

# Low Cholesterol Levels Are Associated With Short-Term Mortality in Older Patients With Ischemic Stroke

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**Background.** The possible relationship between serum total cholesterol (TC) levels and outcome following ischemic stroke is still controversial. We evaluated the association between TC levels and 30-day mortality in a sample of older patients with acute ischemic stroke.

**Methods.** We enrolled 490 older patients with severe ischemic stroke consecutively admitted to University Hospital's Internal Medicine or Geriatrics Department. Stroke type was classified according to the Oxfordshire Community Stroke Project. The data recorded included clinical features, medical history, electrocardiogram, and blood analyses. Patients were divided into three groups by TC levels: group I (TC < 4.1 mmol/L), group II (TC 4.1–5.2 mmol/L), and group III (TC > 5.2 mmol/L).

**Results.** The overall mortality was 27.7%. Mortality was higher in patients with low TC levels (47.4%) compared with those with normal and high TC levels (23.0% and 24.1%, respectively). The odds ratio (OR) for short-term death was 2.17 (95% confidence interval [CI] 1.22–3.85) in group I compared with group III, after adjustment for age and gender. This result did not change after adjustment for possible confounders (OR 2.87; 95% CI 1.23–6.68). A similar trend was observed after adjustment for the Oxfordshire classification, age, and gender (OR 1.67; 95% CI 0.83–3.33).

**Conclusions.** Short-term mortality following ischemic stroke is higher in older participants with low TC levels, independent of a large number of factors. Low TC levels might be useful in identifying frail older participants at high risk of stroke short-term mortality.

THE relationship between serum total cholesterol (TC) levels and ischemic stroke is still a controversial matter, especially in older individuals (1). Some studies have demonstrated a significant association between TC levels and the incidence of ischemic stroke (2–4), while others have found no such association (5,6).

Different clinical trials performed in patients with coronary heart disease (CHD) have shown that therapy with statins is associated with a decrease in the incidence of the principal cardiovascular outcomes, including ischemic stroke (7,8). A 47% reduction in new ischemic stroke has been also demonstrated in older diabetic CHD patients treated with statins (9). Nevertheless, in the Heart Protection Study these effects were obtained irrespective of initial TC concentrations (10); furthermore, the PROSPER (pravastatin in elderly individuals at risk of vascular disease) study has recently shown that in older patients (70–82 years), therapy with statins does not reduce the incidence of fatal and nonfatal stroke (11).

A different and “intriguing” aspect of the relationship between TC and stroke is the possible prognostic value of TC levels in the period following acute ischemic stroke. As yet, only a few studies regarding the effect of TC on survival after stroke have been published, and they have produced different results. In the research of Censori and colleagues

(12), TC levels were not associated with short-term outcome in terms of disability and death, while Dyker and colleagues reported an inverse association between lower TC levels and 3-month, but not 30-day, total mortality (13). More recently, Vauthey and colleagues found that high TC levels were associated with a better prognosis in the early stage (first month) following ischemic stroke (14). In order to contribute to a better comprehension of the possible relationship between TC levels and outcome during the acute phase of stroke, we performed a study to evaluate the association between TC levels and 30-day mortality in a sample of older patients with acute ischemic stroke consecutively admitted to the hospital.

## METHODS

In this retrospective study, 490 older patients (>65 years) with severe ischemic stroke consecutively admitted to the University School Internal Medicine Department (Ferrara) or Geriatric Department (Perugia) in 1996–2000 were included. Since the only outcome of the study was short-term mortality, we decided to exclude patients with minor stroke (Rankin scale <3) or transient ischemic attacks (TIA). Indeed, short-term mortality is extremely low in patients with minor stroke or TIA.

All patients underwent computed tomography of the brain within 72 hours of admission. Stroke type was classified

Table 1. Age, Gender, Total Mortality, and Oxfordshire Community Stroke Project Classification in 469 Older Patients With Ischemic Stroke Divided by TC Levels

Parameter	Group I (TC < 4.1 mmol/L) (n = 79)	Group II (TC 4.1–5.2 mmol/L) (n = 146)	Group III (TC > 5.2 mmol/L) (n = 244)	p
Total mortality (%)	37 (47.4)	33 (23.0)	60 (24.1)	.001
Age	80.7 ± 8.6*	78.2 ± 10.3	77.4 ± 8.6	.02
Gender (female)	40.8	57.9	64.6	.01
TACI	31 (39.3)	45 (30.8)	59 (24.2)	—
PACI	21 (26.5)	45 (30.8)	76 (31.1)	—
POCI	9 (11.4)	6 (4.1)	10 (4.1)	—
LACI	18 (22.8)	50 (34.3)	99 (40.6)	.02

Notes: \**p* = .02 post hoc test group I versus III.

TC = total cholesterol; TACI = total anterior circulation infarction; PACI = partial anterior circulation infarction; POCI = posterior circulation infarction; LACI = lacunar infarction.

according to the system used by the Oxfordshire Community Stroke Project (OCSP) (15) as follows: TACI (total anterior circulation infarction), PACI (partial anterior circulation infarction), POCI (posterior circulation infarction), and LACI (lacunar infarction).

Twenty-one patients could not be classified according to the OCSP categories and/or were currently treated with statins, and were thus excluded from analysis.

For all patients, the data recorded included 1) clinical features of stroke, 2) detailed medical history including vascular risk factors (arterial hypertension, diabetes mellitus, atrial fibrillation [AF], CHD, congestive heart failure [CHF], alcohol abuse, smoking, previous TIA, or stroke), 3) 12-lead electrocardiogram, and 4) routine blood analysis and urine tests. Hypertension was defined as 1) documented history of hypertension, and/or 2) current use of antihypertensive drugs, and/or 3) blood pressure >160/90 mmHg in two or more measurements. Diabetes mellitus was defined as 1) documented history of diabetes, or 2) current use of antidiabetic drugs or insulin, or 3) documented fasting glycemia >126 mg/dL in two or more measurements.

Prevalence of CHD, CHF, AF, and history of previous stroke or TIA was assessed by two investigators (G. Z. and A. C.) according to standardized criteria that use multiple sources of information (clinical examination and chart review). Serum cholesterol, triglycerides, plasma glucose, serum iron, albumin, fibrinogen, blood sedimentation rate (BSR), and white blood cell (WBC) count were measured by standard methods in blood samples from fasting patients on the morning after admission. Patients were divided into three groups by TC levels: group I (TC < 4.1 mmol/L; 160 mg/dL), group II (TC 4.1–5.2 mmol/L; 160–200 mg/dL), and group III (TC > 5.2 mmol/L; 200 mg/dL). According to internationally accepted cut-off values, group I included patients with “low” TC levels (16), group II included patients with “normal-desiderable” TC levels, and group III included patients with “high” TC levels (17).

The study was approved by the local ethical committee.

### Statistical Analysis

The principal characteristics of the patients were compared using analysis of variance (ANOVA) or unpaired Student's *t* test for continuous variables. The chi squared

( $\chi^2$ ) test was used for categorical variables. The odds ratio (OR), estimated by means of multivariate logistic regression method, was used to compare the mortality risk by group of TC levels (groups I, II, and III).

Three different models were constructed.

- Model I included TC group, age and gender as independent variables.
- Model II included TC group, age, gender, and the variables that were significantly associated with the outcome, i.e., hypertension, diabetes, blood glucose, AF, CHD, previous TIA/stroke, smoking, CHF, altered level of consciousness, and hematocrit.
- Model III included TC group, age, gender, and the OSCP classification.

Systat for Windows version 5.0 (Systat, Evanston, IL) and SPSS for Windows version 7.0 (SPSS, Inc., Chicago, IL) statistical packages were used.

### RESULTS

During the study period, 490 older patients with major ischemic stroke were admitted. Their mean age was 78.4 ± 9.2 years and 58.2% were female. On the whole, 130 patients died within 30 days after stroke, with an overall mortality of 27.7%. As reported in Table 1, the mortality rate was significantly higher in patients with TC levels below 160 mg/dL, i.e. group I (47.4%) compared with those with normal and high TC levels (23.0% and 24.1%, respectively). Participants in group I were characterized by older age and higher prevalence of male gender. The OCSP classification is also reported in Table 1; a significant trend toward a lower prevalence of TACI and a higher prevalence of LACI from group I to group III was observed.

The distribution of the principal stroke risk factors and clinical chemistry parameters in the participants divided by TC levels are reported in Table 2. Group I was characterized by a lower prevalence of hypertension, and by a higher prevalence of CHF and AF. No differences in the distribution of diabetes mellitus, smoking, CHD, history of TIA/stroke, and alcohol abuse emerged between the three groups. BSR was significantly higher, while hematocrit was lower in group I compared with group III; no differences

Table 2. Principal Vascular Risk Factors and Biochemical Parameters in 469 Older Patients With Ischemic Stroke Divided by TC Levels

Parameter	Group I (TC < 4.1 mmol/L) (n = 79)	Group II (TC 4.1–5.2 mmol/L) (n = 146)	Group III (TC > 5.2 mmol/L) (n = 244)	p
	(%)	(%)	(%)	
Hypertension	56.8	68.7	76.6	.005
Diabetes mellitus	23.7	29.2	25.3	.60
Smokers	27.7	28.2	26.8	.90
CHD	52.1	40.7	40.2	.10
CHF	19.4	10.3	6.9	.008
EKG–AF	44.4	31.2	24.7	.005
Previous TIA/stroke	27.0	25.0	26.5	.90
Alcohol abuse	6.7	6.5	5.4	.80
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	
Blood glucose (mmol/L)	6.6 ± 3.0	7.54 ± 3.7	7.4 ± 3.0	0.10
Serum iron (µmol/L)	11 ± 7.7	12.1 ± 6.6	13 ± 6.7	0.10
Fibrinogen (µmol/L)	13.2 ± 5.3	13.4 ± 4.32	13.4 ± 4.0	0.90
BSR (mm/h)	32 ± 27*	26 ± 24	25 ± 18	0.03
WBC (× 10 <sup>3</sup> /mmc)	10.3 ± 5.3	10.1 ± 8.5	9.7 ± 3.9	0.60
Hematocrit (%)	38.1°	39.6	41	0.01

Notes: \*p = .02 post hoc test group I versus III; †p = .001 post hoc test group I versus III.

CHD = coronary heart disease; CHF = congestive heart failure; TIA = transient ischemic attack; BSR = blood sedimentation rate; WBC = white blood cells; TC = total cholesterol; EKG–AF = electrocardiogram–atrial fibrillation; SD = standard deviation.

were found in blood glucose, serum iron, fibrinogen, and WBC count across the three groups.

Results of multivariate logistic regression analysis in the participants divided by TC levels are reported in Table 3. The OR for short-term death was 2.17 (95% confidence interval [CI] 1.22–3.85) in group I compared with group III after adjustment for age and gender (model 1); this result did not substantially change after adjustment for the principal stroke risk factors (OR 2.87; 95% CI 1.23–6.68; model 2). A similar but not significant trend was observed after adjustment for age, gender, and the OCSF classification (OR 1.67; 95% CI 0.83–3.33).

When the OR was calculated after stroke stratification for OCSF stroke type, the association between TC levels and total mortality was not significant, with the exception of the PACI group (OR 3.41; 95% CI 1.03–11.24).

**DISCUSSION**

We evaluated the possible relationship between TC levels, measured within 24 hours after admission to hospital, and short-term mortality in a sample of older patients affected by ischemic stroke. The main finding of this study is that mortality was higher in patients with low TC levels (<4.1 mmol/L); this association was independent of a large number of prognostic factors, but not of the OCSF stroke-type classification. Only three previous studies have been specifically focused on the relationship between TC levels and the outcome after ischemic stroke, and they reported conflicting results. Corsari and colleagues did not find any association between TC levels and functional outcome at 30 days, evaluated according to a modified Rankin scale (12). Dyker and colleagues reported an inverse association between lower TC levels and 3-month mortality independent of the OCSF classification (13). These authors could not demonstrate any relationship between TC levels and short-term mortality in the different OCSF groups, and

concluded that cholesterol might be a marker for long-term rather than short-term survival (13). More recently, Vauthey and colleagues found that high TC levels (>6.5 mmol/L) were associated with a better short-term outcome (including lower mortality) after controlling for different prognostic factors (14). Nevertheless, some important differences between that study and the present study must be acknowledged: 1) the mortality rate was very different (1.8%–4.1% vs 27%) likely due to different mean age (adult vs older participants), and different severity of the strokes (consecutive first-ever vs consecutive “major” strokes); 2) the OCSF classification was not included in the multivariate analysis; and 3) the cut-off values used for TC in that study were much different. In the present study, we divided our patients into three groups (low, normal-desiderable, and high TC levels) according to international literature (16,17).

The possible mechanisms linking low TC levels and short-term mortality after stroke have not been established. The first possibility is that TC might directly influence the evolution of ischemic stroke. A protective effect of cholesterol has been proposed based on experimental studies. Cholesterol is essential for normal cell membrane fluidity, but high TC levels enhance platelet aggregation (18); furthermore, high TC levels reduce the large artery responsiveness to vasodilatory stimuli (19). On the other hand, in vitro studies have shown that cholesterol retards the effects of oxidative stress on cerebral tissue, and also increases the tolerance of cultured cardiomyocytes to anoxia (20,21). Data from our sample argue against the hypothesis of a neuroprotective effect of cholesterol; indeed, after multivariate adjustment, participants with high TC levels tendentially had higher mortality compared with the participants with “normal” TC levels (see Table 3).

A second possibility is that low TC levels might be a marker of other factors affecting stroke outcome. For example, TC and apoprotein levels are known to decrease

Table 3. Multivariate Logistic Regression Analysis for Total Mortality in 469 Older Patients With Ischemic Stroke

	OR	CI 95%
Model 1		
Group I	2.17	1.22–3.85
Group II	0.83	0.49–1.40
Group III	Reference	—
Model 2		
Group I	2.87	1.23–6.68
Group II	0.61	0.27–1.40
Group III	Reference	—
Model 3		
Group I	1.67	0.83–3.33
Group II	0.63	0.34–1.15
Group III	Reference	—

Notes: Model 1: age, gender; Model 2: age, gender, hypertension, diabetes, blood glucose, atrial fibrillation, coronary heart disease, previous transient ischemic attack/stroke, smoking, congestive heart failure, altered level of consciousness, hematocrit; Model 3: age, gender, Oxfordshire Community Stroke Project classification.

OR = odds ratio; CI = confidence interval.

significantly during the acute phase (22,23), and therefore might decrease after stroke in proportion to severity of brain damage. However, this is not a likely explanation of our results. We measured TC levels within 24 hours after admission to hospital, and, according to previous studies, these values should reflect prestroke TC levels in each patient (24,25). Moreover the results did not change after adjustment for two markers of acute inflammation such as BSR and WBC count (data not shown).

A third possible explanation is that TC levels might reflect a “poor health” status, which might be responsible for higher mortality after stroke. Several studies have shown that, in older participants, low TC levels are associated with an increased risk of all-cause mortality (26,27); furthermore, much evidence supports the hypothesis that this association is due to the TC-lowering effect of chronic diseases (28,29). In our sample, low TC levels were associated with older age, higher BSR, higher prevalence of CHD, CHF, AF, and with more-severe stroke type (TACI). These data may suggest that patients belonging to group I were frail or at least “more frail” compared with groups II and III. We advance the hypothesis that the association between low TC levels and higher mortality might be explained by a greater prevalence of the frailty syndrome (30,31) among the patients with low TC.

In spite of the apparent discrepancy, our data do not contradict the findings of Aronow and colleagues. On one hand, cholesterol levels may be associated with the incidence of ischemic stroke (4), and therapy with statins may reduce the incidence of ischemic stroke in older patients (9). On the other hand, among older patients with acute ischemic stroke, low cholesterol levels may be associated with short-term mortality, as they may reflect a state of frailty preceding the acute disease.

Two important limitations of the present study should be finally acknowledged. First, since we do not know the TC levels before the onset of stroke in our patients, we cannot exclude that they changed as a consequence of the

cerebrovascular event. However, this is a limitation that is likely true for the majority of stroke patients seen in clinical practice from whom the only value of TC available is the one measured after hospital admission. Second, we do not have a standardized measure of comorbidity in our patients, and it is known that higher comorbidity levels are associated with poor outcome in older patients (32). Third, we did not evaluate routinely high-density lipoprotein cholesterol (HDL-C) levels. HDL-C levels are negatively associated with the incidence of ischemic stroke (33); furthermore, low levels have been associated with acute inflammation (22) and with poor outcome in older patients (34). The measurement of this metabolic parameter would add important data to our topic of study.

### Conclusion

Our data suggest that short-term mortality after ischemic stroke is higher in older patients with low TC levels, independent of a large number of prognostic factors, but not of the clinical stroke-type classification. Low TC levels might be useful in identifying frail older individuals at high risk of short-term mortality after acute ischemic stroke.

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