Association between non-high-density lipoprotein cholesterol and haemorrhagic transformation in patients with acute ischaemic stroke

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Abstract

Background: It is unclear whether non-high-density lipoprotein cholesterol (Non-HDL-C) is associated with haemorrhagic transformation (HT) after acute ischaemic stroke (AIS). We aimed to explore the association between Non-HDL-C and HT, as well as compare the predictive values of Non-HDL-C and low-density lipoprotein cholesterol (LDL-C) for HT. Methods: We consecutively enrolled AIS patients within 7 days of stroke onset. Participants were divided into four categories according to quartiles of Non-HDL-C. HT was assessed by follow-up brain imaging. We assessed the association between Non-HDL-C, LDL-C and HT in multivariate logistic regression analysis. Results: A total of 2043 patients were included, among whom 232 were identified as HT. Compared with the highest quartiles, the first, second and third quartiles of Non-HDL-C were associated with increased risk of HT (adjusted Odds ratios [ORs] 1.74 [95% Confidence Interval [CI] 1.09-2.78], 2.01[95% CI 1.26-3.20], and 1.76 [95% CI 1.10-2.83], respectively, P for trend=0.024). Similar results were found for LDL-C. There was significant interaction between Non-HDL-C and age ( P for interaction=0.021). The addition of Non-HDL-C and LDL-C to conventional factors significantly improved predictive values (Non-HDL-C, net reclassification index [NRI] 0.24, 95%CI 0.17-0.31, P<0.001; LDL-C, NRI 0.15, 95%CI 0.08-0.22, P=0.03). Conclusions: Low Non-HDL-C was associated with increased risks of HT. In addition, Non-HDL-C has similar effects as LDL-C for predicting HT. Keywords: Non-high-density lipoprotein cholesterol, Haemorrhagic transformation, Acute ischaemic stroke

Background

Haemorrhagic transformation (HT) is a common complication after acute ischaemic stroke (AIS), occurring in about 10%-40% of patients[1]. The presence of HT may contribute to poor outcome in stroke patients[2]. A number of factors associated with HT have been reported, including age, stroke severity, atrial fibrillation and thrombolysis.

Although dyslipidaemia is known as an important risk factor of stroke[3], the association between the serum lipid levels and HT has not been well established. Prior studies have stated that low level of low-density lipoprotein cholesterol (LDL-C) could increase HT in patients with AIS[4-6], whereas the relationship between non-high-density lipoprotein cholesterol (Non-HDL-C) and HT is still not clear. As
a composite marker, Non-HDL-C includes the triglyceride-rich lipoproteins such as chylomicrons, LDL, very-low-density lipoproteins, and their remnant[7]. Recent studies demonstrated that Non-HDL-C was more strongly associated with cardiovascular diseases than LDL-C[8-10]. However, whether Non-HDL-C is superior to LDL-C for predicting HT has not been studied. Therefore, we aimed to explore the association between Non-HDL-C and HT, as well as compare the predictive values of Non-HDL-C and LDL-C for HT in patients with AIS.

Methods

Study Population

We consecutively enrolled ischaemic stroke patients within 7 days of stroke onset between January 2016 and September 2018 based on the Chengdu Stroke Registry Database, which has been described in details.[11] All patients were clinically diagnosed as ischaemic stroke based on the World health Organization criteria[12], and finally confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan. Patients were not eligible if they: (1) were diagnosed with HT based on the initial head CT on admission, or (2) did not undergo later CT or MRI scan; or (3) lacked lipid profile test within 24 hours after admission.

Data collection

Baseline information including patients’ demographics, stroke severity on admission, medical history, current smoking, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, lipid parameters, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, thrombolysis and thrombectomy were collected. Medical history contained hypertension, diabetes mellitus, hyperlipidaemia and atrial fibrillation. Stroke severity on admission was evaluated using the National Institutes of Health Stroke Scale (NIHSS)[13].

Lipid parameters

Blood samples were collected within 24 hours after hospital admission, and serum lipid parameters, including total cholesterol (TC), triglycerides (TG), HDL-C and LDL-C, were tested in the Department of Laboratory Medicine, West China Hospital. Non-HDL-C levels were determined by subtracting serum HDL-C levels from total cholesterol[14].
Assessment of HT

HT was defined as haemorrhage within the infarcted area or parenchyma hemorrhage outside the infarct zone that was present on a second CT or MRI (usually within 7±2 days after admission), but not on head CT or MRI on admission, based on the European Cooperative Acute Stroke Study II criteria.[15] Additionally, HT was classified into symptomatic or no symptomatic HT group based on whether patients experienced any neurological deterioration. [16] HT was identified separately by two researchers (YW and QS), and a third researcher (CW) was consulted when a disagreement occurred.

Statistical analysis

Participants were divided into four categories according to quartiles of Non-HDL-C. Continuous variables are described as means with the standard deviations or median with interquartile ranges, and categorical variables are presented as proportions frequencies with percentages. Differences in continuous data were assessed using Student’s t test, ANOVA test, the Mann–Whitney U test or the Kruskal–Wallis test and differences in categorical data were assessed using the chi-squared test or Fisher’s exact test. Univariate analysis was carried out to identify possible risk factors for HT. We further performed multivariate logistic regression analysis to assess the association between Non-HDL-C or LDL-C and HT. The odds ratio (OR) and 95% confidence interval (CI) was calculated. We created two models. Model 1 adjusted for age and sex. Model 2 adjusted for other potential confounding variables besides age and sex on model 1. Multivariable spline regression model was used to test nonlinear relationship between LDL-C, Non-HDL-C and HT. In addition, C statistics and net reclassification index[17] were calculated to evaluate the predictive value of adding Non-HDL-C or LDL-C to conventional risk factors model. In addition, we performed stratified analyses to explore potential indicators that may modify the relationship between Non-HDL-C and HT. The significance of interaction was tested by the likelihood ratio test. All statistical analyses were performed using SPSS 22.0 (IBM, Chicago, IL, USA), R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA). Two-sided values of $P < 0.05$ were considered statistically significant.

Results
Baseline characteristics

In all, 2206 consecutive patients with ischaemic stroke within 7 days were admitted to our hospital during the study period and 2043 patients were included in this study (Figure 1). Of these 2043 patients, the mean age was 65 ± 14 years, and 63.1% were males.

Demographic and clinical characteristics of participants based on Non-HDL-C quartiles are summarized in Table 1. Non-HDL-C levels ranged from 0.59 to 10.03 mmol/L (mean value, 3.14 mmol/L). Patients were divided into four categories based on Non-HDL-C quartiles: Q1, <2.35 mmol/L; Q2, 2.35–3.06 mmol/L; Q3, 3.07–3.83 mmol/L and Q4 3, >3.83 mmol/L. As shown in table 1, patients in the lowest quartile were more likely to be older, have a higher proportion of atrial fibrillation, have higher NIHSS scores and HDL-C compared with those in the highest quartile of Non-HDL-C. In addition, patients in the highest quartile were more likely to be have a higher proportion of hypertension, diabetes mellitus, have higher SBP, DBP, glucose, TG, TC and LDL-C compared with those in the lowest quartile of Non-HDL-C.

Of the 2043 patients, 232 (11.4%) were identified as HT, of whom 34 (1.7%) were symptomatic HT. Incidence of HT was 14.0% in quartile1, 11.5% in quartile2, 12.3% in quartile3, and 7.1% in quartile4 for LDL-C (P=0.003), and was 14.8% in quartile1, 13.1% in quartile2, 11.2% in quartile3, and 6.3% in quartile4 for Non-HDL-C (P<0.001).

Association of Non-HDL-C and LDL-C with HT, symptomatic HT

In the univariate analysis, age (P<0.001), males (P<0.001), atrial fibrillation (P<0.001), smoking (P=0.033), alcohol consumption (P=0.049), TOAST classification (P<0.001), NIHSS scores on admission (P<0.001), SBP (P<0.001), DBP (P=0.048), thrombolysis (P<0.001), thrombectomy (P<0.001), TG (P<0.001), TC (P=0.003), HDL-C (P=0.005), LDL-C (P<0.001) and Non-HDL-C (P<0.001) were significantly associated with HT (Table 2). In addition, only age (P=0.017), atrial fibrillation (P<0.001), NIHSS scores on admission (P<0.001), TC (P=0.047) and Non-HDL-C (P=0.028) were significantly related to symptomatic HT (Supplemental Table 1).

Table 3 shows the association between quartiles of Non-HDL-C or LDL-C and HT. After adjusting for age and sex in model 1, patients in the lower Non-HDL-C quartiles were associated with increased
risks of HT ($P$ for trend $<0.001$). Compared with the highest quartiles, the first, second and third quartiles of Non-HDL-C were associated with increased risk of HT (adjusted ORs 1.74 [95% CI 1.09-2.78], 2.01 [95% CI 1.26-3.20], and 1.76 [95% CI 1.10-2.83], respectively) after adjusting for age, sex, NIHSS scores on admission, atrial fibrillation, smoking, alcohol consumption, SBP, thrombolysis, thrombectomy and TOAST classification in model 2. However, the only significant association was found between the third quartiles of Non-HDL-C and symptomatic HT (adjusted ORs 3.82 [95% CI 1.05-13.85]) after adjusting for age and NIHSS scores on admission (Supplemental Table 2).

After adjusting age and sex in model 1, patients in the lower LDL-C quartiles were associated with increased risks of HT ($P$ for trend $<0.001$). Compared with the highest quartiles, the first and third quartiles of LDL-C were associated with increased risks of HT (adjusted ORs 1.57 [95% CI 1.00-2.47] and 1.82 [95% CI 1.16-2.87]), but not the second quartiles (adjusted ORs 1.51 [95% CI 0.95-2.40]) after adjusting for age, sex, NIHSS scores on admission, atrial fibrillation, smoking, alcohol consumption, SBP, thrombolysis, thrombectomy and TOAST classification in model 2 (Table 3). No obvious relationship was found between LDL-C and symptomatic HT after adjusting for age and NIHSS scores on admission (Supplemental Table 2).

Using a multiple-adjusted spline regression, no nonlinear trend was found between Non-HDL-C, LDL-C and HT (Figure 2). When adding Non-HDL-C or LDL-C to Model2, the c-statistics were 0.79 (95%CI 0.77-0.80, $P<0.001$) for Non-HDL-C and 0.78 (95%CI 0.77-0.80, $P<0.001$) for LDL-C (Table 4). In addition, when adding Non-HDL-C, LDL-C to model 2 containing conventional risk factors significantly improved predictive ability (Non-HDL-C, net reclassification index 0.24, 95%CI 0.17-0.31, $P<0.001$; LDL-C, net reclassification index 0.15, 95%CI 0.08-0.22, $P=0.03$) (Table 4).

**Patients Age Affects the Relationship between Non-HDL-C and HT**

Age is an interaction factor between Non-HDL-C and HT ($P=0.021$). Limiting the analysis to younger patients (<60) showed a significant negative relationship between Non-HDL-C and HT (OR 0.64, 95%CI 0.47-0.87, $P<0.01$), whereas this relationship was no longer significant in older patients ($\geq$60) (Table 5). After adjustment for potential confounding variables, we found that the relationship between Non-HDL-C and HT did not change by sex, base NIHSS score, atrial fibrillation, smoking,
alcohol consumption, SBP, reperfusion therapy (thrombolysis/thrombectomy) and stroke subtype (all 
P for interaction > 0.05) (Table 5).

Discussion
In the present study, we found low Non-HDL-C was associated with an increased risk of HT in patients 
with AIS after adjustment for known risk factors. In addition, Non-HDL-C has similar effects as LDL-C 
for predicting HT. 

Some studies showed that Non-HDL-C was a good biomarker for predicting cardiovascular events[7, 
18, 19]. Despite these data, the role of the Non-HDL-C for HT is still not clear in patients with 
ischaemic stroke. In the present study, low Non-HDL-C was independently associated with increased 
risks of HT. In addition, no robust association was observed between LDL-C and HT. Prior studies[4, 
20] have shown that low LDL-C was related to greater risk for HT; however, these studies included 
patients with ischaemic stroke receiving intravenous or intra-arterial rt-PA and mechanical 
recanalization. Conversely, other research[21-23] stated that LDL-C on admission was not associated 
with intracerebral hemorrhage after intravenous thrombolysis. In our study, we found lower LDL-C 
was significantly related to higher risks of HT in the univariate analysis, but this association was 
attenuated after adjusting for risk factors, suggesting a possible mediating effect of unmeasured 
confounders. Further studies are needed to clarify the association especially in general AIS patients. 
The mechanisms that explain the association of cholesterol and HT are uncertain, but there are some 
possible explanations as follows. First, cholesterol may play a great role in keeping the integrity of 
cerebral vascular vessel. It is reported that low level of cholesterol could cause the increased 
permeability of the erythrocyte membrane[24], and even contribute to the leakage and rupture of 
vessels wall[25]. Second, cholesterol is likely to affect aggregation of platelet. Some studies have 
shown that low level of cholesterol might lead to decreased platelet aggregation, and then increase 
the risk of bleeding[26]. Third, abnormal blood lipid levels could result in the increased plasma 
viscosity and whole blood viscosity, and then cholesterol would be accumulated in endothelium, 
thereby exciting the sympathetic nervous system and renin angiotensin system, with the injury of 
vascular wall[27, 28]. Further studies are needed to verify the mechanism between serum lipid levels
and HT.

Although increasing evidence[8-10] indicated that Non-HDL-C was superior to LDL-C in terms of predicting the risk of cardiovascular disease, we found Non-HDL-C has similar predictive values as LDL-C for HT in AIS. The addition of Non-HDL-C or LDL-C to a conventional risk factor model could improve predictive ability for HT, suggesting that Non-HDL-C could be a potential predictive marker for HT as well as LDL-C. Furthermore, Non-HDL-C is more accurate and reliable when measured in the non-fasting state compared with LDL-C[29]. In addition, some guidelines on the management of blood cholesterol has recommended that Non-HDL-C could be as a primary goal in the primary and secondary prevention of cardiovascular disease[30-32].

In this study, we found Non-HDL-C was negatively associated with HT in younger stroke patients. In older stroke patients, Non-HDL-C is also negatively related to HT although there was no significant difference. One possible explanation for the difference is that malnutrition is more commonly seen in elderly population[33] and malnutrition might lead to decreased serum cholesterol.[34] In addition, there are other factors that may contribute to the occurrence of HT. Older people usually present arterial stiffness that recently has been recognised as a possible risk factor for HT.[35]

Interestingly, our study found that SBP on admission was significantly lower in patients with HT (140 ± 23 mmHg) than those without HT (146 ± 23 mmHg), which is in line with some previous studies.[36-38] A possible explanation might be that slightly elevated blood pressure could provide an adequate cerebral blood supply, and thereby reduce the damage to blood-brain barrier due to ischemia and hypoxia,[39] which may prevent the occurrence of HT. A much-debated question is whether blood pressure is related to HT. Some studies[40-43] showed elevated SBP was associated with increased risks of HT, whereas other studies[44-46] did not observe the association. In addition, recent studies have reported that blood pressure variability, rather than the single measure of blood pressure on admission, is an emerging risk factor for HT.[47-49] More research is needed in this field.

Our study has some limitations. First, patients presented with HT at admission were excluded. Therefore, the results might not be generalizable to all ischaemic stroke patients. However, the proportion of patients with HT at admission is low (3.9%) in this study. Second, this study was just an
observational, single-centre study, so the findings might not be generalized to the whole Chinese population. Third, although we struggled to obtain medical history, there might be some omissions. Therefore, the results of this study should be interpreted cautiously.

In conclusion, low Non-HDL-C was independently associated with an increased risk of HT. In addition, Non-HDL-C has similar effects as LDL-C for predicting HT. These findings suggest that patients with low Non-HDL-C or LDL-C are prone to haemorrhagic transformation and those might be considered in practice to reduce the risk of haemorrhagic transformation. Further large sample size studies are needed to confirm these findings.

**Abbreviations**

HT: haemorrhagic transformation; AIS: acute ischaemic stroke; Non-HDL-C: non-high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; OR: Odds ratio; ORs: Odds ratios CI: Confidence interval; NRI: net reclassification index; CT: Computed tomography; MRI: Magnetic resonance imaging; SBP: systolic blood pressure; DBP: diastolic blood pressure; TOAST: the Trial of ORG 10172 in Acute Stroke Treatment; NIHSS: National Institutes of Health Stroke Scale; TC: total cholesterol, TG: triglycerides.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by The Biomedical Research Ethics Committee of West China Hospital, Sichuan University, and conformed to local and international ethical criteria. Informed consent was not required since the study was observational and retrospective in nature.

**Consent for publication**

Participants consent for publication: Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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None

**Author Contributions**
Ming Liu and Bo Wu designed the study, guided the data analysis and revised the manuscript. Yanan Wang, Quhong Song, Yajun Cheng and Ye Chen collected the clinical data. Yanan Wang, Quhong Song and Chenchen Wei collected the imaging data. Yanan Wang and Junfeng Liu performed statistics analysis. Yanan Wang and Quhong Song drafted the manuscript. All authors revised the manuscript and approved the final version.

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**Availability of data and materials**

The data used in this study are available from the corresponding author upon reasonable request.

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Tables
Table 1 Baseline characteristics of participants according to Non-HDL-C quartiles
| Characteristics                          | Quartiles of Non-HDL, mmol/l | P-value |
|-----------------------------------------|------------------------------|---------|
|                                         | Q1. <2.35                   | Q2. 2.35-3.06 | Q3. 3.07-3.83 | Q4. >3.83 |         |
|                                         | n=514                       | n=510    | n=511    | n=508    |         |
| Age, (Mean ± SD), years                 | 66 ± 15                     | 65 ± 14  | 65 ± 14  | 63 ± 14  | <0.001<sup>a</sup> |
| Male, n (%)                             | 327 (63.6%)                 | 341 (66.9%) | 321 (62.8%) | 301 (59.3%) | 0.093<sup>b</sup> |
| Medical history                          |                             |          |          |          |         |
| Hypertension, n (%)                     | 269 (52.3%)                 | 265 (52.0%) | 297 (58.1%) | 301 (59.3%) | 0.030<sup>b</sup> |
| Diabetes mellitus, n (%)                | 129 (25.1%)                 | 109 (21.4%) | 91 (17.8%) | 138 (27.2%) | 0.002<sup>b</sup> |
| Hyperlipidaemia, n (%)                  | 14 (2.7%)                   | 19 (3.7%)  | 17 (3.3%) | 25 (4.9%) | 0.293<sup>b</sup> |
| Atrial fibrillation, n (%)              | 97 (18.9%)                  | 62 (12.2%) | 44 (8.6%) | 32 (6.3%) | <0.001<sup>b</sup> |
| Smoking, n (%)                          | 213 (41.4%)                 | 220 (43.1%) | 223 (43.6%) | 208 (40.9%) | 0.787<sup>b</sup> |
| Alcohol consumption, n (%)              | 142 (27.6%)                 | 141 (27.6%) | 142 (27.8%) | 135 (26.6%) | 0.971<sup>b</sup> |
| TOAST classification                     |                             |          |          |          |         |
| Large-artery atherosclerosis, n (%)     | 151 (29.4%)                 | 156 (30.6%) | 179 (35.0%) | 185 (36.4%) | <0.001<sup>b</sup> |
| Small-artery occlusion, n (%)           | 84 (16.3%)                  | 112 (22.0%) | 132 (25.8%) | 156 (30.7%) |         |
| Cardioembolic, n (%)                    | 150 (29.2%)                 | 130 (25.5%) | 97 (19.0%) | 57 (11.2%) |         |
| Undetermined aetiology, n (%)           | 108 (21.0%)                 | 93 (18.2%)  | 87 (17.0%) | 98 (19.3%) |         |
| Other aetiology, n (%)                  | 21 (4.1%)                   | 19 (3.7%)  | 16 (3.1%) | 12 (2.4%) |         |
| NIHSS on admission, median (IQR)        | 6 (2-13)                    | 6 (2-11)  | 5 (2-11) | 5 (2-10) | 0.002<sup>c</sup> |
| SBP, (Mean ± SD), mmHg                  | 141 ± 22                    | 144 ± 23  | 147 ± 24 | 151 ± 23 | <0.001<sup>a</sup> |
| DBP, (Mean ± SD), mmHg                  | 82 ± 14                     | 85 ± 14   | 87 ± 15  | 88 ± 15  | ≤0.001<sup>a</sup> |
| Glucose, (Mean ± SD), mmol/L            | 7.61 ± 2.92                 | 7.67 ± 3.06 | 7.62 ± 2.96 | 8.98 ± 4.44 | <0.001<sup>a</sup> |
| Thrombolysis, n (%)                     | 31 (6.0%)                   | 22 (4.3%)  | 21 (4.1%) | 33 (6.5%) | 0.216<sup>b</sup> |
| Thrombectomy, n (%)                     | 33 (6.4%)                   | 24 (4.3%)  | 22 (4.3%) | 23 (4.5%) | 0.386<sup>b</sup> |
| Lipid profile                           |                             |          |          |          |         |
| TG, (Mean ± SD), mmol/L                 | 1.11 ± 0.72                 | 1.36 ± 0.84 | 1.74 ± 1.03 | 2.53 ± 1.88 | <0.001<sup>a</sup> |
| TC, (Mean ± SD), mmol/L                 | 3.14 ± 0.55                 | 3.97 ± 0.41 | 4.63 ± 0.41 | 5.81 ± 0.84 | <0.001<sup>a</sup> |
| HDL-C, (Mean ± SD), mmol/L              | 1.29 ± 0.41                 | 1.25 ± 0.36 | 1.23 ± 0.36 | 1.19 ± 0.35 | 0.001<sup>a</sup> |
| LDL-C, (Mean ± SD), mmol/L              | 1.58 ± 0.40                 | 2.33 ± 0.30 | 2.87 ± 0.36 | 3.79 ± 0.77 | <0.001<sup>a</sup> |
| Non-HDL, (Mean ± SD), mmol/L            | 1.86 ± 0.36                 | 2.72 ± 0.20 | 3.40 ± 0.22 | 4.62 ± 0.78 | <0.001<sup>a</sup> |

Abbreviations: TOAST, the Trial of ORG 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC,
total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol.

a ANOVA test

b Chi-squared test

c Kruskal–Wallis test

Table 2 Univariate analysis to identify risk factors associated with haemorrhagic transformation in patients with acute ischaemic stroke
| Characteristic                          | Total patients (n=2043) | With HT (n=232) | Without HT (n=1811) | P-value  |
|----------------------------------------|-------------------------|----------------|---------------------|----------|
| Age (Mean ± SD), years                 | 65 ± 14                 | 68 ± 14        | 64 ± 14             | <0.001   |
| Males, n (%)                           | 1290 (63.1%)            | 113 (48.7%)    | 1177 (65.0%)        | <0.001   |
| Medical history, n (%)                 |                         |                |                     |          |
| Hypertension, n (%)                    | 1132 (55.4%)            | 115 (49.5%)    | 1017 (56.2%)        | 0.864    |
| Diabetes mellitus, n (%)               | 467 (22.9%)             | 52 (22.4%)     | 415 (22.9%)         | 0.528    |
| Hyperlipidaemia, n (%)                 | 75 (3.7%)               | 7 (3.0%)       | 68 (3.8%)           | 0.574    |
| Atrial fibrillation, n (%)             | 235 (11.5%)             | 69 (29.7%)     | 166 (9.2%)          | <0.001   |
| Smoking, n (%)                         | 864 (42.3%)             | 83 (35.8%)     | 781 (43.1%)         | 0.033    |
| Alcohol consumption, n (%)             | 560 (27.4%)             | 51 (22.0%)     | 509 (28.1%)         | 0.049    |
| TOAST classification                   |                         |                |                     |          |
| Large-artery atherosclerosis, n (%)    | 671 (32.8%)             | 73 (31.5%)     | 598 (33.0%)         | <0.001   |
| Small-artery occlusion, n (%)          | 484 (23.7%)             | 4 (1.7%)       | 480 (26.5%)         |          |
| Cardioembolic, n (%)                   | 434 (21.2%)             | 111 (47.8%)    | 323 (17.8%)         |          |
| Undetermined aetiology, n (%)          | 386 (18.9%)             | 40 (16.1%)     | 346 (19.3%)         |          |
| Other aetiology, n (%)                 | 68 (3.3%)               | 4 (1.7%)       | 64 (3.5%)           |          |
| NIHSS on admission, median (IQR)       | 5 (2-10)                | 11(6-18)       | 5 (2-10)            | <0.001   |
| SBP, (Mean ± SD), mmHg                 | 146 ± 23                | 140 ± 23       | 146 ± 23            | <0.001   |
| DBP, (Mean ± SD), mmHg                 | 85 ± 15                 | 84 ± 16        | 86 ± 15             | 0.048    |
| Glucose, (Mean ± SD), mmol/L           | 7.97 ± 3.45             | 8.16 ± 2.52    | 7.94 ± 3.55         | 0.233    |
| Thrombolysis, n (%)                    | 107 (5.2%)              | 27 (11.6%)     | 80 (4.4%)           | <0.001   |
| Thrombectomy, n (%)                    | 102 (5.0%)              | 24 (10.3%)     | 78 (4.3%)           | <0.001   |
| Lipid profile                          |                         |                |                     |          |
| TG, (Mean ± SD), mmol/L               | 1.68 ± 1.32             | 1.37 ± 1.01    | 1.72 ± 1.35         | <0.001   |
| TC, (Mean ± SD), mmol/L               | 4.38 ± 1.13             | 4.18 ± 1.11    | 4.41 ± 1.14         | 0.003    |
| HDL-C, (Mean ± SD), mmol/L            | 1.24 ± 0.37             | 1.32 ± 0.44    | 1.23 ± 0.36         | 0.005    |
| LDL-C, (Mean ± SD), mmol/L            | 2.64 ± 0.95             | 2.44 ± 0.86    | 2.66 ± 0.95         | <0.001   |
| Non-HDL-C, (Mean ± SD), mmol/L        | 3.14 ± 1.11             | 2.86 ± 1.05    | 3.18 ± 1.11         | <0.001   |

Abbreviations; NHISS, National Institutes of Health Stroke Scale; SBP; systolic blood pressure; DBP; diastolic blood pressure; TG; triglyceride; TC; total cholesterol; LDL-C; low-density lipoprotein cholesterol; HDL-C; high-density lipoprotein cholesterol. Non-HDL-C; non-high-density lipoprotein cholesterol.
a Student’s t test
b Chi-squared test
c Mann-Whitney Test

Table 3 Association of quartiles of Non-HDL-C, LDL-C and haemorrhagic transformation

| Variables                                           | Crude | Model 1 | Model 2 |
|-----------------------------------------------------|-------|---------|---------|
|                                                     | OR    | 95% CI  | P-value | OR    | 95% CI  | P-value | OR    | 95% CI  | P-value |
| Non-HDL-C                                           |       |         |         |       |         |         |       |         |         |
| Q1: <2.35 mmol/L                                    | 2.5   | 1.6     | <0.001  | 2.60  | 1.68    | <0.001  | 1.74  | 1.09    | 0.01    |
|                                                     | 8     | 7-3.9   | 0.001   | 4.03  | -       | 0.01    | -     | 2.78    | 0.01    |
| Q2: 2.35 - 3.06 mmol/L                              | 2.2   | 1.4     | <0.001  | 2.34  | 1.50    | <0.001  | 2.01  | 1.26    | 0.00    |
|                                                     | 5     | 5-3.5   | 0.001   | -     | 3.66    | 0.01    | -     | 3.20    | 0.00    |
| Q3: 3.07 - 3.83 mmol/L                              | 1.8   | 1.1     | <0.007  | 1.88  | 1.19    | <0.001  | 1.76  | 1.10    | 0.01    |
|                                                     | 7     | 6-2.9   | 0.007   | 2.97  | -       | 0.01    | -     | 2.83    | 0.01    |
| Q4: >3.83 mmol/L                                    | 1.0   | 1.0     | 1.0     | 1.00  | 1.00    | 0.13    | 1.00  | 0.07    | 0.11    |
|                                                     | 0     | 0-1.0   | 0.0     | -1.0  | -       | 0.0     | 2     | -       | 0.0     |
| Age (years)                                         | 1.0   | 1.0     | 1.0     | 1.01  | 1.00    | 0.13    | 1.00  | 0.12    | 0.05    |
|                                                     | 1     | 0-1.0   | 0.0     | 1.01  | -1.0    | 0.0     | 1.00  | -       | 0.0     |
| Sex (female/male)                                   | 0.5   | 0.4     | <0.006  | 0.52  | 0.35    | 0.00    | 0.52  | 0.78    | 0.00    |
|                                                     | 3     | 2-0.7   | 0.006   | 0.52  | -       | 0.00    | 0.52  | 0.78    | 0.00    |
| NIHSS                                               | 1.0   | 1.0     | <0.001  | 1.1   | 0.6     | 0.9     | 1.1   | 0.6     | 0.9     |
|                                                     | 8     | 6-1.1   | 0.001   | 1.1   | 0.6     | 0.9     | 1.1   | 0.6     | 0.9     |
| Atrial fibrillation                                 | 1.6   | 1.1     | 0.0     | 3.0   | 3-3.4   | 0.01    | 3.0   | 3-3.4   | 0.01    |
|                                                     | 8     | 6-3.2   | 11      | 6     | 3-3.4   | 0.01    | 6     | 3-3.4   | 0.01    |
| Smoking                                             | 1.5   | 0.9     | 0.0     | 2.3   | 9-2.3   | 0.05    | 2.3   | 9-2.3   | 0.05    |
|                                                     | 4     | 3-0.9   | 0.0     | 2.3   | -       | 0.05    | 2.3   | -       | 0.05    |
| Alcohol consumption                                 | 0.9   | 0.6     | 0.9     | 0.6   | 0.5     | 0.55    | 0.6   | 0.5     | 0.55    |
|                                                     | 9     | 5-1.5   | 0.0     | 0.6   | 0.5     | 0.55    | 0.6   | 0.5     | 0.55    |
| SBP (mmHg)                                          | 0.9   | 0.9     | 0.0     | 0.9   | 0.9     | 0.0     | 0.9   | 0.9     | 0.0     |
|                                                     | 9     | 8-1.0   | 0.02    | 0.9   | 0.9     | 0.0     | 0.9   | 0.9     | 0.0     |
| Thrombolysis                                        | 2.0   | 1.2     | 0.0     | 2.0   | 1.2     | 0.0     | 2.0   | 1.2     | 0.0     |
|                                                     | 7     | 5-3.4   | 0.05    | 2.0   | 1.2     | 0.0     | 2.0   | 1.2     | 0.0     |
| Thrombectomy                                        | 1.8   | 1.0     | 0.0     | 1.8   | 1.0     | 0.0     | 1.8   | 1.0     | 0.0     |
|                                                     | 1     | 5-3.1   | 0.01    | 1.8   | 1.0     | 0.0     | 1.8   | 1.0     | 0.0     |
| TOAST classification (cardioembolic/non cardioembolic)| 2.0  | 1.4     | <0.001  | 2.0   | 1.4     | <0.001  | 2.0   | 1.4     | <0.001  |
|                                                     | 7     | 5-2.9   | 0.001   | 2.0   | 1.4     | <0.001  | 2.0   | 1.4     | <0.001  |

LDL-C
| Q1: <1.99 mmol/L | 2.2 | 1.4 | <0.05 | 2.26 | <0.01 | 1.48 | 1.57 | 1.00 | 0.04 |
|------------------|-----|-----|-------|------|-------|------|------|------|------|
|                  | 0   | 3.3 | 0.001 | 3.44 | 2.47  |
| Q2: 1.99 - 2.56 mmol/L | 1.7 | 1.1 | 0.00 | 1.77 | 0.01 | 1.14 | 1.51 | 0.95 | 0.07 |
|                  | 0   | 2.6 | 0.17  | 2.75 | 2.40  |
| Q3: 2.57 - 3.24 mmol/L | 1.8 | 1.1 | 0.00 | 1.85 | 0.00 | 1.20 | 1.82 | 1.16 | 0.00 |
|                  | 3   | 2.8 | 0.06  | 2.85 | 2.87  |
| Q4: >3.24 mmol/L  | 1.0 | 1.0 | 1.00 | 1.01 | 1.00 | 0.12 | 9   |
| Age (years)      | 2   | 0.7 | <0.001 | 1.01 | 1.00 | 0.02 | 9   |
| Sex (female/male)| 0.5 | 0.4 | <0.001 | 0.53 | 0.35 | 0.00 | 2   |
| NIHSS            | 0.5 | 0.4 | <0.001 | 0.53 | 0.35 | 0.00 | 2   |
| Atrial fibrillation | 1.6 | 1.1 | 0.00 | 1.11 |
| Smoking          | 1.5 | 0.9 | 0.00 | 0.9  |
| Alcohol consumption | 0.9 | 0.6 | 0.90 | 0.9  |
| SBP (mmHg)       | 0.9 | 0.6 | 0.90 | 0.9  |
| Thrombolysis     | 2.0 | 1.2 | 0.00 | 0.06 |
| Thrombectomy     | 1.8 | 1.0 | 0.00 | 0.33 |
| TOAST classification (cardioembolic/non cardioembolic) | 2.1 | 1.5 | <0.001 | 0.80 |

Abbreviations: OR, odds ratio; CI, confidence interval; Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment.

Table 4 C statistics and net reclassification index for HT by Non-HDL-C, LDL-C among patients with acute ischaemic stroke.
| Variable                  | C statistics (95%CI) | P-value | NRI (95%CI)   | P-value |
|---------------------------|----------------------|---------|---------------|---------|
| Non-HDL-C                 | 0.59 (0.55-0.63)     | <0.001  | NA            | NA      |
| LDL-C                     | 0.57 (0.53-0.61)     | 0.001   | NA            | NA      |
| Non-HDL-C + Model 2       | 0.79 (0.77-0.80)     | <0.001  | 0.24 (0.17-0.31) | <0.001 |
| LDL-C + Model 2           | 0.78 (0.77-0.80)     | <0.001  | 0.15 (0.08-0.22) | 0.03    |

Model 2 adjusted for age, sex, National Institutes of Health Stroke Scale scores on admission, atrial fibrillation, smoking, alcohol consumption, systolic blood pressure, thrombolysis, thrombectomy and the Trial of ORG 10172 in Acute Stroke Treatment classification. NRI, net reclassification improvement.

Table 5 Stratified logistic regression analysis to identify variables that modify the correlation between Non-HDL-C and haemorrhagic transformation.
|                              | OR (95% CI), P-value* | P for interaction* |
|------------------------------|-----------------------|--------------------|
| **Age**                      |                       |                    |
| <60                          | 0.64 (0.47-0.87), P<0.001 | 0.021             |
| ≥60                          | 0.95 (0.81-1.12), 0.523 |                    |
| **Sex**                      |                       |                    |
| Male                         | 0.78 (0.64-0.96) 0.021 | 0.188             |
| Female                       | 0.95 (0.78-1.15) 0.586 |                    |
| **Baseline NIHSS score**     |                       |                    |
| <15                          | 0.90 (0.76-1.06) 0.217 | 0.363             |
| ≥15                          | 0.78 (0.59-1.02) 0.069 |                    |
| **Atrial Fibrillation**      |                       |                    |
| No                           | 0.82 (0.69-0.96) 0.016 | 0.151             |
| Yes                          | 1.05 (0.78-1.40) 0.760 |                    |
| **Smoking**                  |                       |                    |
| No                           | 0.89 (0.74-1.06) 0.190 | 0.655             |
| Yes                          | 0.83 (0.66-1.04) 0.109 |                    |
| **Alcohol consumption**      |                       |                    |
| No                           | 0.91 (0.78-1.07) 0.261 | 0.160             |
| Yes                          | 0.71 (0.53-0.97) 0.032 |                    |
| **SBP**                      |                       |                    |
| < 140                        | 0.91 (0.74-1.11) 0.338 | 0.404             |
| ≥140                         | 0.80 (0.66-0.98) 0.031 |                    |
| **Reperfusion therapy**      |                       |                    |
| (Thrombolysis/Thrombectomy)  |                       |                    |
| No                           | 0.86 (0.74-1.01) 0.070 | 0.944             |
| Yes                          | 0.88 (0.62-1.24) 0.452 |                    |
| **Stroke subtype**           |                       |                    |
| Non-cardioembolic            | 0.79 (0.66-0.95) 0.013 | 0.134             |
| Cardioembolic                | 0.99 (0.79-1.25) 0.953 |                    |

*Above model adjusted for age, sex, National Institutes of Health Stroke Scale scores on admission, atrial fibrillation, smoking, alcohol consumption, systolic blood pressure, thrombolysis, thrombectomy and Stroke subtype. In each case, the model is not adjusted for the stratification variable.*

**Figures**
2206 consecutive patients with acute ischemic stroke within 7 days

Exclusion (n=163)
85 patients with HT on admission;
67 patients without a second CT or MRI scan
11 patients without lipid profile results within 24 h after admission

Final sample (n=2043)
1811 patients without HT
232 patients with HT

Figure 1
Study patients flow chart. HT: haemorrhagic transformation.
Figure 2

Relationship of Non-HDL-C (A), LDL-C (B) with risk of haemorrhagic transformation after acute ischaemic stroke. Risk of haemorrhagic transformation and 95% confidence intervals determined using the generalized additive model.

Supplementary Files
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Supplemental Table 2.doc