An Elevated High-Density Lipoprotein Cholesterol Levels Is Associated with Favorable Outcomes of Patients with Small-Artery Occlusion

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Abstract

**Background:** The relationship between high-density lipoprotein (HDL) cholesterol and small-artery occlusion (SAO) is not well understood.

**Methods:** A total of 3067 consecutive patients with SAO were recruited from Tianjin Huanhu Hospital between January 01, 2008, and December 31, 2015. HDL values at admission were classified into four groups according to quartiles (<0.92, 0.92–1.08, 1.08–1.28, and ≥1.28). Patients were followed up to 12 months after stroke. Prognoses, represented by modified Rankin scale (mRS), were estimated via HDL quartiles upon admission utilizing multivariate logistic regression analysis. Meanwhile, we conducted additional subgroup analyses to investigate associations according to age.

**Results:** Among 3067 patients, 2284 (74.5%) were classified as having favorable outcomes, 783 (25.5%) had a composite of poor outcomes, recurrent stroke, myocardial infarction or vascular death within 12 months. After adjustment for possible confounders, HDL levels in the two highest quartiles (1.08–1.28 and ≥1.28) were correlated with the 12-month primary outcome of patients with SAO (1.08–1.28, 0.587; 95% CI, 0.394-0.873; P = 0.009; ≥1.28, 0.448; 95% CI, 0.291-0.688; P < 0.001). However, a direct correlation was found in patients aged 45–75 years (1.08–1.28, P = 0.033; ≥1.28, P = 0.001). Similar to the primary outcome, a direct correlation was also found in patients aged 45–75 years with a 12-month secondary outcomes (≥1.28 mmol/L, p = 0.001).

**Conclusions:** An elevated HDL cholesterol level in patients with SAO is an independent predictor of a favorable prognosis 12 months after SAO. However, the association was only present in patients aged 45–75 years.

**Keywords:** High-Density Lipoprotein Cholesterol, Stroke, Outcome, Small-Artery Occlusion.
Background

Stroke is a disease with high mortality and incidence rates worldwide; thus, it is an important health topic and is associated with an increased global economic burden [1,2]. Ischemic stroke events account for 71% of global stroke cases, and are classified into five subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [3,4]. Small-artery occlusion (SAO), one subtype caused by the occlusion of the branches of small penetrating arteries, accounts for 25% of ischemic stroke cases [5]. Despite its association with lower mortality and disability rates, the prevalence and progression of SAO is associated with motor dysfunction, including falls, as well as progressive cognitive decline, vascular dementia, and vascular parkinsonism. Furthermore, cerebral small vessel diseases such as SAO present a risk that can impair the quality of life. [6-8]. Although the pathophysiology of SAO is not clear, it is crucial to identify risk factors and explore ways to improve the quality of life for patients and reduce stroke burden [5,9].

Several studies have identified risk factors strongly associated with SAO prognoses including irregular glucose metabolism, fibrinogen abnormalities, and lipid metabolism disorders [7,10,11,12]. In particular, studies evaluated the role of dyslipidemia factors, including elevated low density lipoprotein (LDL) cholesterol, triglycerides (TG), total cholesterol (TC), and decreased high-density lipoprotein (HDL) cholesterol. A strong correlation between LDL cholesterol level, coronary heart disease, and stroke has been demonstrated by numerous studies [11-13]. While reports have revealed that TG and TC levels are associated with lacunar infarction [14,15,16], there have been few investigations evaluating HDL cholesterol levels that can predict ischemic stroke; moreover, the outcomes are inconsistent. It is imperative to clarify this association and provide appropriate clinical guidance. The aim of this study was to investigate the association between HDL levels and SAO prognoses in patients with stroke categorized by
Methods

Study population

Consecutive patients with stroke were chosen from a hospital-based registry established in Tianjin Huanhu Hospital, a specialized neurology hospital in Tianjin, China. We reviewed and extracted detailed information on patients from the registry between January 01, 2008, and December 31, 2015. Patients who had their first ischemic stroke event within 7 days of onset and whose medical history, behavioral factors, family history, neurological examination, standard 12-lead echocardiography, standardized blood tests, and imaging (magnetic resonance imaging or computed tomography) results led to a subsequent SAO diagnosis were included in our study; in addition, our inclusion criteria also required HDL values to be provided upon admission. Patients with a stroke classification of atherothrombotic, cardioembolic, and other or undetermined causes according to TOAST criteria were excluded from our analysis. Other exclusion factor included no data on lipids and lack of follow-up.

Among the 17,980 patients diagnosed with ischemic stroke according to World Health Organization criteria [17], 3483 were diagnosed with SAO upon admission; thus, the 14,497 patients with non-SAO strokes were excluded from our study. After excluding patients that did not have HDL data on blood lipids collected upon admission, missing follow-up reports or other reasons, 3067 patients with SAO remained that met all the inclusion criteria and were analyzed in the present study (Figure 1). Patients were classified into three subgroups according to age (<45 years, n = 140; ≥45 and <75 years, n = 2054; ≥75 years, n = 312).

Patients were evaluated for SAO by two experienced neurologists. SAO cases categorized as lacunar infarcts using other classification systems [18] were diagnosed based on the
following criteria: The patient exhibited one of the traditional clinical lacunar syndromes without evidence of cerebral cortical dysfunction. Patients also had a relevant brain stem or subcortical hemispheric lesion < 1.5 cm in diameter detected via computed tomography or magnetic resonance imaging. Additionally, no potential cardiac sources for embolism were present and stenosis was less than 50% in an ipsilateral artery. A history of diabetes mellitus or hypertension further supported the clinical diagnosis. All patients included in present study were diagnosed with Small-artery occlusion, those with a poor prognosis for survival (loss of consciousness or severe comorbidities), those with preexisting disabilities of the extremities were excluded from this study.

Demographic and clinical assessment

Baseline information and stroke risk factors were obtained from a record of clinical history within 24 hours of admission; information included age, sex, medical history, and detailed demographic data. Biochemical variables in the blood were measured following a fasting period of at least eight hours on the first day after admission and were analyzed in a certified central laboratory.

HDL values were classified into four quartiles (<0.92, 0.92–1.08, 1.08–1.28 and ≥1.28 mmol/L), since quartile classification is the most common statistical layering method. Hypertension was documented for patients with a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on the seventh day after stroke onset, systolic and diastolic blood pressures of 140/90 mmHg, and for patients taking antihypertensive medications [15]. Diabetes mellitus was identified in patients with fasting blood glucose levels ≥ 7.0 mmol/L, non-fasting glucose levels ≥ 11.1 mmol/L, a previous diagnosis of diabetes, and/or the use of hypoglycemic agents with a glycated hemoglobin (HbA1c) level ≥ 6.5% at the time of admission [19,20]. Dyslipidemia was characterized in patients being treated with cholesterol-reducing agents as well as in patients with a TG level > 2.26
mmol/L (200 mg/dL) or a TC level > 6.21 mmol/L (240 mg/dL). Individuals who had smoked tobacco products every day for more than a year were defined as current smokers. Alcohol drinkers were defined as those who consumed alcohol at least once per week for more than 1 year. Body mass index (kg/m^2) was calculated at the time of admission, and obesity was defined as a body mass index ≥ 30 kg/m^2 [21]. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) [22].

Functional outcome and follow-up

The primary outcome was prognoses of patients with SAO (favorable or poor prognoses) during a 12-month period after stroke onset. Secondary outcomes included poor prognoses, and composite of recurrent stroke, myocardial infarction (MI) or vascular death within 12 months. The 12-month follow-up was done by telephone interviews or in-person interviews; all results were recorded into our electronic stroke database immediately to ensure reliability. The modified Rankin scale (mRS) was used to evaluate functional outcomes: mRS scores of 0–2 represented favorable prognoses and mRS scores of 3–5 indicated poor prognoses.

Statistical analysis

In this study, continuous variables are presented as means ± standard deviations and categorical variables are reported as counts and proportions. We assessed the significance of intergroup differences using t-tests and one-way analysis of variance tests; chi-squared tests or Fisher’s exact tests were used to determine differences between groups. A multiple logistic regression analysis was used to evaluate the relationship between HDL levels and stroke prognoses with mRS scores. Statistical analyses were performed using the Statistical Package SPSS 24.0. All tests were two-sided, and p values < 0.05 were considered statistically significant.
Results

Baseline demographics and clinical characteristics of study participants

Table 1 outlines the baseline demographics and clinical characteristics according to the HDL quartiles. The mean HDL level of all patients was 1.126 ± 0.31 mmol/L (range, 0.25–6.11 mmol/L). NIHSS scores ranged from 0 to 14. In the present study, we collected data on 3067 patients (2134 men [69.6%]; 933 women [30.4%]). Mean age was 61.94±11.08 years. Among them, 29.5% had diabetes and 64.7% had hypertension. There was a statistically significant difference among the stratifications regarding HDL levels and lipid metabolism disorders (p < 0.05). Patients with HDL levels in the highest quartile were less likely to have diabetes (n = 164, 21.2%) and to smoke (n = 267, 34.5%).

Evaluation of risk factors between groups classified by outcomes

Table 2 describes the comparison of risk factors between different groups classified by outcomes. Among patients, 2284 (74.5%) had an favorable outcome. As it shows the following factors to be independently associated with the 12-month primary outcomes: age, HDL levels, and NIHSS scores (p < 0.001, p = 0.006, p < 0.001, respectively). Younger patients (60.87±10.82) had more favorable outcomes than older patients (64.23±11.00). However, there were no significant associations with other risk factors (sex, hypertension, diabetes, smoking, alcohol consumption, and obesity). In addition, of 3067 patients, 783 (25.5%) had a composite of poor outcomes, recurrent stroke, MI or vascular death within 12 months. Similar to the primary outcome predictors, secondary outcomes were significantly correlated with age, HDL levels, and NIHSS scores (all p values < 0.05). Patients with favorable outcomes were more likely to be the younger (60.87±10.82).

Multivariate logistical regression analyses of HDL groups and outcomes

Table 3 presents the results of the logistic regression analyses of HDL levels and outcome...
variables. As shown in the table, HDL levels in the two higher quartiles (1.08–1.28, ≥1.28) were significantly associated with the 12-month primary outcome as compared with the reference of HDL levels in the lowest quartile (adjusted odds ratio, 1.08–1.28, 0.587; 95% CI, 0.394–0.873; P = 0.009; ≥1.28, 0.448; 95% CI, 0.291–0.688; P < 0.001). Similar to the primary outcome, with 12-month secondary outcomes, patients with HDL levels in the two higher quartiles (1.08–1.28, ≥1.28) had more favorable outcomes (adjusted odds ratio, 1.08–1.28, 0.788; 95% CI, 0.621–0.999; P = 0.049; ≥1.28, 0.713; 95% CI, 0.560–0.909; P = 0.006). Meanwhile, there was a statistically significant association between age and SAO primary and secondary outcome (both P values < 0.001).

Table 4 further shows the association between HDL levels and outcomes according to age. We found a statistically significant direct correlation for the age range of 45–75 years with the primary outcome of stroke (1.08–1.28 mmol/L, p = 0.033; ≥1.28 mmol/L, p = 0.001, respectively). Furthermore, the similar association was found for patients with the secondary outcomes (≥1.28 mmol/L, p = 0.001). However, no association was found between outcomes and the lower HDL stratification with the age range of 45–75 years, neither the primary outcome (0.92–1.08; p = 0.064) nor the secondary outcomes (0.92–1.08; p = 0.305).

Discussion

The present study analyzed the clinical data of patients with SAO according to different age groups using data obtained from a hospital-based stroke registry from Tianjin, located in northern China. The higher HDL stratification levels (1.08–1.28, ≥1.28) were strongly correlated with favorable outcomes of patients with SAO; this clear positive association was observed in patients from 45 to 75 years of age. Our results indicated that elevated HDL cholesterol levels may facilitate a favorable prognosis for patients with SAO. Previous studies have demonstrated that low HDL
cholesterol levels were not only associated with the risk of incident stroke, but also with cerebral small vessel disease [19,23,24,25,26]. In addition, both the Japan Public Health Center study (2017) and the Holmes (2018) study reported an inverse relationship between HDL cholesterol levels and SAO. Furthermore, the Holmes (2018) study provided evidence demonstrating that cholesterol ester transfer proteins mediated higher HDL cholesterol levels and were associated with a lower risk of SAO, genetically [19,25,26]. Our results support these study findings; however, a meta-analysis of randomized controlled trials did not show that raising HDL levels will reduce the risk of stroke, but these results could have been affected by off-target effects of the drugs [27]. Moreover, a Framingham study provided no evidence to support a causal relationship between the role of 47 HDL cholesterol single nucleotide polymorphisms and ischemic stroke [28]; however, compared with the 3067 patients in our study, this previous study only involved 301 participants with ischemic stroke. Differences between our study results and previous studies may be due to patient race, age, and analytic strategies; for instance, the percentage of women was higher in the aforementioned Framingham study, 56% [28], compared with the 30.4% of women in our study. Our analysis revealed an inconsistent association between HDL and stroke similar to previous findings concerning cardiovascular disease [29]. Some randomized controlled trials explored the clinical benefits of elevated HDL cholesterol levels for patients diagnosed with cardiovascular disease by adding niacin to statin therapy. One study showed that elevated HDL levels contributed to the regression of angiographic coronary-artery stenoses [30]; however, another study surprisingly reported no clinical benefits after increasing HDL cholesterol levels for patients with cardiovascular disease and failed to provide evidence for a causal link between extended-release niacin and ischemic stroke [29]. Nevertheless, there are no reported clinical studies analyzing the relationship
between elevated HDL levels and ischemic stroke or ischemic stroke subtypes; thus, further evaluation is needed to clarify these contradictory findings. Nevertheless, our results are valid and may be used to provide clinical guidance in northern China.

Additionally, our previous studies found that hemoglobin A1c levels and high-sensitivity C-reactive proteins (hs-CRPs) were associated with SAO outcomes [10,31]. Although, hyperglycemia and hs-CRPs may be related to endothelial damage and inflammatory responses, thus leading to the occlusion of deep penetrating vessels, dysglycemia may also intensify lipid disorders that can aggravate the inflammatory responses of vessels. Therefore, these risk factors are independent and interrelated, further signifying the importance of evaluating risk factors related to dyslipidemia in clinical practice.

Although there is a significant relationship between HDL cholesterol and SAO, the underlying mechanism is not clear. HDL plays a key role in promoting reverse cholesterol transport from the periphery to the liver. Furthermore, mounting evidence has demonstrated that the reverse cholesterol transport process may provide protection from atherosclerosis, which can lead to lacunar infarcts through artery occlusion [26,32]; in fact, some studies found impaired carbon dioxide (CO₂) vasoreactivity in lacunar infarct patients. While serum HDL cholesterol affects cerebral vasculature CO₂ reactivity by increasing the permeability of the blood-brain barrier, the increased permeability may lead to glial and neuronal damage by allowing blood products to diffuse into the perivascular space[26]. Also, some evidence suggests that HDL cholesterol may activate endothelial nitric oxide synthase to promote endothelial repair, induce angiogenesis, and increase platelet reactivity, anti-inflammatory reactions, and hypercoagulability functions[19,33,34]. Furthermore, modulating HDL levels may be implicated in vascular remodeling and functional recovery [34,35,36].

Our study also found that elevated HDL cholesterol levels were associated with favorable
prognoses only in patients aged from 45 to 75 years after multivariate adjustment, and this association was presented both in the primary outcome group and the secondary outcomes. Similar to our study, Aleksandra et al. found that lower HDL cholesterol levels was significant in middle-aged and elderly persons [23], which may be strongly correlated with the HDL cholesterol’s above-mentioned anti-inflammatory and anti-atherogenic pathophysiology. No association was presented between HDL cholesterol levels with SAO outcomes in the oldest-old patients (≥ 75 years). That might be associate with a higher risk of comorbidity with increasing age, and multiple risk factors acting together may attenuate the impact of any one independent risk or protective factor, such as the protection of HDL cholesterol. Studies have indicated hypertension, hyperglycemia and dyslipidemia were the major risk factors of small artery occlusion in young adults. Nevertheless, the young people have less complication, higher compensatory function and adjustable life style. Controlling weight and alcohol, quit smoking, exercise and good medication compliance can regulate blood pressure, blood glucose and lipid metabolism, which contribute to favorable outcomes in the young.

The clinical information that was collected for a large number of SAO cases, promptly drawn blood samples, and inclusion of adults of any age enhanced the robustness of our study. Our findings suggest the importance of maintaining HDL cholesterol values in higher stratifications using lipid-regulating drugs or proper exercise for patients with SAO. However, there were several limitations to our study. First, we collected clinical information for SAO cases from one hospital in Tianjin; thus the patient population does not represent the general population of China that may otherwise vary by region, diet, lifestyle, and other factors. Furthermore, we did not consider the use of lipid-lowering medications such as statins. The influence of statins on HDL cholesterol values during the follow-up period is unclear and may have affected the outcomes of patients with SAO. In
addition, patients without HDL cholesterol data upon at admission were not included in this study, which may have presented a selection bias. Finally, other limitations were those particularly inherent to retrospective studies.

Abbreviations
CI, confidence interval;
HbA1c, hemoglobin A1c;
HDL-C, High-Density Lipoprotein Cholesterol;
hs-CRP, High-Sensitivity C-Reactive Protein;
LAA, large-artery atherosclerosis;
LDL-C, Low-Density Lipoprotein Cholesterol;
mRS, modified Rankin scale;
NIHSS, National Institutes of Health Stroke Scale;
OR, odds ratio;
SAO, Small-artery occlusion;
TOAST, Trial of ORG10172 in Acute Stroke Treatment;
TC, Total Cholesterol;
TG, Triglycerides

Declarations

Ethics approval and consent to participate

The Ethics Committee of Tianjin Huanhu Hospital approved the study protocol. All patients consent to participate in this observational study. Written informed consent was obtained from each participant according to the demand of Local Ethics Committee of Tianjin Huanhu Hospital. A written consent could be obtained directly from the patient. In some circumstances that the patient was unable to sign because of hemiplegia, a written
consent could be obtained from a family member. The ethics committee approved this procedure.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

All authors declare that they have no competing interests.

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**Authors’ contributions**

JW took part in design of the study, funding obtained, interpretation of the data and revising the manuscript. RH, PL and YW carried out the studies, participated in collecting data. RH, and PL drafted the manuscript. RH and YW performed the statistical analysis and participated in its design. All authors read and approved the final manuscript.

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Tables

Table 1 - Baseline demographics and clinical characteristics according to HDL groups

| Quartile of HDL | <0.92 (n =733) | 0.92 to < 1.08 (n =768) |
|-----------------|----------------|-------------------------|
| Age, years (median values) | 61.42±11.28 | 62.39±11.26 |
| Male sex, n(%)* | 542(73.9) | 511(66.5) |
| Risk factors | | |
| Hypertension, n(%) | 490(66.8) | 479(62.4) |
| Diabetes, n(%)* | 305(41.6) | 213(27.7) |
| Smokers, n(%)* | 305(41.6) | 297(38.7) |
| Alcohol drinkers, n(%) | 120(16.4) | 116(15.1) |
| Obesity, n(%) | 54(7.4) | 48(6.3) |
| Laboratory findings | | |
| TG, mmol/L (median values)* | 2.09±1.48 | 1.76±1.00 |
| TC, mmol/L (median values)* | 4.59±1.82 | 4.87±0.95 |
| HDL-C, mmol/L (median values)* | 0.79±0.97 | 0.99±0.45 |
| LDL-C, mmol/L (median values)* | 2.68±0.79 | 2.90±0.78 |
| NIHSS, n(%) | 0-6 | 538(73.4) | 548(71.4) |
| | 7-14 | 195(26.6) | 220(28.6) |

* Indicates P< 0.05 when comparing between four groups. TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institute of Health stroke scale

Table 2 - Comparison of the risk factors between different groups classified by outcomes
mRS: modified Rankin scale; NIHSS: National Institute of Health stroke scale; HDL, high-density lipoprotein cholesterol;

|                          | mRS≤2 | mRS≥3 | P Value  |
|--------------------------|-------|-------|----------|
| (n=2284)                 | 60.87±10.82 | 64.23±11.00 | <0.001   |
| Male sex, n(%)           | 1596(69.9) | 142(64.0) | 0.068    |
| Hypertension, n(%)       | 1482(64.9) | 135(60.8) | 0.226    |
| Diabetes, n(%)           | 660(28.9)  | 74(33.3)  | 0.166    |
| Smokers, n(%)            | 868(38.0)  | 78(35.1)  | 0.400    |
| Alcohol drinkers, n(%)   | 366(16.0)  | 34(15.3)  | 0.783    |
| Obesity, n(%)            | 151(6.6)   | 13(5.9)   | 0.664    |
| HDL, n(%)                |         |         | 0.006    |
| <0.92                    | 527(23.1)  | 69(31.1)  |          |
| ≥0.92                    | 558(24.4)  | 60(27.0)  |          |
| ≥1.08                    | 597(26.1)  | 54(24.3)  |          |
| ≥1.28                    | 602(26.4)  | 39(17.6)  |          |
| NIHSS, n(%)              |         |         | <0.001   |
| 0-6                      | 1795(78.6) | 75(33.8)  |          |
| ≥7                       | 489(21.4)  | 147(66.2) |          |

|                          |          |          |          |
|--------------------------|----------|----------|----------|
| Primary outcome          | Secondary |          |          |
| OR ( 95% CI )           | P Value  | OR ( 95% CI ) | P Value  |
| Age                      |          |          |          |
| HDL                      |          |          |          |
| <0.92                    | 1.026(1.012-1.039) | <0.001 |          |
| ≥0.92                    | 0.706(0.478-1.042) | 0.079  | 0.9010(1.712-1.140) | 0.079 |
| ≥1.08                    | 0.587(0.394-0.873) | 0.009  | 0.7880(0.621-0.999) | 0.009 |
| ≥1.28                    | 0.448(0.291-0.688) | <0.001 | 0.7130(0.560-0.909) | <0.001 |
| NIHSS                    |          |          |          |
| 0-6                      | 7.165(5.314-9.660) | <0.001 |          |
| ≥7                       |          |          | 2.7962(3.245-3.333) |          |

mRS: modified Rankin scale; NIHSS: National Institute of Health stroke scale; HDL, high-density lipoprotein cholesterol;

Table 3 - Multivariate logistical regression analyses of HDL groups and the
outcome variables

Table 4 - Multivariate logistical regression analyses of HDL groups classified by
age and outcomes
| Primary outcome | HDL | OR(95%CI) | P Value | OR(95%CI) |
|-----------------|-----|-----------|---------|-----------|
| < 0.92          | index |          | 0.672   | 0.650(0.4 |
| ≥ 0.92          | 0.585(0.049-6.971) | 0.672   | 0.650(0.4 | |
| ≥ 1.08          | 2.788(0.404-19.243) | 0.298   | 0.615(0.3 | |
| ≥ 1.28          | 0.000(0.000-) | 0.998   | 0.452(0.2 | |

| NIHSS | OR(95%CI) | P Value | OR(95%CI) |
|-------|-----------|---------|-----------|
| 0-6   | 4.5730.810-25.832) | 0.085   | 8.501(6.0 | |
| ≥ 7   | 4.5730.810-25.832) | 0.085   | 8.501(6.0 | |

| Secondary outcome | Age | OR(95%CI) | P Value | OR(95%CI) |
|-------------------|-----|-----------|---------|-----------|
| < 0.92            | index |          | 0.756   | 1.026(1.0 | |
| ≥ 0.92            | 0.9840.889-1.089 | 0.756   | 1.026(1.0 | |
| ≥ 1.08            | 0.742(0.189-2.911) | 0.668   | 0.868(0.6 | |
| ≥ 1.28            | 2.664(0.803-8.844) | 0.109   | 0.788(0.6 | |
| NIHSS             | 0.691(0.156-3.065) | 0.627   | 0.684(0.5 | |
| ≥ 7               | 2.706(0.983-7.448) | 0.054   | 2.995(2.4 | |

mRS: modified Rankin scale; NIHSS: National Institute of Health stroke scale; HDL, high-density lipoprotein cholesterol;

Figures
Fig. 1 Flow chart of patient selection
SAO: small-artery occlusion

Figure 1

Flowchart for patient selection.