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Achieving low density lipoprotein-cholesterol < 70 mg/dL may be associated with a trend of reduced progression of carotid artery atherosclerosis in ischemic stroke patients

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Abstract

Objective—To assess whether an intensive lipid-lowering strategy is more beneficial on atherosclerotic plaque progression in the stroke survivors.

Methods—We retrospectively assessed data that was prospectively collected on 106 ischemic stroke patients from one academic stroke center. Patients with various degrees of common carotid artery atherosclerosis were followed for one year. Patients were classified into intensive lipid-lowering therapy (ILLT) group if they achieve low-density lipoprotein cholesterol (LDL-c) < 70 mg/dL ($n = 38$) and conventional lipid-lowering therapy (CLLT) group if their LDL-c is within 70–120 mg/dL ($n = 68$) at end of one year. Carotid ultrasound was performed at baseline lipid-lowering therapy and at one year to characterize the plaques.

Results—Mean change in atherosclerotic plaque length was -1.4 mm (95% CI: $[-4.1, 1, 2]$; $P = 0.27$) in ILLT and 1.1 mm in CLLT group (95% CI: $[-0.9, 3.1]$; $P = 0.27$); no difference between groups ($P = 0.40$). Atherosclerotic plaque thickness decreased by 0.2 mm (95% CI: $[-0.4, 0.03]$; $P = 0.09$) in ILLT group; while in CLLT group, thickness increased by 0.02 mm after 1-year therapy (95% CI: $[-0.1, 0.2]$; $P = 0.77$); no difference between groups ($P = 0.28$).

Conclusions—Achieving LDL-c < 70 mg/dL in ischemic stroke patients was associated with a trend of reducing atherosclerotic plaque progression at one year. Future larger studies are warranted.

Keywords

Stroke prevention and control; Atherosclerotic plaque; Dyslipidemia therapy; Vascular ultrasound

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1. Introduction

Stroke is the leading cause of morbidity and mortality in China [1], whereas the etiology of large-artery atherosclerosis accounts up to 50% [2]. Estimated recurrence rate of large-artery atherosclerotic stroke was approximately 20% within 30 days [3]. Lipid-lowering therapy with hydroxymethylglutaryl coenzyme-A reductase inhibitor (i.e. statin) is a recommended pharmacotherapy to prevent recurrent ischemic stroke [4]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial concluded that high dose of statin (80 mg of atorvastatin per day) can reduce the overall incidence of strokes and cardiovascular events after median duration of 4.9 years follow-up [5]. Meta-analysis also shows a reduction of 20 mg/dL low-density lipoprotein cholesterol (LDL-c) at one year produced a highly significant 15% further reduction in major vascular events, including 16% reduction in ischemic strokes [6]. Intensive statin therapy after acute coronary syndrome led to remarkable regression of coronary plaque volume [7,8]. Each 10% reduction in LDL-c was estimated to reduce carotid intima-media thickness by 0.73% per year [9]. But there are knowledge gaps about the impact of intensive lipid-lowering therapy (ILLT) on the progression of atherosclerosis plaques in ischemic stroke patients.

To validate the benefit of ILLT in stroke survivors with identified carotid atherosclerosis, we aimed to investigate the differential progression of carotid atherosclerosis plaques between the ILLT group (LDL-c level < 70 mg/dL) and the conventional lipid-lowering therapy (CLLT) group (LDL-c level within 70–120 mg/dL) in a retrospective cohort with one year follow-up time.

2. Materials and methods

2.1. Study design

We retrospectively assessed data that was prospectively collected on 106 adult stroke patients, whose etiology was thought to be carotid atherosclerosis [10], at Xuanwu hospital stroke center, from January 2013 to December 2014. We excluded pregnant patients or patients have past medical histories of intracranial hemorrhage, hepatic dysfunctions, kidney dysfunctions, and familial hypercholesterolemia.

Patients were assessed by B-mode ultrasound at baseline before therapy and 12 months after treatment to characterize the common carotid atherosclerosis plaques. The parameters of carotid ultrasound include length and thickness on both sides of the common carotid artery at carotid bulbs. All the patients were treated with various types and dose of statins according to the secondary stroke prevention guideline [4]. We divided the patients into ILLT (<70 mg/dL) group and CLLT (70–120 mg/dL) group according to their end-point LDL-c levels at 12 months post-therapy. Blood examinations for lipid levels, homocysteine (HCY) levels and glycemic levels were performed at one year after lipid-lowering therapy. Serum blood biochemistry tests were tested using Hitachi 7600 automated biochemistry analyzer (Hitachi, Ltd, Japan).

This study was approved and conducted in compliance with Institutional Review Board (IRB) of Xuanwu Hospital, Capital Medical University.

2.2. Ultrasound procedures and examination

Carotid ultrasound was performed before the initiation of lipid-lowering treatment and 12 months after treatment with the same ultrasound mode. High-resolution B-mode ultrasound was performed using iU22 (Philips, Netherlands) to evaluate the carotid atherosclerosis plaques with a broadband C3–9 MHz linear ultrasound transducer. Certified sonographers completed ultrasonographic examinations in strict adherence to the Mannheim consensus [11].

Plaque was denoted as a focal structure encroaching into the arterial lumen of >5 mm or 50% of the surrounding carotid intima-media thickness value or demonstrating a thickness > 1.5 mm as measured from the intima–lumen interface to the media–adventitia interface [12]. Plaques were detected on bilateral carotid bulbs. Both length and thickness of plaque were recorded.

2.3. Statistical analysis

Categorical variables were listed as number (percentage). Comparisons of categorical values between the two groups at the baseline were performed by Chi-square test. Normally distributed continuous variables were expressed in mean $\pm$ standard deviation (S.D.), while non-normally distributed continuous variables were expressed in median (interquartile range, IQR). Comparisons of continuous variables between the two groups were performed by the two-sample *t*-test if normally distributed with equal variance between groups; otherwise, *Wilcoxon* rank sum test would be used.

A repeated measure analysis with mixed model was used to compare the ultrasound parameters between the two groups. Types of lipid-lowering therapy strategy, visit time and the interaction of the above factors were measured, and we adjusted age (≥ 60 years vs. <60 years), smoking status (yes vs. no), history of diabetes mellitus (yes vs. no) and history of hypertension (yes vs. no) in the models. All statistical analyses were performed using the SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients' characteristics

One hundred six (38 in ILLT and 68 in CLLT) patients were identified based on the inclusion and exclusion criteria above. The baseline characteristics of subjects were shown in Table 1. There were no significant differences in demographics or past medical history between the two groups (Table 1). The median length of CCA atherosclerosis plaques was 16.2 mm in ILLT group, with IQR as 11.4 mm; and median length was 13.2 mm in CLLT ($P = 0.07$), with IQR as 10.1 mm (Table 1). The thickness of CCA atherosclerosis plaques was 2.3 (0.7) mm and 2.2 (0.7) mm in ITTL group and CTTL group, respectively $P = 0.60$ (Table 1).

3.2. Biochemistry outcomes

LDL-c level in the ILLT group was significantly lower (54(17) mg/dL) as compared to 102(42) mg/dL in the CLLT group ($P < 0.0001$) (Table 2). For total cholesterol, median level

was 109(28) mg/dL and 168(51) mg/dL for the ILLT group and the CLLT group, respectively ($P < 0.0001$). For HDL-c level, it was 40(19) mg/dL in the ILLT group and 49(17) mg/dL in CLLT the group ($P = 0.004$). Triglycerides level was 102(67) mg/dL in the ILLT group and 126 (74) mg/dL in the CLLT group ($P = 0.02$). No differences in fasting plasma glucose (FPG) level or HCY concentrations were seen between the two groups (Table 2).

3.3. Progression of atherosclerotic plaques with lipid-lowering therapy

We adjusted age (≥ 60 years vs. < 60 years), smoking status (yes vs. no), history of diabetes mellitus (yes vs. no) and history of hypertension (yes vs. no) in the mixed model. The association of the progression of atherosclerotic plaques and risk factors were shown in Table 3.

For ILLT group (Table 4): estimated change of CCA atherosclerotic plaques length was -1.4 mm with 95% confidential interval (CI) -4.1 mm to 1.2 mm from baseline ($P = 0.27$). Estimated change of the thickness of CCA atherosclerotic plaques was -0.2 mm with 95% CI from -0.4 mm to 0.03 mm from baseline ($P = 0.09$).

For CLLT group (Table 4): estimated change of CCA length at 1-year observation was 1.1 mm, and 95% CI was from -0.9 mm to 3.1 mm ($P = 0.27$). Estimated change of CCA thickness was 0.02 mm after one year (95%CI: $[-0.1, 0.2]$; $P = 0.77$).

Compared with CLLT, ILLT was associated with lower progression of the carotid atherosclerotic plaques in the stroke survivors after 1-year therapy without reaching a significant level (shown in Table 4 and Fig. 1).

4. Discussion

This retrospective study indicates that achieving LDL-c < 70 mg/dL vs. 70 – 120 mg/dL in ischemic stroke patients was associated with a trend of reduced atherosclerotic plaque progression at one year after statin therapy. Although significant statistical levels were not achieved, our findings provided important preliminary data to plan future randomized controlled clinical trials to formally test the hypothesis that intensive lipid-lowering therapy (LDL-c < 70 mg/dL) is effective in preventing the progress of atherosclerotic plaques and reducing the cardiovascular events.

The target of LDL level in secondary stroke prevention remains obscure. An LDL-c level 100 mg/dL of statin therapy to reduce risks of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerosis is considered as Class I and Level of Evidence B according to the secondary stroke prevention guideline by American Stroke Association; while an LDL-c level < 100 mg/dL is regarded as Class I and Level of Evidence C [4]. A post hoc analysis of SPARCL trial revealed that achieving an LDL-c level of < 70 mg/dL was related to a 28% reduction in risk of stroke (HR, 0.72 ; 95% CI: $[0.59, 0.89]$; $P = 0.002$) without a significant rise in the risk of hemorrhagic stroke (HR, 1.28 ; 95% CI: $[0.78, 2.09]$; $P = 0.34$) in patients with a recent stroke or TIA [13]. Hence, our

study supported intensive lipid-lowering therapy with a target of LDL-c < 70 mg/dL would likely be beneficial in secondary atherosclerotic stroke prevention.

There are several limitations in the study. First, our study is a retrospective study in nature although the data was prospectively collected in the clinical database in our stroke center. Second, although the study showed the trend that LDL-c < 70 mg/dL was associated with limited progression of CCA atherosclerotic plaque, the study failed to reach any statistical significances, which might be due to inadequate power. Third, our database didn't contain adequate data about risk factor management, the side effects and the morphological changes of atherosclerosis plaques, to fully support the beneficial effects of ILLT.

5. Conclusion

Achieving LDL-c < 70 mg/dL may be associated with a trend of reducing atherosclerotic plaque progression in ischemic stroke patients. Our next step is to plan a randomized controlled clinical trial with adequate power to systematically investigate the impact of LDL-c level on the progression of CCA atherosclerotic plaque and clinical cardiovascular events.

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None.

Abbreviations

LDL-c	low-density lipoprotein cholesterol
ILLT	intensive lipid-lowering therapy
CLLT	conventional lipid-lowering therapy
HCY	homocysteine
S.D	standard deviation
IQR	interquartile range
CI	confidential interval

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Fig. 1.

Representative ultrasonography results. (a) and (b) are the baseline and 1-year follow-up ultrasonography results on conventional lipid-lowering therapy, respectively. An isoechoic plaque with the magnitude of 2.02 cm * 0.43 cm at the baseline (a), and was also showed as isoechoic with the magnitude of 2.02 cm * 0.41 cm (b) after one-year therapy. (c) and (d) are baseline and one-year follow-up ultrasonography results on the intensive lipid-lowering therapy, respectively. The hypoechoic plaque with the magnitude of 1.80 cm * 0.57 cm (c) regressed to the magnitude of 1.66 cm * 0.43 cm (d) after one year.

Table 1

Patients' clinical-demographical characteristics at baseline.

Baseline characteristics	ILLT (<i>n</i> = 38)	CLLT (<i>n</i> = 68)	Statistics	<i>P</i> value
Male (%)	31 (81.6%)	43 (63.2%)	3.9 ^a	0.05
Age (mean ± S.D.) (years)	63 ± 11	62 ± 11	1.1 ^b	0.76
Past medical history (%)				
Hypertension	27 (71.1%)	48 (70.6%)	0.003 ^a	1.00
Diabetes mellitus	11 (29.0%)	28 (41.2%)	2.3 ^a	0.32
Coronary heart disease	7 (18.4%)	8 (11.8%)	0.9 ^a	0.35
Hyperlipidemia	14 (36.8%)	22 (32.4%)	0.2 ^a	0.64
Smoking	27 (71.1%)	37 (54.4%)	2.8 ^a	0.09
Ultrasound results of CCA plaque				
Length (median, IQR) (mm)	16.2 (11.4)	13.2 (10.1)	3.3 ^c	0.07
Thickness (median, IQR) (mm)	2.3 (0.7)	2.2 (0.7)	0.3 ^c	0.60

ILLT, intensive lipid-lowering therapy; CLLT, conventional lipid-lowering therapy; S.D., standard deviation; CCA, common carotid artery; IQR, interquartile range.

^a χ^2 -Value.

^b *t*-Value.

^c *H*-value.

Table 2

Biochemistry results.

Blood examination outcomes at 1 year	ILLT (<i>n</i> =38)	CLLT (<i>n</i> = 68)	Statistic	<i>P</i> value
Cholesterol (median, IQR) (mg/dL)	109, 28	168, 51	64.7 ^a	<0.0001
LDL-c (median, IQR) (mg/dL)	54, 17	102, 42	72.5 ^a	<0.0001
HDL-c (median, IQR) (mg/dL)	40, 19	49, 17	8.3 ^a	0.004
Triglycerides (median, IQR) (mg/dL)	102, 67	126, 74	5.7 ^a	0.02
FPG (median, IQR) (mg/dL)	104, 29	106, 80	1 ^a	0.30
HCY (median, IQR) (μmol/L)	13, 6	13, 7	0.4 ^a	0.54

ILLT, intensive lipid-lowering therapy; CLLT, conventional lipid-lowering therapy; IQR, in-terquartile range; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; HCY, homocysteine; FPG, fasting plasma glucose.

^a*H*-value.

Table 3

Association between atherosclerotic plaque progression and lipid-lowering strategy, visit time and risk factors for 1-year data with the mixed-effect models.

	<u>Change of plaque length</u>		<u>Change of plaque thickness</u>	
	<i>F</i> value	<i>P</i> value	<i>F</i> value	<i>P</i> value
LDL < 70 mg/dL vs. LDL ≥ 70 mg/dL	0.71	0.40	1.15	0.28
1-year follow up vs. baseline	0.05	0.82	1.36	0.24
Male vs. female	0.11	0.74	0.72	0.40
≥ 60 years vs. <60 years	1.14	0.29	4.29	0.04
Diabetes vs. non-diabetes	0	0.98	0.35	0.55
Smoking vs. non-smoking	1.49	0.22	1.03	0.31
Interaction of LDL group and visit time	2.37	0.12	2.31	0.13

Table 4

Vascular ultrasound results and estimated changes of common carotid artery plaque under lipid-lowering therapy in 1 year.

	Baseline (median, IQR)		At one year (median, IQR)		Estimated difference vs. baseline (95%CI)		P values vs. baseline		P value between groups
	ILLT	CLLT	ILLT	CLLT	ILLT	CLLT	ILLT	CLLT	
Length (mm)	16.2, 11.4	13.2, 10.1	14.2, 9.5	14.4, 11.9	-1.4 [-4.1, 1.2]	1.1 [-0.9, 3.1]	0.27	0.27	0.40
Thickness (mm)	2.3, 0.7	2.2, 0.7	2.1, 0.8	2.3, 0.7	-0.2 [-0.4, 0.03]	0.02 [-0.1, 0.2]	0.09	0.77	0.28

IQR, interquartile range; CI, confidence interval.