High Cholesterol Levels Are Associated with Improved Long-term Survival after Acute Ischemic Stroke

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Background: Prior statin treatment and high admission cholesterol have been associated with favorable outcome after ischemic stroke (IS), a paradox not completely explained. The aim of this study was to investigate the effect of admission cholesterol levels and the impact of statin treatment on short- and long-term survival after IS. *Methods:* Consecutive patients admitted in 2006 and 2010 were included in the study. Total cholesterol of 4.6 mmol/L or more was defined as high. Logistic regression analysis was performed to assess predictors of 1-month mortality, and Cox proportional hazard regression analysis was applied to investigate predictors of long-term mortality. *Results:* Of 190 patients included in the final analysis, 21 (11%) died within 1 month and 61 (32%) died during 7 years of observation. Low cholesterol was associated with older age, lower blood pressure (BP), presence of angina, and higher risk of death. Three-month, 1-year, and 5-year survival rates were 100%, 98%, and 84%, respectively, in high cholesterol patients, compared with 92%, 87%, and 57% in low cholesterol group ($P = .0001$ with the log-rank test). Mortality risk was increased for patients with low cholesterol (hazard ratio: 1.97; 95% confidence interval [CI]: 1.05-3.69), after adjustment for age and admission National Institutes of Health Stroke Scale score. After further adjustment for angina and admission BP, the effect of cholesterol on mortality risk was still obvious, yet attenuated (hazard ratio: 1.87; 95% CI: .94-3.32). *Conclusions:* High admission cholesterol may be associated with increased long-term survival after IS. Future studies on the temporal profile of cholesterol levels and stroke outcome would be of interest. **Key Words:** Brain ischemia—stroke—fatal outcome—cholesterol—statins.

Introduction

Ischemic stroke (IS) is a leading cause of death and long-term disability in adults worldwide.[1] One-month mortality rates range from 13% to 27% in Europe,[2] and stroke severity is the most powerful predictor of functional outcome and death.[3] One-year survivors have annual mortality rate near 10% for the following 4 years,[4] and age, severity of stroke, cardiac disease, cardioembolic etiology, hypertension, and diabetes are the most important predictors of long-term outcome.[3] Identification of modifiable predictors of long-term outcome has facilitated the selection of appropriate treatment for secondary prevention to improve prognosis. However, despite available treatment strategies, stroke mortality has not changed dramatically over the last 4 decades.[5]

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been associated with reduced recurrence of IS,[6] reduced vascular events in patients with prior IS, and reduced IS in patients with other vascular disease.[7] An Irish study has recently shown beneficial effect

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of acute statin treatment in survival and functional outcome up to 1 year after stroke.[8] Further exploration of interactions among admission cholesterol levels, previous statin treatment, and stroke morbidity has shown a possible "reverse epidemiology" between lipids and outcome.[9] Earlier studies have also indicated a positive association between elevated admission cholesterol at IS onset and improved short-term functional outcome[10] and 10-year survival.[11] In another study, lower total and low-density lipoprotein (LDL) cholesterol levels were independent predictors of poor 3-month functional outcome in men but not in women.[12]

The aim of this study was to further investigate the effect of cholesterol levels and the impact of statin treatment in short- and long-term survival after acute IS.

Methods

Study Design and Population

The study was approved by the Local Ethics Committee. The Karolinska University Hospital in Huddinge is a hospital of reference with approximately 800 beds, serving an ethnically diverse population of around 250,000 persons. We aimed to design a hospital-based register on cerebrovascular diseases based on a standardized protocol including demographic characteristics, vascular risk factors, comorbidities, clinical investigation results, biochemical and neuroimaging data, complications, and outcome. Since 2006, all medical records including previous and current medication and laboratory results are digitalized. Our study was designed as a retrospective, hospital-based, follow-up cohort including all patients admitted in the stroke unit since January 2006. During the initial, pilot phase of patient recruitment, we enrolled 220 patients admitted during 2006 and 120 patients admitted in 2010, to investigate the differences in management of hyperglycemia and their impact on outcome after IS (Nilsson U, Kostulas K, Markaki I, Sjöstrand C, unpublished data). Of 340 patients initially enrolled in this pilot, 37 were excluded because of nonvascular diagnosis (n = 20) or because of admission later than 72 hours from symptom onset (n = 17). Patients with vascular diagnosis other than IS (n = 190) or transient ischemic attack (n = 52), including hemorrhagic stroke (n = 49), transient global amnesia (n = 4), large-vessel dissection without evidence of IS (n = 5), vasculities (n = 2), and sinus thrombosis (n = 1) were also excluded. A total of 190 IS patients were included in the current analysis. Age, gender, etiologic phenotypes, risk factor, and biochemical profile and treatment options on admission and at discharge did not differ significantly between patients admitted in 2006 compared with patients admitted in 2010.

Data Collection

Clinical and biochemical data were obtained by reviewing medical records of all patients. All patients underwent computed tomography and/or magnetic resonance tomography of the brain. To identify the potential mechanism of cerebral infarction, electrocardiography, chest echocardiography, carotid ultrasonography, complete blood count, and blood biochemistry were performed in all patients. When indicated, some patients also underwent magnetic resonance tomography, computed tomography and/or digital subtraction angiography, transesophageal echocardiography, Holter monitoring, and special anticoagulation tests.

Arterial hypertension was considered present when the patients were on antihypertensive treatment on admission or when hypertension was diagnosed by repeated measurements of systemic blood pressure (BP) more than 140/90 mm Hg during hospital stay. Diabetes mellitus was considered present when patients had a known diagnosis and/or were on antidiabetic treatment on admission or had a fasting HbA1c value of 6.5% or more.[13] Atrial fibrillation was considered present when mentioned in patients' medical history or detected during the investigation period. Angina was considered present when mentioned in patients' medical history. All patients smoking any kind of tobacco on a daily basis were coded as smokers, whereas former smokers of at least 3 months without smoking were coded as nonsmokers. Measurements of systolic and diastolic BP and body mass index (BMI) on admission are reported. All patients were classified according to the Causative Classification of Stroke system, a computerized algorithm of Stop Stroke Study–Trial of Org 10172 in Acute Stroke Treatment system,[14] and according to ASCO (A: atherosclerosis, S: small vessel disease, C: cardiac source and O: other cause) phenotypic classification system.[15] Large artery atherosclerosis (LAA), cardioembolic (CE) etiology, small artery occlusion, and cryptogenic disease (CRYPT) comprise the main subgroups reported here. CRYPT by Trial of Org 10172 in Acute Stroke Treatment comprised patients with unidentified cause despite complete work up, and CRYPT by ASCO comprised patients with grade 0 or 3 in all pathologies.

Statistical Analysis

Baseline characteristics were compared with chi-square test for categorical variables, *t* test for normally distributed continuous variables (age, systolic and diastolic BP, BMI, white blood cell count after exclusion of 5 individuals with values over 15×10^9/L, total and LDL cholesterol levels, and hemoglobin), and Wilcoxon–Mann–Whitney test for non-normally distributed variables (admission National Institutes of Health Stroke Scale [NIHSS] score, plasma glucose, and homocysteine). Logistic regression analysis was performed to assess the risk of death at 1 month from IS onset. Univariate analysis was performed for all variables that differed significantly between survivors and deceased patients. Bonferroni

correction was then performed, and all variables with adjusted P values less than .05 were included in the multivariable model. Variables that had no significant effect in multivariable model were removed stepwise. Kaplan–Meier survival curves were produced for each cholesterol quartile and formed 2 clusters illustrating worse survival in patients who belonged in the lower cholesterol quartiles compared with those included in the third and fourth quartiles. For that reason, further analysis was performed after dichotomization of cholesterol values at the second quartile (4.6 mmol/L), to evaluate this difference. Adjusted hazard ratios for mortality at 7 years were calculated with Cox proportional hazard model. Stepwise approach was performed in similar way as in logistic regression analysis. Continuous variables were dichotomized at the 50th percentile, except for age and admission NIHSS score. The proportional hazard assumption was validated using Schoenfeld residuals and the global test. Analyses were performed with Stata statistical software version 12.0.

Results

Study Population

A total of 190 patients with IS were included in the final analysis, the mean age was 74 ± 13 years, and there were slightly more men (55%) than women. Baseline characteristics of all patients are presented in Table 1. During a 7-year observation period (median 30 months), 82 patients (43%) died. Forty-six deaths (56%) were attributed to cardiovascular causes, including myocardial infarction, stroke, heart failure, cardiac arrest, and patients who died within 1 month from the actual ischemic event (n = 21). Infections and malignant diseases accounted each for 7% (n = 6) of all deaths, and data about the cause of death were missing in 23% of the cases (n = 18). Six patients died of various other etiologies. Cumulative rates of mortality were 11% at 1 month and 52% at the end of follow-up period. The annual risk of death was highest in the first year (19%). Patients who survived 1 year from IS onset had an annual mortality rate of approximately 6% during the following years.

Short-term Survival

Cholesterol values were missing in 14 of 21 patients (67%) who died within 1 month from IS onset, and further investigation of the effect of admission cholesterol on short-term outcome was precluded. Patients who died early were significantly older at stroke onset (mean age: 86 ± 8 versus 72 ± 13 years, $P < .0001$) and had higher proportion of women (81% versus 41%, $P = .005$), compared with those who survived the first month after IS. CE etiology was more common among deceased patients, and small artery occlusion was more common among survivors. Deceased patients had higher admission NIHSS score, higher white blood cell count, slightly lower BMI, and lower hemoglobin (data not shown). Univariate logistic regression analysis showed that increased age, female gender, high admission NIHSS score, and CE etiology were associated with increased 1-month mortality. In multivariate analysis, only age (odds ratio: 1.9; 95% confidence interval [CI]: 1.07-3.24 per 5-year increment) and admission NIHSS score (odds ratio: 1.2; 95% CI: 1.09-1.29) were significant predictors of 1-month mortality.

Long-term Survival

Of 169 1-month survivors, 159 had available data on admission cholesterol (mean 4.6 ± 1.1 mmol/L), of whom 84 had admission levels of 4.6 mmol/L or more. Statins were discontinued in only 2 of 47 patients with present treatment on admission and were newly initiated in 60 of 122 patients who had no previous treatment.

Three-month survival rates were 92% and 100% in low and high cholesterol group, respectively; 1-, 2-, and 5-year survival rates were 87%, 81%, and 57%, respectively, in low cholesterol group and 98%, 95%, and 84% in high cholesterol group ($P = .0001$ with the log-rank test, Fig 1). The annual mortality rate in patients with low cholesterol was close to 7% after the first year and reached 58% by the end of observation period. In patients with high cholesterol, the annual mortality was near 3% and reached 31% after 7 years of observation. Baseline characteristics of the patients by cholesterol status are presented in Table 1. Patients with low cholesterol were older, had lower BP, lower admission glucose levels, and more often angina, yet admission NIHSS score did not differ compared with patients with higher cholesterol levels. BMI did not differ between groups, and Pearson correlation coefficient showed no correlation between cholesterol and BMI values (rho = .036). Presence of statin treatment on admission was more common in patients with low cholesterol, whereas patients with high cholesterol had more often statins at discharge.

Univariate Cox regression analysis showed that increased age, high admission NIHSS score, low diastolic BP, presence of angina, low cholesterol, low hemoglobin, and presence of antiplatelet treatment on admission were associated with increased mortality. In multivariate analysis, low admission cholesterol (<4.6 mmol/L) was an independent predictor of long-term mortality (hazard ratio [HR]: 1.97; 95% CI: 1.05-3.69) after adjustment for age and admission NIHSS score. Further adjustment for the presence of angina and for admission BP showed an attenuated, yet still obvious trend toward statistical significance (HR: 1.87; 95% CI: .94-3.32). Investigation of patients with angina showed that cholesterol levels were not associated with the presence of statin treatment (mean cholesterol 3.9 mmol/L in patients with angina

Table 1. *Baseline characteristics of all patients and of 1-mo survivors by cholesterol levels on admission*

	All patients (n = 190)	Cholesterol <4.6 (n = 75)	Cholesterol ≥4.6 (n = 84)	*P* (high versus low cholesterol)
Age, y, mean ± SD	74 ± 13	75 ± 13	69 ± 11	.002
Gender, male, % (n)	55 (104)	60 (45)	58 (49)	.8
Deceased, % (n)	43 (82)	47 (35)	20 (17)	<.0001
Risk factors, % (n)				
Hypertension	63 (119)	64 (48)	60 (50)	.6
Diabetes mellitus	25 (47)	28 (21)	24 (20)	.5
Angina	22 (41)	31 (23)	12 (10)	.004
Smoking	15 (29)	16 (11)	21 (17)	.5
Atrial fibrillation	25 (48)	32 (24)	19 (16)	.06
NIHSS score at admission	3 (6)	3 (5)	2 (4)	.5
SBP, mm Hg, mean ± SD	164 ± 28	160 ± 26	169 ± 29	.04
DBP, mm Hg, mean ± SD	89 ± 16	86 ± 15	93 ± 15	.004
BMI, kg/m^2, mean ± SD	26 ± 4.7	26 ± 4.2	26.5 ± 4.4	.5
Causative subtypes, % (n)				
LAA by TOAST	15 (29)	15 (11)	18 (15)	.6
LAA pure by ASCO	12 (22)	9 (7)	15 (13)	.2
CE by TOAST	33 (63)	32 (24)	27 (23)	.5
CE pure by ASCO	35 (66)	29 (22)	29 (24)	.9
SAO by TOAST	17 (33)	16 (12)	25 (21)	.2
SAO pure by ASCO	22 (42)	21 (16)	30 (25)	.2
CRYPT by TOAST	8 (16)	9 (7)	11 (9)	.8
CRYPT by ASCO	5 (9)	4 (3)	7 (6)	.5
Biochemical profile, mean ± SD				
Total cholesterol, mmol/L	4.6 ± 1.2	3.7 ± .8	5.5 ± .6	<.0001
LDL cholesterol, mmol/L	2.7 ± .9	2 ± .5	3.4 ± .7	<.0001
HDL cholesterol, mmol/L	1.4 ± .4	1.3 ± .3	1.4 ± .5	.07
Triglycerides, mmol/L	1.4 ± .7	1.3 ± .6	1.5 ± .8	.04
WBC count, $\times 10^9$/L	8.3 ± 2.4	8.4 ± 2.3	7.9 ± 2.4	.2
Hemoglobin, g/L	138 ± 14	137 ± 11	140 ± 16	.2
Homocysteine, μmol/L, median (IQR)	14 (6)	14 (6)	13 (5)	.3
Glucose, mmol/L, median (IQR)	6.2 (2)	6 (1.8)	6.5 (2.4)	.09
Treatment, % (n)				
Antiplatelets on admission	47 (90)	56 (42)	38 (32)	.02
Anticoagulants on admission	8 (15)	9 (7)	5 (4)	.3
Statins on admission	26 (49)	36 (27)	19 (16)	.02
Antiplatelets at discharge	—	71 (53)	76 (64)	.4
Anticoagulants at discharge	—	33 (25)	30 (25)	.6
Statins at discharge	—	52 (39)	74 (62)	.004

Abbreviations: BMI, body mass index; CE, cardioembolic; CRYPT, cryptogenic disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IQR, interquartile range; LAA, large artery atherosclerosis; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; SAO, small artery occlusion; SBP, systolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WBC, white blood cells.

and statin treatment at stroke onset [n = 20] versus 4.3 mmol/L in patients with angina, without statin treatment on admission [n = 13]; $P = .3$). Also, Kaplan–Meier survival curves showed similar mortality rates during the first year from IS onset in patients with and without angina.

Separate investigation of LDL cholesterol did not show any association with mortality after adjustment for age and admission NIHSS score. Neither presence of statin treatment at discharge nor newly initiated statins during hospital stay was independently associated with mortality.

Discussion

In this retrospective, hospital-based, pilot cohort of IS patients, low levels of total cholesterol were associated with increased long-term mortality. The observed difference in survival was rather pronounced during the first year from IS onset, and survival curves kept diverging

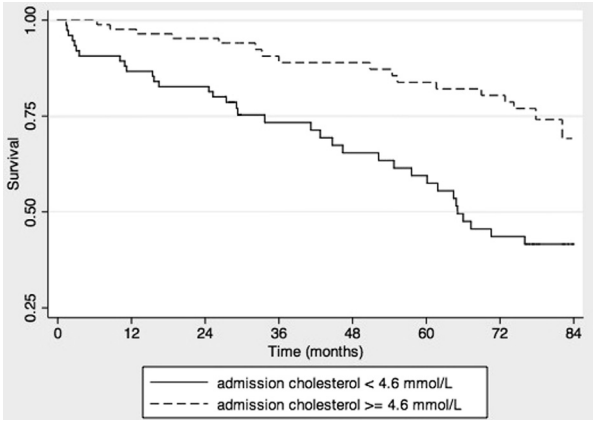

Figure 1. *Kaplan–Meier survival curves for 7-year observation of 1-month survivors by cholesterol status.*

over the whole observation period. Cholesterol levels over 6.5 mmol/L on admission have previously been associated with better early functional outcome at 1 month after acute IS, independently of comorbidities, stroke etiology, and severity of symptoms.[16] A subsequent study did not confirm any effect of admission cholesterol values on functional outcome at 3 months after IS, as measured by the difference of NIHSS scores on admission and at follow-up.[17] Recently, in a national registry study, cholesterol over 4 mmol/L in IS patients who were not on statin treatment on admission was an independent predictor of 3-year survival.[9] Different set-up of the studies and heterogeneous measures of outcome may explain this discrepancy. Inconclusive findings in previous studies may also result by the diversity of cholesterol subclasses with various functional features included in common terms. Evaluation of LDL and HDL particle sizes and subclass distributions in acute IS, performed in a case–control study, showed that small, dense LDL was an independent predictor of IS onset and consecutive in-hospital mortality.[18] In our study, LDL cholesterol was significantly higher in survivors, but an independent association with mortality was not confirmed.

In the present study, we evaluated the levels of total cholesterol measured within 72 hours from IS onset; cholesterol levels of 4.6 mmol/L or more were associated with improved survival. Stroke severity, measured by admission NIHSS score, did not differ between patients with high and low cholesterol; thus, we may hypothesize it is unlikely that cholesterol exerted its effect on mortality by affecting stroke severity. Statin treatment on admission was less common in patients with higher cholesterol; hence, the beneficial effect on survival of this group is unlikely to be attributed to concomitant statin use. Presence of angina may have contributed as a confounder in long-term mortality; however, it was not associated with increased risk during the first year from symptom onset. Possible mechanisms may involve the effect of nutritional status on admission on long-term prognosis. Studies on metabolic balance of stroke patients have shown that low baseline BMI and weight loss are associated with poor outcome.[19] An "obesity paradox" has been suggested to describe the contrasting influence of overweight in patients with chronic diseases compared with healthy population.[20] In a register-based study in Denmark, obesity was associated with reduced mortality and stroke recurrence in over 45,000 stroke patients.[21] In our study, BMI was slightly higher in survivors compared with deceased but did not predict mortality and did not correlate with cholesterol values.

In our cohort, one third of the patients with low cholesterol had a history of angina. This may be attributed to a more intensive dietary and medical lipid-lowering treatment that is indicated in patients with ischemic heart disease.[22] In a large population-based cohort study, stable angina in patients without obstructive coronary artery disease was associated with increased risk for major adverse cardiovascular events, compared with individuals without ischemic heart disease.[23] Patients with low cholesterol had also lower BP in our study, which may reflect the strict control on vascular risk factors, including hypertension, in patients with angina who are overrepresented in that group. In a randomized placebo-controlled trial on the effect of statin treatment in patients without previous cardiovascular diseases, systemic BP was significantly reduced in the treatment arm.[24]

Short-term mortality was also examined in our study, and age and admission NIHSS score were independent predictors of all-cause death at 1 month. Cholesterol values were not available in the majority of patients who died early, which precluded the investigation of cholesterol effect on short-term mortality. Poor clinical status of those patients resulting in limited clinical investigation and blood sampling may explain this lack of data. Presence of statin treatment on admission was investigated as an indirect marker of previous hyperlipidemia, but no association was reported. High total cholesterol has previously been associated with better short-term outcome in terms of in-hospital mortality and functional disability.[10] Another study on IS in the elderly population showed that patients over the age of 85 years had lower prevalence of hyperlipidemia and were more disabled at discharge than younger IS patients, despite lower admission NIHSS score.[25]

Statin treatment before IS in patients with low LDL levels on admission has been associated with better functional outcome at discharge, independently of age and stroke severity, in a small, prospective, hospital-based cohort.[26] Data from a larger, hospital-based, stroke registry have also indicated a correlation between pretreatment with statins and reduced in-hospital mortality and improved functional outcome at discharge of patients with first-ever IS.[27] In the same study, hypercholesterolemia before IS was another factor associated with improved outcome. In the present study, we found that statin

treatment on admission was 3 times more common among 1-month survivors than deceased patients, but an independent association was not confirmed. Concerning long-term survival, statin treatment at discharge was more common among 7-year survivors than deceased patients, but it was not an independent predictor of outcome. A population-based study in France has recently reported that prestroke statin treatment did not affect initial clinical severity but was associated with a nonsignificant, better, early functional outcome after IS.[28] In a recent meta-analysis, prestroke statin use in IS patients was associated with improved 90-day functional outcome and reduced mortality.[29]

Our study has limitations. It is designed as a retrospective analysis of prospectively collected data and, thereby, vulnerable for missing values and confounding bias. The small number of patients restricts adjustment for several confounding factors and investigation of subgroups, and nonsignificant observations are difficult to interpret whether they result from a true lack of association or from lack of power. However, it has been possible to explore the effect of a number of variables on mortality rates, and we report associations that are well in accordance with previously published work of larger scale. We were not able to evaluate possible effects of admission cholesterol on short-term outcome because of missing values in patients who died early, yet we believe that our study contributes with original data in a field of current scientific interest.

In conclusion, in patients with acute IS, higher admission cholesterol levels may be associated with improved long-term survival. Further studies on the temporal profile of cholesterol levels post-IS would be of interest, for more robust evaluation of their effect on survival.

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