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Statins Are Associated With Better Outcomes After Carotid Endarterectomy in Symptomatic Patients

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Background and Purpose—Statins have been associated with a reduction in mortality from noncardiac surgery. This study aimed to determine whether statin use on admission to hospital for carotid endarterectomy was associated with a reduction of in-hospital adverse outcomes.

Methods—Data describing patient characteristics, surgical indication, statin treatment, and in-hospital outcomes of death, ischemic stroke or death and cardiac outcomes were collected from a chart review of all patients (3360) undergoing carotid endarterectomy in Western Canada from January 2000 to December 2001. Outcomes of patients on statins versus those not on statins were compared using logistic regression to account for differences in patient characteristics, and propensity score methods to account for factors influencing patient allocation to statins.

Results—Eight hundred and fifteen of 2031 symptomatic patients and 665 of 1252 asymptomatic patients were on a statin at the time of hospital admission. Statin use by symptomatic patients was associated with reduced in-hospital mortality and in-hospital ischemic stroke or death, but not in-hospital cardiac outcomes (adjusted odds ratio 0.25 [CI, 0.07 to 0.90], 0.55 [CI, 0.32 to 0.95], 0.87 [CI, 0.49 to 1.54], respectively). The improvement in outcomes was robust when tested using propensity score matching. This association was not seen in asymptomatic patients on statins (adjusted odds ratio, in-hospital mortality 0.54 [CI, 0.13 to 2.24]; in-hospital ischemic stroke or death 1.34 [CI, 0.61 to 2.93]; in-hospital cardiac outcomes 1.37 [CI, 0.73 to 2.58]).

Conclusions—These findings are suggestive of a protective effect of statin therapy in symptomatic patients pre-treated at the time of carotid endarterectomy, though this needs confirmation in a randomized controlled trial. (*Stroke*. 2005;36:2072-2076.)

Key Words: carotid endarterectomy ■ neuroprotection ■ outcome ■ perioperative complications ■ statins

Performing carotid endarterectomy for the prevention of stroke has a solid evidence base in patients with symptomatic disease,¹ and an evolving role in asymptomatic disease with the publishing of recent trial results.^{2,3} The effectiveness of the procedure outside of the clinical trial setting depends on a low perioperative complication rate, particularly in categories where the absolute reduction of risk of stroke is more modest (eg, moderate symptomatic stenosis and asymptomatic disease). Therefore, any intervention that may reduce the incidence of perioperative complications may extend the potential benefit of the procedure. Statins have been shown to prevent stroke in clinical trials in different settings^{4,5,6} and have been associated with reduced adverse outcomes in noncardiac surgery.^{7,8} In addition, statins have putative neuroprotective attributes.⁹ The purpose of this observational study was to assess whether statin use before carotid endarterectomy is associated with reduced in-hospital adverse outcomes.

Subjects and Methods

Participants

All carotid endarterectomy cases performed in four Western Canadian provinces from January 2000 to December 2001 were identified from administrative databases. Permission to conduct a chart review of the cases identified was granted by all hospitals performing carotid endarterectomies, following Institutional Review Board approval from the University of Calgary.

Data Collection

Two trained chart reviewers entered study variables and indications for surgery from the charts into an electronic database that is described in detail elsewhere.¹⁰

Study Variables

The exposure variable for the analysis was whether the patient was on statin therapy at time of admission to hospital for carotid endarterectomy. Each statin was assumed to have an equal effect on the outcome¹¹; therefore, all statins were counted together as a single variable for the purposes of the analysis. The chart reviewers were

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TABLE 1. Patient Characteristics by Symptom Status and Statin Use

Characteristic	Asymptomatic (n=1252)				Symptomatic (n=2031)			
	Total	Statin (n=665)	No Statin (n=587)	P Value	Total	Statin (n=815)	No Statin (n=1216)	P Value
Age median (IQR)		71 (65–76)	73 (67–78)			70 (64–76)	73 (66–79)	
Female (%)	443 (35.4)	230 (34.6)	213 (36.3)	0.53	667 (32.8)	262 (32.2)	405 (33.3)	0.59
Atrial fibrillation (%)	116 (9.3)	61 (9.2)	55 (9.4)	0.91	156 (7.7)	63 (7.7)	93 (7.7)	0.95
Previous myocardial infarction (%)	369 (29.5)	237 (35.6)	132 (22.5)	<0.001	499 (24.6)	258 (31.7)	241 (19.8)	<0.001
Congestive heart failure (%)	108 (8.6)	50 (7.5)	58 (9.9)	0.14	139 (6.8)	67 (8.2)	72 (5.9)	0.044
Peripheral vascular disease (%)	508 (40.6)	275 (41.4)	233 (39.7)	0.55	568 (28.0)	269 (33.0)	299 (24.6)	<0.001
Diabetes mellitus (%)	227 (18.1)	129 (19.4)	98 (16.7)	0.22	397 (19.6)	163 (20.0)	234 (19.2)	0.67
Dementia (%)	18 (1.4)	8 (1.2)	10 (1.7)	0.46	35 (1.7)	16 (2.0)	19 (1.6)	0.50
Chronic pulmonary disease (%)	280 (22.4)	131 (19.7)	149 (25.4)	0.016	447 (22.0)	180 (22.1)	267 (22.0)	0.95
Peptic ulcer disease (%)	94 (7.5)	48 (7.2)	46 (7.8)	0.68	179 (8.8)	66 (8.1)	113 (9.3)	0.35
Liver disease (%)	18 (1.4)	5 (0.8)	13 (2.2)	0.03	22 (1.1)	8 (1.0)	14 (1.2)	0.72
Cancer (%)	121 (9.7)	50 (7.5)	71 (12.4)	0.006	203 (10.0)	79 (9.7)	124 (10.2)	0.71
HIV/AIDS (%)	4 (0.3)	1 (0.2)	3 (0.5)	0.26	7 (0.3)	3 (0.4)	4 (0.3)	0.88

IQR indicates interquartile range

provided with both the generic and trade name for each available statin medication to ensure the maximum capture of statin usage prior to surgery. Algorithms were developed to ensure no double counting. No data were collected on dose or duration of treatment, or the potential complications of statin use.

The pre-specified outcomes were in-hospital mortality, in-hospital ischemic stroke or death, and in-hospital cardiac events (a composite of myocardial infarction and unstable angina). Strokes were classified as ischemic or hemorrhagic. The decision to exclude hemorrhagic stroke from the combined stroke or death outcome was made a priori, given the evidence that statins do not affect the incidence of hemorrhagic stroke.⁶

Patient characteristics (patient comorbidities constituting the Charlson index,¹² sex and age), hospital site identifier, and indication for surgery were included in the analysis.

Statistical Analyses

All analyses were performed separately for the asymptomatic and symptomatic indications. Crude rates for each outcome were tested using the Fisher Exact test. Crude odds ratios (ORs) for the association between statin use and each outcome were calculated. Two different logistic regression models were then used to adjust the crude ORs, the first using all patient characteristics, and the second using only significant patient characteristics identified by backward elimination. Given the virtually identical findings from these two modeling approaches, only results from the former are presented. We also performed an adjusted analysis that additionally included dummy variables for hospital site in order to control for possible hospital site factors that may confound the association between statins and outcomes. The area under the receiver-operating characteristic (ROC) curve was determined and reported for each multivariable model that we developed.

Propensity scores for the likelihood of selection to statin use by patient characteristic were determined. Those characteristics associated with either a higher or a lower propensity to be treated with a statin are presented with their respective odds ratios for treatment assignment.¹³ The area under the ROC curve for the propensity score model was also determined. The propensity score was then used in two different ways. In a first propensity analysis, it was included as a further term in the logistic regression model. In our second propensity analysis, propensity score matching between statin and no statin groups was performed using three different matching methods (kernel, stratified, and radius) only for those outcomes which showed significance. This permitted the testing of the robustness of the

treatment effect by reducing any selection bias in its estimation.¹⁴ All analyses were performed using STATA 8 (Statacorp).

Results

Participants

A total of 3360 carotid endarterectomies were performed in four Western Canadian provinces from January 2000 to December 2001, and of these, 3309 (98.5%) were reviewed. The final analysis included 3283 (97.7%) of charts. Twenty-six cases were excluded: 20 attributable to missing demographics and 6 because the side of surgery was not identified. Carotid endarterectomy was performed on 2031 patients with a symptomatic indication, 815 of whom were on a statin. One thousand five hundred eighty-nine of the 2031 symptomatic patients (78.2% of symptomatic patients) had cerebral events and 442 (21.8%) had ocular events. Nine hundred and fifty-five (47.0%) had a transient ischemic attack. Of the 1252 patients with an asymptomatic indication, 665 were on a statin. The patient characteristics are summarized in Table 1 by operative indication.

Propensity for Statin Therapy

Patients had a higher propensity to be on statin therapy with a previous myocardial infarction (OR 1.53; 95% CI 1.38 to 1.70) or peripheral vascular disease (OR 1.19; 95% CI 1.09 to 1.31), and a lower propensity to be on statin therapy with increasing age (OR 0.98; 95% CI 0.98 to 0.99), or with liver disease (OR 0.61; 95% CI 0.41 to 0.93). The area under the ROC curve for the multivariable model predicting statin use was 0.61.

Outcomes by Statin Use

For symptomatic patients, the crude in-hospital mortality rate was 0.4% (3/815) on statin compared with 1.2% (15/1216) not on statin, an absolute risk difference of 0.8% ($P=0.052$) in favor of those on statins. The figures for the outcome of in-hospital ischemic stroke or death were 2.5% (20/815) and

TABLE 2. Crude and Adjusted Odd Ratios of In-Hospital Outcomes by Statin Use for Patients With a Symptomatic Indication for Surgery

Outcome	Crude	Adjusted	Adjusted Plus Propensity Score	Adjusted Plus Propensity Score and Hospital
Death				
Odds Ratio	0.30	0.25	0.25	0.24
95% CI	0.08–1.03	0.07–0.90	0.07–0.89	0.06–0.91
ROC	0.62	0.85	0.85	0.89
Ischemic Stroke or Death				
Odds Ratio	0.59	0.55	0.55	0.55
95% CI	0.34–0.99	0.32–0.95	0.32–0.95	0.31–0.97
ROC	0.56	0.68	0.68	0.76
Cardiac				
Odds Ratio	0.95	0.87	0.87	0.82
95% CI	0.54–1.65	0.49–1.54	0.49–1.54	0.45–1.50
ROC	0.51	0.72	0.72	0.79

Outcome: Crude: statin exposure only; Adjusted: patient characteristics identified in Table 1 included in the logistic regression model; Adjusted plus Propensity Score: as Adjusted, including the propensity score in the logistic regression model; Adjusted plus Propensity Score and Hospital: as Adjusted Plus Propensity Score, including hospital site identifier as a dummy variable in the logistic regression model.

4.1% (50/1216) respectively, an absolute risk difference of 1.6% ($P=0.045$) in favor of those on statins. The figures for the outcome of in-hospital cardiac events were 2.7% (33/1216) for those on statins and 2.6% (21/815) for those not on statins, an absolute risk difference of 0.1% ($P=0.49$).

The crude in-hospital mortality rate for asymptomatic patients was 0.6% (4/665) on statin versus 1.0% (6/587) not on statin, an absolute risk difference of 0.4% in favor of the statin group ($P=0.53$). The figures for the outcome of in-hospital ischemic stroke or death were 2.6% (17/665) and 2.0% (12/587) respectively, an absolute risk difference of 0.6%, favoring those not on statin ($P=0.52$). The figures for the outcome of in-hospital cardiac events were 4.2% (28/665) for patients on statins and 3.1% (18/587) for patients not on statins, an absolute risk difference of 0.9% ($P=0.18$).

The crude in-hospital hemorrhagic stroke rate for symptomatic patients was 0.7% (6/815) on statin versus 0.5% (6/1216) not on statin, an absolute risk difference of 0.2% ($P=0.34$). The crude in-hospital hemorrhagic stroke rate for asymptomatic patients was 0.3% (2/665) on statin versus 0.3% (2/587) not on statin ($P=0.64$).

Tables 2 and 3 summarize the crude and adjusted OR and CI for each outcome by symptomatic and asymptomatic patients, respectively. After adjustment, only patients with a symptomatic indication for surgery who were on a statin had a significant reduction in both in-hospital mortality and in-hospital ischemic stroke or death. These findings were unchanged when the propensity score for statin therapy and hospital site were added to the logistic regression model.

This finding was robust when tested with the three different matching techniques for propensity scoring. When patients were matched to reduce the bias in estimation of potential treatment effect, absolute reductions in in-hospital mortality rate of 0.9% ($P=0.005$), 0.8% ($P=0.034$), and

0.9% ($P=0.016$) associated with statin use were seen using the kernel, stratified, and radius matching methods, respectively. The reductions associated with statin use for the in-hospital ischemic stroke or death rate were 1.7% ($P=0.022$), 1.5% ($P=0.055$), and 1.7% ($P=0.038$), respectively.

Discussion

Among symptomatic patients undergoing carotid endarterectomy, statin use on admission to hospital before surgery was associated with a lower in-hospital mortality rate and a lower in-hospital ischemic stroke or death rate relative to not being on a statin. This finding was robust when adjusted for the relationship between prognostic variables and outcome, for confounding by hospital, and for the propensity of individual patients to be selected to treatment with a statin. This did not extend to cardiac outcomes with symptomatic patients. Meanwhile, there was no evidence of better outcomes associated with statin use among asymptomatic patients undergoing carotid endarterectomy.

Propensity scoring methodology allows firmer inferences to be drawn from observational data. Patients in this study on statins were more likely to have either a known indication (prior myocardial infarct) or a known contraindication (liver disease) in keeping with clinical practice guidelines. However, the area under the ROC for our propensity model indicates that statin use is not fully explained by patient characteristics, age, or gender. This likely reflects factors such as individual physician practice or ability to pay for medications, which were not captured.

The lower in-hospital mortality found among statin users builds on the results of previously published observational studies and a small randomized controlled trial.^{7,8,15} These studies included a predominance of patients undergoing

TABLE 3. Crude and Adjusted Odds Ratios of In-Hospital Outcomes by Statin Use for Patients With a Asymptomatic Indication for Surgery

Outcome	Crude	Adjusted	Adjusted Plus Propensity Score	Adjusted Plus Propensity Score and Hospital
Death				
Odds Ratio	0.59	0.54	0.52	0.68
95% CI	0.16–2.09	0.13–2.24	0.12–2.28	0.14–3.39
ROC	0.57	0.92	0.92	0.95
Ischemic Stroke or Death				
Odds Ratio	1.26	1.34	1.35	1.80
95% CI	0.60–2.65	0.61–2.93	0.62–2.94	0.76–4.24
ROC	0.53	0.65	0.66	0.74
Cardiac				
Odds Ratio	1.39	1.37	1.37	1.39
95% CI	0.76–2.54	0.73–2.58	0.73–2.58	0.72–2.68
ROC	0.54	0.71	0.70	0.77

Outcome: Crude: statin exposure only; Adjusted: patient characteristics identified in Table 1 included in the logistic regression model; Adjusted plus Propensity Score: as Adjusted, including the propensity score in the logistic regression model; Adjusted Plus Propensity Score and Hospital: as Adjusted Plus Propensity Score, including hospital site identifier as a dummy variable in the logistic regression model.

peripheral vascular procedures, and the main outcome of interest was mortality. Our study confirms these findings among carotid endarterectomy cases, and in addition shows a reduction in in-hospital ischemic stroke or death.

The well described lipid-lowering abilities of statins are their principal mechanism of prevention from vascular events. Though beyond the scope of this study, preoperative lipid levels would have helped more accurately determine the role of this effect in the results described. However, if this was the sole reason for the protective effect seen in this study, then it is likely that protection would have been shared across symptom status and extended to cardiac outcomes in symptomatic patients. This, therefore, raises the possibility that the association with a reduction in adverse outcomes was related to the pleiotropic effects of statins.

Statins exhibit many properties that may be protective at time of surgery, including anti-thrombotic actions, the ability to stabilize atherosclerotic plaque, and neuroprotective actions such as preserving cerebral blood flow, attenuating the neuroinflammatory response, and antioxidant activity.⁹ Many of these would be shared across symptomatic and asymptomatic patients. The apparent discrepant benefit for symptomatic patients suggests that our findings may have arisen from plaque stabilizing effects or by a reduction of the neuroinflammatory response.⁹

Limitations of this study include the possibility that a true effect of statin therapy in asymptomatic patients may be hidden by the low frequency of outcomes seen. In addition, none of the statistical methods employed take account of potential hidden biases. Statin use may be a marker for higher quality care, the most obvious of which may be perioperative β -blockade, which is associated with a reduction in perioperative mortality, which we did not assess.¹⁶ However, the adjusted ORs took into account previous myocardial infarction

and congestive heart failure, 2 common indications for β -blocker use. Furthermore, little effect was seen when adjustment was made for hospital site dummy variables, a potential indicator of local quality of care. If higher quality care was the sole reason for improved outcomes among symptomatic patients, then as mentioned previously, this benefit would likely have been seen for cardiac outcomes as well.

These findings suggest a protective effect of statin therapy in recently symptomatic patients undergoing carotid endarterectomy. This is, however, only an observational study, and the extent to which the favorable outcome associations are attributable to statin therapy—as opposed to unmeasured confounders or selection factors—now needs to be explored in rigorously performed randomized controlled trials.

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