Effect of Pitavastatin on Preventing Ischemic Complications with Carotid Artery Stenting: A Multicenter Prospective Study—EPOCH-CAS Study

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Abstract

Purpose Periprocedural ischemic stroke is one problem associated with carotid artery stenting (CAS). This study was designed to assess whether preoperative statin therapy reduces the risk of periprocedural ischemic complications with CAS.

Methods In this prospective study at 11 centers, patients with carotid artery stenosis (symptomatic $\geq 50\%$, asymptomatic $\geq 80\%$) and a high risk of carotid endarterectomy but without previous statin treatments were divided into two groups by low-density lipoprotein cholesterol (LDL-C)

levels. With LDL-C ≥ 120 mg/dl, the pitavastatin-treated (PS) group received pitavastatin at 4 mg/day. With LDL-C < 120 mg/dl, the non-PS group received no statin therapy. After 4 weeks, both groups underwent CAS. Frequencies of new ipsilateral ischemic lesions on diffusion-weighted imaging within 72 h after CAS and cerebrovascular events (transient ischemic attack, stroke, or death) within 30 days were assessed.

Results Among the 80 patients enrolled, 61 patients (PS group, $n = 31$; non-PS group, $n = 30$) fulfilled the inclusion criteria. New ipsilateral ischemic lesions were identified in 8 of 31 patients (25.8 %) in the PS group and 16 of 30 patients (53.3 %) in the non-PS group ($P = 0.028$). Cerebrovascular events occurred in 0 patients in the PS group and in 3 of 30 patients (10.0 %) in the non-PS group ($P = 0.071$). Multivariate analyses demonstrated the pitavastatin treatment ($\beta = 0.74$, 95 % confidence interval 0.070–1.48, $P = 0.042$) to be an independent factor for decreasing post-CAS ischemic lesions.

This study was conducted on behalf of the EPOCH-CAS Investigators. The members of EPOCH-CAS Investigators are given in [Appendix](#).

Trial Registration: UMIN Clinical Trials Registry: UMIN000004113. <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&receptno=R000004946&type=summary&language=E>.

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Conclusion Pretreatment with pitavastatin significantly reduced the frequency of periprocedural ischemic complications with CAS.

Keywords Statin therapy · Carotid artery stenting · Diffusion-weighted imaging · Pitavastatin · Ischemic complication

Introduction

Carotid artery stenting (CAS) for carotid artery stenosis has been effective not only in patients at high risk, but also those at conventional risk for carotid endarterectomy (CEA), and it is becoming an alternative to CEA [1]. However, the incidence of periprocedural stroke (particularly ischemic stroke) is higher with CAS than with CEA [1, 2]. Factors that influence periprocedural ischemic complications in CAS include use of a protection device, stent design, technical expertise, patient age, and plaque characteristics [3–8].

In addition to the antihyperlipidemic effects, 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (statins) have the pleiotropic effects, including plaque stabilization, improvement of endothelial function, reduction in vascular inflammation, reduction of platelet aggregation, and thrombus deposition [9–11]. Statins can reduce periprocedural complications when administered before coronary intervention [12]. However, it has not been sufficiently investigated whether statins reduce periprocedural complications with CAS. We therefore investigated whether pre-CAS pitavastatin therapy could reduce the frequency of periprocedural ischemic complications with CAS.

Methods

Study Population and Design

The EPOCH-CAS (Effect of Pitavastatin On preventing isCHemic complications with CAS) study was a prospective study conducted at 11 medical centers in Japan. The study was approved by each hospital research ethics committee. All patients provided written informed consent before participation in this study.

The EPOCH-CAS study included patients who had $\geq 50\%$ symptomatic or $\geq 80\%$ asymptomatic carotid artery stenosis at a high risk for CEA and with no history of statin treatment (Table 1).

Patients were divided into two groups on the basis of serum low-density lipoprotein cholesterol (LDL-C) levels

Table 1 Inclusion criteria, exclusion criteria, and criteria for CEA high risk

Inclusion criteria

- (1) Patient is scheduled to undergo CAS more than 4 weeks after study enrollment
- (2) Angiography findings of $\geq 50\%$ symptomatic or $\geq 80\%$ asymptomatic carotid artery stenosis according to the North American Symptomatic CEA Trial criteria
- (3) High risk of CEA

Exclusion criteria

- (1) History of or under lipid-lowering treatment with a statin
- (2) Severe liver dysfunction or biliary obstruction
- (3) Severe renal dysfunction
- (4) Any active inflammatory disorder such as connective tissue disease
- (5) Nonatherosclerotic carotid disease
- (6) Treatment with cyclosporine
- (7) MRI contraindicated for reasons such as pacemaker insertion
- (8) Considered ineligible for study participation for any other reason by the investigator or subinvestigator

Criteria for CEA high risk (at least one factor required)

- (1) Severe left ventricular dysfunction with congestive heart failure (New York Heart Association (NYHA) class III/IV) and/or left ventricular ejection fraction $< 30\%$
- (2) Recent myocardial infarction (> 24 h and < 4 weeks)
- (3) Unstable angina
- (4) Open-heart surgery within 6 weeks of study enrollment
- (5) Coexisting severe coronary artery disease requiring open-heart surgery
- (6) Severe pulmonary disease
- (7) Contralateral carotid occlusion
- (8) Contralateral laryngeal nerve palsy
- (9) Previous radical neck surgery or radiation therapy to the neck
- (10) Recurrent stenosis after CEA
- (11) High cervical internal carotid artery lesion or common carotid artery lesions below the clavicle
- (12) Age ≥ 75 years
- (13) Judged to be high risk by physician for any reasons other than the above

CEA carotid endarterectomy, MRI magnetic resonance imaging

at the time of enrollment. Patients with LDL-C ≥ 120 mg/dl were provided 4 mg/day of pitavastatin and underwent CAS 4 weeks later (pitavastatin-treated [PS] group). Patients with LDL-C < 120 mg/dl received no statin therapy and underwent CAS 4 weeks later (non-PS group). This is because Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2007 recommended that LDL-C level be < 120 mg/dl for patients with carotid artery stenosis. Patients in both groups underwent CAS in a nonblinded manner. Blood samples were collected on the day before CAS in both groups.

CAS Procedure

Dual antiplatelet therapy (aspirin [100 mg] and clopidogrel [75 mg] or cilostazol [200 mg]) was initiated at least 1 week before CAS and continued for at least for 30 days after CAS. Use of an embolic protection device (EPD) was mandatory, but the type was unrestricted. The type of stent used was also not restricted. Pre- and postdilation were performed when necessary during the procedure.

Magnetic Resonance Imaging Technique

Diffusion-Weighted Imaging (DWI)

Each center was allowed to use scanners with field strengths of 1.5 or 3 T, as long as the same scanner and the same imaging parameters were used in both groups. The imaging protocol included the same DWI sequences ($b = 0, 1,000 \text{ s/mm}^2$; section thickness 5.0 mm; gap 1 mm); apparent diffusion coefficient maps were obtained in all cases. The protocol specified magnetic resonance (MR) imaging scans to take place within 1 week before CAS and within 12–72 h after CAS. The window/level setting during evaluation was set on the basis of previously published standards for DWI [13]. Two board-certified neuroradiologists independently and blindly analyzed all scans, and they evaluated the number of lesions measuring $<10 \text{ mm}$ and $\geq 10 \text{ mm}$ separately, as well as the vascular distribution. DWI positivity was defined by at least one new bright lesion on DWI that had not been detected at baseline. Differences in assessment were resolved by consensus.

MR Plaque Imaging

MR imaging for plaque characterization was performed on 1.5 or 3 T scanners. For each patient, follow-up studies were performed with the same imaging unit as the baseline study. A 2D T1-weighted fast spin-echo sequence was performed before and after 4-week statin treatment using a black blood double inversion recovery preparation pulse and a fat-saturation pulse. The signal intensities were measured with the region of interest drawn over the carotid plaque at the most severely stenotic level. The signal intensity ratio of the plaque relative to adjacent muscle was calculated.

End Points

The primary end point of this study was the incidence of new ipsilateral ischemic lesions on DWI, and the secondary end point was the occurrence of cerebrovascular events (defined as transient ischemic attack, stroke, or death)

within 30 days after CAS. Stroke was defined as a neurological deficits that persisted for more than 24 h.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation for continuous variables and as frequencies for categorical variables. Continuous variables were compared by the two sample t test or the Wilcoxon rank sum test, and categorical variables by the χ^2 test or Fisher's exact test. A multiple logistic regression analysis was constructed to identify independent predictors of new ipsilateral ischemic lesions on DWI. Statistical significance was defined as a two-sided P value of <0.05 . JMP version 9 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Study Profile

A total of 80 patients were enrolled (PS group, $n = 44$; non-PS group, $n = 36$) from July 2010 to September 2012. Eight patients withdrew from the study for the following reasons: canceled CAS, 3 patients in the PS group (malignant tumor in 2 and ileus in 1); emergency CAS, 1 in the PS group and 1 in the non-PS group; and stopped pitavastatin therapy (3 in the PS group—creatinine kinase elevation in 2 and patient preference in 1) (Fig. 1). Two patients who underwent emergency CAS because of minor ischemic stroke during the waiting period were discharged without any neurological sequela.

CAS was performed successfully in all 72 patients (PS group, $n = 37$; non-PS group, $n = 35$) meeting the inclusion criteria. Eleven patients (six in the PS group and five in the non-PS group) were excluded because they were in violation of the DWI protocol, as follows: preprocedural DWI more than 1 week before CAS, 4 in the PS group and 4 in the non-PS group; no preprocedural DWI, 1 in the PS group; different slice thickness (7 mm), 1 in the PS group; and preprocedural DWI more than 1 week before CAS with different slice thickness (3 mm), 1 in the non-PS group. A total of 61 patients (PS group, $n = 31$; non-PS group, $n = 30$) underwent the primary end-point analyses (Fig. 1).

In these 61 patients, cholesterol levels were significantly different between the two groups. At the time of study enrollment, LDL-C and total cholesterol levels were significantly higher in the PS group than in the non-PS group; in contrast, on the day before CAS, LDL-C and total cholesterol levels were significantly lower in the PS group than in the non-PS group (Table 2). The findings of MR

Fig. 1 Study profile. *PS* pitavastatin treated, *CAS* carotid artery stenting, *LDL-C* low-density lipoprotein cholesterol, *DWI* diffusion-weighted imaging

Table 2 Changes of lipids levels at the baseline and before CAS

Lipid	Baseline			Before CAS		
	PS group (n = 31)	Non-PS group (n = 30)	P value	PS group (n = 31)	Non-PS group (n = 30)	P value
Total cholesterol, mg/dl	218 ± 29	175 ± 51	0.0001	135 ± 23	166 ± 34	0.0001
Triglycerides, mg/dl	127 ± 55	133 ± 77	0.69	96 ± 44	133 ± 72	0.02
HDL cholesterol, mg/dl	47 ± 12	48 ± 17	0.83	47 ± 12	48 ± 19	0.77
LDL cholesterol, mg/dl	145 ± 22	93 ± 21	<0.0001	69 ± 16	91 ± 24	0.0001

Data are presented as mean ± standard deviation

CAS carotid artery stenting, *PS* pitavastatin treated, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

Table 3 Changes of signal intensity ratio in the MR plaque imaging

PS group (n = 31)			Non-PS group (n = 30)			P value (PS vs. non-PS) at baseline	P value (PS vs. non-PS) at pre-CAS
Baseline	Before CAS	P value (vs. baseline)	Baseline	Before CAS	P value (vs. baseline)		
1.327 ± 0.268	1.368 ± 0.344	0.6089	1.368 ± 0.344	1.333 ± 0.297	0.2070	0.9854	0.6202

Data are presented as mean ± standard deviation

MR magnetic resonance, *PS* pitavastatin treated, *CAS* carotid artery stenting

plaque imaging were similar between both groups in each analysis at both baseline and before CAS (Table 3). There were also no significant differences in the signal intensity ratio between the pre- and poststatin treatment times in the PS group. Other baseline clinical characteristics and procedural data did not differ significantly between the groups (Table 4).

New Ischemic Lesions on DWI

New ipsilateral ischemic lesions were detected in 24 of the 61 patients (39.3 %); the DWI-positive rate was significantly lower in the PS group (25.8 %, 8 of 31 patients) than in the non-PS group (53.3 %, 16 of 30 patients; $P = 0.028$) (Table 5).

Table 4 Demographics and baseline characteristics

Characteristic	PS group (<i>n</i> = 31)	Non-PS group (<i>n</i> = 30)	<i>P</i> value
Male, <i>n</i> (%)	26 (83.9)	29 (96.7)	0.09
Age, year	72 ± 9	74 ± 8	0.31
Degree of stenosis (%)	79 ± 11	79 ± 12	0.97
History, <i>n</i> (%)			
Symptomatic stenosis	14 (45.2)	14 (46.7)	0.91
Ischemic heart disease	5 (16.1)	4 (13.3)	0.76
Hypertension	21 (67.7)	19 (63.3)	0.72
Diabetes mellitus type 2	12 (38.7)	6 (20.0)	0.11
Hyperlipidemia	31 (100.0)	0 (0.0)	<0.0001
Current or past smoker	18 (58.1)	16 (53.3)	0.71
High risk for CEA			
CHF and/or known severe LVEF	0 (0.0)	0 (0.0)	–
Recent MI	0 (0.0)	0 (0.0)	–
Unstable angina	2 (6.5)	2 (6.7)	0.97
Open heart surgery needed within 6 wk	0 (0.0)	0 (0.0)	–
Coexisting severe coronary artery disease	1 (3.2)	1 (3.3)	0.98
Severe pulmonary disease	0 (0.0)	0 (0.0)	–
Contralateral carotid occlusion	1 (3.2)	1 (3.3)	0.98
Contralateral laryngeal nerve palsy	0 (0.0)	0 (0.0)	–
Previous radical neck surgery or radiation therapy to the neck	0 (0.0)	2 (6.7)	0.14
Recurrent stenosis after CEA	0 (0.0)	0 (0.0)	–
High cervical ICA lesions or CCA lesions below the clavicle	10 (32.3)	10 (33.3)	0.93
Age >75 years	7 (22.6)	11 (36.7)	0.23
Physician judgment	9 (29.0)	7 (23.3)	0.61
EPD			
Distal balloon protection			
PercuSurge (PerS)	0 (0.0)	1 (3.3)	0.31
Distal filter protection			
Angioguard RX	1 (3.2)	0 (0.0)	0.32
FilterWire EZ (FW)	23 (74.2)	26 (86.7)	0.22
Spider FX	3 (9.7)	0 (0.0)	0.08
Multiple protection (proximal protection (PP) + distal protection)			
PP + FW	2 (6.5)	0 (0.0)	0.16
PP + PerS	1 (3.2)	1 (3.3)	0.98
PP + FW + PerS	1 (3.2)	2 (6.7)	0.53

Table 4 continued

Characteristic	PS group (<i>n</i> = 31)	Non-PS group (<i>n</i> = 30)	<i>P</i> value
Stent			
Open cell			
Precise	10 (32.3)	14 (46.7)	0.25
Protégé	1 (3.2)	0 (0.0)	0.32
Closed cell			
Carotid Wallstent	20 (64.5)	16 (53.3)	0.37

Data are presented as mean ± standard deviation or *n* (%)

PS pitavastatin treated, CEA carotid endarterectomy, CHF chronic heart failure, LVEF left ventricular ejection fraction, MI myocardial infarction, ICA internal carotid artery, CCA common carotid artery

Table 5 New DWI-positive lesions on posttreatment scans

Lesion	PS group (<i>n</i> = 31)	Non-PS group (<i>n</i> = 30)	<i>P</i> value
Ipsilateral new lesion (at least one new lesion)	8 (25.8 %)	16 (53.3 %)	0.028
Ipsilateral single new lesions	5 (16.1 %)	3 (10.0 %)	–
Ipsilateral multiple new lesions	3 (9.7 %)	13 (43.3 %)	–
Ipsilateral and nonipsilateral (contralateral or posterior circulation) new lesion	8 (25.8 %)	17 (56.7 %)	0.014

DWI diffusion-weighted imaging, PS pitavastatin treated

In three patients (two in the PS group and one in the non-PS group), new ischemic lesions were also observed on the contralateral side, and three patients from the non-PS group showed ischemic lesions in the posterior circulation. In five patients, except for one patient in the non-PS group, ischemic lesions were also observed on the ipsilateral side. When we included the contralateral side and the posterior circulation lesion, the DWI positivity rate was also significantly lower in the PS group than in the non-PS group ($P = 0.014$) (Table 5).

The mean number of ischemic lesions was 4.67 (range 1–42): the median number of lesions was 1 (range 1–8) in the PS group and 2 (range 1–42) in the non-PS group. The multiple lesion rates on the ipsilateral side were 9.7 % (3 of 31 patients) in the PS group and 43.3 % (13 of 30 patients) in the non-PS group. One patient with transient ischemic attack and 2 patients with minor stroke in the non-PS group had multiple lesions (3, 12, and 42 lesions, respectively). Other DWI-positive lesions were all asymptomatic.

As to lesion size, 5 lesions were 10–20 mm in diameter, and all other lesions were under 10 mm. One minor stroke patient had 4 lesions of ≥ 10 mm. Another lesion of ≥ 10 mm was asymptomatic.

Table 6 Cerebrovascular events within 30 days

Event	PS group (<i>n</i> = 31)	Non-PS group (<i>n</i> = 30)	<i>P</i> value
Cerebrovascular events	0	3 (10.0 %)	0.071
Stroke	0	2 (6.7 %)	0.144
Transient ischemic attack	0	1 (3.3 %)	0.305
Death	0	0	–

PS pitavastatin treated

Cerebrovascular Events

Of 61 patients, three patients (4.9 %), all of whom belonged to the non-PS group, had cerebrovascular events; this included transient ischemic attack in one patient (1.6 %) and minor ischemic stroke in two patients (3.3 %). In the both patients with stroke, the symptoms completely disappeared within 30 days. No deaths occurred in either group. As a result, cerebrovascular events tended to occur less frequently in the PS group than in the non-PS group ($P = 0.071$) (Table 6).

Independent Factors Related to New Ischemic Lesions on DWI

To determine whether the pitavastatin treatment decreased the post-CAS ischemic complications, multivariate analyses were performed using the post-CAS development of new ipsilateral DWI-positive lesion as the dependent variable. Independent variables were PS group, degree of stenosis, symptomatic stenosis, pre-CAS LDL-C levels, pre-CAS signal intensity ratio on MR plaque imaging, type of EPDs, and use of closed cell stents, all of which could potentially affect the post-CAS occurrence of ischemic complications. Multivariate analyses revealed that the PS group ($\beta = 0.74$, 95 % confidence interval 0.070–1.48, $P = 0.042$) and degree of carotid stenosis ($\beta = 0.095$, 95 % confidence interval 0.030–0.18, $P = 0.023$) were independently associated with less frequent occurrence of post-CAS ipsilateral ischemic lesions (Table 7).

Discussion

In the field of percutaneous coronary intervention, statin administration before intervention has already been reported to decrease periprocedural complications. A randomized study in elective coronary intervention patients indicated that the occurrence of periprocedural complications was significantly lower in the atorvastatin therapy group compared to the placebo group [12]. The mechanisms underlying the beneficial effects of atorvastatin are not completely clear. Such results are presumably the result of the pleiotropic effects of statins.

Table 7 Factors affecting the incidence of new ischemic lesions on DWI (multivariate analysis)

Factor	β	95 % confidence interval	<i>P</i> value
PS group	0.74	0.070 to 1.48	0.042
Degree of stenosis at baseline	0.095	0.030 to 0.18	0.023
Symptomatic stenosis	−0.2359	−0.95 to 0.48	0.51
LDL-C before CAS	0.0012	−0.027 to 0.030	0.93
Signal intensity ratio in MR plaque imaging before CAS	0.66	−1.49 to 2.97	0.55
EPD (distal protection)	0.59	−0.29 to 1.57	0.20
Stent (closed cell)	0.37	−0.30 to 1.08	0.30

DWI diffusion-weighted imaging, *PS* pitavastatin treated, *LDL-C* low-density lipoprotein cholesterol, *CAS* carotid artery stenting, *EPD* embolic protection device

To our knowledge, only two retrospective studies have reported the possible benefits of statins on CAS. Groschel et al. [14] reported that the periprocedural cardiovascular events rate in 180 CAS cases was significantly lower than in various prestatin treatment groups (4 %) than in the non-prestatin therapy group (15 %).

Verzini et al. [15] provided a retrospective analysis of 1,083 consecutive CAS cases. Statin use was associated with a reduction in risk of perioperative stroke and death (odds ratio 0.327; 95 % confidence interval 0.13–0.80, $P = 0.016$). Our study showed that the cerebrovascular event rate in the PS group was not significantly lower than in the non-PS group. Nevertheless, a significant difference was evident on DWI, so if the number of patients were increased, a significant difference even for the cerebrovascular event might be identified.

Kastrup et al. [16] reported that the number of new DWI lesions was significantly higher in patients who developed a stroke than in patients without neurological deficit. Major stroke patients had multiple lesions larger than 20 mm in diameter, whereas all patients with minor stroke had multiple new lesions smaller than 10 mm in diameter. In our study, two minor stroke patients also had multiple lesions (12 and 42); the size of lesions was also smaller than 10 mm in diameter except for 4 lesions of 10–20 mm.

Several investigators, using DWI to detect clinically silent embolic lesions after protected CAS, have reported new DWI lesions at frequencies of 6.7–73 % [8, 17–21]. A substudy of the International Carotid Stenting Study (ICSS) reported that new DWI lesions occurred in 62 of 124 patients (50 %) in the stenting group [18]. In a DWI-positive CAS group (62 patients), single lesions were seen in 18 (15 %), multiple lesions in 44 (35 %), and stroke in 8 (6 %). New DWI lesions were present in 73 % in an EPD group and 34 % in a group without EPD. In this study, EPD

was used in all cases, and new DWI lesions occurred in 25.8 % (8 of 31) in the PS group, which was much lower compared with 56.7 % (17 of 30) in the non-PS group in this study and 73 % in EPD group in the ICSS study. Moreover, both the ICSS study and the non-PS group in this study showed that CAS-related embolisms much more frequently occurred as multiple lesions, whereas the frequency of multiple lesions was much lower than that of single lesion in the PS group. These findings suggest that preprocedural statin therapy is effective for reduction of both number and occurrence rate of ischemic lesions.

In our study, there was a significant difference in LDL-C and total cholesterol levels between the two groups. However, several authors reported that dyslipidemia or hyperlipidemia did not affect the post-CAS DWI-positive lesion occurrence [19, 21]. Our study also revealed that an independent factor for post-CAS new DWI-positive lesions was pitavastatin treatment, but not LDL-C level. Taken together, these findings suggest that the statin therapy reduced post-CAS DWI-positive lesions with the pleiotropic effects other than improving cholesterol profiles.

In our study, we chose pitavastatin out of many statins because only pitavastatin can reportedly stabilize the carotid plaque within 1 month after administering statins. Nakamura et al. [10] reported that plaque stabilization of unstable carotid plaque significantly occurred by pitavastatin therapy within 1 month on ultrasonography. Yoshimura et al. [8] reported that unstable plaque on time-of-flight MR angiography was associated with more ipsilateral ischemic lesions on DWI after CAS. One possible explanation for the lower DWI-positive rate in the PS group in this study is plaque stabilization as a consequence of the pitavastatin administration. However, in our study, there was no significant difference in MR plaque imaging findings between pre- and poststatin treatment in the PS groups. This result suggests that the lower DWI-positive rate in the PS group may not be due to plaque stabilization but rather to other pleiotropic effects. Otherwise, MR plaque imaging in the current study may not be suitable for detecting the short-term changes in plaque stability. We have evaluated plaque stability using T1-weighted MR plaque imaging because several reports described that high-signal plaques on T1-weighted images predict silent ischemic lesions after CAS [22, 23]. However, ultrasound may be much more sensitive than MR plaque imaging regarding plaque stability. Therefore, it would be expected that ultrasound is also added in the protocol in a future study.

New ischemic lesions, even without corresponding focal deficit, might lead to long-term clinical consequences, including cognitive decline and dementia [24]. Thus, reducing ischemic lesions as much as possible is essential in CAS. For this purpose, statins are promising.

There are some limitations in this study, as follows. This study had a nonrandomized design with a relatively small

sample size; there were significant differences in LDL-C levels between the groups; different stents and EPDs were used; DWI was performed by different MR imaging machines; pre-CAS DWI scan was performed within 1 week before CAS; and efficacy of antiplatelet agents was not evaluated. Despite these limitations, this is to our knowledge the first prospective study at multiple centers to demonstrate that pretreatment with pitavastatin decreases the incidence of ischemic complication after CAS. Future randomized control trials are now warranted.

Conclusion

Pretreatment with pitavastatin significantly reduced periprocedural ischemic complications with CAS.

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Conflict of interest The authors declare that they have no conflict of interest.

Appendix

The investigators and institutions participating in the EPOCH-CAS study were as follows: Ishinkai Yao General Hospital, Yao, Osaka (Katsutoshi Takayama, MD, Kaoru Myouchin, MD, Ryota Kimura, MD, Shinichiro Kurokawa, MD); Osaka Medical College, Takatsuki, Osaka (Naokado Ikeda, MD, Terumasa Kuroiwa, MD, Toshihiko Kuroiwa, MD); Kyoto First Red Cross Hospital, Kyoto (Keisuke Imai, MD, Masashi Hamanaka, MD); Kokura Memorial Hospital, Fukuoka (Masanori Gomi, MD, Ichiro Nakahara, MD); Shiroyama Hospital, Habikino, Osaka (Kosuke Miyake, MD, Kenichi Murao, MD); Suzuka General Hospital, Suzuka, Mie (Ryuta Yasuda, MD, Kenji Kawaguchi, MD); Suzuka Kaisei Hospital, Suzuka, Mie (Kazuhide Hamada, MD, Kenji Kanamaru, MD); Nara Medical University, Kashihara, Nara (Takeshi Wada, MD, Ichiro Nakagawa, MD, Masahiko Sakamoto, MD, Toshiaki Taoka, MD, Hiroyuki Nakase, MD, Kimihiko Kichikawa, MD); Mie University Graduate School of Medicine, Tsu, Mie (Hiroshi Tanemura, MD, Naoki Toma, MD, Masayuki Maeda, MD, Hidenori Suzuki, MD, Waro Taki, MD); Yagi Neurosurgical Hospital, Osaka (Hiroyuki Ohnishi, MD, Hirokatsu Taniguchi, MD); Wakayama Medical University, Wakayama (Arisa Umesaki, MD, Osamu Masuo, MD, Naoyuki Nakao, MD).

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