Total cholesterol affects the outcome in anterior cerebral artery-occluded acute ischemic stroke patients treated with thrombolysis

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Abstract

Object In this study, we investigated whether certain types of lipid profiles are major contributors to disease outcomes. **Methods** At two stroke medical centers, among 13,285 hospitalized patients treated with thrombolysis, thrombectomy, or conventional care, two hundred and seventy-six anterior cerebral artery-occluded acute ischemic stroke (AIS) patients were screened. We examined the plasma lipid profiles by using the cutoff values from a receiver operating characteristic (ROC) curve. A multivariate logistic regression or Fisher's exact test was used to compare the outcome and risk events. The modified Rankin scale (mRS) score was used to assess the major clinical outcome of the patients 3 months after disease onset. Mortality and symptomatic intracranial hemorrhage (sICH) were both evaluated as risk factors. The disease outcome was examined by analyzing symptom improvement at discharge. **Results** In the anterior cerebral artery-occluded AIS (NIHSS ≥ 10) patients treated by intravenous (IV) thrombolysis, a total cholesterol (TC) level greater than 5.07 mmol/L predicted a poor outcome (OR 3.55, 95% CI 1.21,10.46, $p = 0.021$). **Conclusion** In anterior cerebral artery-occluded AIS patients, the TC level is a highly promising screening factor for predicting the outcome of IV thrombolysis.

Background

Atherosclerotic cardiovascular disease and its clinical manifestations, such as ischemic cerebrovascular disease and coronary artery disease, are the leading cause of morbidity and mortality worldwide^{1 2, 3}. In most epidemiological cohort studies, the total cholesterol (TC) levels are well known to be associated with the cause of stroke. An increased risk of intracerebral hemorrhage (ICH) is closely associated with lower cholesterol levels⁴. Patients with higher TC levels are susceptible to ischemic stroke⁵⁻¹⁰. Therefore, determining whether certain types of plasma lipid profiles play critical roles in causing stroke is important. Lower HDL-C and TG levels have been used as two important parameters to independently predict a better survival rate after intravenous (IV) thrombolysis treatment in a retrospective analysis¹¹, and it has been well documented that patients can greatly benefit from this treatment. Lower low-density lipoprotein cholesterol (LDL-C) levels were found to be associated with ICH, while high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels do not differ between stroke patients with or without ICH¹². It is apparent that different types of biological lipoproteins are associated with certain disease types and their prognosis or consequences. Over the past decade, few studies have focused on the association between TC levels and prognosis in stroke patients. Thus, identifying the association between an individual's plasma lipid profile and prognosis in AIS is critical.

In this study, we evaluated the association between the lipid profiles and prognosis in AIS patients. We analyzed the relationship between cholesterol levels and prognosis following thrombolysis. Subsequently, we compared the effect of cholesterol on three common AIS management strategies (thrombolysis, thrombectomy and conventional treatment). Importantly, we found that the lipid profiles presented in

patients' plasma can be used as indicators to predict the overall outcome of severe anterior cerebral artery-occluded AIS patients only among patients treated with IV thrombolysis.

Methods

Patients and methods

This retrospective study was approved by the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University and the First People's Hospital of Changzhou, Soochow University. The requirement for individual patient consent or consent from the patients' relatives was waived, and the patients' information was anonymized prior to analysis. In total, 13,285 AIS patients treated with thrombolysis, thrombectomy, or conventional care between December 2010 and May 2015 at Xinhua Hospital and The First People's Hospital of Changzhou were recruited for this study. Among these patients, 396 patients received IV thrombolysis management, 98 patients received endovascular mechanical thrombectomy, and 12,791 patients were treated by conventional procedures not including thrombolysis or thrombectomy. Due to our specific patient selection requirements (National Institutes of Health Stroke Scale [NIHSS] score ≥ 10 , anterior artery occlusion, and age < 80 years), the final results reported in the present study include a total of 276 patients. Among these patients, 78 patients were in the endovascular thrombectomy group, 95 patients were in the IV thrombolysis group, and 103 patients were in the conventional care group. The detailed screening processes are shown in Figure 1.

According to the baseline NIHSS score, which is a clinical measure of neurologic deficit with a range of 0 (no deficit) to 42 (maximum possible deficit), patients with a score of 10 or more, representing a greater than 80% likelihood of a major arterial occlusion¹³, were identified. A stroke neurologist clinically assessed all patients upon admission. Cranial computed tomography (CT) was obtained prior to IV recombinant tissue plasminogen activator (rt-PA) treatment to rule out intracranial hemorrhage.

IV rt-PA thrombolysis treatment was initiated within 4.5 hours of the onset of stroke symptoms, and mechanical thrombectomy treatment was initiated within 6 hours as we previously reported¹⁴⁻¹⁶. The conventional care group consisted of patients who were subject to high risks during thrombolysis or thrombectomy or whose families did not consent to treatment. The time between onset and admission was less than 6 hours.

Patient treatment

The main inclusion criteria were as follows: 1. an NIHSS score ≥ 10 at admission; 2. imaging evidence revealing that the occlusion site was the anterior cerebral artery; and 3. analysis of the full lipid profile (including TG, TC, HDL-C and LDL-C) within 24 hours of stroke onset. The exclusion criteria included uncontrolled hypertension, severe sensitivity to radiographic contrast agents, and CT or magnetic resonance imaging (MRI) evidence of intracranial hemorrhage.

The patients in the thrombectomy group were treated as previously described¹⁴⁻¹⁶. The technical details of the endovascular procedure have also been described in a previous study. Upon admission, a stroke neurologist examined all patients; cranial CT or multimodal MR angiography was performed on patients prior to each intervention to confirm the diagnosis of large-vessel occlusion and rule out intracranial hemorrhage. All interventional treatments were initiated within the first 6 hours of stroke onset. For the thrombolysis treatment, we followed the American Heart Association (AHA) guidelines¹⁷ as described in a previous study¹⁶. The patients in the conventional care group were treated with lipid-lowering drugs via oral administration. The CT scans were reviewed during hospitalization, and if intracranial hemorrhage occurred, anticoagulation therapy was ceased, and the treatment plan was adjusted. No thrombolysis or thrombectomy management was performed in the conventional care patient group.

The intracranial hemorrhagic transformations were divided into clinically silent or symptomatic and then further classified into different categories. Hemorrhage was scored using the Pessin criteria and formalized based on the European Cooperative Acute Stroke Study (ECASS) trials (hemorrhagic infarction types 1 and 2 and parenchymal hematoma types 1 and 2)¹⁸⁻²⁰. Symptomatic intracranial hemorrhage was defined as any parenchymal hematoma subarachnoid hemorrhage or intraventricular hemorrhage associated with a worsening of the NIHSS score by four or more points within 24 h²¹. CT and MR images are very useful tools for evaluating the infarct lesion in the brain. The Alberta Stroke Program Early CT Score (ASPECTS) was used as a grading system to standardize the quantification of the CT images²². As the ASPECTS criteria were not included in the treatment guidelines of our two centers, ASPECTS was not measured immediately before the rt-PA treatment and did not affect the choice of management strategy. ASPECTS was evaluated by two neurosurgeons at the initial stage of this retrospective study (C.J.G., Y.L., and Y.P. contributed to this work). The stroke mechanism was viewed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The subtypes of AIS were defined at the 3-month follow-up as follows: cardioembolic, large-vessel atherosclerosis, other (uncommon etiologies), or undetermined²³. When no etiology was found or two diagnoses were possible, the etiology was classified as undetermined. The outcome at 3 months was evaluated by the modified Rankin scale (mRS) score either at a face-to-face visit or by telephone. Favorable outcomes were defined as a score of 0 to 2, and unfavorable outcomes were defined as a score of 3 to 6.

First, the mRS score at 3 months (the major outcome variable) was evaluated in the patients in the thrombolysis group with TC $\leq$ 5.07 mmol/L or $>$ 5.07 mmol/L. Then, the mRS score was compared with that in the thrombectomy group, the thrombolysis group, and the conventional care group. We also checked for symptom improvement after different management techniques. To evaluate the degree to which the symptoms improved after treatment, we compared the clinical improvement (discharge NIHSS score - admission NIHSS score $\geq$ 4) and the marked improvement (discharge NIHSS score - admission NIHSS score $\geq$ 10) rates of the patients among the treatment groups. Additionally, the difference in sICH and mortality risk between the thrombectomy (or thrombolysis) and conventional care groups was evaluated. The following data were also collected: age, gender, stroke reason, time between onset and needle, blood pressure at admission, plasma glucose and lipid profiles, medical history, documented occlusion site, and mRS score at 3 months.

Statistical analysis

The baselines and main outcomes are described as the means and standard deviations; the qualitative data are described as numbers and percentages. The lipid profiles were stratified using the cutoff values from the receiver operating characteristic (ROC) curve. For comparisons between different therapies, a Chi-square test or 2-sided Fisher's exact test was used (significance was set as $p < 0.05$). The independent prognostic value of the lipid profiles, the associations among the different management options, and symptomatic improvement or some other risk events were analyzed by a bivariate logistic regression analysis. All statistical analyses were performed using SAS software (version 9.4, SAS Institute).

Results

Prognostic factors of the clinical outcome in thrombolysis patients

Because blood lipids are reportedly inflammatory mediators and have been considered high risk factors of stroke, we examined the lipid profiles in plasma by using the cutoff values from the ROC curve. In this study, for the severe anterior cerebral artery-occluded AIS patients treated with thrombolysis, the cutoff values of TG, TC and LDL-C were 1.65 mmol/L (sensitivity 71.4%, specificity 87.5%), 5.07 mmol/L (sensitivity 83.3%, specificity 58.5%), and 3.01 mmol/L (sensitivity 63.5%, specificity 81.2%), respectively.

To determine whether the lipid profiles are predictors of the disease outcome, a univariate logistical regression was conducted. As shown in Table 1, a higher TC level (>5.07 mmol/L) can be clearly used as a predictor of a worse outcome (OR 3.55, 95% CI 1.21,10.46), while the TG and LDL-C levels are not suitable for predicting the disease outcome. Other parameters, such as the baseline ASPECTS (OR 0.54, 95% CI 0.39,0.76), admission NIHSS score (OR 1.14, 95% CI 1.00,1.29), plasma glucose level (OR 1.25, 95% CI 1.03,1.52), and systolic (OR 1.03, 95% CI 1.01,1.06) and diastolic (OR 1.04, 95% CI 1.01,1.08) pressure, were also considered associated with the disease outcome three months after disease onset. To determine the major contributors to the disease outcome three months after the disease onset, a multivariate logistic regression was conducted including the variables of systolic pressure, TC, admission ASPECTS and admission NIHSS score. By examining all clinical assessments and evaluations, it was found that the TC level (OR 6.64, 95% CI 1.84,23.96) is closely associated with the disease outcome of the patients (Table 1).

Population baseline

We also sought to determine whether the lipid profiles affect the prognosis of AIS patients who receive other types of treatment, such as mechanical thrombectomy and conventional treatment. In total, 13,285 hospitalized AIS patients were screened at Xinhua Hospital and The First People's Hospital of Changzhou between December 2010 and May 2015. After the screening, 276 patients treated with 3 different management methods were chosen, as shown in Figure 1. Of these patients, 95 patients received IV rt-PA thrombolysis treatment (thrombolysis group), 78 patients underwent endovascular thrombectomy treatment (thrombectomy group), and the remaining 103 patients were managed by conventional care without IV rt-PA treatment or thrombectomy (control group). The mean ages of the patients in these 3 groups ranged from 60 to 70 years (the average age of the thrombolysis patients was 67.25 years, the average age of the thrombectomy patients was 61.41 years, and the average age of the conventional care patients was 65.14 years; Table 2). Nearly half of the patients' symptoms were caused by large-artery atherosclerosis in the thrombectomy (46.15%) and thrombolysis (43.16%) groups, while 82.41% of the stroke cases resulted from large-artery atherosclerosis in the conventional care group. The detailed baseline characteristics of these three groups are listed in Table 2.

Clinical outcome

To determine whether TC affected the overall outcome, the mRS score of the patients in the different treatment groups at 3 months was analyzed based on the TC cutoff value. In addition to our previous analysis, a TC level > 5.07 mmol/L corresponded to a 3.55-fold greater possibility of an unfavorable

outcome compared with that of a TC level ≤ 5.07 mmol/L (OR 3.55, 95% CI 1.21-10.46) in the thrombolysis group. The rate of unfavorable outcome was 65.00% (13 of 20) with a TC level > 5.07 in the thrombectomy group but 53.40% (31 of 58) in the patients with a TC level ≤ 5.07 in the thrombectomy group. The risk of unfavorable outcome among the patients with a TC level > 5.07 was 1.65 times (95% CI 0.49-5.61) greater than that among the patients with a TC level ≤ 5.07 in the control group, although this difference was not statistically significant. The distribution of mRS scores at 3 months within the different groups is shown in Figure 2. There was no significant prognostic improvement among the patients with a TC level ≤ 5.07 in the thrombectomy group (OR 0.62, 95% CI 0.22-1.77).

As shown in Table 4, the TC cutoff value among the different therapy groups was analyzed. The severe AIS patients with a TC level ≤ 5.07 significantly benefited from thrombectomy (OR 0.12, 95% CI 0.04-0.37) and thrombolysis (OR: 0.24, 95% CI 0.09-0.62) compared with the patients in the conventional care group. The outcome of the patients with a TC level > 5.07 did not significantly improve compared with that in the patients in the conventional care treatment group; and the thrombolysis treatment was associated with even worse outcomes (OR 1.41, 95% CI 0.25-7.84 Table 4). However, the mechanical thrombectomy treatment corresponded to a significant improvement in prognosis (OR 0.08, 95% CI 0.01-1.07, Table 4).

Clinical improvement

The clinical improvement rate in the thrombolysis group was 56.67% (17 of 30 patients) (OR 9.79, 95% CI 2.14-44.70) of that in the control group among patients with a TC level > 5.07 mmol/L. However, among the patients with a TC level ≤ 5.07 mmol/L, a clinical improvement rate of 75.38% (49 of 65 patients) was observed in the thrombolysis group (OR 14.71, 95% CI 5.52-39.21) as shown in Supplementary Table 1. Compared with the control group, in the thrombectomy group, 15 (75.00%) of 20 patients with a TC level > 5.07 mmol/L achieved clinical improvement (OR 23.69, 95% CI 3.57-157.39), and 47 (81.03%) of 58 patients with a TC level ≤ 5.07 mmol/L achieved clinical improvement (OR 21.50, 95% CI 6.81-67.87) (Supplementary Table 1).

Among the patients with a TC level > 5.07 mmol/L, the rate of marked improvement in the thrombolysis group was 20% (6 of 30 patients), which was significantly lower (OR 0.07, 95% CI 0.01-0.78) than that in the thrombectomy group. Among the patients with a TC level ≤ 5.07 mmol/L, the rate of marked improvement in the thrombolysis group increased to 38.64% (25 of 65 patients), which was not significantly different from that in the thrombectomy group (OR 0.50, 95% CI 0.21-1.21) as shown in Supplementary Table 2.

Mortality and sICH

The mortality rate of the patients with a TC level > 5.07 mmol/L was 13.30% (4 of 30 patients) in the thrombolysis group and did not show a significant advantage compared with that in the control group (OR 0.60, 95% CI 0.08-4.32). The mortality rate of the patients with a TC level ≤ 5.07 mmol/L increased to 20% (13 of 65 patients) in the thrombolysis group (OR 0.67, 95% CI 0.24-1.85 compared with the control group) as shown in Table 5. Four (20%) of 20 patients with a TC level > 5.07 mmol/L died in the thrombectomy group (OR 23.69, 95% CI 3.57-157.39, compared with the control group), and eleven (18.97%) of 58 patients with a TC level ≤ 5.07 mmol/L died in the thrombectomy group (OR 0.43, 95% CI 0.14-1.34, compared with the control group) (Table 5).

The symptoms of intracranial hemorrhage during therapy were considered risk factors for a disability outcome. In total, 6 (6.30%) and 9 (11.54%) patients suffered from sICH within 24 hours of treatment in the thrombolysis and thrombectomy groups, respectively, as shown in Supplementary Table 3. Two sICH (1.85%) occurred 24 hours after conventional care. Considering the TC cutoff value (5.07 mmol/L), there were no significant differences between the thrombolysis and thrombectomy groups as shown in Table 6.

Discussion

The type of lipid profile and lipid accumulation at the location of cerebral large-artery occlusion have been reported to be critical factors of disease outcome. The efficacy of IV thrombolysis in large-artery occluded AIS patients is still controversial. Despite the extensive studies that have been conducted, the association between lipid profiles and AIS prognosis is highly controversial and remains unclear^{4,8,11,12,24-26}. Thus, excluding patients with severe illnesses, we questioned whether other factors interfere with the efficiency of IV thrombolysis. As a result, our data demonstrated that the TC level was an independent prognostic factor for IV thrombolysis. Higher TC levels (> 5.07 mmol/L) independently predicted poor outcomes after thrombolysis treatment in severe anterior cerebral artery-occluded AIS patients.

Furthermore, our study aimed to identify the association between the patterns of plasma lipids and the outcome and prognosis of AIS and determine whether the best treatment strategy is either thrombolysis or mechanical thrombectomy. By performing a ROC curve analysis, we determined the relationships between the outcome of AIS and the plasma lipid profiles. More importantly, we provide a relatively definitive boundary that can help predict the outcome of disease based on plasma lipid levels. The

threshold TC level of 5.07 mmol/L can be used as an indicator to predict disease outcome 3 months after disease onset among patients managed by IV thrombolysis.

A retrospective analysis of 1066 AIS patients reported that there was no association between lipid profiles and 3-month mRS scores or sICH²⁷. Additionally, other studies have shown that lower plasma TC, TG and HDL-C levels can each independently predict a poor 3-month outcome²⁶. In contrast, as described elsewhere, a higher HDL-C level has also been shown to be associated with a favorable outcome at 3 months¹¹. However, unexpectedly, higher HDL-C and TG levels were independently correlated with increased mortality in the same study¹¹. Our data clearly show that there is a close association between TC, but not TG and HDL-C, and the outcome of disease. In agreement with other studies, we did not observe an obvious association between the lipid profiles and sICH. Because the administration of statin can lower cholesterol levels, our data support the notion that lowering cholesterol levels does not affect the sICH risk in patients treated with IV thrombolysis.

The mechanism underlying the association between higher TC levels and poor 3-month outcome remains unclear. High plasma TC levels have been shown to be strongly associated with atherosclerosis stroke in large sample cohort studies performed by other researchers^{9, 10}. The unfavorable outcome observed in AIS patients receiving IV thrombolysis might be caused by large-vessel atherosclerosis²⁸⁻³⁰, which is closely associated with high levels of TC.

It is a general consensus that the poor artery recanalization of thrombolysis in stroke patients caused by atherosclerosis might lead to a poor prognosis³¹. The clinical outcome of severe AIS patients (NIHSS ≥ 10) treated by thrombectomy does not significantly differ between patients divided by the TC threshold (> 5.07 mmol/L and ≤ 5.07 mmol/L) (Table 3). To further confirm whether the TC levels influence the clinical outcome after thrombectomy treatment in severe anterior cerebral artery-occluded AIS patients, we replotted the ROC curve based on another TC cutoff value obtained through the thrombectomy database. The subsequent multivariable logistic regression including the new TC cutoff value still did not reveal a significant difference as shown in Supplementary Table 3. Therefore, the efficacy of thrombectomy might not be linked to cholesterol levels given the excellent recanalization rate of the thrombectomy procedure. However, this result seems to contradict the lack of association between atherosclerosis and outcome in our logistic regression model. Thus, we speculate that the etiological classification is a subjective measurement that might represent some deviation. The artificial etiological classification might not truly reflect the real condition of AIS patients. Our data suggest that the TC level could be a much more informative parameter that accurately reflects the atherosclerosis status of patients. Thus, in severe anterior cerebral artery-occluded AIS patients, the TC level might be a useful screening parameter for IV thrombolysis.

Finally, as stated in the materials and methods section, the included patient samples might be insufficient and could limit the strength of our study. However, the data collected are significant according to the ROC curve analysis. Nonetheless, further work is needed for prospective clinical trial verification.

Conclusions

In anterior cerebral artery-occluded AIS (NIHSS ≥ 10) patients, a TC level greater than 5.07 mmol/L can be considered a threshold for predicting a poor outcome following IV thrombolysis treatment, and if the TC level of an AIS patient is above this threshold, it is recommended that the physician choose an appropriate therapeutic strategy, such as mechanical thrombectomy. The determination of the TC levels is a useful screening method for the prediction of the outcome of IV thrombolysis.

Declarations

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Disclosures

The authors report that there are no conflicts of interest concerning the materials or methods used in this study or the findings reported in this paper.

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Tables

Table 1. Comparison of patients with favorable and unfavorable outcomes at 3 months in the thrombolysis group

Characteristics	Favorable	Unfavorable	Univariate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)*
Gender				
Male	18 (56.25)	34 (53.97)	0.91 (0.39,2.15)	
Female	14 (43.75)	29 (46.03)	1.00	
Age (years)				
≤60	11 (34.38)	13 (20.63)	1.00	
60-70	7 (21.88)	20 (31.75)	2.42 (0.74,7.84)	
>70	14 (43.75)	30 (47.62)	1.81 (0.65,5.05)	
ASPECTS (mean ± SD) †	9.09 ± 1.03	7.10 ± 2.44	0.54 (0.39,0.76)	0.44 (0.29,0.67)
Occluded vessel‡				
MCA_M1	11 (34.38)	43 (68.25)	1.00	
MCA_M2	18 (56.25)	15 (23.81)	0.21 (0.08,0.55)	
Other	3 (9.38)	5 (7.94)	0.36 (0.29,0.43)	
Cause of stroke				
Cardiogenic embolism	15 (46.88)	24 (38.10)	1.00	
Large-artery atherosclerosis	9 (28.13)	32 (50.79)	2.22 (0.83,5.93)	
Other	0 (0.00)	1 (1.59)	-	
Undetermined	8 (25.00)	6 (9.52)	0.47 (0.14,1.62)	
Time				
Onset to arrival (mean ± SD)	71.88 ± 39.74	69.62 ± 40.12	1.00 (0.99,1.01)	
Onset to treatment (mean ± SD)	175.47 ± 68.30	157.24 ± 45.10	0.99 (0.99,1.00)	
NIHSS upon admission (mean ± SD)	13.28 ± 3.12	14.97 ± 3.99	1.14 (1.00,1.29)	1.19 (1.01,1.40)
Systolic (mean ± SD)	139.78 ± 16.56	151.94 ± 23.43	1.03 (1.01,1.06)	1.05 (1.01,1.09)
Diastolic (mean ± SD)	74.09 ± 9.88	80.97 ± 14.67	1.04 (1.01,1.08)	
Plasma glucose (mean ± SD)	6.75 ± 2.40	8.20 ± 3.00	1.25 (1.03,1.52)	
Total plasma cholesterol				
≤5.07	27 (84.38)	38 (60.32)	1.00	1.00
>5.07	5 (15.63)	25 (39.68)	3.55 (1.21,10.46)	6.64 (1.84,23.96)
Plasma triglycerides				
≤1.65	28 (87.50)	46 (73.02)	1.00	
>1.65	4 (12.50)	17 (26.98)	2.59 (0.79,8.47)	
Low-density lipoprotein cholesterol				
≤3.01	30 (93.75)	59 (93.65)	1.00	
>3.01	2 (6.25)	4 (6.35)	1.02 (0.18,5.87)	
Atrial fibrillation				
No	17 (53.13)	40 (63.49)	1.00	
Yes	15 (46.88)	23 (36.51)	0.65 (0.27,1.54)	
Diabetes				
No	26 (81.25)	47 (74.60)	1.00	
Yes	6 (18.75)	16 (25.40)	1.48 (0.51,4.23)	
Hypertension				
No	11 (34.38)	20 (31.75)	1.00	
Yes	21 (65.63)	43 (68.25)	1.13 (0.46,2.78)	

* This analysis was performed by using a logistic regression.

† ASPECTS = Alberta Stroke Program Early CT Score.

‡ MCA_M1 = M1 segment of the middle cerebral artery; MCA_M2 = M2 segment of the middle cerebral artery.

Table 2. Baseline characteristics

Variable	Thrombolysis (n = 95)	Thrombectomy (n = 78)	Control (n = 103)	P-value*
Age (years; mean $\pm$ SD)	67.25 $\pm$ 8.96	61.41 $\pm$ 14.10	65.14 $\pm$ 10.87	0.0034
Gender (%)				
Male	52 (54.74)	47 (60.26)	61 (56.48)	0.7606
Female	43 (45.26)	31 (39.74)	47 (43.52)	
Baseline ASPECTS (Mean $\pm$ SD)*	7.77 $\pm$ 2.28	5.85 $\pm$ 2.91	7.03 $\pm$ 2.90	<0.0001
24 hour ASPECTS (Mean $\pm$ SD)	5.19 $\pm$ 3.03	3.28 $\pm$ 2.75	4.68 $\pm$ 2.65	<0.0001
Occluded vessel (%) †				
MCA_M1	53 (55.79)	54 (69.23)	37 (34.26)	<0.0001
MCA_M2	34 (35.79)	8 (10.26)	58 (53.70)	
ICA	3 (3.16)	3 (3.85)	9 (8.33)	
ICA/MCA	4 (4.21)	13 (16.67)	4 (3.70)	
Cause of stroke (%)				
Cardiogenic embolism	39 (41.05)	34 (43.59)	13 (12.04)	<0.0001
Large-artery atherosclerosis	41 (43.16)	36 (46.15)	89 (82.41)	
Other	1 (1.05)	5 (6.41)	0 (0.00)	
Undetermined	14 (14.74)	3 (3.85)	6 (5.56)	
NIHSS score upon admission (Mean $\pm$ SD)‡	14.41 $\pm$ 3.78	18.44 $\pm$ 3.81	16.16 $\pm$ 6.00	<0.0001
Systolic (Mean $\pm$ SD)	147.84 $\pm$ 22.05	142.54 $\pm$ 25.99	152.14 $\pm$ 25.17	0.0476
Diastolic (Mean $\pm$ SD)	78.65 $\pm$ 13.59	83.82 $\pm$ 13.72	81.71 $\pm$ 15.02	0.0148
Serum glucose (Mean $\pm$ SD)	7.71 $\pm$ 2.89	8.17 $\pm$ 3.98	9.91 $\pm$ 4.83	0.0003
Total cholesterol (Mean $\pm$ SD)	4.61 $\pm$ 0.97	4.49 $\pm$ 0.91	4.81 $\pm$ 1.10	0.1026
Triacylglycerol (Mean $\pm$ SD)	1.38 $\pm$ 0.88	1.74 $\pm$ 0.95	1.60 $\pm$ 1.06	0.0022
Low-density lipoprotein cholesterol (Mean $\pm$ SD)	2.66 $\pm$ 0.72	2.14 $\pm$ 0.64	2.89 $\pm$ 0.70	<0.0001
Atrial fibrillation (%)				
No	57 (60.00)	42 (53.85)	92 (85.19)	<0.0001
Yes	38 (40.00)	36 (46.15)	16 (14.81)	
Hypertension (%)				
No	31 (32.63)	36 (46.15)	31 (28.70)	0.0410
Yes	64 (67.37)	42 (53.85)	77 (71.30)	
Diabetes (%)				
No	73 (76.84)	67 (85.90)	68 (62.96)	0.0015
Yes	22 (23.16)	11 (14.10)	40 (37.04)	

* Determined using a Chi-square test or 2-sided Fisher's exact test.

* ASPECTS = Alberta Stroke Program Early CT Score.

† MCA_M1 = M1 segment of the middle cerebral artery; MCA_M2 = M2 segment of the middle cerebral artery;
ICA = internal carotid artery.

‡ NIHSS = National Institutes of Health Stroke Scale.

Table 3. Comparison of the major outcome variable (mRS score) among different therapies and usual management.

Group	mRS score* ≤2 (%)	mRS score >2 (%)	OR (95% CI) †	T value	P-value
Thrombolysis				5.30	0.02
TC > 5.07‡	5 (16.7%)	25 (83.3%)	3.55 (1.21 10.46)		
TC ≤ 5.07	27 (41.5%)	38 (58.5%)	1		
Thrombectomy				0.80	0.37
TC > 5.07	7 (35.0%)	13 (65.0%)	0.62 (0.22 1.77)		
TC ≤ 5.07	27 (46.6%)	31 (53.4%)	1		
Control				0.64	0.42
TC > 5.07	4 (16.7%)	33 (83.3%)	1.65 (0.49 5.61)		
TC ≤ 5.07	11 (10.8%)	55 (89.2%)	1		

* mRS score = modified Rankin scale score.

† This analysis was performed by using a logistic regression.

‡ TC = total cholesterol.

Table 4 Comparison of the major outcome variable (mRS score) among different therapies and usual management

Group	TC > 5.07*			TC ≤ 5.07		
	mRS score† ≤ 2 (%)	mRS score > 2 (%)	OR (95% CI)	mRS score ≤ 2 (%)	mRS score > 2 (%)	OR (95% CI) ‡
Thrombolysis	5 (16.67)	25 (83.33)	1.41 (0.25,7.84)	27 (41.54)	38 (58.46)	0.24 (0.09,0.62)
Thrombectomy	7 (35.00)	13 (65.00)	0.08 (0.01,1.07)	27 (46.55)	31 (53.45)	0.12 (0.04,0.37)
Control	4 (10.81)	33 (89.19)	1.00	11 (16.67)	55 (83.33)	1.00

* TC = total cholesterol.

† mRS score = modified Rankin scale score.

‡ This analysis was performed by using a logistic regression.

Table 5. Comparison of death among different therapies and usual management

Group	TC > 5.07*			TC ≤ 5.07		
	Alive (%)	Dead (%)	OR (95% CI)	Alive (%)	Dead (%)	OR (95% CI) †
Thrombolysis	26 (86.67)	4 (13.33)	0.60 (0.08,4.32)	52 (80.00)	13 (20.00)	0.67 (0.24,1.85)
Thrombectomy	16 (80.00)	4 (20.00)	0.08 (0.01,0.81)	47 (81.03)	11 (18.97)	0.43 (0.14,1.34)
Control	27 (72.97)	10 (27.03)	1.00	48 (72.73)	18 (27.27)	1.00

* TC = total cholesterol

†This analysis was performed by using a logistic regression.

Table 6 Comparison of sICH among different therapies and usual management

Group	TC > 5.07*			TC≤5.07		
	No-sICH (%)†	sICH (%)	OR (95% CI)	No-sICH (%)	sICH (%)	OR (95% CI) ‡
Thrombolysis	27 (90.00)	3 (10.00)	0.94 (0.03,30.85)	62 (95.38)	3 (4.62)	0.79 (0.16,4.07)
Thrombectomy	18 (90.00)	2 (10.00)	1.00	51 (87.93)	7 (12.07)	1.00
Control	37 (100.00)	0 (0.00)	-	64 (96.97)	2 (3.03)	0.36 (0.04,3.11)

* TC = total cholesterol

† sICH = symptomatic intracranial hemorrhage

‡ This analysis was performed by using a logistic regression.

Figures

Figure 1

Patient screening workflow. This figure illustrates the patient selection criteria. The 13,285 hospitalized acute ischemic stroke patients were divided into three groups according to the management type received. The NIHSS score, occlusion site, follow up, age and TC were used as screening criteria. AIS = acute ischemic stroke; ACA = anterior cerebral artery; ICA = internal carotid artery; MCA_M1 = M1 segment of middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale; TC = total cholesterol.

Figure 2

Outcomes of patients managed by different therapies. The numbers and percentages of patients in the management cohorts indicating the distribution of mRS scores. TC = total cholesterol, mRS = modified Rankin Scale.