Elevated Serum Cholesterol Is a Risk Factor for Both Coronary Heart Disease and Thromboembolic Stroke in Hawaiian Japanese Men

Implications of Shared Risk

Richard Benfante, PhD; Katsuhiko Yano, MD; Lie-Ju Hwang, PhD; J. David Curb, MD; Abraham Kagan, MD; Webster Ross, MD

Background and Purpose

The relation between total serum cholesterol level and thromboembolic or nonhemorrhagic stroke is controversial. The Honolulu Heart Program cohort of Japanese-American men provides data which show that elevated serum cholesterol is an independent predictor of thromboembolic stroke as well as coronary heart disease (CHD). The data are presented to suggest that the association of elevated cholesterol with stroke is sometimes underestimated or underreported partly because of competing or shared risk with CHD, the other major atherosclerotic end point.

Methods

The data are based on 6352 men (aged 51 to 74 years) at baseline examination (1971 to 1974) who were free of clinical CHD and stroke and who were followed an average of 15 years for new cases of both end points. Relative risks of serum cholesterol for CHD and thromboembolic stroke were calculated, controlling for other major cardiovascular covariates.

Results

There was a continuous and progressive increase in both CHD and thromboembolic stroke rates with increasing levels of serum cholesterol. The relative risk between the highest and lowest quartiles of serum cholesterol was 1.7 (95% confidence interval, 1.4 to 2.0) for CHD and 1.4 (95% confidence interval, 1.1 to 1.9) for thromboembolic stroke. There was a decline in the difference in relative risks between CHD and thromboembolic stroke in older men (aged 60 years and older) compared with younger men (aged younger than 60 years).

Conclusions

These data provide additional evidence that elevated serum cholesterol should be considered a primary risk factor for thromboembolic stroke, presumably through its effect on both coronary and cerebrovascular atherosclerosis. It is suggested that this association is sometimes underestimated or underreported partly because of shared or competing risk with CHD, the clinical manifestation of atherosclerosis that generally occurs earlier in life and with greater frequency than thromboembolic stroke. *(Stroke. 1994;25:814-820.)*

Key Words • atherosclerosis • cholesterol • coronary heart disease • risk factors

The public health impact of elevated serum cholesterol is usually described in terms of its effect on the pathogenesis of atherosclerosis and subsequent coronary heart disease (CHD). Atherosclerosis also plays a primary role in the biological etiology of the most common form of stroke (thromboembolic [TE]), yet elevated serum cholesterol is usually not mentioned as a primary risk factor for this disease, and stroke is seldom factored into public health impact and policy statements regarding the effects of elevated serum cholesterol. 1 With TE stroke being the leading cause of neurological disability in the United States and the third leading cause of death, 2 it would seem important to further elucidate the association of elevated serum cholesterol with this disease and reasons why the relevance of the association may currently be underestimated.

Many myocardial infarctions and cerebral infarctions (TE strokes) share a common biological mechanism in which a clot (thrombus) becomes lodged in either a coronary, cerebral, or carotid artery narrowed by advanced atherosclerosis. The subsequent loss of blood supply results in a temporary or permanent loss of tissue function in the area served by the affected artery. With elevated serum cholesterol being a primary biological component in the development of atherosclerosis, one might expect a good association between elevated serum cholesterol and TE stroke for much the same reason that a strong and consistent association exists with CHD. Yet prospective studies examining the association of elevated serum cholesterol and TE stroke have yielded equivocal results. A few studies have indicated a direct association, 3–5 and others have shown little or no association. 6,7 Some earlier studies in the Honolulu Heart Program did not report a significant association, although the association became stronger with increased follow-up. 8,9

There is reason to suspect that the tenuous nature of this association may be partly related to the developmental sequence of atherosclerosis. Atherosclerotic lesions are first established in the aorta, then in the coronary arteries, and later in the cerebrovascular and
The time lag in the development of atherosclerosis in the cerebral arteries compared with the coronary arteries is commensurate with the fact that TE stroke generally occurs much later in life than CHD; ie, approximately half of CHD cases occur before age 65, whereas approximately 75% of TE stroke cases occur after age 65.2 It is reasonable that the time lag in TE stroke incidence, along with the competing risk effects of earlier onset of CHD, requires a substantial follow-up period to identify an association between elevated serum cholesterol and TE stroke.

With these points in mind, we had the opportunity to examine the 15-year incidence of both CHD and TE stroke in the Honolulu Heart Program cohort of 6352 Japanese-American men between the ages of 51 and 74 years and free of diagnosed CHD and stroke at examination 3 (1971 to 1974). The purpose of this study is to further elucidate the relation between elevated serum cholesterol and TE stroke by studying a population with a relatively lower incidence of CHD compared with the mainland United States but a comparable stroke incidence.

Subjects and Methods

Study Cohort

The Honolulu Heart Program is an ongoing, prospective study of CHD and stroke among men of Japanese ancestry born between 1900 and 1919 and living on the island of Oahu, Hawaii, in 1965. Details of the method of recruiting the study cohort, procedures of baseline examinations, laboratory tests, and follow-up procedures are described elsewhere.14 Briefly, 8006 men participated in the initial examination carried out during 1965 to 1968. A second examination was carried out 2 years after the first. A third comprehensive examination was carried out 6 years after the first, during the years 1971 to 1974, and was used as the baseline for this study. At this examination, 6860 of the original cohort of 8006 men participated. All men who had clinical evidence of previous myocardial infarction or stroke at the examination or by surveillance of hospital discharge records between examinations were excluded, leaving 6352 men available for this analysis.

Examination Procedures

Physical examinations and interviews that focused on the cardiovascular system were performed. The examination included an electrocardiogram and an interview with a physician, which provided the ascertainment of prevalent cardiovascular disease. The characteristics measured at the third examination that were used in the present analysis include total serum cholesterol, systolic blood pressure (SBP), current cigarette smoking status (smoker/nonsmoker), history of diabetes (yes/no) (predominantly late-onset type II diabetes, with only 2% of 1263 men with diabetes being insulin dependent), adiposity as measured by body mass index (BMI) (weight [kilograms]/[height [square meters]), and current alcohol use (drinker/nondrinker). Nonfasting serum cholesterol values were determined at the Kuakini Medical Center in Honolulu using a standard automated colorimetric procedure (Auto Analyzer N24a method).15 High- and low-density lipoprotein lipid profiles were not performed.

Identification of Incident Cases

New cases of CHD and TE stroke were identified by continuous, thorough surveillance of hospital discharge records, obituaries in local newspapers, and death certificates. A panel of physicians reviewed all records to confirm diagnoses of cardiovascular disease and other causes of death. Detailed accounts of the differential diagnosis of CHD and stroke in the Honolulu Heart Program have been previously described.8,9,17 For CHD the study end point was definite CHD, defined as documented CHD death or nonfatal myocardial infarction, confirmed by electrocardiogram and/or cardiac enzyme measurements. Definitive diagnostic assessment of hospital findings by a neurologist led to the identification of stroke end points, which met specific written criteria.14,17 Follow-up surveillance covered a 17-year period that began in the fall of 1971 and continued through the end of 1988. Because the examination covered a period of 3 years, the mean duration of follow-up was approximately 15 years. Less than 2% of the cohort was lost to follow-up during the study period. Computed tomographic (CT) scan was first used for stroke diagnosis in 1976; after 1980 CT scan was performed in 93% of stroke cases, with a diagnostic CT confirmation rate of 99% for intracranial hemorrhage and 70% for TE stroke. Even before the advent of CT scan, nearly all cases had lumbar puncture for the presence or absence of blood in the cerebrospinal fluid, and most cases had some objective evidence by nuclear brain scan, cerebral angiography, etc; only 13% were diagnosed solely on the basis of clinical symptoms. No distinction was made between atherothrombotic infarction and cardioembolic infarction because in some cases adequate information for this distinction was unavailable from hospital records and because the prevalence of atrial fibrillation on electrocardiogram at exam 1 was very low (0.08%), and the occurrence of stroke shortly after acute myocardial infarction was quite uncommon in this study cohort. Our neurologist estimated that cardioembolic infarction accounted for less than 10% of total TE stroke.

Statistical Analysis

To compare the relative incidence between CHD and TE stroke, age-adjusted incidence rates of CHD and TE stroke were calculated by the person-years of exposure approach for the total cohort and two different age groups, ie, a middle-aged group of persons aged 51 to 59 years (n=3480) and an older group of persons aged 60 to 74 years (n=2872). The direct method was used for age adjustment of rates, with the total population at risk at exam 3 used as the standard.

To compare levels of serum cholesterol and other major cardiovascular risk factors in persons with incident CHD and TE stroke and in noncases (those with neither CHD nor TE stroke), age-adjusted means were calculated by generalized linear models including age as a covariate. To evaluate age-adjusted bivariate or multivariate relative risks of serum cholesterol for CHD and TE stroke during an average 15 years of follow-up, analyses of separate Cox proportional hazards models were made with respect to the different end points. The cutoff date is the end of 1988 for all end points. The event time is defined as the time from the date of exam 3 to the date of onset of incident cases. The censoring time for deaths is computed as (death date minus exam 3 date). For those still alive at the end of 1988, the censoring time is the follow-up time since exam 3. Multivariate comparisons were made by controlling for selected covariates, which included age, SBP, BMI, smoking, history of diabetes, and alcohol drinking. Estimates of relative risks of high to low levels of serum cholesterol were based on the corresponding regression coefficient associated with the difference of two median values in the first and last quartiles of serum cholesterol (ie, 80 mg/dL or 2.07 mmol/L). The same rule applied to the other continuous covariates SBP and BMI. As for dichotomous covariates (eg, smoking, diabetes, and alcohol drinking), the relative risk estimate is simply the natural exponent of the associated regression coefficient. A test of differences in relative risk levels between cardiovascular disease end points was determined by taking the natural exponent of the difference in the Cox regression coefficients of the comparison groups. The standard error of this difference was used to calculate 95% confidence intervals (CIs).
TABLE 1. Coronary Heart Disease and Thromboembolic Stroke Incidence Rates* per 1000 Person-Years and Case-Fatality Rates During 15 Years of Follow-up: The Honolulu Heart Program

<table>
<thead>
<tr>
<th>Age at Exam 3, y</th>
<th>51-59 (n=3480)</th>
<th>60-74 (n=2872)</th>
<th>Total Cohort (n=6352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD IR</td>
<td>5.5</td>
<td>7.5</td>
<td>6.3</td>
</tr>
<tr>
<td>CFR, %</td>
<td>39</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>TE stroke IR</td>
<td>1.7</td>
<td>4.2</td>
<td>2.7</td>
</tr>
<tr>
<td>CFR, %</td>
<td>11</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Rate ratio       3.2  3.5  1.8  4.5  2.3  4.0

IR indicates incidence rate (per 1000 person-years); CFR, case-fatality rate (percentage of incident cases that were fatal); CHD, coronary heart disease; and TE, thromboembolic.

*IR includes subjects who experienced both CHD and TE stroke at some time during the follow-up period (7% of total cases). In such cases person-years are accrued until specified end point occurred.

Results

During an average of 15 years of follow-up, there were 252 new cases of TE stroke and 575 cases of definite CHD in the 6352 men aged 51 to 74 years who were initially free of clinically diagnosed myocardial infarction and stroke at baseline. Among the two case groups there were 56 persons who experienced both CHD and TE stroke events at some time during the follow-up period. Of these, there were 17 instances in which CHD and stroke occurred during the same general cardiovascular episode.

Table 1 shows that CHD incidence rates were 6.3/1000 person-years compared with 2.7/1000 person-years for TE stroke. This resulted in an overall rate ratio of CHD to TE stroke of 2.3. For men aged younger than 60 years at baseline, CHD rates were 5.5/1000 person-years compared with 1.7/1000 person-years for TE stroke. For men aged 60 years and older the comparative rates were 7.5 and 4.2/1000 person-years, respectively. The rate ratio of CHD to TE stroke declined from 3.2 to 1.8 in the younger compared with the older men. The overall case-fatality rate for persons who developed clinical CHD was 52%, four times higher than that for TE stroke at only 13%.

Table 2 shows age-adjusted mean values for serum cholesterol and other major cardiovascular risk factors in persons at baseline who would eventually develop TE stroke or CHD compared with the noncase group. Serum cholesterol levels were significantly higher in persons who developed TE stroke or CHD compared with persons who would develop neither end point. Persons who developed CHD had slightly higher serum cholesterol levels (224.4 mg/dL or 5.8 mmol/L) compared with persons who developed TE stroke (220.7 mg/dL or 5.71 mmol/L), but the difference was not statistically significant. Persons who developed TE stroke or CHD also had significantly higher values for SBP, BMI, smoking prevalence, and history of diabetes. The higher values for SBP and smoking prevalence in incident TE stroke compared with CHD were statistically significant (P<.01). Prevalence of alcohol drinking was lower in the cardiovascular groups compared with the noncase group. The difference in alcohol drinking prevalence between the incidence groups was not statistically significant.

The Figure shows CHD and TE stroke incidence rates by quartiles of serum cholesterol during the 15-year follow-up period. For both end points there was a continuous and graded increase in disease rates by increasing level of cholesterol. The age-adjusted relative

TABLE 2. Age-Adjusted Mean Values for Serum Cholesterol and Other Cardiovascular Risk Factors in Subjects With Incident Thromboembolic Stroke* or Definite Coronary Heart Disease* and Noncases

<table>
<thead>
<tr>
<th>Variable</th>
<th>TE Stroke (n=226)</th>
<th>CHD (n=542)</th>
<th>Noncases (n=5567)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>220.7†</td>
<td>224.4‡</td>
<td>214.5</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>(5.71)†</td>
<td>(5.80)‡</td>
<td>(5.55)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>148.9†</td>
<td>143.9‡</td>
<td>135.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4‡</td>
<td>24.4‡</td>
<td>23.6</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>50.5‡</td>
<td>39.4‡</td>
<td>33.4</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>30.9‡</td>
<td>27.8‡</td>
<td>18.6</td>
</tr>
<tr>
<td>Alcohol drinkers, %</td>
<td>66.8</td>
<td>63.2‡</td>
<td>70.5</td>
</tr>
</tbody>
</table>

TE indicates thromboembolic; CHD, coronary heart disease; and BP, blood pressure.

*Occurred as either the first or only major clinical event. Does not include 17 subjects who experienced both end points as part of the same general cardiovascular episode.

†Subjects with neither CHD nor TE stroke.

‡P<.01, based on f test for difference in mean values between case and noncase groups.
Table 3. Age-Specific Multivariate Relative Risks* of Serum Cholesterol for Thromboembolic Stroke and Coronary Heart Disease\textsuperscript{a} During 15 Years of Follow-up (Based on Cox Proportional Hazards Model)

<table>
<thead>
<tr>
<th>Age at Exam 3, y</th>
<th>CHD</th>
<th>TE stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-59</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>60-74</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Total Cohort</td>
<td>1.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**RR** indicates relative risk; **CI**, 95% confidence interval; **CHD**, coronary heart disease; and **TE**, thromboembolic.

*RR is based on the difference in risk between median values in the first and last quartiles of serum cholesterol (80 mg/dL or 2.07 mmol/L). Covariates include age, systolic blood pressure, body mass index, smoking, history of diabetes, and alcohol drinking.

includes persons experiencing both end points at some time during the follow-up period (7% of total cases).
to find that elevated serum cholesterol predicts TE stroke as well. In the current study the other major risk factors for CHD also predict TE stroke. Again, this should not be surprising when both clinical end points share common elements in their etiology. Some of the results of this study may provide clues as to why elevated serum cholesterol has only infrequently been reported as a primary risk factor for stroke associated with atherosclerosis (ie, TE, atherothrombotic, ischemic, and nonhemorrhagic stroke) in other studies.

The Natural History of Atherosclerosis and the Problem of Competing Risk

A case can be made that the usual lack of strong association of elevated serum cholesterol with atherosclerotic-type strokes may partly be due to a strong competing risk effect of CHD. For example, the results of this study and other major prospective studies of cardiovascular disease show that clinical CHD tends to occur earlier in life and with much greater frequency than does stroke.2 This pattern of occurrence follows the reported normal sequence of progressive atherosclerosis, in which atherosclerotic plaque becomes established first in the aorta, then in the coronary arteries, and years later in the cerebral arteries.10-13 The greater frequency of occurrence of CHD earlier in life compared with stroke provides the basis for a reduced statistical association of serum cholesterol with stroke. For example, many individuals with elevated serum cholesterol and at high risk for stroke may die of CHD before an episode of stroke can occur. In the case of the present study, the overall case-fatality rate for CHD is 52%, four times higher than that for TE stroke. In addition, those individuals who survive myocardial infarction or who suffer from severe angina often undergo radical risk factor intervention to prevent further atherosclerotic events from occurring. This provides the basis for a further reduction in the association of elevated serum cholesterol with stroke.

The relative risk patterns in the current study for serum cholesterol in CHD and TE stroke are also in general accord with a competing risk scenario. The relative risk of serum cholesterol is significant for both end points, but for the total cohort the relative risk for TE stroke is diminished (1.4) compared with that for CHD (1.7). The ratio of CHD to stroke rate is much higher in younger men (aged younger than 60 years) compared with older men. For men aged 60 years or older, a group in which the rate differential is smaller, the relative risks for CHD (1.8) and TE stroke (1.6) are more similar. It is interesting to note that the relative risk and CI of elevated serum cholesterol for TE stroke in older men (1.6 [1.1 to 2.3]) are very similar to those for CHD in middle-aged men (1.6 [1.1 to 2.0]). This may partly reflect the time lag required for accumulation of enough stroke cases later in life to recognize an association.

It may be relevant here to summarize the general pattern of CHD and stroke in the Honolulu Heart Program compared with other major study cohorts. The prevalence and incidence of CHD in this cohort were somewhat higher (40% to 100%) than those among indigenous Japanese men in Japan but were much lower than those among US white men.23-25 On the other hand, the prevalence and incidence of stroke (both hemorrhagic and TE) were much lower (approximately one third) than those among indigenous Japanese men and were nearly equal to those among US white men.26-27 Furthermore, the associations of major risk factors with CHD and stroke were very similar to those found for US white men.19,28 It may be that the somewhat lower overall CHD rate together with an overall higher stroke rate in this cohort was advantageous in finding an association between elevated serum cholesterol and TE stroke.

The finding that the relative risk for CHD remained undiminished in the older men is in agreement with earlier studies in the Honolulu Heart Program.28-30 Other prospective studies have indicated that the association of elevated serum cholesterol and CHD decreases with age, although this is puzzling because elevated cholesterol levels are considered a necessary biological ingredient in atherosclerosis, a pathological process that usually progresses with age in the absence of intervention. Theoretical reasons that have been suggested to help explain this discrepancy include different selective attrition effects on cohorts studied during different time periods, different intervention effects, and other demographic and methodological factors. A more detailed discussion of possible reasons why some
Differential Classification of Stroke and Potential Effect on Relative Risk Associations

There are several other ways that the statistical association between elevated serum cholesterol and atherosclerotic stroke may be artificially reduced. One is to lump cases of hemorrhagic stroke with those of atherosclerotic stroke. The reported negative association of serum cholesterol with hemorrhagic stroke would necessarily dilute the association between elevated serum cholesterol and stroke when the classification criterion for stroke is total stroke, as is often the case. For TE stroke there is another classification criterion that could affect relative risk associations with elevated serum cholesterol. The major subgroups of TE stroke are large- and small-vessel strokes. The latter type of TE stroke is usually not associated with atherosclerosis, the primary association being with hypertension. The large-vessel type of stroke is primarily associated with atherosclerosis. Because it is technically difficult in many studies to differentiate between large- and small-vessel strokes, they are lumped into a single category of TE stroke. Such is the case in the present study. The inclusion of an unknown number of small-vessel strokes that are not related to atherosclerosis per se would also tend to diminish the association of elevated serum cholesterol and TE stroke. The lack of association between elevated serum cholesterol and cerebral infarction in a large cohort of men in Japan is thought to be due to a predominance of small-vessel-type infarctions in that population. In the future, with more effective technical means of differentiating between these stroke subgroups, we may be able to show stronger associations between those strokes that are more related to atherosclerosis and elevated serum cholesterol levels.

The results of this study strongly suggest that elevated serum cholesterol should be considered a major risk factor for TE stroke as well as CHD. The lack of consistently strong associations in previous studies may be related to problems in the statistical modeling of elevated serum cholesterol with TE stroke. Among these are a potentially strong competing risk effect from CHD, inclusion of some TE strokes in stroke case groups that are not primarily related to atherosclerosis, insufficient follow-up time to accumulate enough cases of a relatively late-onset disease, and preventive effects of intervention or treatment in persons with other atherosclerotic clinical manifestations. Future studies will have to be of a fairly innovative nature in attempting to deal with the complex problems of competing risk and comorbidity that increase as cohorts age. To consider this association too lightly may be to underestimate the public health impact of elevated serum cholesterol levels on overall morbidity and mortality as well as economic and social costs of subsequent treatment and disability.

Acknowledgments

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