Higher Total Serum Cholesterol Levels Are Associated With Less Severe Strokes and Lower All-Cause Mortality
Ten-Year Follow-Up of Ischemic Strokes in the Copenhagen Stroke Study

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Background and Purpose—Evidence of a causal relation between serum cholesterol and stroke is inconsistent. We investigated the relation between total serum cholesterol and both stroke severity and poststroke mortality to test the hypothesis that hypercholesterolemia is primarily associated with minor stroke.

Methods—In the study, 652 unselected patients with ischemic stroke arrived at the hospital within 24 hours of stroke onset. A measure of total serum cholesterol was obtained in 513 (79%) within the 24-hour time window. Stroke severity was measured with the Scandinavian Stroke Scale (0 = worst, 58 = best); a full cardiovascular risk profile was established for all. Death within 10 years after stroke onset was obtained from the Danish Registry of Persons.

Results—Mean ± SD age of the 513 patients was 75 ± 10 years, 54% were women, and the mean ± SD Scandinavian Stroke Scale score was 39 ± 17. Serum cholesterol was inversely and almost linearly related to stroke severity: an increase of 1 mmol/L in total serum cholesterol resulted in an increase in the Scandinavian Stroke Scale score of 1.32 (95% CI, 0.28 to 2.36, P = 0.013), meaning that higher cholesterol levels are associated with less severe strokes. A survival analysis revealed an inverse linear relation between serum cholesterol and mortality, meaning that an increase of 1 mmol/L in cholesterol results in a hazard ratio of 0.89 (95% CI, 0.82 to 0.97, P = 0.01).

Conclusions—The results of our study support the hypothesis that a higher cholesterol level favors development of minor strokes. Because of selection, therefore, major strokes are more often seen in patients with lower cholesterol levels. Poststroke mortality, therefore, is inversely related to cholesterol. (Stroke. 2007;38:2646-2651.)

Key Words: cholesterol • mortality • prognosis • stroke

The stroke-cholesterol relation is complex and contains several paradoxes.1–4 Whereas total cholesterol is a well-documented risk factor for coronary disease,5,6 evidence of a relation between cholesterol and risk of stroke is inconsistent.7–11 In search of an explanation for this paradox, it has been noted that most large-scale studies on cholesterol and stroke risk have not differentiated between ischemic and hemorrhagic stroke, nor did they differentiate among various subtypes of ischemic stroke.8–11 It has been suggested that cholesterol may increase the risk of only certain types of infarcts3,12–14 and that low cholesterol predisposes to hemorrhagic stroke,1,9,15 thus attenuating an association between cholesterol and all stroke.

Despite the increasing risk of cardiovascular disease with increasing cholesterol5,6 and the decreasing risk of stroke with cholesterol-lowering agents,16 a higher cholesterol value has been associated with a better outcome in several studies.17–19 These paradoxical observations would be explainable as a whole if hypercholesterolemia could be linked to minor stroke (mainly small-vessel stroke) with a fairly good prognosis while not being linked to major stroke (mainly hemorrhagic and large-vessel and/or embolic strokes) with a poorer prognosis.

Based on a 10-year follow-up study of 652 patients with well-characterized acute stroke, the aim of the present study was to test the hypothesis that hypercholesterolemia is primarily associated with minor stroke caused by small-vessel occlusion.

Subjects and Methods
This was a retrospective study based on data from the community-based Copenhagen Stroke Study. The Copenhagen Stroke Study has been described in detail elsewhere.20,21 In brief, all patients sustaining a stroke in a well-defined area of Copenhagen with 240 000 inhabitants were admitted to a 62-bed stroke unit at the same hospital. The inclusion period was March 1992 to November 1993. No preselection of patients was performed, because all who had experienced a stroke in the area were brought to the stroke unit of our
hospital, regardless of age, stroke severity, or comorbid diseases. In our community, all who experience symptoms of a stroke or transient ischemic attack (TIA) including nursing home residents) are urged to immediately seek hospital treatment. General practitioners were instructed to hospitalize all patients with stroke or TIA. Hospital care is free, and a very high proportion (88%) of stroke patients in the area was admitted to this hospital during the time of inclusion. On admission, all patients were offered a standardized evaluation program, computed tomography (CT) scan, ECG, a battery of blood tests including total serum cholesterol, and a cardiovascular risk factor evaluation by a standardized questionnaire. Information was obtained from relatives or caregivers when needed. The study was approved by the ethics committee.

Stroke was defined according to World Health Organization criteria.22 TIs or subarachnoid hemorrhages were not included. The Scandinavian Stroke Scale (SSS) was used to assess stroke severity on admission. SSS evaluates level of consciousness; eye movement; power in the arm, hand, and leg; orientation; apraxia; facial paresis; and gait on a total score from 0 (worst) to 58 (best). CT determined stroke type (hemorrhage/infarct). Lesion size was measured as the largest diameter visible on the CT scan.

The following prognostic factors were investigated in the statistical analyses: age, sex, initial stroke severity (on SSS), diabetes mellitus, atrial fibrillation (AF), ischemic heart disease (IHD), hypertension, previous stroke, preexisting disability, alcohol consumption, smoking, and total serum cholesterol. Diabetes was considered present when a patient had known diabetes mellitus on admission or when the plasma glucose value was ≧11 mmol/L on admission or during the hospital stay. AF was diagnosed when present on the admission ECG. Information concerning other disabling diseases was obtained on admission and included disabling diseases other than previous stroke (eg, amputation, multiple sclerosis, severe dementia, heart failure, latent or persistent respiratoty insufficiency). IHD was present when a patient had a history of IHD or when IHD was diagnosed during the hospital stay. Hypertension was present when a patient had received antihypertensive treatment before admission or when hypertension was diagnosed during the hospital stay by repeated detection of blood pressure ≧160/95 mm Hg. Smoking was coded when a patient smoked any kind of tobacco on a daily basis. Former smokers were coded as nonsmokers. Intake of alcohol was coded when consumed daily. Total serum cholesterol was determined in a blood sample drawn on admission to the hospital. Total serum cholesterol concentration was determined enzymatically on a Hitachi 717 analyzer.

Only patients admitted within 24 hours after stroke onset were included in the study. Patients with hemorrhage and/or those younger than 40 years were not included. Patients with hemorrhagic infarcts were considered to have had ischemic stroke and hence were included in the study. Statins were not prescribed for secondary prevention in patients included in this study, as evidence of a preventive effect was not established at the time of inclusion.

Follow-Up

Information on the date of death within 10 years after stroke onset was obtained from the Danish Central Registry of Persons. The follow-up was performed during the year 2003 ending November 3 (censoring date). Six patients had immigrated to another country and were lost to follow-up.

Statistical Analyses

Statistical analyses were performed with the statistical software R package. Identification of significant predictors of SSS score and total serum cholesterol were found by means of multiple linear regression models. We applied generalized additive regression models to identify the functional form of the continuous predictors. Tests of linearity were based on a likelihood ratio test between models including a restricted cubic spline and a linear term.

Survival analysis was applied to identify predictors of death according to the Cox proportional-hazards model with age as delayed entry. Emphasis was placed on the possible effect of cholesterol level on survival. Missing observations were analyzed for informative absence to justify a listwise deletion, and hence, that analysis of complete cases would lead to unbiased parameter estimates. We did not find any evidence to reject the hypothesis that observations were missing at random. In all statistical analyses, the significance of predictors was based on likelihood ratio tests at a significance level of 5%.

Results

Baseline characteristics of the patients included in the study are listed in Table 1. Of the 652 patients who arrived within 24 hours of stroke onset, a measure of total serum cholesterol was obtained for 513 (79%) patients. Mean±SD age was 74.8±10.5 years, 54% were women, and the mean±SD SSS score was 38.6±16.8. Patients who had no measurement of total serum cholesterol within 24 hours did not differ significantly in regard to age (74.5±9.9 years, P=0.8), sex (57% were women, P=0.6), and stroke severity (SSS score,
40.5±15.8, P=0.16) compared with those who had. Total serum cholesterol was significantly higher in women and patients with other comorbidities and significantly lower in patients with AF.

A multiple linear-regression model was applied to estimate the partial effect of cholesterol on SSS score while controlling for the remaining risk factors listed in Table 1. These results appear in Table 2. An increase in total serum cholesterol of 1 mmol/L on average resulted in an increase in the SSS score of 1.32 (P=0.013), meaning that a higher cholesterol level is associated with less severe stroke. This is illustrated in Figure 1: an increase in SSS scores (ie, improvement in stroke severity) mirrored an increase in cholesterol value. Increasing age, previous stroke, diabetes, and, in particular, AF all had a significant decreasing effect on SSS; ie, they were significantly associated with more severe strokes (Table 2).

Infarct size expressed as the largest infarct diameter on CT scan (infarcts were visible on CT scans for 330 patients) were inversely significantly correlated with SSS score (correlation coefficient −0.46, P<0.001) meaning that a small infarct was associated with a high SSS score and vice versa.

Table 3 shows mean infarct diameter and mean total serum cholesterol values for the stroke subtypes: carotid artery circulation strokes (lobar infarcts and basal ganglia/ internal capsule/external capsule infarcts) and vertebrobasilar circulation strokes. It appears that infarcts located subcortically were smaller than those with cortical involvement. In line with the results of our linear-regression model (Table 2), total serum cholesterol was higher in patients with subcortical (and smaller) infarcts no matter the localization. In patients with AF, infarcts appeared to be larger but total serum cholesterol was lower compared with patients without AF. AF was identified as a confounder, as it was univariately related to both stroke severity (ie, SSS score) and total serum cholesterol. In multivariate analysis, we found that AF was an independent predictor of SSS score (P=0.006) and a weak predictor of total serum cholesterol value (P=0.045).

The mortality rates within 7 days, 30 days, 1 year, 5 years, and 10 years were 7.2%, 15.2%, 29.4%, 57.3%, and 80.7%, respectively. For the patients who died during the 10-year follow-up, an estimated 74% died of cardiac causes (33%) or cerebral stroke (53%). The reason why the percentage sums to 86% (instead of 74%) is that several possible causes of death are given for each patient. In the survival analysis, while adjusting for the confounders and risk factors listed in Table 1, we found that an increase in cholesterol of 1 mmol/L resulted in a hazard ratio of 0.89 (95% CI, 0.82 to 0.97, P=0.01); thus, an increase in cholesterol improved survival. This is illustrated in Figure 2, wherein a decreasing proba-
bility of death with increasing total serum cholesterol is illustrated.

When the first 30 days after the onset of ischemic stroke were excluded from the analyses, a similar association with all-cause mortality remained significant \((P < 0.001)\), though more moderate. The mean ± SD cholesterol value of the patients who died within the first 30 days after stroke onset was 5.67 ± 1.55 mmol/L compared with 6.02 ± 1.34 mmol/L for those patients who survived the first 30 days after stroke onset. This difference in cholesterol is of borderline significance \((P = 0.06)\).

IHD, previous stroke, and decreasing SSS (ie, more severe strokes) were significantly associated with an increasing probability of death. In a univariate analysis of AF, we found a hazard ratio of 1.85 \((P < 0.001)\), ie, an 85% increase in hazard for patients with AF. However, when adjusting for the confounders and risk factors listed in Table 1, including total serum cholesterol, we did not identify AF as a significant predictor of mortality in our survival analysis.

**Discussion**

We found an inverse and almost linear independent association between concentrations of total serum cholesterol and stroke severity. Because stroke severity (SSS score) is closely related to infarct size, our findings suggest that higher cholesterol levels are associated with smaller strokes. Accordingly, we also found an inverse and almost linear association between total serum cholesterol and mortality:

![Figure 2. Probability of death with increasing total serum cholesterol: hazard ratio = 0.89 for a 1-unit increase in cholesterol. The curve was adjusted so that the hazard ratio was unity for the lowest observed cholesterol level (1.5 mmol/L). The histogram shows the distribution of cholesterol levels.](image-url)
higher cholesterol levels were associated with lower mortality rates. Hence, the result of our study supports the hypothesis that hypercholesterolemia primarily is associated with minor strokes due to small-vessel occlusion.

Weaknesses and Limitations
Total serum cholesterol measurement was not available within 24 hours after stroke in 21% of the patients, but the influence of this deficiency is most likely of minor importance because these patients did not differ from the others with respect to age, sex, and stroke severity. Cholesterol is known to be a phase reactant, which decreases with increasing stroke severity. A number of studies have shown that the total serum cholesterol value obtained within 48 hours reflects usual cholesterol levels. Some studies, however, have found the total serum cholesterol value obtained within 48 hours to be slightly decreased or increased compared with cholesterol levels 3 months after stroke. Importantly, however, there was no statistically significant correlation between stroke severity and an alteration in the lipid profile. Because we excluded patients who arrived >24 hours after stroke onset and our blood samples were collected within a narrow 24-hour time frame, we consider bias in this respect as unlikely. Blood samples were taken on admission at various times of the day and night and not in a fasting state. However, total cholesterol is not influenced by fasting in the short term, so we did not expect an influence of fasting on our measurements. Small infarcts may elude detection on CT scans, especially within the first few days after stroke, and the size of the hypodensity reflecting an infarct may change within the first weeks. For this reason, we decided to measure stroke severity by means of a neurological score (SSS) and not by infarct size. Because the SSS score is directly correlated to infarct size, we believe it is justified to consider minor strokes as reflecting small-vessel occlusion. As shown in Figure 2, patients with either very low or very high cholesterol concentrations were relatively scarce (<4 mmol/L = 5%, >8 mmol/L = 6%), and our statistical estimates are therefore encumbered by uncertainty at the lower and upper extremes of the range of cholesterol. Hence, our conclusions relate to patients with concentrations of cholesterol within a range of 4 to 8 mmol/L (89% of our population).

We had no information about the use of statins in this study. However, we did not prescribe statins for secondary prevention, because evidence of a preventive effect in patients with stroke had not been established either at the time of inclusion or within the subsequent 10-year follow-up period. Use of statins for prevention of IHD was still unusual at the time of inclusion in our study. Furthermore, IHD was not related to stroke severity, and total serum cholesterol was higher in patients with IHD. For these reasons, we do not expect that the use of statins confounded the result of our study.

Cholesterol and Stroke Severity
The inverse relation between stroke severity and cholesterol is a new observation that has not been reported before. In our search of the literature, we found no studies in which quantitative assessment of initial stroke severity was included in the analysis of the cholesterol-stroke relation. We suggest that cholesterol plays a more prominent role in the development of small-vessel disease of the brain (and thereby less severe strokes) than in disease processes leading to occlusion of large vessels of the brain. It is noteworthy in this context that patients with AF (related to embolic and more severe strokes) had markedly lower cholesterol values than did patients without AF. In support of these findings, a recent larger case-control study reported that cholesterol measured within a week after stroke was higher in patients with lacunar stroke (small, deep infarcts <15 mm on magnetic resonance imaging) compared with patients with atherothrombotic and cardioembolic strokes, the latter having the lowest concentrations of serum cholesterol. In this study, a delay in blood sampling of >2 to 3 days might have disproportionately decreased cholesterol in some patients. An association between serum cholesterol and ischemic stroke subtypes has also been shown in 2 other studies, with patients with cardioembolic strokes having the lowest levels of total serum cholesterol as also indicated in our study.

Cholesterol and Stroke Survival
Higher serum cholesterol concentrations were also associated with lower short-term mortality after stroke in 3 other studies. The authors of those studies suggested a neuroprotective role for cholesterol as an explanation of their paradoxical finding. In those studies, stroke severity was not measured, so this important factor (that significantly influenced survival in our study) was not included in their statistical analysis of outcome after stroke. Instead, we suggest that higher cholesterol favors the development of small-vessel disease and thereby less severe strokes associated with lower mortality. In several large-scale studies, all-cause mortality was inversely related to cholesterol: lower cholesterol was associated with higher all-cause mortality and higher cholesterol was associated with lower all-cause mortality. The reasons for these results remain unclear. The findings in our study may contribute to an understanding of these results: higher cholesterol favors the development of minor stroke associated with lower mortality. Hence, among individuals with higher cholesterol values, there will be an overrepresentation of future patients with minor strokes and consequently, due to selection, major strokes (associated with higher mortality) will be overrepresented in individuals with lower cholesterol.

Cholesterol and Stroke Risk
Although cholesterol is a well-documented risk factor for coronary disease, the association between cholesterol and risk of stroke is less clear. Some studies concluded that total serum cholesterol was associated with stroke, whereas others reached the opposite conclusion. The indications from our study of a relation between total serum cholesterol and small-vessel/minor stroke may help explain the controversy. Unlike myocardial infarction, ischemic stroke is a composite of several heterogeneous pathophysiologic entities in which the influence of cholesterol, as indicated by our study, is variable. Hence, our study suggests that cholesterol
has a greater influence on the development of strokes caused by small-vessel occlusion than on disease processes that cause occlusion of larger vessels. In that case, it might be difficult to demonstrate an unambiguous relation between total cholesterol and risk of stroke.

It has been discussed whether the preventive effect of statins is due to lowering of cholesterol or non–cholesterol-lowering effects, such as plaque stabilization, modification of inflammatory responses, thrombus formation, etc. Our study suggests that the cholesterol-lowering effect of statins may play a role, particularly in the prevention of milder stroke subtypes.

Conclusions

The results of our study support the hypothesis that higher total serum cholesterol favors the development of minor stroke. Due to selection, therefore, major strokes are more often seen in patients with lower total serum cholesterol levels. All-cause mortality, therefore, is inversely related to total serum cholesterol.

Disclosures

None.

References

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