

Statins Reduce Neurologic Injury in Asymptomatic Carotid Endarterectomy Patients

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Background and Purpose—Statins are neuroprotective in a variety of experimental models of cerebral injury. We sought to determine whether patients taking statins before asymptomatic carotid endarterectomy exhibit a lower incidence of neurological injury (clinical stroke and cognitive dysfunction).

Methods—A total of 328 patients with asymptomatic carotid stenosis scheduled for elective carotid endarterectomy consented to participate in this observational study of perioperative neurological injury.

Results—Patients taking statins had a lower incidence of clinical stroke (0.0% vs 3.1%; $P=0.02$) and cognitive dysfunction (11.0% vs 20.2%; $P=0.03$). In a multivariate regression model, statin use was significantly associated with decreased odds of cognitive dysfunction (odds ratio, 0.51 [95% CI, 0.27–0.96]; $P=0.04$).

Conclusions—Preoperative statin use was associated with less neurological injury after asymptomatic carotid endarterectomy. These observations suggest that it may be possible to further reduce the perioperative morbidity of carotid endarterectomy.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00597883 (*Stroke*. 2013;44:1150-1152.)

Key Words: carotid stenosis ■ cognitive dysfunction ■ statins ■ stroke

The introduction of statins has reduced the natural history risk of asymptomatic carotid artery stenosis to such a level that the benefit of carotid endarterectomy (CEA) for those with high-grade stenosis is almost of negligible benefit.¹ It remains unclear whether statins are actually neuroprotective in humans.

The Asymptomatic Carotid Surgery Trial suggested a reduction in the periprocedural risk of stroke and death from 6% to 2% for those “on lipid-lowering agents.”² However, administrative data from Canada on 1252 asymptomatic CEAs failed to demonstrate a protective effect for statins.³ The effect of statins on postoperative cognitive dysfunction has not been studied previously. The aim of this study was to determine whether statins are neuroprotective in a cohort of asymptomatic CEA patients by evaluating statin use and neurological injury, defined by both clinical stroke and significant cognitive dysfunction.

Materials and Methods

Patients

A total of 328 asymptomatic elective CEA patients with high-grade carotid artery stenosis were enrolled with written informed consent in this institutional review board-approved observational study. Two-hundred patients were taking statins at the time of surgery, and 124 were not. A reference group was used to account for trauma of

surgery, effects of general anesthesia, and practice effect associated with repeated neurocognitive testing, as described previously.⁴ Patients were examined with a previously described battery of neuropsychometric tests preoperatively and 1 day postoperatively.⁴ Four patients had a perioperative clinical stroke defined by significant clinical manifestations and radiographic infarcts detected by magnetic resonance imaging ($n=2$) or computerized axial tomography ($n=2$) and were excluded from neuropsychometric analysis. A total of 324 asymptomatic patients completed the entire battery of neuropsychometric tests at both time points. The neuropsychometric tests evaluate a variety of cognitive domains, including verbal memory, visuospatial organization, motor function, and executive action, as described previously.⁴

A variety of factors affect the neuropsychometric performance of patients after CEA, but only age >75 years and diabetes mellitus have been shown previously to significantly and independently affect performance.⁵ Other factors that might also affect performance, but have not been shown to independently affect performance, were evaluated as well. These included years of education, body mass index, history of smoking, extensive peripheral vascular disease, hypertension, and duration of cross-clamping of the carotid artery. We have included these factors in our univariate and multivariate analyses.

Anesthesia and Surgery

As described previously,⁴ the surgical technique, anesthetic management, and indications for CEA have remained constant at this institution over the duration of this study, as described previously.⁴

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Drs Heyer and Connolly had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical Analyses

Neuropsychometric performance was calculated, as described previously.^{4,6} Patients were considered to have cognitive dysfunction based on 2 criteria to account for both focal and global/hemispheric deficits: ≥ 2.0 -SD worse performance than the reference group in ≥ 2 cognitive domains or ≥ 1.5 -SD worse performance than the reference group in all 4 cognitive domains.

Statistics were performed using R environment (R Development Core Team, Vienna, Austria). For univariate analyses, Student *t* test, Wilcoxon rank-sum test, Fisher exact test, Pearson χ^2 test, and simple logistic regression were used where appropriate. The α level was adjusted for multiple hypotheses using the Benjamini and Hochberg method to control for the false discovery rate.⁷ A multiple logistic regression model was constructed to identify independent predictors of cognitive dysfunction. All of the factors with $P < 0.20$ in a simple univariate logistic regression were entered into the final model. Model fit and calibration were confirmed with the likelihood ratio test, Hosmer-Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. The sample mean was imputed in the event of missing values for predictor variables. $P \leq 0.05$ was considered significant.

Results

There were no differences in patient characteristics between those taking and not taking statins (Table 1). Patients taking statins had a significantly lower incidence of perioperative stroke (0.0% vs 3.1%; $P = 0.02$) and a significantly lower incidence of cognitive dysfunction (11.0% vs 20.2%; $P = 0.03$) compared with patients not taking statins. The final logistic regression model included statin use and body mass index (Table 2). Statin use was associated with significantly decreased odds of cognitive dysfunction (odds ratio, 0.51 [95% CI, 0.27–0.96]; $P = 0.04$). No other variables were significant in the model.

Discussion

Although some preliminary data suggest that preoperative and perioperative statin use may be associated with a lower incidence of perioperative stroke in symptomatic patients undergoing CEA, the data for asymptomatic patients are nearly nonexistent.^{2,3} This study demonstrates for the first time that statin use is associated with a lower incidence of perioperative neurological injury in asymptomatic patients, as defined by both clinical stroke and cognitive dysfunction. Our previous studies in CEA patients have confirmed that the degree

Table 2. Univariate and Multivariate Logistic Regression Models

Characteristic	Univariate		Multivariate	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age >75, y	1.01 (0.98–1.05)	0.51		
Education, y	0.97 (0.88–1.06)	0.46		
BMI	0.94 (0.87–1.01)	0.13	0.96 (0.88–1.03)	0.24
History of smoking	0.99 (0.51–2.00)	0.99		
Hypertension	1.30 (0.70–2.46)	0.41		
Diabetes mellitus	0.87 (0.36–1.88)	0.73		
PVD	0.69 (0.32–1.38)	0.31		
Cross-clamp duration, min	1.00 (0.98–1.02)	0.99		
Statin use	0.49 (0.26–0.91)	0.02	0.51 (0.27–0.96)	0.04

BMI indicates body mass index; and PVD, peripheral vascular disease.

of cognitive dysfunction reported in this study is associated with actual brain injury,⁸ and studies by other groups suggest that postoperative cognitive dysfunction can be predictive of not only disability and early retirement but even early death.⁹ Thus, we feel that the witnessed protection is clinically significant.

Finally, we recognize the limitations of our study. The reasons for prescription and duration of statin use were not recorded. Although there are advantages of a single-center study in terms of consistency in surgical/anesthetic technique, as well as neuropsychometric evaluation, there are limitations associated with the applicability of our results to a generalized population. Therefore, all of these weaknesses would be addressed by a multicenter trial, which is critical in determining the clinical significance of these findings.

Conclusions

Statin use is associated with less neurological injury, as defined by both clinical stroke and cognitive dysfunction, after asymptomatic CEA. These observations, if confirmed in prospective trials, suggest that it may be possible to further reduce the perioperative morbidity of CEA.

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Disclosures

None.

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Table 1. Patient Characteristics: No Statin and Statins

Characteristic	No Statins (n=124)	Statins (n=200)	P Value
Age >75 y	33.1%	25.5%	0.18
Education, y	14.7±3.1	14.7±3.5	0.09
BMI	26.3±3.8	27.5±4.9	0.07
History of smoking	65.3%	73.5%	0.15
Hypertension	44.4%	56.5%	0.04
Diabetes mellitus	16.1%	20.5%	0.41
PVD	25.8%	32.0%	0.29
Cross-clamp duration, min	41.3±16.6	45.5±18.5	0.05
Cognitive dysfunction	20.2%	11.0%	0.04

Data show the mean±SD unless otherwise specified.

BMI indicates body mass index; and PVD, peripheral vascular disease.

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