Dose-Dependent Effect of Statin Pretreatment on Preventing the Periprocedural Complications of Carotid Artery Stenting

Jeong-Ho Hong, MD; Sung-Il Sohn, MD; Jaehyuk Kwak, MD; Joonsang Yoo, MD; Hyuk Won Chang, MD; O-Ki Kwon, MD; Cheolkyu Jung, MD; Inyoung Chung, MD; Hee-Joon Bae, MD; Ji Sung Lee, PhD; Moon-Ku Han, MD

Background and Purpose—We investigated whether statin pretreatment can dose dependently reduce periprocedural complications in patients undergoing carotid artery stenting because of symptomatic carotid artery stenosis.

Methods—We enrolled a consecutive series of 397 symptomatic carotid artery stenosis (≥50% stenosis on conventional angiography) treated with carotid artery stenting at 2 tertiary university hospitals over a decade. Definition of periprocedural complications included any stroke, myocardial infarction, and death within 1 month after or during the procedure. Statin pretreatment was divided into 3 categories according to the atorvastatin equivalent dose: none (n=158; 39.8%), standard dose (<40 mg of atorvastatin, n=155; 39.0%), and high dose (≥40 mg; n=84; 21.2%). A multivariable logistic regression analysis with the generalized estimating equation method was used to investigate independent factors in periprocedural complications.

Results—The patients' mean age was 68.7 years (81.6% men). The periprocedural complication rates across the 3 categories of statin use were 12.0%, 4.5%, and 1.2%. After adjustment, a change in the atorvastatin dose category was associated with reduction in the odds of periprocedural complications for each change in dose category (standard-dose statin: odds ratio, 0.24; 95% confidence interval, 0.07–0.81; high-dose statin: odds ratio, 0.11; 95% confidence interval, 0.01–0.96; *P* for trend=0.01). Administration of antiplatelet drugs was also an independent factor in periprocedural complications (OR, 0.18; 95% CI, 0.05–0.69).

Conclusions—This study shows that statin pretreatment may reduce the incidence of periprocedural complications dose dependently in patients with symptomatic carotid artery stenting. **(*Stroke*. 2017;48:1890-1894. DOI: 10.1161/STROKEAHA.117.016680.)**

Key Words: cerebral infarction ■ carotid stenosis ■ cerebrovascular disorders ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ stroke

A recent randomized trial showed that periprocedural complications occurred at similar rates in carotid endarterectomy (CEA) and carotid artery stenting (CAS). However, the incidence of periprocedural complications other than myocardial infarction was higher in CAS than in CEA.[1]

Statins are used widely given their pleiotropic and cholesterol-lowering effect; these drugs reduce the incidence of stroke and of myocardial infarction in stroke patients.[2,3] Statin pretreatment reduced the incidence of myocardial infarction after percutaneous coronary interventions[4,5] and the risk of perioperative stroke and mortality after CEA.[6,7] However, few studies have reported on whether statin use before CAS reduced periprocedural complications.[8–11] In addition, no specific statin dose has been recommended in carotid interventions, unlike for acute coronary interventions; for patients undergoing percutaneous coronary interventions, high-dose statin before percutaneous coronary interventions is recommended for reducing the risk of periprocedural complications.[12] It is also unknown whether statin pretreatment has dose-dependent effects on periprocedural complication risk in patients with CAS. Here, we investigated whether statin pretreatment is associated with a reduction of periprocedural complications and whether statin has dose-dependent effects on periprocedural complication risks in patients undergoing CAS for symptomatic carotid stenosis.

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From the Department of Neurology (J.-H.H., S.-I.S., J.K., J.Y.); Department of Radiology (H.W.C.), Keimyung University School of Medicine, Dongsan Medical Center, Daegu, Korea; Department of Neurology (I.C., H.-J.B., M.-K.H.), Department of Neurosurgery (O.-K.K.), and Department of Radiology (C.J.), Seoul National University Bundang Hospital, Seongnam, Korea; and Clinical Trial Center, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea (J.S.L.).

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Correspondence to Moon-Ku Han, MD, PhD, Department of Neurology, Stroke Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do, 463–707, Korea. E-mail mkhan@snu.ac.kr

Subjects and Methods

Selection of Study Patients and Data Collection

Our study population was collected retrospectively from a prospective CAS registry of 2 tertiary university hospitals, between July 2003 and June 2013. Eligibility criteria for the current investigation were the following. (1) Patients treated with CAS for symptomatic carotid stenosis, defined as a transient ischemic attack, transient monocular visual loss, or any ischemic stroke affected by a relevant carotid artery within 180 days before procedure. (2) Patients with carotid artery stenosis of >50%, as measured by the North American Symptomatic Carotid Endarterectomy Trial[13] criteria on conventional catheter angiography. Patients with inaccessible vessels for revascularization or who had recently (<7 days) stroke of a size sufficiently large to predict hemorrhagic conversion during the procedure were excluded. Life expectancy of <1 year or any acute, serious medical problem was also criteria for exclusion.

We obtained demographics, vascular risk factors, current medication regimes, and procedural characteristics from the CAS registry database. Neurological examination was performed by independent neurologists or neurosurgeons immediately and again 24 hours after the stenting procedure, and daily thereafter, until discharge from the hospital. After discharge, a 30-day clinical event history was obtained by neurologists or neurosurgeons during outpatient clinic visits or by trained nurses by telephonic interviews.

The statin name and dose were ascertained by self-reporting or hospital record review. Patients were accordingly categorized into no-statin, standard-dose (≤40 mg), and high-dose statin groups (> 40 mg) according to the atorvastatin-equivalent dose, based on the lipid reduction fraction at the time of CAS, independently of the duration of therapy.[14,15] Data from subjects with complete lipid profiles were used for comparison of patients in the 3 groups. The data were collected prospectively to monitor the quality of stroke care. The study was approved by the local institutional review boards of each center.

Periprocedural complications were defined as the composite outcome of any stroke, myocardial infarction, or death because of any cause during or within 1 day after the CAS procedure (immediate procedural events) and 1 to 30 days after the procedure (30-day clinical events). Stroke was defined as an acute neurological deficit with focal signs and symptoms on neurological examination, regardless of symptom duration, and classified as ischemic or hemorrhagic, based on computed tomography or magnetic resonance imaging. Myocardial infarction was defined by the third universal definition.[16] Ischemic heart disease was defined as a composite variable of myocardial infarction, unstable angina, percutaneous coronary interventions, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty.

Table 1. Baseline Characteristics of Patients Undergoing Stenting for Symptomatic Carotid Artery Stenosis

	Total (n=397)	No Statin (n=158)	Standard-Dose Statin (n=155)	High-Dose Statin (n=84)	*P* Value
Age, y	68.7±9.9	68.5±9.4	69.1±10.7	68.3±9.4	0.79
Sex (men), n (%)	324 (81.6%)	135 (85.4%)	119 (76.8%)	70 (83.3%)	0.13
Vascular risk factors					
Hypertension	275 (69.3%)	98 (62.0%)	109 (70.3%)	68 (81.0%)	0.009
Diabetes mellitus	169 (42.6%)	67 (42.4%)	64 (41.3%)	38 (45.2%)	0.84
Dyslipidemia	99 (24.9%)	11 (7.0%)	59 (38.1%)	29 (34.5%)	<0.0001
Smoking	182 (45.8%)	74 (46.8%)	71 (45.8%)	37 (44.0%)	0.92
Atrial fibrillation	30 (7.6%)	8 (5.1%)	16 (10.3%)	6 (7.1%)	0.21
Ischemic heart disease	80 (20.2%)	37 (23.4%)	21 (13.5%)	22 (26.2%)	0.03
Myocardial infarction	30 (7.6%)	13 (8.2%)	9 (5.8%)	8 (9.5%)	0.54
Unstable angina	53 (13.4%)	24 (15.2%)	14 (9.0%)	15 (17.9%)	0.11
PCI	26 (6.5%)	13 (8.2%)	8 (5.2%)	5 (6.0%)	0.53
CABG	14 (3.5%)	9 (5.7%)	3 (1.9%)	2 (2.4%)	0.16
PTCA	5 (1.3%)	2 (1.3%)	2 (1.3%)	1 (1.2%)	—
Acute carotid stenting	43 (10.8%)	20 (12.7%)	15 (9.7%)	8 (9.5%)	0.64
Procedure within 2 wk of onset	241 (60.7%)	96 (60.8%)	88 (56.8%)	57 (67.9%)	0.25
Pre-stenting medication					
Antiplatelet therapy	383 (96.5%)	147 (93.0%)	152 (98.1%)	84 (100%)	0.008
Severity of lesional stenosis	80.9±11.9	81.1±12.5	80.5±12.2	81.1±10.6	0.90
50–69%	44 (11.1%)	20 (12.7%)	19 (12.3%)	5 (6.0%)	
70–89%	221 (55.7%)	81 (51.3%)	87 (56.1%)	53 (63.1%)	0.34
≥90%	132 (33.2%)	57 (36.1%)	49 (31.6%)	26 (31.0%)	
Contralateral stenosis > 50%	96 (24.2%)	37 (23.4%)	42 (27.1%)	17 (20.2%)	0.48
Post-stenting dilatation	135 (34.0%)	49 (31.0%)	56 (36.1%)	30 (35.7%)	0.59
Embolic protection device	355 (89.4%)	137 (86.7%)	143 (92.3%)	75 (89.3%)	0.28

CABG indicates coronary artery bypass graft; PCI, percutaneous coronary intervention; and PTCA, percutaneous transluminal coronary angioplasty.

Table 2. Periprocedural Complications Within 30 Days After Stenting for Symptomatic Carotid Artery Stenosis

	Total (n=397)	No Statin (n=158)	Standard-Dose Statin (n=155)	High-Dose Statin (n=84)	*P* Value
Periprocedural complications, n (%)	27 (6.8)	19 (12.0)	7 (4.5)	1 (1.2)	0.002
Immediate procedural events	16 (4.0)	11 (7.0)	5 (3.2)	0 (0)	0.026
Ischemic stroke	8 (2.0)	5 (3.2)	3 (1.9)	0 (0)	
Hemorrhagic stroke	6 (1.5)	4 (2.5)	2 (1.3)	0 (0)	
Myocardial infarction	1 (0.3)	1 (0.6)	0 (0)	0 (0)	
Death	2 (0.5)	2 (1.3)	0 (0)	0 (0)	
30-d clinical events	14 (3.5)	10 (6.3)	3 (1.9)	1 (1.2)	0.046
Ischemic stroke	4 (1.0)	4 (2.5)	0 (0)	0 (0)	
Hemorrhagic stroke	1 (0.3)	0 (0)	0 (0)	1 (1.2)	
Myocardial infarction	3 (0.8)	1 (0.6)	2 (1.3)	0 (0)	
Death	7 (1.8)	6 (3.8)	1 (0.6)	0 (0)	

Procedure Protocol

All patients requiring CAS who were admitted to 2 different hospitals were treated following the same guidelines.[17] Dual antiplatelet therapy with aspirin plus clopidogrel was administered routinely for at least 7 days before the procedure. For urgent CAS, aspirin and a loading dose of clopidogrel (300 mg) were administered. An intravenous bolus injection of 3000 U heparin was given after femoral artery puncture. Cerebral embolic protection devices were used in most of the procedures. Post-stenting balloon dilatation was used at the discretion of the operators. Afterward, at least 1 antiplatelet drug was administered for ≥1 year.

Statistical Analysis

Variables were presented as means±SDs, medians (interquartile range), or frequencies (percentages) as appropriate. $P<0.05$ was considered to indicate significance. Statistical analyses were performed using SAS Statistical software, version 9.2 for Windows (SAS, Cary, NC). To compare baseline characteristics and periprocedural complications among the 3 groups according to the pre-treatment statin dose, Pearson χ^2 test was used for categorical variables, ANOVA for parametric variables, and the Kruskal–Wallis test for nonparametric variables because the periprocedural period was relatively short. Multivariable logistic regression analysis using the generalized estimating equation method, with predefined variables (quartile of recruitment) and the potential confounders that were significantly associated with periprocedural complication in a bivariate analysis ($P<0.2$), was performed to predict the occurrence of periprocedural complications and to consider the center effect.

Results

Finally, 397 CAS cases were enrolled; the mean age was 68.7±9.9 years and 324 cases (81.6%) included men. In total, 239 cases (60.2%) received statins; atorvastatin was the most commonly used statin (n=191; 80.0%). Statin drugs and doses used before CAS are summarized in Table I in the online-only Data Supplement.

There were 39.8% cases in the no-statin, 39.0% in the standard-dose, and 21.1% in the high-dose groups. At baseline, there were significant differences in the proportion of hypertension, dyslipidemia, and ischemic heart disease and pre-treatment with antiplatelet drugs among the groups ($P<0.05$). Although 2 centers used a CAS protocol following the same guidelines, antiplatelet drugs were not administered before CAS in 3.5% of cases (n=14): these cases were enrolled in the early phase of the 10-year CAS registry, and most involved urgent procedures. Urgent carotid stenting was performed in 43 cases (10.8%), and the proportion of acute carotid stenting did not differ among the 3 groups (Table 1).

High- and standard-dose statin use was associated with periprocedural complication reduction within 30 days, as compared with the no-statin group (12.0% versus 4.5% versus 1.2%; $P=0.002$). When we divided the data into immediate procedural events and 30-day clinical events, these trends remained unchanged (Table 2). After adjusting for

Table 3. Multivariable Logistic Regression Analysis With Generalized Estimating Equation Method of Prediction for Periprocedural Complications Within 30 Days After Stenting for Symptomatic Carotid Artery Stenosis

	OR	95% CI	*P* Value
Male	0.57	0.21–1.54	0.27
Hypertension	1.85	0.74–4.62	0.19
Ischemic heart disease	0.70	0.24–2.05	0.52
Dyslipidemia	1.34	0.37–4.94	0.66
Antiplatelet	0.18	0.05–0.69	0.01
Quartile of recruitment			
1–100	Reference		
101–199	0.75	0.29–1.98	0.56
200–298	0.49	0.14–1.68	0.26
299–397	0.35	0.09–1.37	0.13
Statin			
No-statin use	Reference		
Standard-dose statin (atorvastatin <40 mg)*	0.24	0.07–0.81	0.02
High-dose statin (atorvastatin ≥40 mg)*	0.11	0.01–0.96)	0.046

Based on lipid reduction fraction, statin drug and dose were substituted by atorvastatin equivalent dose. CI indicates confidence interval; and OR, odds ratio.

*$P=0.01$ for linear trend effect of statin dose

Table 4. Lipid Profiles Stratified According to Statin Dose

	Total (92.5%; 347/375)	No Statin (89.5%; 136/152)	Standard-Dose Statin (92.5%; 135/146)	High-Dose Statin (98.7%; 76/77)	*P* Value
Total cholesterol	174.0±43.7	171.9±37.9	179.5±50.6	167.9±39.5	0.14
Triglyceride	132.9±76.1	133.5±76.9	138.6±84.4	121.7±56.6	0.3
HDL	42.1±10.6	42.5±11.3	42.2±9.7	41.5±11.0	0.8
LDL	103.1±35.6	100.4±29.2	108.5±42.0	98.4±32.8	0.07

Data are shown for subjects with a complete lipid profile. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

confounders, including sex, hypertension, ischemic heart disease, hyperlipidemia, and antiplatelet pretreatment, as well as the quartile of recruitment (as a learning curve effect; ie, time dependent) and a center effect, statin pre-treatment remained an independent predictor of periprocedural complications after CAS. There was a linear trend effect of the statin dose (standard-dose statin: odds ratio, 0.24; 95% CI, 0.07–0.81; high-dose statin: odds ratio, 0.11, 95% CI, 0.01–0.96; *P* for trend=0.01), but no significant difference in the lipid profiles among the 3 groups (Tables 3 and 4).

Discussion

Our study indicated a dose-dependent effect of statins on risk reduction for periprocedural complications after CAS, independent of baseline lipid profiles. Considering that arterial stenting may induce platelet activation, thrombosis, and inflammation within the vessel wall,[18,19] embolic events are more important periprocedural complications during CAS than during CEA.[20,21] Recently, evidence has increasingly indicated that premorbid statin use can significantly decrease the rate of cardiovascular and cerebrovascular events after vascular procedures and CEA, as well as secondary stroke events.[4–7,22–25] However, current guidelines for the management of patients with carotid artery disease also do not recommend statin use, or a specific dose before CAS for carotid artery stenosis, because of a lack of evidence.[17]

In our study, 6.8% of cases had experienced periprocedural complications within 1 month of the procedure; this rate is similar to that reported in previous clinical trials that enrolled patients with symptomatic CAS.[20,26] However, the incidence rate was only 3.3% (8/239) in the high- and standard-dose groups. Our novel findings of the dose-dependent effect of statins on the risk of periprocedural complications in symptomatic patients undergoing CAS may involve various mechanisms. Symptomatic carotid arteries have unstable or vulnerable plaques that can cause thrombotic and embolic complications during CAS. Statin pre-treatment improves atheroma stability[27,28] and can reduce the embolic debris during CAS.[29]

Several studies have shown congruent findings on the relationship between the reduction of the risk of periprocedural complications in CAS and statin pretreatment.[8,9,11] Patti et al[10] conducted randomized controlled studies evaluating the clopidogrel load and high-dose statin reload in statin-treated patients undergoing CAS: this strategy reduced 50% of the ischemic event risk. However, these results cannot be generalized to only symptomatic patients because of the heterogeneity and relatively small number of subjects and do not clarify the appropriate statin dose.

In our study, cholesterol levels were not different in patients with and without periprocedural complications, in agreement with a previous study.[11] Ibrahimi et al[32] assessed the correlation between plaque stability by meta-analysis, based on echogenicity during ultrasound imaging and lipid profile changes, but found no such relationship. Our results suggest pleiotropic effects of antithrombotic and profibrinolytic pathways, mediated by statins, which are dose dependent, similar to the cholesterol-lowering properties of statins.[33,34]

This study has several limitations. Given its nonrandomized retrospective design, our findings should be interpreted cautiously. The patient selection leans toward less challenging patients and could thus misrepresent the risks in the excluded patients. Moreover, our patients were limited to only symptomatic CAS patients. Patients with clinically asymptomatic carotid stenosis may also have unstable plaque; thus, our findings should be validated in asymptomatic cohorts. We could not evaluate asymptomatic embolic infarction by diffusion-weighted images of the brain after the procedure in our retrospective study. Our subjects were collected at 2 different centers over a period of ≈10 years, which may have influenced our findings.[35] We therefore adjusted for the center and learning curve effects as confounders during multivariable logistic regression analysis, using the generalized estimating equation method. Finally, this study was not powered to address different statin regimens.

Although we cannot suggest the pre-CAS statin treatment duration for patients with symptomatic carotid stenosis, we demonstrated that statin pretreatment before CAS for symptomatic carotid stenosis can reduce periprocedural complications dose dependently. We recommend the use of a high-dose statin before CAS in patients with symptomatic carotid stenosis.

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Disclosures

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