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## Statins Reduce Neurologic Injury in Asymptomatic Carotid Endarterectomy Patients

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### Abstract

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

**Methods**—Three hundred twenty-eight (328) patients with asymptomatic carotid stenosis scheduled for elective CEA consented to participate in this observational study of perioperative neurologic 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 (OR: 0.51 [0.27-0.96],  $P=0.04$ ).

**Conclusions**—Pre-operative statin use was associated with less neurologic injury following asymptomatic CEA. These observations suggest that it may be possible to further reduce the perioperative morbidity of CEA.

Clinical Trial Registration-URL: <http://www.ClinicalTrials.gov>. Unique Identifier: NCT00597883.

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#### Disclosures

Drs. Eric J. Heyer and E. Sander 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.

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Search terms: [13] cerebrovascular disease/stroke, [49] carotid stenosis, [76] carotid endarterectomy

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## I. Introduction

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<sup>1</sup>. It remains unclear whether statins are actually neuroprotective in humans.

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

## II. Materials and Methods

### Patients

Three hundred twenty-eight (328) asymptomatic elective CEA patients with high-grade carotid artery stenosis were enrolled with written informed consent in this IRB-approved observational study ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) NCT00597883). Two hundred (200) 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 previously described<sup>4</sup>\_ENREF\_8. Patients were examined with a previously described battery of neuropsychometric tests pre-operatively and 1 day post-operatively<sup>4</sup>. Four (4) 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. Three hundred twenty-four (324) asymptomatic patients completed the entire battery of neuropsychometric tests at both time points. The neuropsychometric tests evaluate a variety of cognitive domains – verbal memory, visuo-spatial organization, motor function, and executive action – as previously described<sup>4</sup>.

A variety of factors affect the neuropsychometric performance of patients after CEA, but only age >75 and diabetes mellitus have been previously shown to significantly and independently affect performance<sup>5</sup>\_ENREF\_10. 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 (BMI), history of smoking, extensive peripheral vascular disease (PVD), hypertension, and duration of cross-clamping of the carotid artery. We have included these factors in our uni- and multi-variate analyses.

### Anesthesia and Surgery

As previously described<sup>4</sup>, the surgical technique, anesthetic management, and indications for CEA have remained constant at this institution over the duration of this study, as previously described<sup>4</sup>\_ENREF\_8

### Statistical Analyses

Neuropsychometric performance was calculated, as described previously<sup>4,6</sup>\_ENREF\_5. Patients were considered to have cognitive dysfunction based on two criteria to account for both focal and global/hemispheric deficits\_ENREF\_11: (1) 2SD worse performance than

reference group in two or more cognitive domains or (2) 1.5SD worse than the reference group in all four cognitive domains.

Statistics were performed using R environment (R Development Core Team, Vienna, Austria, 2008). For univariate analyses, Student's t-test, Wilcoxon rank sums test, Fisher's exact test, Pearson's  $\chi^2$  test, and simple logistic regression were used where appropriate. The alpha level was adjusted for multiple hypotheses using the Benjamini and Hochberg method to control for the false discovery rate (FDR)<sup>7</sup>. A multiple logistic regression model was constructed to identify independent predictors of cognitive dysfunction. All 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.  $P < 0.05$  was considered significant.

### III. Results

#### Neurologic Injury & Statin Use

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 to patients not taking statins. The final logistic regression model included statin use and BMI (Table 2). Statin use was associated with significantly decreased odds of cognitive dysfunction (OR: 0.51 [0.27-0.96],  $P=0.04$ ). No other variables were significant in the model.

### IV. Discussion

While some preliminary data suggests that pre- and perioperative statin use may be associated with a lower incidence of perioperative stroke in symptomatic patients undergoing CEA, the data for asymptomatic patients is nearly non-existent<sup>2,3</sup>. This study demonstrates for the first time that statin use is associated with a lower incidence of perioperative neurologic injury in asymptomatic patients as defined by both clinical stroke and cognitive dysfunction. Our previous studies in CEA patients have confirmed that the degree of cognitive dysfunction reported in this study is associated with actual brain injury<sup>8</sup>, and studies by other groups suggest that post-operative cognitive dysfunction can be predictive of, not only disability and early retirement, but even early death<sup>9</sup>. We thus 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 was not recorded. While 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 applicability of our results to a generalized population. Therefore, all of these weaknesses would be addressed by a multi-center trial, which is critical in determining the clinical significance of these findings.

### V. Conclusions

Statin use is associated with less neurologic injury, as defined by both clinical stroke and cognitive dysfunction, following 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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**Table 1**

Patient Characteristics – No Statin and Statins\*.

	No Statins N=124	Statins N=200	P
Age >75 years	33.1%	25.5%	0.18
Education, years	14.7±3.1	14.7±3.5	0.09
BMI <sup>†</sup>	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 <sup>†</sup>	25.8%	32.0%	0.29
Cross Clamp Duration, mins	41.3±16.6	45.5±18.5	0.05
Cognitive Dysfunction	20.2%	11.0%	0.04

\* Mean ± standard deviation.

<sup>†</sup> BMI indicates body mass index; PVD indicates peripheral vascular disease.

**Table 2**

Univariate and Multivariate Logistic Regression Models.

	<b>Univariate Odds Ratio</b>	<b>P</b>	<b>Multivariate Odds Ratio</b>	<b>P</b>
Age >75, years	1.01 (0.98-1.05)	0.51		
Education, years	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, mins	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; PVD indicates peripheral vascular disease.