhage and intracerebral hemorrhage by serum cholesterol quintiles separately for hypertensive ($N=3,225$) and normotensive ($N=4,606$) men to examine the possible interaction between serum cholesterol and blood pressure for risk of hemorrhagic stroke. The incidence rates of subarachnoid hemorrhage and intracerebral hemorrhage were highest for men with serum cholesterol in the lowest quintile, while no consistent trend of incidence rates was found for men with serum cholesterol in the other four quintiles among either the hypertensive or the normotensive men. However, the inverse association between serum cholesterol and hemorrhagic stroke was significant only for intracerebral hemorrhage in normotensive men ($p=0.001$) and was of only borderline significance for intracerebral hemorrhage in hypertensive men. A formal statistical test for the interaction revealed no significant contribution to the risk of hemorrhagic stroke.

**Discussion**

We found a significant inverse association between serum cholesterol and intracerebral hemorrhage after controlling for age and other risk factors. A similar inverse association was also observed for subarachnoid hemorrhage, but this association was neither as consistent as that for intracerebral hemorrhage nor was it significant. The increased risk of hemorrhagic stroke was noted only for men with serum cholesterol in the lowest quintile ($<189$ mg/dl). Further breakdown of men with low serum cholesterol ($<200$ mg/dl) indicated that the risk of hemorrhagic stroke was highest for those with the lowest serum cholesterol ($<160$ mg/dl). These findings suggest a threshold effect. The inverse association was stronger for normotensive than for hypertensive men, although there was no statistical evidence for an interaction of blood pressure and serum cholesterol.

The inverse association of serum cholesterol with hemorrhagic stroke has been reported in several population studies in Japan $^1$- $^4$ as well as in earlier studies of Japanese men in Honolulu. $^5$ $^6$ A few other studies in Japan have reported a U-shaped relation between serum cholesterol and hemorrhagic stroke. $^{15}$-$^{17}$ In those studies, however, the relation between serum cholesterol and hemorrhagic stroke was not investigated separately for subarachnoid hemorrhage and intracranial hemorrhage. Also, the possible interaction between serum cholesterol and blood pressure was not examined.

In the United States and other Western countries, epidemiologic investigations of risk factors for stroke have focused on thromboembolic stroke (cerebral infarction) rather than on hemorrhagic stroke mainly because of the relative scarcity of the latter condition. $^{18}$-$^{21}$ It is generally accepted that the importance of serum cholesterol as a risk factor for stroke is much weaker and less consistent than its firmly established predictive value for coronary heart disease. The Framingham Study reported a significant inverse association between low density lipoprotein cholesterol and stroke (both atherothrombotic brain infarction and other types) in a multivariate analysis, but only for women. $^7$ In another report of the Framingham Study, hypertension and cigarette smoking were found to be significant risk factors for subarachnoid hemorrhage, but nothing was mentioned about serum cholesterol. $^{22}$ More recently, Iso et al $^8$ reported an inverse association between serum total cholesterol and death from intracranial hemorrhage on the basis of 6 year follow-up data for 350,977 men screened for the MRFIT. That study showed a significantly higher mortality from intracranial hemorrhage only for men with very low serum cholesterol ($<160$ mg/dl). That study also suggested an interaction between serum cholesterol and blood pressure for the risk of fatal intracranial hemorrhage. There was a strong inverse association among hypertensive men (diastolic blood pressure of $\geq 90$ mm Hg) and no association among normotensive men. The inverse association was not observed for subarachnoid hemorrhage.

Our findings are similar to those in the MRFIT except that the inverse association between serum cholesterol and hemorrhagic stroke was stronger

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**TABLE 4.  Age-Adjusted Incidence Rates (per 1,000 Person-Years) of Hemorrhagic Stroke According to Quintiles of Serum Cholesterol for Men Hypertensive and Normotensive at Initial Examination of Honolulu Heart Program**

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Subarachnoid hemorrhage</th>
<th>Intracerebral hemorrhage</th>
<th>Subarachnoid hemorrhage</th>
<th>Intracerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>No.</td>
<td>Rate</td>
<td>n</td>
</tr>
<tr>
<td>I</td>
<td>588</td>
<td>7</td>
<td>0.77</td>
<td>14</td>
</tr>
<tr>
<td>II</td>
<td>631</td>
<td>7</td>
<td>0.69</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>635</td>
<td>4</td>
<td>0.39</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>652</td>
<td>2</td>
<td>0.19</td>
<td>8</td>
</tr>
<tr>
<td>V</td>
<td>719</td>
<td>7</td>
<td>0.61</td>
<td>10</td>
</tr>
</tbody>
</table>

Test for association

$^{*}$ Lowest quintile vs. other 4 quintiles combined, using Cox regression with age as covariate.

Hypertensive, men with average blood pressure $\geq 140/90$ mm Hg or on antihypertensive medication; normotensive, men with average blood pressure of $<140/90$ mm/Hg and not on antihypertensive medication.

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$^*$ Lowest quintile vs. other four quintiles combined, using Cox regression with age as covariate.
among normotensive than among hypertensive men, although the incidence rate of hemorrhagic stroke was much higher for the latter within each serum cholesterol quintile. This suggests that although hypertension is the most important risk factor for hemorrhagic stroke, very low serum cholesterol appears to be an underlying condition that can facilitate weakening of the arterial wall and lead to the rupture of small intraparenchymal cerebral arteries.

It is possible that the discrepancy between the two studies regarding the interaction between blood pressure and serum cholesterol for the risk of hemorrhagic stroke may be explained by our longer follow-up (18 vs. 6 years). During a long follow-up, a substantial portion of men normotensive at the initial examination would become hypertensive, thus increasing the risk of hemorrhagic stroke. Such misclassification might cause a spurious inverse association between serum cholesterol and hemorrhagic stroke among normotensive men. In our study, 30% of the men normotensive at the initial examination had become hypertensive 6 years later at the third examination. However, a significant inverse association (p<0.05) was still noted between serum cholesterol and intracerebral hemorrhage for men who remained normotensive at the third examination.

The biologic mechanism of the harmful effects of low serum cholesterol upon cerebral arteries is not well understood. There is, however, some evidence that very low serum cholesterol plays a role in the pathogenesis of intracerebral hemorrhage through its adverse effects upon erythrocyte fragility and the development of arterionecrosis.

Low serum cholesterol may also be a manifestation of inadequate nutrition, especially of a low intake of animal protein and fat. It is known that farmers in northern Japan, where cerebral hemorrhage is prevalent, have very low serum cholesterol and also eat little animal food. Furthermore, in a study of trends for coronary heart disease and stroke and their risk factors in Japan, it was found that the decline in the incidence of stroke between 1963 and 1983 in rural communities of northeast Japan paralleled an increase in the intake of animal protein and an increase in serum cholesterol during the same period. In the same study, serum cholesterol was inversely associated with cerebral hemorrhage.

In a comparative epidemiologic study of stroke in Japan and Hawaii, it was found that incidence of stroke (both hemorrhagic and thromboembolic) was three times as high in Japan as in Japanese-Americans in Hawaii, despite nearly equal average blood pressures. Intake of animal protein was much higher in Hawaii and was inversely related to stroke incidence in both places. Also, the average serum cholesterol and fat intake were substantially higher in Hawaii than in Japan. It was suggested that low serum cholesterol (which might reflect poor nutrition, especially inadequate intake of animal food) could enhance the vulnerability of small intraparenchymal cerebral arteries and lead to the development of stroke in the presence of hypertension. These findings are consistent with the results of experimental studies using stroke-prone spontaneously hypertensive rats.

It is possible that the apparent inverse association between serum cholesterol and the risk of intracerebral hemorrhage may be a consequence of the competing risk. Since individuals with low serum cholesterol are less likely to die prematurely from coronary heart disease, they are therefore more prone to experience stroke, which is more common in the elderly. However, this is a rather unlikely explanation because an inverse association was not observed between serum cholesterol and the risk of thromboembolic stroke, which occurs much more commonly than hemorrhagic stroke in the elderly.

Thus, although an inverse association between serum cholesterol and intracerebral hemorrhage has been shown in several prospective studies (including ours), there still remains the relative lack of biologically plausible explanations for this association. Low serum cholesterol might be a marker for a disease characterized by vessel fragility and an increased risk of hemorrhagic stroke. Even though we assume a causal relation between low serum cholesterol and an increased risk of intracerebral hemorrhage, the public health implications of such a finding would depend on the characteristics of the population.

In the United States and other Western countries, where both average serum cholesterol and the prevalence of coronary heart disease are high, hemorrhagic stroke occurs much less commonly than thromboembolic stroke. Furthermore, the inverse association between serum cholesterol and hemorrhagic stroke is nonlinear and is limited to men with very low levels of serum cholesterol (<160 mg/dl). Taking account of these limitations together, the overall adverse effect of low serum cholesterol on the risk of stroke appears to be relatively small in terms of population-attributable risk. Therefore, our findings should not preclude the current public health policy of recommending the reduction of serum cholesterol for the prevention of coronary heart disease in the United States.

In Japan and other Asian countries, however, the risk of stroke is as much as three times higher than in the United States, and hemorrhagic stroke may account for more than one third of all strokes. As the population's average serum cholesterol is low, the appropriate public health goal should be to maintain optimal levels of serum cholesterol (probably around 200 mg/dl), which would not increase the risk of either stroke or coronary heart disease.

References


**Key Words** • Asian Americans • cerebral hemorrhage • cholesterol • hypertension
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