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Low levels of high-density lipoprotein cholesterol in patients with atherosclerotic stroke: A prospective cohort study

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ABSTRACT

Objective: The purpose of this study was to evaluate the influence of baseline high-density lipoprotein cholesterol (HDL-C) on initial stroke severity and clinical outcomes in acute ischemic stroke.
Methods: From August 2006 through December 2011, patients with acute atherosclerotic ischemic stroke were included. Total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and HDL-C were checked and National Institutes of Health Stroke Scale (NIHSS) scores were obtained at admission. The primary outcomes were a composite end point of all-cause mortality, recurrent stroke, or occurrence of ischemic heart disease during follow-up.
Results: Overall, 3093 subjects (mean age 66.8 years) were included and 675 patients (22%) had low HDL-C (≤35 mg/dL) at admission. These patients had higher NIHSS scores. After adjusting for all clinical factors in multivariate logistic analysis, low HDL-C at admission (OR, 1.79, 95% CI, 1.40–2.29) was significantly associated with higher stroke severity (NIHSS score > 6). During the follow-up period, 280 patients (9%) developed one of the components of the composite end point, including 76 (11.3%) in patients with low HDL-C and 204 (8.4%) in patients with normal HDL-C at admission ($p < 0.001$). In multivariate Cox regression analysis, after adjusting for all clinical factors, low HDL-C at admission (HR, 1.41, 95% CI, 1.02–1.95) was a significant independent predictor of the composite end point.
Conclusions: Low baseline HDL-C (≤35 mg/dL) at admission was associated with higher stroke severity and poor clinical outcome during follow-up in patients with atherosclerotic ischemic stroke.

Despite advances in treatment, ischemic stroke is still one of the major causes of death in industrialized countries. Patients with ischemic stroke have a significantly higher risk of recurrent cardiovascular events and mortality during follow-up after surviving their first-ever stroke [1,2]. Previous studies have identified several independent risk factors, such as increasing age and stroke severity, for mortality and stroke recurrence during follow-up [3,4]. Although the role of dyslipidemia as a risk factor for stroke is controversial, recent evidence suggests that increased low-density lipoprotein cholesterol (LDL-C) or decreased high-density lipoprotein cholesterol (HDL-C) is associated with atherosclerotic stroke [5–8]. The beneficial effect of statin treatment to lower LDL-C was proven in a clinical trial to prevent recurrent ischemic stroke and cardiovascular events after stroke [9]. However, the influence of HDL-C on clinical outcomes after stroke is still uncertain. HDL is the lipoprotein responsible for reverse cholesterol transport that transfers cholesterol from peripheral tissues back to the liver. In addition to being a cholesterol transportation vehicle, HDL directly protects against atherosclerosis through anti-oxidant, anti-inflammatory and anti-thrombotic effects [10–12]. Preclinical evidences suggest that HDL may be a neuroprotective agent that decreases stroke severity. A previous study demonstrated that acute reconstituted HDL infusion reduced the area of brain damage in both an excitotoxic lesion model and middle cerebral artery occlusion model in rats, and the benefits of HDL on decreasing neuronal

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damage were most likely due to its antioxidant effect [13]. Given these beneficial properties of HDL, we hypothesized that: (1) low HDL-C levels would be associated with higher stroke severity; and (2) low HDL-C would influence the clinical outcomes in patients with atherosclerotic stroke. We therefore performed a prospective cohort study including stroke patients with atherosclerotic origin and evaluated the influence of HDL-C on the prognosis in these patients.

1. Methods

1.1. Study subjects

We prospectively collected data from patients with acute ischemic stroke and transient ischemic attack (TIA) that were admitted to our hospital from August 2006 through December 2011. Based on the clinical symptoms and neuroimaging findings, stroke subtypes were determined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification as large artery atherosclerosis, small vessel occlusion, cardiac embolism, other etiologies, and undetermined [14]. Subjects fulfilling the following criteria were recruited for the present study: (1) age 18 years or older (2) no lipid lowering drug use prior to admission; and (3) stroke or TIA due to large artery atherosclerosis and small vessel occlusion.

The patients' demographic data, vascular risk factors, previous disease history, medications before admission, laboratory tests, and follow-up information after enrollment were collected according to a predetermined protocol. To avoid drugs' effects on lipid levels, only patients without any lipid lowering therapy prior to admission were included in this study. Blood tests, including complete blood count, creatinine levels, total cholesterol, triglycerides, LDL-C and HDL-C were obtained within 24 h after admission. The LDL-C and HDL-C levels were determined using a Hitachi 7600 Automatic Biochemistry Analyzer. LDL-C was determined with direct assay and HDL-C was determined with the polyethylene glycol-modified enzymes/α-cyclodextrin sulfate (PEGME) assay. Hypertension was present when a patient had either received antihypertensive treatment before admission or had a systolic blood pressure $>$140 mmHg or a diastolic blood pressure $>$90 mmHg for at least 3 times during the hospital stay. Diabetes was present when a patient had either received antidiabetic treatment before admission or had a fasting blood glucose level $\geq$126 mg/dL or random blood glucose level $\geq$200 mg/dL if the patient also exhibits classic diabetic symptoms during the hospital stay. Ischemic heart disease was defined as a history of physician-diagnosed coronary heart disease, myocardial infarction, angina pectoris, or unstable angina. Atrial fibrillation was diagnosed when present on the admission electrocardiography. Stroke severity was evaluated based on the National Institutes of Health Stroke Scale (NIHSS) score at admission. Medications prescribed at discharge were categorized as "medications at discharge". Antiplatelet drug use was defined as documentation that the patient was given aspirin, clopidogrel, dipyridamole or ticlopidine, alone or in combination. Anticoagulation drug use was defined as documentation that the patient was given warfarin or dabigatrin. Antihypertensive drug use was defined as documentation that the patient was given diuretic, calcium antagonist, angiotensin converting enzyme inhibitor, angiotensin receptor antagonist or beta-blocker, alone or in combination. Antidiabetic drug use was defined as documentation that the patient was given sulfonylurea, metformin, thiazolidinedione, alpha-glucosidase inhibitor or insulin, alone or in combination. Lipid lowering drug use was defined as documentation that the patient was taking statin, fibrate, nicotinic acid, cholestyramine or ezetimibe, alone or in combination.

1.2. Follow-up

All patients were followed after enrollment. If the patients survived to discharge, they were followed at outpatient clinics or by telephone interviews given by trained research assistants when they could not attend the clinics. The primary outcomes for the present study were a composite end point of all-cause mortality, recurrent stroke, or occurrence of ischemic heart disease, whichever came first. Recurrent stroke was defined as the sudden appearance of a new neurological deficit indicating different vascular territories or a worsening of previous neurological deficits and fitting the definition of TIA, ischemic, or hemorrhagic stroke. All cases of recurrence were verified by neurologists. The diagnosis of ischemic heart disease was based on physician-diagnosed myocardial infarction, unstable angina, or angina requiring hospitalization for a coronary revascularization procedure. The medical information was obtained from all available medical records or by telephone interviews with the patients or families. Each patient was followed up either to the day of occurring one of the components of the composite end point or to December 31, 2011. This study was approved by the Institutional Review Board of our hospital, and informed consent was obtained from the each study participant.

1.3. Statistical analysis

Continuous variables were presented as means $\pm$ standard deviations (SDs) or medians with interquartile ranges, and categorical variables were presented as numbers and percentages. The clinical characteristics of the groups were compared using the chi-square test with or without Yates' correction for categorical variables and the unpaired Student's t test or Mann–Whitney rank sum test for continuous variables. A 2-tailed p value < 0.05 was considered significant. We used logistic regression analysis to identify the clinical factors associated with higher stroke severity at admission (NIHSS score $>$ 6). Kaplan–Meier curves were constructed and stratified by HDL level ($\leq$vs $>$ 35 mg/dL) or by isolated and non-isolated HDL-C. Comparisons were made using the log-rank test. Cox regression analysis was used to identify predictors of composite end point. Multivariate analysis was performed on all baseline characteristics. Hazard ratio (HR) or odds ratio (OR) and their 95% confidence intervals (CI) were calculated. All analyses were performed using the SAS statistical package (version 9.2 for Windows; SAS Institute, Cary, NC, USA).

2. Results

During the study period, 3093 subjects with ischemic stroke or TIA qualified for this study (Fig. 1). The mean age was 66.8 years, 62% were men and 49% had a stroke due to large artery atherosclerosis. Among them, 675 patients (22%) had HDL-C $\leq$ 35 mg/dL at admission. The baseline clinical characteristics of the patients with low HDL-C ($\leq$35 mg/dL) and normal HDL-C ($>$35 mg/dL) are shown in Table 1. A higher percentage of the patients with low HDL-C were male, had diabetes and smoked. They also had lower serum levels of cholesterol and LDL-C, but higher levels of triglycerides and creatinine. After adjusting for all clinical factors in multivariate logistic analysis, we found that male gender, creatinine, triglycerides and NIHSS score at admission were associated with low HDL-C. At admission, the patients with low HDL-C had significantly higher NIHSS scores than the patients with normal HDL-C (6.4 ± 7.1 vs. 5.3 ± 6.1, $p < 0.001$). In multivariate logistic analysis, after adjusting for all clinical factors, we found that low HDL-C (OR, 1.79, 95% CI, 1.40–2.29) was significantly associated with increased stroke severity as defined by a NIHSS score $>$ 6 at admission

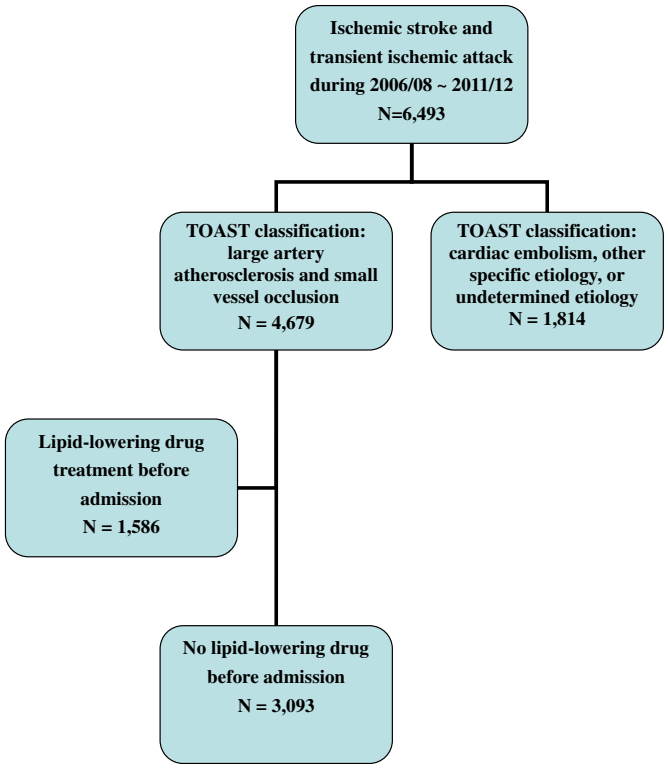

Fig. 1. Flow chart for the inclusion and exclusion of study participants.

Table 1
Clinical characteristics of the patients with low and normal HDL-C.

Variable	Low HDL ($n = 675$)	Normal HDL ($n = 2418$)	p Value
Age (years)	65.9 ± 12.2	67.7 ± 11.6	<0.001
Male	523 (77)	1389 (57)	<0.001
Hypertension	520 (77)	1914 (79)	0.235
Diabetes mellitus	380 (56)	1120 (46)	<0.001
Current smoker	362 (54)	924 (38)	<0.001
Previous stroke	201 (30)	615 (25)	0.024
Ischemic heart disease	48 (7)	148 (6)	0.350
Atrial fibrillation	18 (3)	60 (2)	0.786
Leukocyte count at admission ($10^3/\mu L$)	8.4 ± 2.8	8.2 ± 2.8	0.025
Creatinine (mg/dL)	1.5 ± 1.1	1.3 ± 1.0	<0.001
Lipid profile			
Total cholesterol (mg/dL)	174.4 ± 41.0	199.6 ± 45.4	<0.001
Triglyceride (mg/dL)	178.0 ± 111.0	134.7 ± 84.5	<0.001
Low-density lipoprotein (mg/dL)	117.1 ± 36.1	133.2 ± 40.3	<0.001
High-density lipoprotein (mg/dL)	30.8 ± 3.9	48.5 ± 10.3	<0.001
National Institutes of Health Stroke	6.4 ± 7.1	5.3 ± 6.1	<0.001
Scale score at admission (NIHSS)	4 (2–8)	3 (1–6)	
Large artery atherosclerosis	361 (53)	1162 (48)	0.013
Recombinant tissue plasminogen activator (rt-PA)	11 (2)	37 (2)	0.853
Medications at discharge			
Antiplatelet drug	601 (89)	2224 (92)	0.018
Anticoagulation drug	16 (2)	47 (2)	0.488
Antihypertensive drug	227 (34)	848 (35)	0.470
Antidiabetic drug	307 (45)	935 (39)	0.001
Lipid lowering drug	283 (42)	1142 (47)	0.015
Mean follow-up period (months)	29.6 ± 19.4	32.4 ± 19.0	0.001

Data are presented as mean ± standard deviation or number (percentage). NIHSS score is presented as mean ± standard deviation and median (interquartile range).

(Table 2). The mean follow-up period was 32.7 ± 19.4 months, ranging from 1 day to 53 months. During the follow-up period, 280 patients (9%) developed one of the components of the composite end point, including 76 patients (11.3%) in the low HDL-C group and 204 patients (8.4%) in the normal HDL-C group ($p < 0.001$) (Table 3). The Kaplan–Meier analysis showed a significantly worse clinical outcome in the patients with low HDL-C during follow-up (Fig. 2). In multivariate Cox regression analysis, after adjusting for all clinical factors and medications at discharge, low HDL-C at admission (HR, 1.41, 95% CI, 1.02–1.95) was a significant independent predictor of the composite end point (Table 4). We further divided the study subjects by gender. In men, low HDL-C (HR, 1.63, 95% CI, 1.10–2.42) was a significant predictor, but no association with the composite end point was found in women (HR, 1.04, 95% CI, 0.56–1.95). Specifically looking at the all-cause mortality, low HDL-C at admission (HR, 1.68, 95% CI, 1.15–2.44) was an even stronger independent predictor for mortality.

Because isolated low HDL-C with normal LDL-C and triglyceride is a common lipid phenotype in Asians, we further analyzed the prevalence of isolated low HDL-C and its influence on prognosis in our patients. The patients with low HDL-C were divided into 2 mutually exclusive groups according to lipid levels: isolated low HDL-C (HDL $\leq$ 35 mg/dL and LDL $<$ 160 mg/dL and triglyceride $<$ 200 mg/dL) and non-isolated low HDL-C (HDL $\leq$ 35 mg/dL combined with LDL $\geq$ 160 mg/dL and/or triglyceride $\geq$ 200 mg/dL). Overall, in the 675 patients with low HDL-C, 441 patients (65%) had isolated low HDL-C and 234 (35%) had non-isolated low HDL-C. The baseline clinical characteristics were similar between the 2 groups except that the patients with isolated low HDL-C were older (67.5 ± 12.3 vs. 62.6 ± 11.5 years, $p < 0.001$) and had a higher percentage of previous stroke (33% vs. 23%, $p = 0.006$). The total cholesterol (158.1 ± 30.0 vs. 205.2 ± 41.8 mg/dL, $p < 0.001$), LDL-C (107.7 ± 27.5 vs. 135.1 ± 43.1 mg/dL, $p < 0.001$) and triglyceride levels (124.6 ± 37.0 vs. 281.2 ± 131.7 mg/dL, $p < 0.001$) were significantly lower in the patients with isolated low HDL-C. A lower percentage of these patients were treated with lipid lowering drugs at discharge (27% vs. 69%, $p < 0.001$). During follow-up, the composite end point occurred in 53 (12%) patients in the isolated low HDL-C group, and 23 patients (9.8%) in the non-isolated low HDL-C group ($p = 0.392$). Kaplan–Meier analysis showed a similar clinical outcome (log-rank test, $p = 0.347$) in patients with isolated low HDL-C and non-isolated low HDL-C during follow-up (Fig. 3).

3. Discussion

The major findings of this study were: (1) a lower level of HDL-C (≤35 mg/dL) at admission was associated with increased stroke

Table 2
Multivariate logistic regression analysis for the risk factors of increased stroke severity (NIHSS > 6).

Risk factors	NIHSS score > 6	
	Or (95% CI)	p Value
Age (per year)	1.03 (1.02–1.04)	0.001
Diabetes mellitus (yes or no)	1.33 (1.11–1.60)	0.003
Previous stroke (yes or no)	2.36 (1.95–2.85)	<0.001
Atrial fibrillation (yes or no)	1.88 (1.15–3.06)	0.012
Leukocyte count at admission (per $10^3/\mu L$)	1.15 (1.11–1.18)	<0.001
Low HDL-C (vs. normal)	1.79 (1.40–2.29)	<0.001

Adjusted for age, sex, hypertension, diabetes mellitus, smoking, previous stroke, ischemic heart disease, atrial fibrillation, leukocyte count, creatinine, total cholesterol, triglycerides, LDL-C, HDL-C and NIHSS score.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table 3
Follow-up results in the patients with low and normal HDL-C at admission.

	n	Composite end point	Death	Stroke	Ischemic heart disease
Low HDL-C	675	76 (11.3)*	59	15	2
Male	523	56	40	14	2
Female	152	20	19	1	0
Normal HDL-C	2418	204 (8.4)	146	57	1
Male	1389	124	89	34	1
Female	1029	80	57	23	0

Data are presented as number (percentage). *$p < 0.001$ compared with normal HDL-C group.
HDL-C, high-density lipoprotein cholesterol.

Table 4
Multivariate Cox regression analysis for the independent predictors of composite end point.

Predictors	Composite end point	
	HR (95% CI)	*p* Value
Age (per year)	1.04 (1.03–1.05)	<0.001
Previous stroke	1.63 (1.26–2.12)	<0.001
Leukocyte count at admission (per $10^3/\mu L$)	1.04 (1.00–1.09)	0.026
Creatinine (per 1 mg/dL)	1.12 (1.03–1.23)	0.009
NIHSS score at admission (per 1 score)	1.04 (1.02–1.06)	<0.001
Low HDL-C (vs. normal)	1.41 (1.02–1.95)	0.038

Adjusted for age, sex, hypertension, diabetes mellitus, smoking, previous stroke, ischemic heart disease, atrial fibrillation, leukocyte count, creatinine, total cholesterol, triglycerides, LDL-C, HDL-C and medications use at discharge.
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; HR, hazard ratio.

severity; (2) a lower level of HDL-C at admission independently predicted adverse clinical outcomes in the male patients with atherosclerotic stroke; (3) in our patients with low HDL-C, 65% had low HDL-C without other lipid abnormalities, and these patients were treated less with lipid lowering drugs at discharge; (4) isolated low HDL-C was as strongly associated with the risk of adverse clinical outcome as non-isolated low HDL-C in our patients.

3.1. Low HDL-C and stroke severity

Previous studies demonstrated that lower baseline HDL-C levels increase the risk of ischemic stroke [7,8]. However, the relationship between baseline HDL-C levels and stroke severity is uncertain. In the stroke patient population without any prior lipid lowering therapy in this study, we found that low HDL-C at admission (≤35 mg/dL) was a predictor of increased stroke severity. In a previous study including ischemic stroke of all subtypes, the authors found that low HDL-C (≤35 mg/dL) was associated with a higher stroke severity only in the younger patient cohort (≤50 years) [15]. However, the interpretation of the data in that study was limited by its small sample size. In another cohort of young adults (≤50 years) with ischemic stroke, higher HDL-C levels, independent of the stroke etiology, were associated with a smaller infarct size estimated from imaging studies and less stroke severity as represented by NIHSS score [16]. However, that study recruited patients with all ischemic stroke subtypes, including cardiac embolism and undetermined etiology, and some of the patients received prestroke statin treatment. The strength of our study is that we included a large sample size of pure atherosclerotic stroke patients without any previous lipid lowering therapy. Our results confirmed the association of baseline HDL-C level with increased stroke severity in atherosclerotic stroke patients. The benefits of administering purified or recombinant HDL in the acute stage of ischemic stroke to decrease infarct volume and neurological deficit were proven in an animal study [13]. Further clinical trials are necessary to evaluate the neuroprotective effect of HDL-C in humans.

3.2. Low HDL-C and stroke outcomes

Lower HDL-C is an important risk factor for cardiovascular disease independent of the effects of LDL-C. A recent study in patients with coronary artery disease suggested that low levels of HDL-C are associated with increased recurrent cardiovascular events even when LDL-C is reduced to 70 mg/dL with a statin [17]. Moreover, there is mounting evidence that increasing HDL-C levels has potential in reducing the risk of cardiovascular events and improving clinical outcomes. We found that a low baseline level of HDL-C was an independent predictor of adverse clinical outcomes in patients with atherosclerotic stroke. Several other studies have reported similar clinical observations. In an observation study of 1847 patients with acute ischemic stroke treated with intravenous thrombolysis, lower HDL-C levels in the first 24 h of stroke onset was independently associated with 3-month mortality [18]. In 260 acute ischemic stroke patients in the Fukuoka Stroke Registry, HDL-C <40 mg/dL at admission was an independent predictor of recurrent ischemic stroke after 12 months of follow-up [19]. In SAMURAI rt-PA Registry, a higher HDL-C level was an independent predictor of a favorable outcome (modified Rankin Scale score ≤ 1) at 3-month follow-up in 489 acute ischemic patients treated with intravenous recombinant tissue plasminogen activator [20]. The results from the current and other studies all demonstrate that

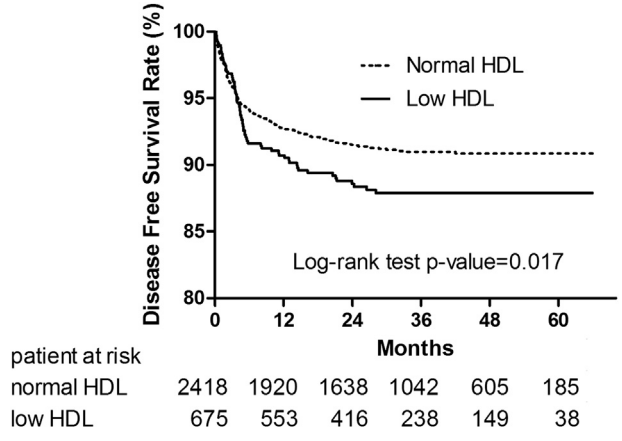

Fig. 2. Kaplan–Meier curve for probability of disease-free survival stratified by low (≤35 mg/dL) and normal (>35 mg/dL) HDL-C levels.

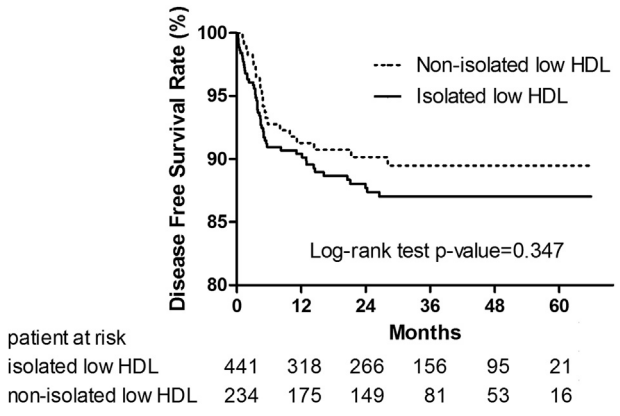

Fig. 3. Kaplan–Meier curve for probability of disease-free survival stratified by isolated and non-isolated low HDL-C.

HDL-C is an important prognostic indicator in ischemic stroke patients.

3.3. Isolated low HDL-C

We found that isolated low HDL-C was a common lipid phenotype in our study population, accounting for approximately 65% of the patients with low HDL-C. Although the patients with isolated low HDL-C had a similar risk of adverse clinical outcomes as those with non-isolated low HDL-C, these patients received significantly less lipid lowering medications at discharge (27% vs 69%, $p < 0.001$). Data from studies in the Asia-Pacific region have shown that the prevalence of isolated low HDL-C is significantly higher in Asian than in non-Asian populations [21]. In Asians, this phenotype is as strongly associated with cardiac risk as low HDL-C with other lipid abnormalities [21]. The clinical importance of isolated low HDL-C should be emphasized not only because this lipid phenotype is associated with future risk, but also because only a few physicians consider therapeutic interventions for this dyslipidemia because HDL-C is not a treatment target for either primary or secondary prevention in current lipid guidelines [22,23]. Currently, lifestyle modification is the most important strategy to manage isolated low HDL-C. Pharmacological therapies, including niacin, fibrates, and statins, could also be considered in these patients. Cholesteryl ester transfer protein inhibitor has shown promise in the treatment of this dyslipidemia, however the clinical benefits need to be proven in clinical trials [24].

3.4. Limitation

The major limitation of the study is that we did not have the information of the pre-stroke lipid levels of these patients. The HDL-C we measured after stroke may not represent the true baseline levels before stroke. It is controversial about the stability of lipid levels after stroke. A previous study demonstrated that HDL-C levels decreased by 18% after acute stroke compared to the pre-stroke levels [25]. However, some studies suggested that lipid levels obtained immediately after acute stroke still could represent the baseline values. Kargman et al. reported that post-stroke lipid levels, including HDL-C, remained constant within 24 h to 4 weeks after acute ischemic stroke and could represent its baseline concentration [26]. The other study also found that the lipid levels determined within 12–48 h after acute stroke can reflect the patients' baseline lipid levels [27]. Second, the association between low HDL-C and poor clinical outcome might not be directly related to the effects of HDL-C on atherosclerosis. HDL-C itself is a marker of chronic inflammation [28] and associated with functional disability [29] in older population. The low HDL-C level might just reflect a poor general health condition in these patients. Further studies are necessary to include the data of C reactive protein and albumin to see if HDL-C is a real independent prognostic indicator. Third, we found low HDL-C was a significant predictor of outcome only in men but not in women. HDL-C level varies with gender and ethnicity. Women usually have higher HDL-C levels than men, but this gender difference is less prominent in Asia [30,31]. A different cut-off value of low HDL-C in women could be calculated after recruiting more female patients in our study. Previous study [31] also demonstrated that HDL-C levels were lower in Asians than those in the western countries. That is also why we chose a lower HDL-C cut-off value ($\leq$35 mg/dL) in our study. Finally, the possible different influence of LDL-C or HDL-C on ischemic and hemorrhagic stroke could not be evaluated in the current study because the event rate of hemorrhagic stroke during follow-up was too small, yielding less statistical power to see the association between HDL-C and hemorrhagic stroke.

3.5. Conclusions

In conclusion, this observational study indicates that lower baseline HDL-C level is a predictor of ischemic stroke severity. Low HDL-C level ($\leq$35 mg/dL) is associated with adverse clinical outcomes in male patients with atherosclerotic stroke. Isolated low HDL-C was a common lipid phenotype in our population. Although isolated low HDL-C was as associated with the risk of composite end point as non-isolated low HDL, this lipid phenotype was significantly less treated.

Disclosure

None.

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