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Low-Density Lipoprotein Cholesterol Levels Are Associated With Subsequent Stented-Territory Ischemic Stroke After Carotid Artery Stenting: A Single Center Retrospective Study

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ABSTRACT

Objective: The role of low-density lipoprotein cholesterol (LDL-C) after carotid artery stenting (CAS) is not well known with respect to stented-territory infarction (STI) and in-stent restenosis (ISR). We hypothesized that LDL-C levels after CAS might be independently associated with STI and ISR.
Methods: We conducted a retrospective study for patients with significant extracranial carotid stenosis who were subjected to CAS between September 2013 and May 2021. LDL-C levels were measured after 6 and 12 months following CAS. The association between STI and ISR, and LDL-C was explored using Cox proportional-hazard model.
Results: Of 244 patients enrolled, STI and ISR were observed in 11 (4.5%) and 10 (4.1%) patients, respectively. In multivariable analysis, higher white blood cell count (hazard ratio [HR], 1.408 per 10^3/mm³; 95% confidence interval [CI], 1.085–1.828; p=0.010), higher LDL-C levels after 12 months (HR, 1.037 per 1 mg/dL; 95% CI, 1.011–1.063; p=0.005), and ISR (HR, 13.526; 95% CI, 3.405–53.725; p<0.001) were independent predictors of STI. Diabetes (HR, 4.746; 95% CI, 1.026–21.948; p=0.046), smaller stent diameter (HR, 0.725 per 1 mm; 95% CI, 0.537–0.980; p=0.036), and higher LDL-C levels after 12 months (HR, 1.031 per 1 mg/dL; 95% CI, 1.007–1.055; p=0.011) were independent predictors of ISR.
Conclusion: We showed that LDL-C levels after 12 months independently predict STI and ISR after CAS. It is necessary to investigate the optimal target LDL-C level for STI prevention through well designed research in the future.

Keywords: Low-density lipoprotein; Carotid stenosis; Stents; Ischemic stroke

INTRODUCTION

Carotid artery stenosis, mostly caused by atherosclerosis, is an important factor contributing to stroke. Dyslipidemia is a major risk factor for atherosclerotic carotid disease. Uncontrolled low-density lipoprotein cholesterol (LDL-C) levels are associated with the progression of

carotid diseases, and controlling LDL-C levels with a statin can effectively reduce the risk of future strokes.[1,2] Lowering LDL-C to target levels reduces the risk of stroke recurrence.[1-3] However, in clinical settings, achievement of LDL-C target levels is not sufficient.[4,5]

Carotid artery stenting (CAS) is an important strategy for the treatment of carotid artery stenosis. High circulating LDL-C levels are associated with relevant embolization after CAS.[6] Furthermore, pre-procedural LDL-C lowering, especially in patients with unstable carotid plaques has been associated with less acute in-stent restenosis (ISR). Pre-interventional LDL-C lowering can also mediate protective effects against peri-interventional stroke, myocardial infarction (MI), and death.[7] CAS is associated with not only the peri-procedural risk but also long-term ISR and stented-territory infarction (STI). The use of statins can reduce the risk of cardiovascular events, including ischemic stroke and cardiac-related mortality after CAS.[8] Various guidelines now recommend specific target levels of LDL-C associated with atherosclerotic cerebrovascular diseases. However, such levels are not defined for specific conditions, such as for patients subjected to CAS who are at a high risk of subsequent stroke.[9]

Maintaining low LDL-C levels after CAS may be crucial for preventing STI and ISR after CAS. Here, we investigated LDL-C levels after six and twelve months following CAS. We compared the levels between patients diagnosed with STI or ISR and those who were not. Factors associated with STI and ISR were also investigated.

MATERIALS AND METHODS

1. Participants

Patients with extracranial carotid diseases who were admitted to the stroke center of Asan Medical Center and were subjected to CAS between September 2013 and May 2021 were retrospectively reviewed. Patients were included if they met the following criteria: 1) age ≥18 years; 2) symptomatic extracranial carotid stenosis ≥50% or asymptomatic stenosis ≥70% diagnosed by digital subtraction angiography (DSA). The following patients were excluded: those who had 1) not LDL-C follow-up data; 2) never followed-up with any imaging tests for restenosis; 3) non-atherosclerotic stenosis including arterial dissection, or Takayasu arteritis; 4) atrial fibrillation or history of cardioembolism; 5) recurrent stroke in multiple vascular territory or vascular territory other than stented vessel; and 6) recurrent strokes or restenosis occurring within one year after stenting. The flowchart of the study population is shown in **Fig. 1**. Baseline characteristics were collected from medical records. Laboratory results including complete blood cell count and C-reactive protein, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), and LDL-C levels were measured after the day of admission with at least eight hours of fasting. Brain magnetic resonance imaging and magnetic resonance angiography (MRA) or computed tomography angiography (CTA) were performed on the study subject to confirm the presence of ischemic lesions and symptomatic stenosis, and ischemic strokes with stenosis >50% in the corresponding artery were classified as symptomatic stenosis. EKG was performed on all subjects, and if non-lacunar infarction was present in other vascular territory corresponding to stenosis, holter monitoring and echocardiography were additionally performed to rule out the possibility of cardioembolism. Informed consent was not obtained from patients due to the retrospective nature of this study. The ethics committee of the Asan Medical Center approved this study (IRB No. 2022-0348).
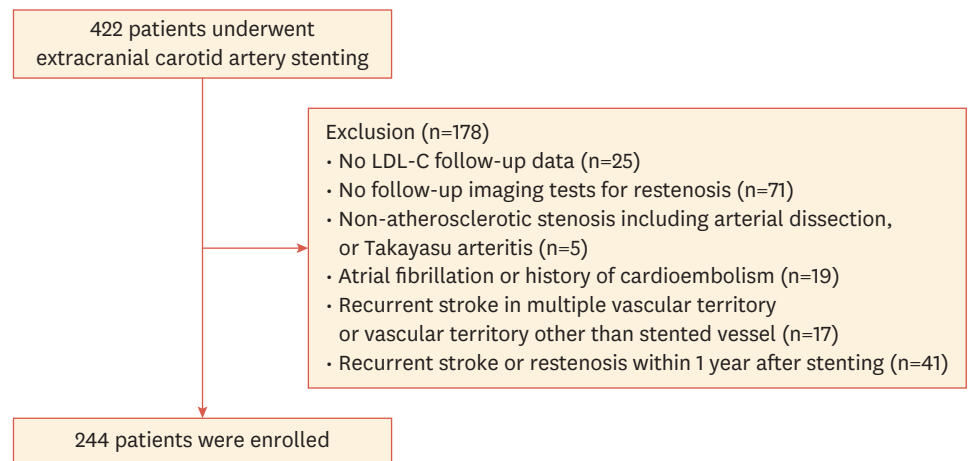
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┌─────────────────────────────────┐
│      422 patients underwent      │
│ extracranial carotid artery stenting │
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Exclusion (n=178)
· No LDL-C follow-up data (n=25)
· No follow-up imaging tests for restenosis (n=71)
· Non-atherosclerotic stenosis including arterial dissection,
  or Takayasu arteritis (n=5)
· Atrial fibrillation or history of cardioembolism (n=19)
· Recurrent stroke in multiple vascular territory
  or vascular territory other than stented vessel (n=17)
· Recurrent stroke or restenosis within 1 year after stenting (n=41)

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┌─────────────────────────────────┐
│     244 patients were enrolled   │
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Fig. 1. Flowchart of the study population.
LDL-C, Low-density lipoprotein cholesterol.

2. CAS and post-stent treatment

CAS was performed by highly experienced neuro-interventionists. Protégé (Covidien), Precise (Cordis), and Acculink (Abbott Laboratories) stents were used on the discretion of the neuro-interventionists. The number, maximum diameter, design (open- or closed-cell type), and length of the stent inserted were recorded. Dual antiplatelet with aspirin 100 mg and clopidogrel 75 mg daily was used before and after CAS. After CAS, dual antiplatelet was maintained for at least 1 year, after which it was changed to mono antiplatelet based on the physician's discretion of our stroke center. A statin was administered based on the decision of the attending neurologist. The potency of statin was categorized as low, moderate, and high. High-intensity statin was defined as atorvastatin ≥40 mg or rosuvastatin ≥20 mg daily; and moderate-intensity statin was defined as atorvastatin 10–20 mg rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 2–4 mg daily. The following are classified as low-intensity statins: simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, fluvastatin 20–40 mg, and pitavastatin 1 mg.[10] The control of risk factors was based on the center protocol; however, the final decision was made by the attending physician.

3. LDL-C levels and neuroimaging follow-up studies

LDL-C levels were measured at follow-ups after six and twelve months following CAS during a routine visit to an outpatient clinic. Blood samples were collected after at least eight hours of fasting. The LDL-C levels were classified into categories according to whether they were adjusted to targets below 70 mg/dL or below 100 mg/dL after 6 and 12 months.[11]

Follow-up neuroimaging studies were performed CTA, carotid duplex ultrasonography (CDU), MRA, or DSA. It was determined by the attending neurologist, depending on the location of stenosis, plaque nature such as calcification, and other comorbidities such as chronic kidney disease. STI was defined as a newly developed ischemic stroke in the stented artery territory observed on diffusion-weighted imaging during the follow-up period with a corresponding newly developed neurological deficit (**Fig. 2**). After work-up for the etiology of newly developed ischemic stroke, patients with multi-territory infarction caused by cardioembolism, or perforator territory infarctions caused by small vessel was not counted as STI. Restenosis higher than 50% of the residual stenosis after stent insertion during
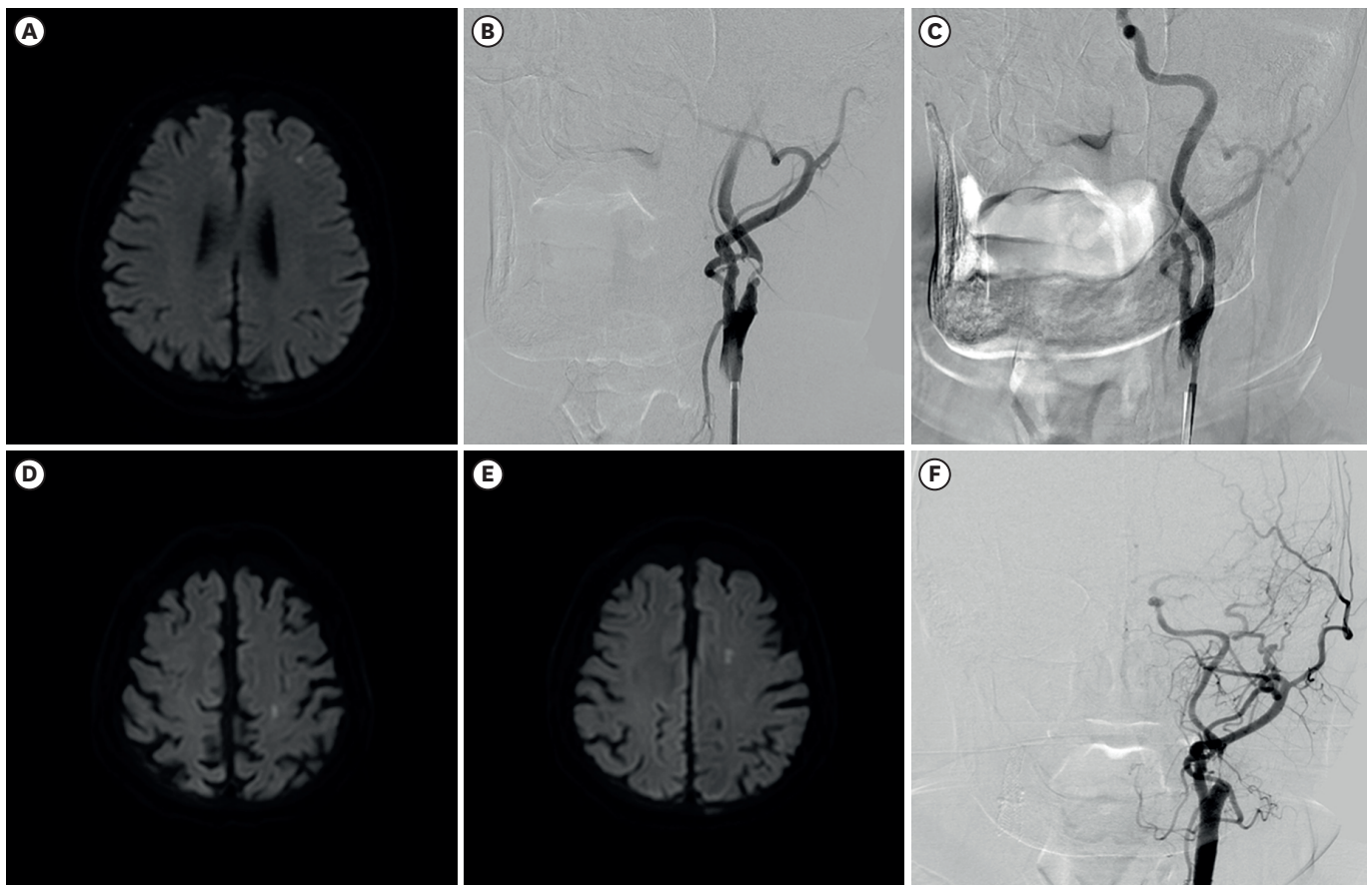
Fig. 2. Representative case of stented-territory infarction associated in-stent restenosis. Initial DWI demonstrates acute ischemic stroke on the left frontal cortex (A). Initial conventional cerebral angiography shows severe stenosis on the left proximal ICA (B). After CAS, left carotid angiography shows improved ICA flow (C). Two years after CAS, DWI for dysarthria reveals newly developed stented-territory infarctions on the left frontal lobe (D-E). Follow-up cerebral angiography demonstrates in-stent restenosis on the left proximal ICA (F).
DWI, diffusion-weight imaging; ICA, internal carotid artery; CAS, carotid artery stenting.

follow-up was considered as ISR, regardless of the neuroimaging modality used. However, the identical imaging modality was used at immediately after CAS and at follow-up to define restenosis higher than 50%. As the association between LDL-C control (LDL-C levels examined during follow-ups conducted at six and twelve months after CAS) and clinical outcomes were investigated, incidences of ISR and STI after 12 months of LDL-C follow-up measurements were considered in the recent study.

4. Statistical analysis

We compared baseline characteristics and laboratory findings, including lipid profile, the potency of statin, and follow-up LDL-C levels between patients with and without STI. A similar comparison was performed between those with and without ISR. Continuous or numerical variables were expressed as the mean (standard deviation) or median (interquartile range [IQR]) and were compared using a Student's *t*-test or Mann–Whitney U test. Categorical variables were analyzed via a chi-square test or Fisher's exact test. The Cox proportional-hazard model was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for study outcomes according to the LDL-C levels. In univariable analysis, LDL-C was analyzed not only as a continuous variable but also as a categorical variable depending on whether the target level was achieved. After univariable analysis for

STI and ISR, variables with potential association (*p*<0.10) and age and sex were entered to the multivariable analysis. The value of *p*<0.05 was considered statistically significant. In multivariable analysis, the LDL-C level used only one of the continuous or categorical variables to consider clinical significance and avoid multi-collinearity. Model 1 used LDL-C level as a continuous variable only. Model 2 and 3 used LDL-C ≥70 mg/dL or ≥100 mg/dL as a categorical variable, respectively. Changes in LDL-C levels according to STI or ISR were analyzed by repeated measures analysis of variance. All statistical analyses were performed with SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

During the study period, we screened 422 patients who underwent extracranial carotid artery stent implantation. Of these, 178 patients were excluded (25 patients who had no LDL-C follow-up data, 71 patients did not undergo follow-up imaging after stenting, 5 patients had non-atherosclerotic stenosis, 19 patients had atrial fibrillation and 17 patients had recurrent stroke in multiple vascular territory or vascular territory other than stented vessel, and 41 patients had stroke or ISR before one year of CAS). Hence, 244 patients (201 men, 82.4%) were included in the final analysis, with a mean age (standard deviation) of 67.5 (9.0) years. The median follow-up period for study was 27 months (IQR, 16–50). LDL-C levels were measured at six and twelve months in 227 and 206 patients, respectively. After six months following CAS, 197 patients (86.8%) and 87 (38.3%) showed LDL-C levels below 100 mg/dL and below 70 mg/dL, respectively. After twelve months following CAS, 171 patients (83.0%) and 84 patients (40.8%) showed LDL-C levels lower than 100 mg/dL and 70 mg/dL, respectively (**Fig. 3**). In 47 patients (24.9%), LDL-C level was maintained below 70 mg/dL at 6 and 12 months, whereas in 83 patients (43.9%), LDL-C level was continuously maintained above 70 mg/dL. None of patients continuously maintained LDL-C <70 mg/dL had STI and ISR. The Kaplan-Meier curves indicate that the group continuously maintained LDL-C level above 70mg/dL had a lower probability of surviving during follow-up (**Fig. 4**). Symptomatic stenosis was observed in 177 patients
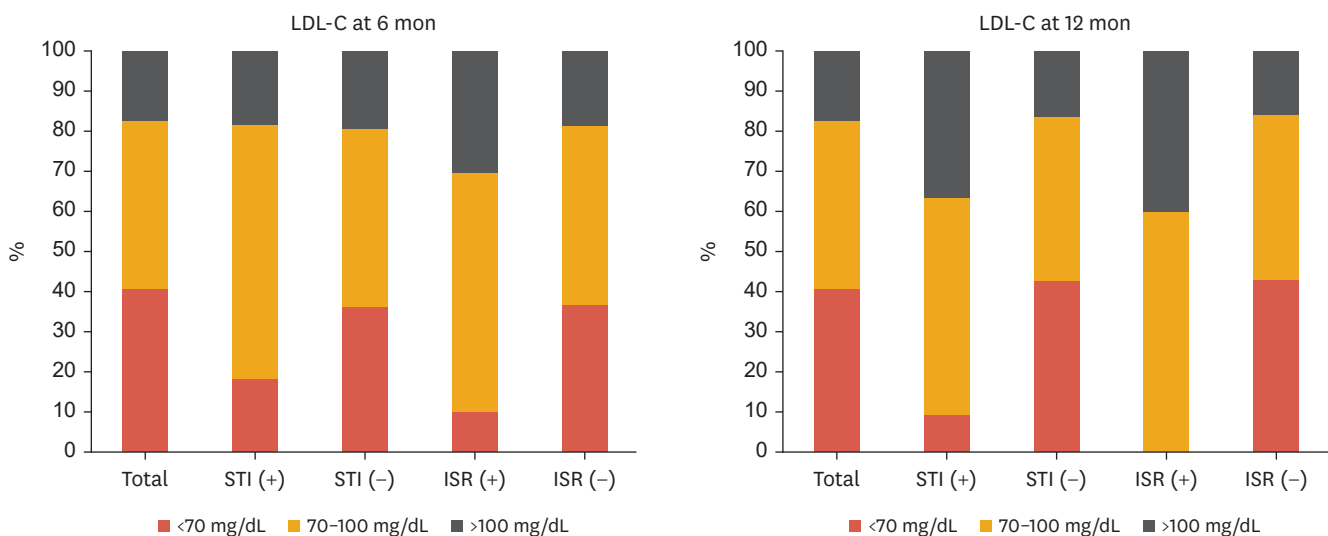

Fig. 3. LDL-C goal attainment rates after six months (A) and twelve months (B) (based on target LDL-C levels).
LDL-C, low-density lipoprotein cholesterol; STI, stented-territory infarction; ISR, in-stent restenosis.
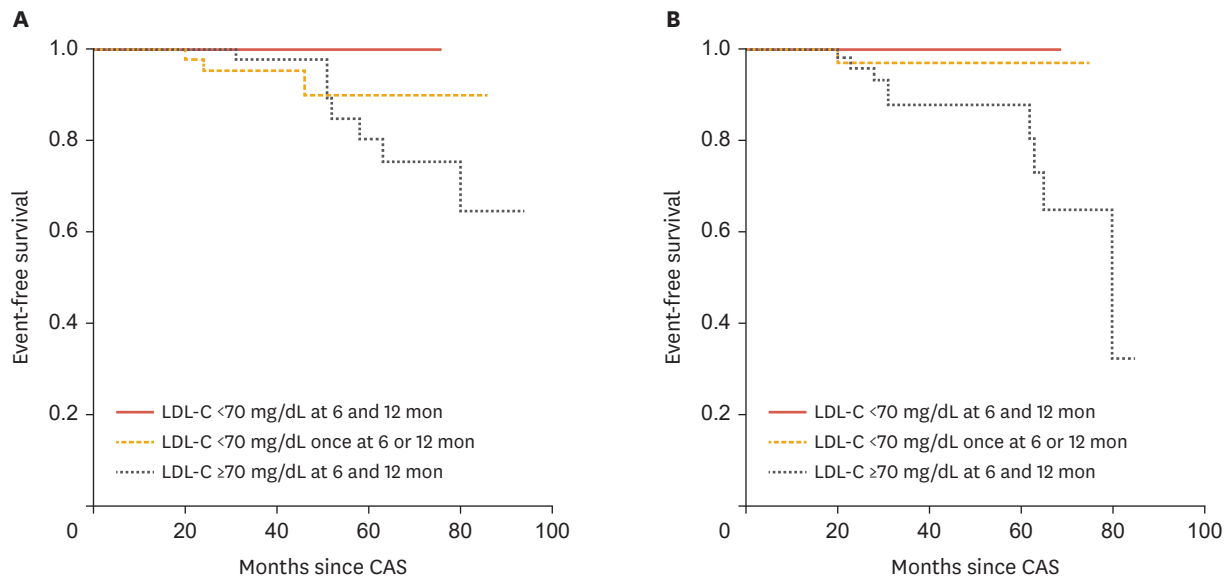
Fig. 4. Kaplan–Meier survival curve for stent-territory infarction (A) and in-stent restenosis (B).
LDL-C, low-density lipoprotein cholesterol; CAS, carotid artery stenting.

(72.5%). Although only 49.6% patients were diagnosed with dyslipidemia before stenting, all patients were administered statin therapy after CAS. Follow-up neuroimaging modalities used to diagnose ISR were CTA (58.2%), CDU (32.8%), DSA (6.1%), and MRA (2.9%). Other baseline characteristics in study population are summarized in **Table 1**.

2. Predictors of STI

After one year, STI after was observed in 11 (4.5%) patients. Univariable analysis demonstrated that smaller stent diameter (HR, 0.757 per 1 mm; 95% CI, 0.577–0.992; p=0.044), higher WBC counts (HR, 1.298 per 10^3/mm^3; 95% CI, 1.029–1.638; p=0.028), higher LDL-C levels after twelve months (HR, 1.039 per 1 mg/dL; 95% CI, 1.016–1.062; p=0.001), higher LDL-C percent change from baseline to twelve months (HR, 1.013 per 1%; 95% CI, 1.000–1.026; p=0.046), and ISR (HR, 15.113; 95% CI, 4.582–49.853; p<0.001) were associated with STI. With the LDL-C level as continuous variable, multivariable analysis showed that higher WBC counts (HR, 1.408 per 10^3/mm^3; 95% CI, 1.085–1.828; p=0.010), LDL-C levels after twelve months (HR, 1.037 per 1 mg/dL; 95% CI, 1.011–1.063; p=0.005), and ISR (HR, 13.526; 95% CI, 3.405–53.725; p<0.001) were independent predictors of STI. With the LDL-C level as categorical variable, multivariable analysis showed that higher WBC counts (HR, 1.543 per 10^3/mm^3; 95% CI, 1.163–2.047; p=0.003), LDL-C levels over 100 mg/dL after twelve months (HR, 7.686; 95% CI, 1.635–36.124; p=0.010), and ISR (HR, 21.986; 95% CI, 5.295–91.295; p<0.001) were independent predictors of STI (**Table 2**). LDL-C level over 70 mg/dL after twelve months was not associated with STI (HR, 2.718; 95% CI, 0.310–23.801; p=0.367). When divided into 3 groups according to whether the LDL-C level was continuously maintained at 6 months and 12 months, Cox proportional analysis could not be applied because STI and ISR did not occur in the group continuously maintained LDL-C below 70 mg/dL. Patients without STI showed a continuous decrease in LDL-C levels, whereas patients with infarction showed elevated LDL-C levels after twelve months (**Fig. 5A**).

3. Predictors of ISR

After one year, ISR was observed in 10 (4.1%) patients. Univariable analysis demonstrated that smaller stent diameter (HR, 0.708 per 1 mm; 95% CI, 0.538–0.931; p=0.013), higher

Table 1. Baseline characteristics associated with stented-territory infarction and in-stent restenosis observed one year after carotid artery stenting

Variables	Total (n=244)	Stented-territory infarction			In-stent restenosis		
		Yes (n=11)	No (n=233)	p	Yes (n=10)	No (n=234)	p
Age (yr)	67.47±9.01	67.45±7.95	68.01±8.71	0.836	65.50±9.98	68.09±8.61	0.356
Male	201 (82.4)	10 (90.9)	191 (82.0)	0.695	8 (80.0)	193 (82.5)	0.691
Hypertension	168 (68.9)	6 (54.5)	162 (69.5)	0.325	7 (70.0)	161 (68.8)	1.000
Diabetes	98 (40.2)	6 (54.5)	92 (39.5)	0.357	6 (60.0)	92 (39.3)	0.206
Dyslipidemia	121 (49.6)	6 (54.5)	115 (49.4)	0.737	4 (40.0)	117 (50.0)	0.749
CAD	80 (32.8)	4 (36.4)	76 (32.6)	0.754	3 (30.0)	77 (32.9)	1.000
Previous stroke	81 (33.2)	4 (36.4)	77 (33.0)	1.000	4 (40.0)	77 (32.9)	0.734
Smoking	118 (48.4)	7 (63.6)	111 (47.6)	0.300	4 (40.0)	114 (48.7)	0.750
Symptomatic stenosis	177 (72.5)	6 (54.5)	171 (73.4)	0.180	7 (70.0)	170 (72.6)	1.000
Multiple stents	5 (2.0)	1 (9.1)	4 (1.7)	0.208	0 (0.0)	5 (2.1)	1.000
Stent diameter (mm)	6.82±1.91	6.52±2.53	7.13±1.86	0.449	5.98±2.47	7.15±1.86	0.170
Stent length (mm)	33.71±10.65	30.45±12.74	34.70±9.93	0.173	29.00±10.75	34.74±10.01	0.078
Open-cell stent	218 (89.3)	9 (81.8)	209 (89.7)	0.331	9 (90.0)	209 (89.3)	1.000
Laboratory findings							
WBC (×10³/mm³)	7.28±2.14	8.73±2.84	7.21±2.00	0.017	7.78±1.93	7.26±2.07	0.438
Hemoglobin (g/dL)	13.30±1.65	12.63±1.81	13.30±1.69	0.197	13.11±1.40	13.28±1.71	0.756
Platelet (×10³/mm³)	241.59±75.7	240.45±95.41	238.93±68.49	0.944	255.50±109.42	238.29±67.73	0.446
CRP (mg/dL)	0.51±1.39	0.36±0.38	0.47±1.22	0.754	0.40±0.32	0.47±1.22	0.846
TC (mg/dL)	158.33±42.94	164.80±57.31	158.02±42.28	0.610	151.18±31.11	158.64±43.40	0.592
HDL-C (mg/dL)	44.04±10.82	41.91±16.23	43.24±10.68	0.794	40.00±13.15	43.31±10.86	0.350
LDL-C (mg/dL)	86.41±34.45	93.82±41.89	86.45±33.70	0.484	83.50±18.41	86.92±34.57	0.757
TG (mg/dL)	141.87±37.19	145.36±52.37	141.71±36.41	0.751	138.40±30.24	142.03±37.45	0.763
Follow-up lab							
LDL-C at 6 mon (mg/dL)	79.70±24.67	86.40±23.41	79.29±24.54	0.370	96.60±30.90	78.82±23.95	0.024
LDL-C at 12 mon (mg/dL)	77.33±25.91	103.55±38.80	77.50±24.95	0.001	103.10±28.24	77.66±25.78	0.003
LDL-C <70 mg/dL at 6 mon	87/227 (38.3)	2/10 (20.0)	85/217 (39.2)	0.324	1/10 (10.0)	86/217 (39.6)	0.093
LDL-C <100 mg/dL at 6 mon	197/227 (86.8)	9/10 (90.0)	188/217 (86.6)	1.000	7/10 (70.0)	190/217 (87.6)	0.131
LDL-C <70 mg/dL at 12 mon	84/206 (40.8)	1/11 (9.1)	83/195 (42.6)	0.030	0/10 (0.0)	84/196 (42.9)	0.006
LDL-C <100 mg/dL at 12 mon	171/206 (83.0)	7/11 (63.6)	164/195 (84.1)	0.095	6/10 (60.0)	165/196 (84.2)	0.069
LDL-C percent change from baseline to 6 mon	4.14±43.41	1.22±28.57	4.39±44.00	0.690	16.68±34.93	3.56±43.74	0.352
LDL-C percent change from baseline to 12 mon	−0.85±38.79	24.73±60.15	−2.29±36.94	0.024	25.84±32.23	−2.21±38.67	0.025
LDL-C level at 6 and 12 mon				0.041			0.004
<70 mg/dL both times	47/189 (24.9)	0 (0.0)	47 (26.3)		0 (0.0)	47 (26.3)	
<70 mg/dL only once	59/189 (31.2)	3 (30.0)	56 (31.3)		1 (10.0)	58 (32.4)	
≥70 mg/dL both times	83/189 (43.9)	7 (70.0)	76 (42.5)		9 (90.0)	74 (41.3)	
Statin intensity				0.463			0.227
Low	78 (32.0)	5 (45.5)	73 (31.3)		4 (40.0)	74 (31.6)	
Moderate	112 (45.9)	5 (45.5)	107 (45.9)		6 (60.0)	106 (45.3)	
High	54 (22.1)	1 (9.1)	53 (22.7)		0 (0.0)	54 (23.1)	
High intensity statin	54 (22.1)	1 (9.1)	53 (22.7)	0.464	0 (0.0)	54 (23.1)	0.123
Follow-up period, mon	27 (16–50)	50 (23–57)	26 (16–48)	0.088	30 (22–62)	20 (13–40)	0.021
In-stent restenosis	10 (4.1)	5 (45.5)	5 (2.1)	<0.001			
Stented-territory infarction	11 (4.5)				5 (50.0)	6 (2.6)	<0.001

Data are presented as mean ± standard deviation, number (percentages), or median (interquartile range).
CAD, coronary artery disease; WBC, white blood cells; CRP, C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.

LDL-C levels after twelve months (HR, 1.039 per 1 mg/dL; 95% CI, 1.013–1.065; p=0.003), and higher LDL-C percent change from baseline to twelve months (HR, 1.019 per 1%; 95% CI, 1.004–1.034; p=0.013) were associated with ISR. With the LDL-C level as continuous variable, multivariable analysis showed that diabetes (HR, 4.746; 95% CI, 1.026–21.948; p=0.046), smaller stent diameter (HR, 0.725 per 1 mm; 95% CI, 0.537–0.980; p=0.013), and higher LDL-C levels after twelve months (HR, 1.031 per 1 mg/dL; 95% CI, 1.007–1.055; p=0.011) were independent predictors of ISR (**Table 3**). With the LDL-C level as categorical variable, multivariable analysis showed that diabetes (HR, 4.720; 95% CI, 1.079–20.648; p=0.039), and smaller stent diameter (HR, 0.704 per 1 mm; 95% CI, 0.521–0.951; p=0.022) were

Table 2. Factors associated with stented-territory infarction

Variables	Univariable analysis			Multivariable analysis								
				Model 1			Model 2			Model 3		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (per year)	1.003	0.933–1.079	0.934	1.049	0.962–1.145	0.278	1.055	0.965–1.153	0.237	1.049	0.943–1.167	0.379
Male	2.432	0.311–19.022	0.397	4.754	0.533–42.430	0.163	6.206	0.683–56.382	0.105	5.264	0.498–55.669	0.168
Hypertension	0.679	0.207–2.230	0.523									
Diabetes	2.311	0.690–7.738	0.174									
Dyslipidemia	1.306	0.395–4.319	0.661									
CAD	1.590	0.461–5.486	0.463									
Previous stroke	2.834	0.761–10.549	0.120									
Smoking	1.292	0.372–4.483	0.687									
Symptomatic stenosis	1.579	0.870–2.866	0.133									
High intensity statin*	0.468	0.060–3.677	0.417									
Multiple stents	4.399	0.555–34.874	0.161									
Stent diameter (per 1 mm)	0.757	0.577–0.992	0.044	0.775	0.530–1.134	0.190	0.852	0.588–1.236	0.399	0.884	0.642–1.218	0.452
Stent length (per 1 mm)	0.957	0.906–1.010	0.113									
Open-cell stent	1.503	0.310–7.279	0.613									
WBC (per $10^3/mm^3$)	1.298	1.029–1.638	0.028	1.408	1.085–1.828	0.010	1.543	1.163–2.047	0.003	1.417	1.078–1.863	0.012
Hemoglobin (per 1 g/dL)	0.684	0.468–1.133	0.108									
Platelet (per $10^3/mm^3$)	1.000	0.992–1.009	0.941									
CRP (per 1 mg/dL)	0.878	0.387–1.992	0.755									
TC (per 1 mg/dL)	0.999	0.986–1.013	0.912									
HDL-C (per 1 mg/dL)	0.986	0.932–1.044	0.633									
LDL-C (per 1 mg/dL)	1.001	0.985–1.017	0.927									
TG (per 1 mg/dL)	0.997	0.981–1.012	0.684									
LDL-C at 6 mon (per 1 mg/dL)	1.006	0.984–1.028	0.587									
LDL-C at 12 mon (per 1 mg/dL)	1.039	1.016–1.062	0.001	1.037	1.011–1.063	0.005						
LDL-C percent change from baseline to 6 mon (per 1%)	0.999	0.989–1.010	0.877									
LDL-C percent change from baseline to 12 mon (per 1%)†	1.013	1.000–1.026	0.046									
LDL ≥70 mg/dL at 6 mon‡	1.538	0.320–7.379	0.591									
LDL ≥100 mg/dL at 6 mon§	0.673	0.085–5.346	0.708									
LDL ≥70 mg/dL at 12 mon‡	4.792	0.608–37.752	0.137									
LDL ≥100 mg/dL at 12 mon§	3.252	0.941–11.234	0.062				7.686	1.635–36.124	0.010	2.718	0.310–23.801	0.367
LDL-C level at 6 and 12 mon	N/A											
<70 mg/dL both times												
<70 mg/dL only once												
≥70 mg/dL both times												
In-stent restenosis	15.113	4.582–49.853	<0.001	13.526	3.405–53.725	<0.001	21.986	5.295–91.295	<0.001	14.302	4.309–47.474	<0.001

HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; WBC, white blood cells; CRP, C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; N/A, not available.

Model 1: LDL-C was included as only continuous variable; Model 2: LDL-C was included as only categorical variable (LDL ≥100 mg/dL at 12 months); Model 3: LDL-C was included as only categorical variable (LDL ≥70 mg/dL at 12 months).

*Reference for high intensity statin were low and medium intensity statin; †This parameter was not included in the multivariable analysis to avoid multi-collinearity; ‡Reference for LDL ≥70 mg/dL was LDL <70 mg/dL; §Reference for LDL ≥100 mg/dL was LDL <100 mg/dL.
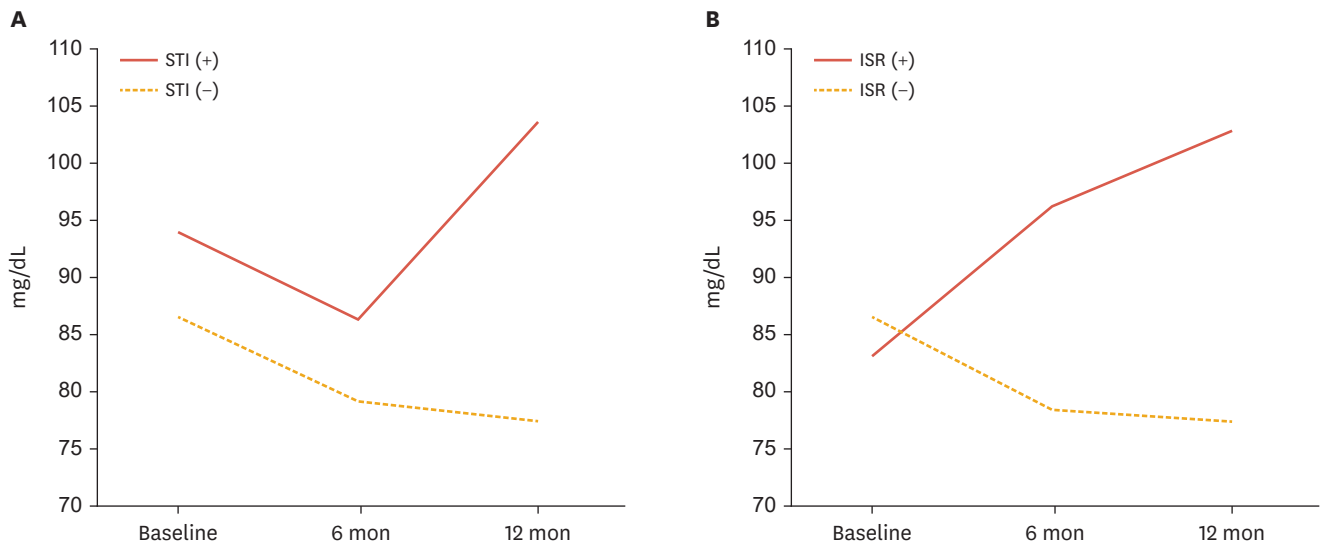
Fig. 5. Changes in low-density lipoprotein cholesterol levels according to stroke territory infarction (A) and ISR (B).
STI, stented-territory infarction; ISR, in-stent restenosis.

independent predictors of ISR. Patients without ISR showed a continuous decrease in LDL-C levels, whereas patients with ISR showed a continuous increase in LDL-C levels (**Fig. 5B**).

DISCUSSION

In the present study, we demonstrated that LDL-C levels observed after twelve months were independently associated with STI as well as ISR. In addition, patients without STI or ISR had better control of LDL-C levels for one year after CAS. Among clinical variables, WBC count and ISR were also identified as predictors of STI. In terms of ISR, diabetes and smaller stent diameter were also independent predictors. The advantages of this study compared to those of previous studies include the demonstration of the LDL-C levels as an important factor in the prognosis after CAS and the results were obtained after adjusting most of the clinical variables.

Renal insufficiency, male sex, age >70 years, a lesion located at the carotid bifurcation, and symptomatic stenosis are known factors for the prediction of STI after CAS. However, the role of dyslipidemia and LDL-C, which are important therapeutic target, remains unelucidated.[12,13] Although a previous study has reported that dyslipidemia is a predictor of recurrent ipsilateral ischemic stroke,[14] another long-term follow-up study has shown that it cannot be considered a predictor.[15] In a study conducted in Korea, fewer ischemic strokes were observed in patients with dyslipidemia.[16] Regarding the cholesterol profile, LDL-C levels are related to new diffusion-weighted image lesions observed in the acute phase immediately after CAS.[17] However, a long-term follow-up study demonstrated that low HDL-C level was an independent predictor of stroke, MI, and all-cause mortality after CAS, whereas LDL-C level was not.[18] Since that study was conducted before the effect of high-intensity statin was elucidated sufficiently, the LDL-C level was maintained above 120 mg/dL. This can be attributed to the lack of an association between LDL-C levels and stroke.

In terms of ISR, restenosis was associated with dyslipidemia in a previous clinical trial.[19] Similar to STI, HDL-C is a predictor of ISR.[20] However, we observed that LDL-C levels examined

Table 3. Factors associated with in-stent restenosis

Variables	Univariable analysis			Multivariable analysis					
				Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (per year)	0.973	0.903–1.049	0.476	1.044	0.951–1.147	0.365	0.998	0.913–1.091	0.960
Male	0.671	0.136–3.295	0.623	0.717	0.116–4.432	0.720	0.648	0.112–3.767	0.629
Hypertension	1.621	0.408–6.450	0.493						
Diabetes	4.085	0.995–16.775	0.051	4.746	1.026–21.948	0.046	4.720	1.079–20.648	0.039
Dyslipidemia	0.822	0.231–2.926	0.762						
CAD	0.849	0.211–3.421	0.818						
Previous stroke	2.696	0.711–10.217	0.145						
Smoking	0.352	0.086–1.443	0.147						
Symptomatic stenosis	0.782	0.199–3.070	0.725						
High intensity statin*	N/A								
Multiple stents	N/A								
Stent diameter (per 1 mm)	0.708	0.538–0.931	0.013	0.725	0.537–0.980	0.036	0.704	0.521–0.951	0.022
Stent length (per 1 mm)	0.946	0.894–1.001	0.056	1.014	0.928–1.107	0.764	1.003	0.926–1.086	0.945
Open-cell stent	2.805	0.350–22.483	0.331						
WBC (per 10^3/mm³)	1.124	0.827–1.527	0.455						
Hemoglobin (per 1 g/dL)	0.849	0.567–1.271	0.426						
Platelet (per 10^3/mm³)	1.004	0.996–1.012	0.372						
CRP (per 1 mg/dL)	0.915	0.357–2.346	0.853						
TC (per 1 mg/dL)	0.991	0.975–1.007	0.255						
HDL-C (per 1 mg/dL)	0.984	0.922–1.049	0.621						
LDL-C (per 1 mg/dL)	0.990	0.970–1.009	0.301						
TG (per 1 mg/dL)	0.991	0.974–1.008	0.305						
LDL-C at 6 mon (per 1 mg/dL)	1.011	0.991–1.031	0.281						
LDL-C at 12 mon (per 1 mg/dL)	1.039	1.013–1.065	0.003	1.031	1.007–1.055	0.011			
LDL-C percent change from baseline to 6 mon (per 1%)	1.000	0.990–1.010	0.956						
LDL-C percent change from baseline to 12 mon (per 1%)[†]	1.019	1.004–1.034	0.013						
LDL ≥70 mg/dL at 6 mon[‡]	3.159	0.392–25.466	0.280						
LDL ≥100 mg/dL at 6 mon[§]	1.536	0.380–6.206	0.547						
LDL ≥70 mg/dL at 12 mon[‡]	N/A								
LDL ≥100 mg/dL at 12 mon[§]	3.466	0.961–12.502	0.058				3.368	0.855–13.257	0.082
LDL-C level at 6 and 12 mon	N/A								
<70 mg/dL both times									
<70 mg/dL only once									
≥70 mg/dL both times									

HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; WBC, white blood cells; CRP, C-reactive protein; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; N/A, not available.
Model 1: LDL-C was included as only continuous variable; Model 2: LDL-C was included as only categorical variable (LDL ≥100 mg/dL at 12 months).
*Reference for high intensity statin were low and medium intensity statin; [†]This parameter was not included in the multivariable analysis to avoid multi-collinearity; [‡]Reference for LDL ≥70 mg/dL was LDL <70 mg/dL; [§]Reference for LDL ≥100 mg/dL was LDL <100 mg/dL.

after twelve months were associated with restenosis, similar to the association of LDL-C with ISR in coronary artery disease.[21-23] Higher levels of LDL-C are associated with increased carotid IMT and progression of carotid artery atherosclerosis.[24,25] The mechanisms underlying restenosis differ according to the time of onset. Early restenosis is caused by vascular injury, neointimal hyperplasia, and vascular remodeling, whereas in the late stage, the progression of atherosclerosis is the main cause.[26] High levels of LDL-C stimulate inflammation, damage vascular endothelial cells, and promote the deposition of cholesterol in the blood vessel wall.[27] Hence, since atherosclerosis is an important factor for predicting ISR during the long-term follow-up period (more than one year) after CAS, we speculated that high LDL-C levels affect the ISR. ISR eventually leads to STI after CAS. However, ISR was not present in 54.5% (6 of 11) of patients with STI. Thus, we tried to find out whether there were differences in clinical characteristics according to the presence of ISR among STI patients. But, no statistically significant difference was found due to the small sample size and low event rate (**Supplementary Table 1**). As this is an important issue further investigation focusing on this issue may be needed.

Therefore, it is very important to control the LDL-C level to prevent STI and ISR. Since treatment options for increasing HDL cholesterol levels are limited, it is necessary to focus on the reduction of LDL-C levels using appropriate statins. In the current guidelines, target LDL-C levels of <70 mg/dL are recommended to reduce the risk of major cardiovascular events in patients with ischemic stroke or transient ischemic attack and atherosclerotic disease (intracranial, carotid, aortic, or coronary).[9] However, no specific guidelines have been established for LDL-C control after CAS. We have tried to evaluate the difference of STI or ISR between the patients who consistently maintained LDL-C <70 mg/dL and other patients. However, Cox proportional analysis could not be applied because STI and ISR did not occur in the group consistently maintained LDL-C below 70 mg/dL. The LDL-C control rate in actual clinical practice is low. In our study, after six months following CAS, 87 patients (38.3%) showed LDL-C levels below 70 mg/dL. After 12 months following CAS, 84 patients (40.8%) showed LDL-C levels lower than 70 mg/dL. This control rate is low considering the clinical guidelines. However, the real-world data shows a control rate similar to that observed in our study. In a previous study with diabetic patients, the control rate among all patients of dyslipidemia was 18.8%, whereas it was 61.1% among those being treated considering target LDL-C levels of less than 100 mg/dL.[28] In a study conducted in Korea, less than 50% of patients achieved LDL-C target levels (LDL-C <70 mg/dL in patients with stroke, acute coronary syndrome, coronary heart disease, and peripheral artery disease, and LDL-C <100 mg/dL in patients with diabetes). In particular, only 34.5% of patients with stroke reached the target levels, consistent with the results of this study.[5] Another study reported that the higher the risk levels of cardiovascular disease were, the lower the control rate of dyslipidemia[4]. Therefore, our study results seem to reflect current real-world clinical practice, suggesting that LDL-C levels should be controlled more aggressively according to the guidelines. Our study showed that LDL-C levels decreased continuously from six to twelve months in the patient group without STI and ISR as well as that higher the LDL-C level, the better predicts the occurrence of STI and ISR. Therefore, LDL-C follow-up should be conducted after CAS.

Our study has several limitations. First, the design of the study was retrospective, and as the enrollment period was long, the strategy for LDL-C lowering was not identical throughout the period. Therefore, we couldn't analyze the effect of change in the guidelines or lipid lowering medication. However, in the subgroup analysis, more clinical events occurred in the early enrolled patients group because of longer follow-up, but LDL-C levels at 6 and 12 months were similar for early and late enrolled patients (**Supplementary Table 2**). Second, various imaging modalities were used to identify restenosis. Therefore, the actual stenosis degree of the subjects may differ based on the diagnostic method, which may introduce selection bias. However, it may also reflect clinical settings, wherein the diagnostic imaging differs depending on the location of the stenosis or other vascular abnormalities. Third, we chose to define restenosis as ≥50% stenosis. Even if 50% stenosis was used to define ISR in some studies, an alternative definition of ≥70% stenosis on CDU was more commonly used by other studies.[29-31] Fourth, LDL-C levels at the time of STI and ISR were not measured. Thus, the degree of LDL-C control at the time of the event was not known. However, on a sequential basis, LDL-C control within 12 months after CAS affects the development of ISR and, consequently is related to the subsequent STI. Therefore, the strength of this study is that it showed that controlling LDL-C levels for one year after CAS could predict future stroke events or ISR. It will be necessary to investigate the possibility of a legacy effect through additional prospective research in the future. Finally, the possibility that the failure of antiplatelet treatment influenced the outcome could not be excluded. However, aspirin and clopidogrel were maintained after CAS, and clinical evidence required to alter antiplatelet according to resistance in CAS is insufficient.

In conclusion, our results demonstrated that LDL-C levels within 12 months independently predict STI as well as ISR after CAS. Since the optimal target LDL-C level for STI prevention is not conclusive, it is necessary to investigate the target LDL-C level through well designed research in the future.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics according to the in-stent restenosis in patients with stented-territory infarction

Click here to view

Supplementary Table 2

Baseline characteristics according to study enroll period

Click here to view

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