CLINICAL RESEARCH STUDIES

From the Society for Vascular Surgery

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy

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Objective: **There is increasing evidence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce cardiovascular and cerebrovascular events through anti-inflammatory, plaque stabilization, and neuroprotective effects independent of lipid lowering. This study was designed to investigate whether statin use reduces the incidence of perioperative stroke and mortality among patients undergoing carotid endarterectomy (CEA).**
Methods: **All patients undergoing CEA from 1994 to 2004 at a large academic medical center were retrospectively reviewed. The independent association of statin use and perioperative morbidity was assessed via multivariate logistic regression analysis.**
Results: **CEA was performed by 13 surgeons on 1566 patients (987 men and 579 women; mean age, 72 ± 10 years), including 1440 (92%) isolated and 126 (8%) combined CEA/coronary artery bypass grafting procedures. The indication for CEA was symptomatic disease in 660 (42%) cases. Six hundred fifty-seven (42%) patients received a statin medication for at least 1 week before surgery. Statin use was associated with a reduction in perioperative strokes (1.2% vs 4.5%; $P < .01$), transient ischemic attacks (1.5% vs 3.6%; $P < .01$), all-cause mortality (0.3% vs 2.1%; $P < .01$), and median (interquartile range) length of hospitalization (2 days [2-5 days] vs 3 days [2-7 days]; $P < .05$). Adjusting for all demographics and comorbidities in multivariate analysis, statin use independently reduced the odds of stroke threefold (odds ratio [95% confidence interval], 0.35 [0.15-0.85]; $P < .05$) and death fivefold (odds ratio [95% confidence interval], 0.20 [0.04-0.99]; $P < .05$).**
Conclusions: **These data suggest that perioperative statin use may reduce the incidence of cerebrovascular events and mortality among patients undergoing CEA. (J Vasc Surg 2005;42:829-836.)**

Carotid stenosis is established as the leading cause of stroke-related morbidity, which accounts for the foremost cause of adult disability, the second most significant cause of dementia, and the third most common cause of death in Western nations.[1,2] Carotid endarterectomy (CEA) remains the "gold standard" treatment for asymptomatic and symptomatic carotid stenosis in the prevention of cerebrovascular events.[3,4] Over the last two decades, there has been dramatic improvement in postoperative outcomes after CEA.[5] Despite the documented safety of CEA, carotid angioplasty and stenting has been introduced as a minimally invasive alternative treatment of carotid artery disease and is challenging the accepted role of the conventional surgical treatment of this patient population.[6] Therefore, continued reduction in CEA-related morbidity is necessary to maintain CEA as the gold standard therapy for occlusive carotid disease.

CEA-related strokes may result from dislodged embolic plaque during carotid manipulation, watershed ischemia during carotid cross clamping, or postoperative thrombosis and embolism.[7,8] Reduction of all phenomena may be necessary to achieve a reduction in perioperative strokes. Recently, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been shown to stabilize arterial plaques, improve cerebrovascular autoregulation and blood flow, and serve as neuroprotectants in both in

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vitro and in vivo experimental studies.[9-12] Statins have also been shown to be effective agents in the primary and secondary prevention of stroke in patients with known vascular disease.[13-16] The purpose of this study was to examine the role of statin therapy in perioperative outcomes after CEA, including cerebrovascular events, myocardial infarction (MI), mortality, cranial nerve injury, and length of hospital stay.

METHODS

All patients who underwent CEA between 1994 and 2004 at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center were identified. Patient demographics, clinical presentation, radiologic records, operative notes, and clinical outcomes were retrospectively obtained and available for review in all cases. All clinical, operative, and outcome variables were defined and documented by the surgeon at the time of operation. No variables or outcomes were retrospectively defined. Patients were classified as smokers if they were active smokers at the time of operation. Symptomatic disease was documented when patients experienced transient ischemic attacks (TIAs) or stroke documented by a neurologist as attributed to carotid artery stenosis. All comorbidities were recorded from the admission history and physical and the discharge summary. Plaques were defined as ulcerative if documented on the carotid imaging report or clearly noted in the operative report. Patients were classified as receiving shunts or patches if operative notes documented the use of an intraluminal shunt or carotid patch, respectively. Chronic renal insufficiency was defined as a serum creatinine level greater than 1.4 mg/dL on hospital admission in the absence of acute renal pathology. Patients using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for at least 1 week before surgery were classified as statin users. Patients were determined to be receiving a statin if they were already taking the medication at the time of their preoperative evaluation, which occurred at least 1 week before surgery. For the subset of patients who were already admitted to the hospital and underwent CEA surgery without an outpatient evaluation, statin users were defined by their admission medication list as reported by their admitting service before surgery. The degree of carotid stenosis was defined by two concordant studies, including duplex ultrasonography, cerebral angiography, and magnetic resonance angiography. For the purposes of this study, percentage stenosis was defined as the average of the two imaging modalities. New-onset postoperative neurologic deficits lasting less than 24 hours were defined as TIAs. Deficits lasting longer than 24 hours were classified as postoperative stroke. All complications occurring within 30 days of CEA (MI, pulmonary embolism, cranial nerve deficits, and neck hematoma) were considered perioperative morbidities. In the setting of perioperative stroke, a neurologist was routinely consulted and documented the presence of stroke. MI was defined by the vascular surgeon or intensive care physician at the time of the event and was documented when there was clinical evidence of either unstable angina or an acute change in cardiac output in the setting of electrocardiogram changes and increased cardiac enzymes.

For intercohort comparison, continuous data were compared via two-way analysis of variance for continuous data and Mann-Whitney U test for categorical data. Percentages were compared via χ^2 tests. The univariate association of statin use and perioperative stroke, MI, and death was assessed via logistic regression analysis (StatView; SAS Institute, Cary, NC). The independent association of statin use with perioperative stroke, MI, and death was assessed via multivariate logistic regression analysis (StatView). All covariables associated with stroke or death (Pvalue $< .10$ in univariate analysis) were included in the multivariate logistic regression model (StatView).

RESULTS

Patient population. CEA was performed on 1566 patients at the Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center between 1994 and 2004, including 126 (8%) patients who underwent a combined CEA/coronary artery bypass grafting (CABG) procedure. The operations were performed by 13 attending surgeons, including 10 vascular surgeons and 3 neurosurgeons. There were 987 (63%) male and 579 (37%) female patients, with a mean age of 72.2 ± 9.9 years; this population included 1408 (90%) white, 142 (9%) black, 14 (1%) Asian, and 2 (0.1%) Hispanic individuals. Comorbidities included hypertension in 1247 (80%), hyperlipidemia in 787 (50%), coronary artery disease in 765 (49%), diabetes mellitus in 407 (26%), smoking in 372 (24%), history of MI in 296 (17%), history of CABG in 268 (17%), history of atrial fibrillation in 153 (10%), congestive heart failure in 128 (8%), and chronic renal insufficiency in 87 (6%) patients. In every case, the operated stenosis was greater than 50%, and it was greater than 70% in 94.8% and greater than 80% in 83.8% of cases. An ulcerated plaque was noted in 215 (19%) cases.

The indication for operation was symptomatic disease in 660 (42%) patients, including a history of stroke in 226 (14%), TIAs in 434 (28%), and asymptomatic stenoses in 906 (58%) cases. The technical details of the operation varied with surgeon preference. Intraluminal shunts were used in 1195 (76.3%) cases, and patch closure was performed in 860 (54.9%) cases. The operation was performed with patients under general anesthesia in 1447 (92.4%) and under cervical block in 119 (7.6%) cases.

At the time of operation, 657 (42%) patients were taking a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) drug. The agents included atorvastatin in 332 patients (mean dose, 20 ± 10 mg/d), simvastatin in 189 patients (mean dose, 20 ± 10 mg/d), pravastatin in 91 patients (mean dose, 30 ± 20 mg/d), lovastatin in 32 patients (mean dose, 30 ±10 mg/d), and fluvastatin in 13 patients (mean dose, 30 ±10 mg/d). Patients taking statins were significantly younger, were more often male, and more frequently had hyperlipidemia, coronary artery disease, hypertension, and a history of smoking. Chronic renal insufficiency, symptomatic carotid disease, and the use of a

Table I. Patient demographics, clinical presentation, radiologic characteristics, and operative variables in the statin and nonstatin treatment groups

Variable	*Statin (n = 909)*	*Nonstatin (n = 657)*	P *value*
Age (y)	70 ± 10	74 ± 10	.001*
Male	436 (66%)	551 (61%)	.020†
Left side	346 (53%)	425 (47%)	.021†
% Stenosis	84% ± 10%	86% ± 10%	.001
Symptomatic disease	228 (35%)	432 (47%)	<.001†
TIA presentation	156 (24%)	278 (31%)	.003†
Stroke presentation	72 (11%)	154 (17%)	.001†
Caucasian	589 (90%)	818 (90%)	.567†
DM	186 (28%)	221 (24%)	.075†
HTN	561 (85%)	686 (75%)	.001†
Atrial fibrillation	29 (4%)	44 (4%)	.693†
CHF	56 (9%)	72 (8%)	.667†
Hyperlipidemia	533 (81%)	254 (28%)	<.001†
CAD	376 (57%)	389 (43%)	<.001†
History of MI	148 (23%)	148 (16%)	.002†
Smoker	196 (30%)	176 (19%)	.001†
CRI	24 (4%)	63 (7%)	.005†
Contralateral stenosis	137 (21%)	150 (17%)	.028†
Ulceration	78 (12%)	137 (15%)	.695†
Local anesthesia	45 (6.8%)	74 (8.1%)	.341†
Selective shunting	78 (12%)	91 (10%)	.241†
Shunt	501 (76%)	694 (76%)	.966†
Surgical frequency (n/3 mo)	11 ± 6	10 ± 6	.114*
Graft	312 (47%)	55 (60%)	.001†
CABG/CEA	60 (9%)	66 (7%)	.179†

Data are n (%) unless otherwise noted.
TIA, Transient ischemic attack; *DM,* diabetes mellitus; *HTN,* hypertension; *CHF,* congestive heart failure; *CAD,* coronary artery disease; *MI,* myocardial infarction; *CRI,* chronic renal insufficiency; *CABG,* coronary artery bypass grafting; *CEA,* carotid endarterectomy.
Statin users more frequently had left-sided disease, hypertension, hyperlipidemia, CAD, a history of MI, a history of smoking, and contralateral stenosis; were younger; and were more frequently male. Statin users less frequently had symptomatic disease, CRI, and carotid patching (graft).
*Two-way analysis of variance.
†Chi-square test.

carotid patch were more frequent in patients not taking statins (Table I).

Perioperative morbidity. There were 21 (1.3%) perioperative deaths and 49 (3.1%) perioperative strokes. MIs occurred in 25 (1.6%), cranial nerve deficits in 66 (2.3%), and neck hematomas in 36 (2.3%) cases. The mean length of stay was 3 days. Univariate analysis revealed that statin use was associated with a reduction in perioperative strokes (1.2% vs 4.5%; $P < .01$), perioperative TIAs (1.5% vs 3.6%; $P < .01$), mortality (0.3% vs 2.1%; $P < .01$), and the median (interquartile range) length of hospitalization (2 days [2-5 days] vs 3 days [2-7 days]; $P < .05$; Table II).

In multivariate analysis of perioperative stroke, adjusting for all comorbidities that were associated with stroke in univariate analysis (symptomatic carotid disease, chronic atrial fibrillation, hyperlipidemia, intraluminal shunt and patch grafting use, and combined CEA/CABG), statin use remained independently associated with a threefold reduction in the odds of perioperative stroke (odds ratio [95% confidence interval], 0.29 [0.14-0.61]; $P < .05$; Table III). This decrease in perioperative stroke rate observed with statin use persisted regardless of the year of surgery (Fig 1). Symptomatic carotid stenosis and combined CEA/CABG were associated with an increased risk of stroke (Table III).

Table II. Outcome comparison of statin and nonstatin treatment groups after carotid endarterectomy

Outcome	*Statin (n = 657)*	*Nonstatin (n = 909)*	P *value*
Stroke	8 (1.2%)	41 (4.5%)	.002
Cranial nerve deficit	29 (4.4%)	38 (4.1%)	.823
MI	8 (1.2%)	19 (2.1%)	.191
Mortality	2 (0.3%)	19 (2.1%)	.002

Data are n (%) unless otherwise noted.
MI, Myocardial infarction.
Patients receiving statin therapy at the time of carotid endarterectomy experienced a lower rate of stroke and mortality.

In multivariate analysis of perioperative mortality, adjusting for all comorbidities that were associated with mortality in univariate analysis (percentage carotid stenosis, hypertension, chronic atrial fibrillation, coronary artery disease, congestive heart failure, chronic renal insufficiency, use of β-blockers, and combined CEA/CABG), statin use remained independently associated with a sevenfold reduction in the odds of perioperative death (odds ratio [95% confidence interval], 0.14 [0.03-0.62]; $P < .05$; Table IV). β-Blocker use was also independently associated with a decreased risk of perioperative mortality, whereas chronic atrial fibrillation, chronic renal insufficiency, and combined CEA/CABG were associated with an increased risk of mortality (Table IV).

DISCUSSION

CEA has proven to be the treatment of choice for symptomatic and asymptomatic carotid artery stenosis and is the most frequently performed noncardiac vascular procedure. However, postoperative complications of CEA, including stroke and mortality, remain significant risks associated with this procedure, with pooled estimates ranging as high as 4% to 8%.[3,4] Our data suggest that perioperative statin therapy significantly reduces the risks of these adverse outcomes in patients undergoing CEA. Statin use was associated with a lower 30-day rate of stroke, TIA, and all-cause mortality. These results were supported by multivariate regression analysis, which adjusted for potential cofounders and found that statin therapy was independently associated with a threefold and fivefold reduction in the risk for stroke and mortality, respectively.

There is a lot of speculation regarding potential mechanisms to account for statins' reduction in cerebrovascular events. Statins effectively reduce plasma concentrations of low-density-lipoprotein cholesterol, which has long been an established risk factor in the pathogenesis of coronary heart disease.[17] However, there has been

Table III. Univariate and multivariate association of clinical, radiographic, and surgical variables with perioperative stroke after carotid endarterectomy

	Univariate		*Multivariate*	
Variable	*Odds ratio (95% CI)*	P *value*	*Odds ratio (95% CI)*	P *value*
Age	0.99 (0.97-1.02)	.692		
Male	1.14 (0.63-2.07)	.667		
Caucasian	1.17 (0.42-3.29)	.767		
Right CEA	0.62 (0.35-1.10)	.105		
Symptomatic carotid stenosis	1.77 (1.03-3.12)	.048	2.14 (1.15-4.03)	.017
% Stenosis	1.02 (0.99-1.05)	.231		
Ulcerative plaque	0.85 (0.36-2.02)	.712		
Contralateral carotid stenosis	0.72 (0.32-1.62)	.424		
Diabetes	1.63 (0.90-2.93)	.105		
Hypertension	1.16 (0.56-2.43)	.681		
Chronic atrial fibrillation	2.36 (0.91-6.13)	.078	2.51 (0.96-6.93)	.067
Hyperlipidemia	0.43 (0.23-0.79)	.006	0.58 (0.29-1.16)	.123
Coronary artery disease	1.23 (0.70-2.17)	.468		
Congestive heart failure	1.55 (0.65-3.72)	.323		
Active smoker	0.96 (0.49-1.89)	.898		
Chronic renal insufficiency	1.47 (0.52-4.21)	.464		
Statin use	0.29 (0.14-0.61)	.001	0.41 (0.18-0.93)	.033
ACE inhibitor use	1.57 (0.86-2.84)	.140		
Calcium channel blocker use	1.06 (0.56-1.98)	.867		
β-Blocker use	0.91 (0.51-1.62)	.751		
Vascular surgeon	2.05 (0.49-8.55)	.323		
Local anesthesia	1.06 (0.37-2.99)	.919		
Intraluminal shunt	2.83 (1.11-7.17)	.029	2.10 (0.75-5.88)	.157
Carotid patch	1.94 (1.05-3.58)	.034	1.32 (0.66-2.65)	.424
Combined CEA/CABG	3.87 (1.97-7.61)	.001	5.54 (2.58-11.7)	.001

CI, Confidence interval; *CEA,* carotid endarterectomy; *ACE,* angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting.
Statin use was independently associated with a lower risk of perioperative stroke. Symptomatic carotid stenosis and combined CEA/CABG were associated with an increased risk of stroke.

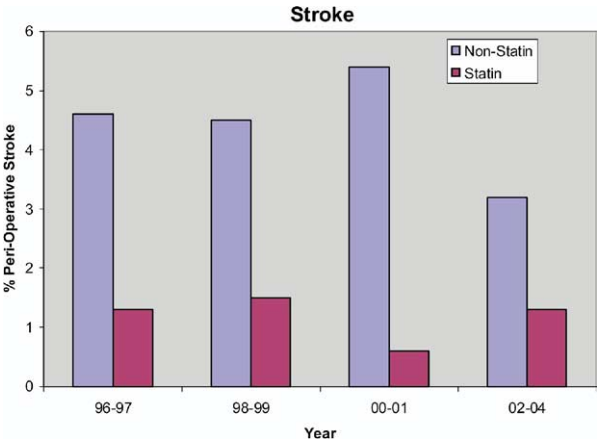

Fig 1. Incidence of postoperative stroke after carotid endarterectomy as a function of statin vs no statin use over time. The postoperative stroke rate remained lower in patients receiving statins, regardless of the year of operation.

debate as to the extent that hyperlipidemia contributes to cerebrovascular disease and the risk of stroke. Epidemiologic and large observational studies have not consistently demonstrated an association between cholesterol levels and all causes of stroke.[18] Nevertheless, the results of numerous clinical trials over the past decade have found that statin therapy reduces the risk of cerebrovascular events in high-risk medical patients.[13-16] A recent meta-analysis of all randomized trials testing statin drugs including more than 90,000 patients found a 21% risk reduction for stroke, which was closely correlated with reductions in levels of low-density-lipoprotein cholesterol.[16] These findings are supported by several reports showing that statin therapy slows the progression of carotid atherosclerosis and reduces carotid intima-media thickness.[19,20] Moreover, the large randomized Heart Protection Study trial, comprising more than 20,000 patients with occlusive arterial disease, showed that statin therapy significantly reduced the number of patients who had strokes or TIAs and subsequently required CEA or angioplasty.[15] Still, It is interesting to note that when 3200 patients from this large study with known pre-existing cerebrovascular disease were evaluated by subgroup analysis, statin therapy was not found to be associated with a reduction in the secondary stroke rate. It is difficult to compare these results with those of the present study, given the differences in the demographic and perioperative risk profile of our patients. Furthermore, the risks for cerebrovascular disease and adverse neurologic sequelae differ between medical and surgical patients.

It has come to light through numerous in vitro and in vivo studies over recent years that statins have other beneficial effects that are independent of lipid lowering. These

Table IV. Univariate and multivariate association of clinical, radiographic, and surgical variables with perioperative mortality after carotid endarterectomy

	Univariate		*Multivariate*	
Variable	*Odds ratio (95% CI)*	P *value*	*Odds ratio (95% CI)*	P *value*
Age	1.01 (0.97-1.06)	0.647		
Male	0.64 (0.27-1.51)	.309		
Caucasian	0.96 (0.22-4.11)	.957		
Right CEA	0.51 (0.20-1.27)	.146		
Symptomatic carotid stenosis	0.68 (0.27-1.69)	.406		
% Stenosis	1.07 (1.01-1.39)	.021	1.06 (0.99-1.14)	.097
Ulcerative plaque	0.02 (0.01-1.12)	.972		
Contralateral carotid stenosis	2.26 (0.91-5.65)	.081		
Diabetes	1.43 (0.57-3.59)	.443		
Hypertension	0.41 (0.17-0.99)	.048	0.30 (0.16-1.18)	.091
Chronic atrial fibrillation	5.02 (1.64-15.3)	.004	3.88 (1.05-14.4)	.042
Hyperlipidemia	0.62 (0.26-1.51)	.293		
Coronary artery disease	3.39 (1.24-9.30)	.018	2.42 (0.71-8.27)	.158
Congestive heart failure	3.60 (1.30-9.99)	.014	1.83 (0.58-5.70)	.299
Active smoker	1.06 (0.39-2.92)	.906		
Chronic renal insufficiency	7.11 (2.69-18.8)	.001	5.41 (1.67-17.5)	.005
Statin use	0.14 (0.03-0.62)	.009	0.21 (0.05-0.96)	.044
ACE inhibitor use	0.31 (0.72-1.34)	.118		
Calcium channel blocker use	0.63 (0.21-1.89)	.414		
β-Blocker use	0.24 (0.07-0.83)	.024	0.26 (0.07-0.98)	.468
Vascular surgeon	1.69 (0.22-17.5)	.610		
Local anesthesia	1.28 (0.29-5.56)	.541		
Intraluminal shunt	0.98 (0.36-2.69)	.968		
Carotid patch	0.74 (0.31-1.79)	.485		
Combined CEA/CABG	11.1 (4.64-26.8)	.001	14.7 (5.47-39.7)	.001

CI, Confidence interval; *CEA*, carotid endarterectomy; *ACE*, angiotensin-converting enzyme; *CABG*, coronary artery bypass grafting.
Statin and β-blocker use was independently associated with a lower risk of perioperative mortality. Chronic atrial fibrillation, chronic renal insufficiency, and combined CEA/CABG were associated with an increased risk of mortality.

non–lipid-mediated, or pleiotropic functions of statins include diverse cellular effects, including increased endothelial nitric oxide synthase (eNOS) expression; reduced production of endothelin 1 and reactive oxygen species; reduction in inflammatory molecules, including C-reactive protein, cytokines, chemokines, adhesion molecules, and C-reactive protein; reduction of intravascular thrombosis; and regulation of vascular smooth muscle cell migration and proliferation.[21-26] The clinical benefits of these pleiotropic effects during the CEA perioperative period may derive through several means. Statins' upregulation of eNOS can help control vasomotor tone, inhibit leukocyte and platelet adhesion, and maintain a thromboresistant interface between the bloodstream and the vessel wall.[10,11,27] These effects on the vascular endothelium might consequently protect the brain during the operation by improving collateral blood flow and enhancing cerebral arterial vasodilation during states of compromised blood flow, as well as by preventing carotid thrombosis and embolism during the postoperative period. This is supported by several animal models of ischemic stroke, which showed that statin therapy reduced infarct size by up to 46% through upregulating eNOS and improving cerebral blood flow.[27,28] Another potential source of cerebral protection attributable to statin pleiotropy during the CEA perioperative period is the stabilization of carotid atheromatous plaques. Many in vitro and in vivo data have shown that statin therapy suppresses numerous inflammatory processes that degrade the extracellular matrix, promote thrombosis, and lead to plaque disruption.[8-10,12,21-24] Statin therapy taken during the preoperative period may therefore stabilize carotid plaques that would otherwise be disrupted, embolize, and lead to a perioperative stroke. Several recent studies support this conclusion by showing that carotid plaques taken from patients after CEA had significantly lower levels of matrix metalloproteinases 1, 2, and 9 and interleukin 6, along with fewer macrophages and higher collagen contents, if they were taking a preoperative statin medication.[29,30]

A host of clinical studies have been published during the past several years that support the use of statin therapy to reduce complications after vascular surgery. In two separate retrospective studies, perioperative statin therapy was associated with a significant reduction in the 30-day and 1-year mortality after CABG surgery.[31,32] Statin use was also independently associated with a reduced risk of 30-day and 6-month mortality in patients undergoing percutaneous coronary interventions.[33] In patients undergoing elective abdominal aortic aneurysm (AAA) repair, Kertai et al[34] found that statin therapy was associated with a significantly lower incidence of perioperative mortality. Abbruzzese et al[35] found that statin therapy was associated with improved secondary graft patency in patients undergoing autogenous infrainguinal bypass procedures but that it did not affect

perioperative mortality, major morbidity, or primary patency rates. Several other reports have recently been published that have looked at perioperative statin therapy in combined patients undergoing major noncardiac vascular surgery, including both emergent and elective AAA repair, lower extremity revascularization procedures, and CEA. Two of these articles[36,37] were reports of retrospective case-control studies that found a significant reduction in perioperative mortality and cardiovascular complications in patients receiving statin therapy. Durazzo et al[38] published the only prospective trial in which 100 patients undergoing major noncardiac surgery were randomized to atorvastatin or placebo for 45 days, irrespective of their serum cholesterol levels. Patients taking statins during the perioperative period in this study were found to have a threefold decrease in the rate of cardiovascular events (8.0% vs. 26%; $P = .031$), including acute MI, ischemic stroke, and unstable angina. However, because this study was heterogeneous and contained a very limited number of CEA cases, no conclusions could be made about statins' ability to reduce postoperative strokes after this specific procedure.

This is the first study to show a direct reduction in cerebrovascular events after CEA. Patients in our statin cohort had lower rates of stroke and mortality even though they had more cardiovascular risk factors, including hypertension, hyperlipidemia, coronary artery disease, a history of MI, male sex, and smoking history. This increase in cardiac morbidity among statin users might explain why no significant differences were found in the incidence of MI among cohorts, even though previous studies suggested that statins reduce postoperative cardiac complications.[36-38] Multivariate analysis confirmed that statin therapy was independently associated with a reduction in the risk of stroke and death, even after adjusting for all significant variables found in our study, including symptomatic disease, combined CEA/CABG, β-blocker use, chronic atrial fibrillation, and chronic renal insufficiency. Nevertheless, other confounders might have been present that were not identified and adjusted for in our multivariate analysis. The validity of our findings, like most published studies of perioperative statin therapy to date, is limited by the retrospective design of the study. There was demographic heterogeneity between statin and nonstatin cohorts in this study, and the duration of statin therapy before CEA was unknown. Similarly, the difference in median length of hospital stay between cohorts may have been influenced by other factors that were not accounted for. Another main limitation was that perioperative serum lipid levels were not obtained and/or were not compared between statin and nonstatin cohorts. Ultimately, large prospective randomized trials will be needed to look at the influence of statin therapy on the primary end points of stroke, MI, and death after CEA, CABG, AAA repair, lower extremity bypass grafting, carotid stenting, or any other endovascular revascularization procedure.

Moreover, it needs to be established how long patients need to receive statin therapy before these procedures to gain the drug's benefit. Our study included patients in the statin cohort if they had been taking the medication for at least 1 week before surgery and continued taking it during the 30-day postoperative period. However, other reports have documented that patients need to receive the medication for as long as 3 years to gain a stroke-reduction benefit.[15,39]

Finally, are the potential benefits of statin therapy enough to justify recommending that every patient be given medication during the perioperative period, regardless of the serum cholesterol levels? A recent study looking at the safety of perioperative statin use in high-risk patients undergoing vascular surgery found no increased risk of rhabdomyolysis or myopathy.[40] It seems reasonable to conclude that statin therapy might become a standard agent to prescribe for most patients undergoing major vascular procedures in the future.

CONCLUSION

The results of this retrospective study suggest that the incidence of cerebrovascular events and mortality in the first 30 days after CEA can be significantly reduced with the perioperative use of statins. Prospective randomized trials will be needed to confirm the results of this study and to determine the optimal use of statin therapy for the surgical patient.

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DISCUSSION

Dr Richard Powell (*Lebanon, NH*). I think your results are quite provocative. Could you postulate, since it seems unlikely that the 30-day stroke and death rate was decreased because of the anticholesterol effects of the statins, what are the other possible mechanisms?

The second question I had is whether or not you saw any form of dose-response relationship. Were the patients who were on higher dose of statins likely to even gain a more beneficial effect than patients on lower doses?

Dr Brooke. To answer your first question, there are several effects that are associated with statin therapy, such as the upregulation of nitric oxide production, which may help lower stroke rates. Nitric oxide has numerous effects, including vasodilation and control of vasomotor tone. There is also a known association between nitric oxide upregulation and protecting the endothelial surface during procedures, including preventing the attachment of platelets and clotting factors. Thus, upregulation of nitric oxide may be a very potent protective factor that is augmented by statins.

There is also a whole cascade of anti-inflammatory effects of statin therapy that have been demonstrated. In vitro and in vivo experiments have found that statins decrease levels of interleukins, matrix metalloproteinases, and other by-products of inflammation. So there may be a potent plaque stabilization effect that can be contributing to the reduction of stroke rates.

To answer your second question, we found that the mean dose for most patients in this study was at the lower end of the dose spectrum. However, we didn't perform a dose-effect correlation in our analysis.

Dr Enrico Ascher *(Brooklyn, NY)*. What were the causes of stroke in the statin and nonstatin patients: were they similar?

Dr Brooke. Our analysis didn't differentiate between the potential etiologies of stroke.

Dr John Chang (*Roslyn, NY*). When you do carotid surgery, do you patch them? Do you close the arteriotomy with a primary closure? Our study indicates that patch angioplasty using the proximal greater saphenous vein has shown long-term beneficial effects in terms of patency and recurrent stenosis.

My second question is to ask you whether or not you would like to extend your study on a group that has milder disease, a nonsurgical population, to treat them with statins for the long-term study of beneficial effects of statin on the plaque to see

whether or not there is evidence of regression, in comparison to the control group that was not treated with statins?

Dr Brooke. The technical details of the operation were at the discretion of the operating surgeon, and approximately 55% of patients had a patch repair. There was no difference between the percent of patients taking statin vs no statin who underwent a patch repair.

To answer the second part of your question, I believe you were asking in regard to statin therapy for carotid stenting?

Dr Chang. Besides putting a statin therapy on a patient with carotid endarterectomy or stent procedure, how about putting statin therapy on a population with a mild to moderate degree of asymptomatic stenosis? By putting statins in that population with a mild to moderate degree of disease, one can concentrate that statin therapy may slow the progression of disease or even regress the plaque. That's my question.

Dr Brooke. Certainly I think that statin therapy would be important for patients in the early stages of vascular disease. It clearly should be part of the overall approach to risk factor modification in the vascular patient population. In medically managed patients, for example, it has been shown that statin therapy can reduce the incidence of primary stroke rates significantly. So I think prophylactic statin therapy may theoretically prevent some patients from ultimately going to surgery. That's what some of the large randomized trials have already demonstrated. But what's less known is what statin therapy will do for a surgical patient during the perioperative period and how statins are working during the perioperative period, and that was the purpose of this study.

Dr Richard Cambria (*Boston, Mass*). Aside from the cardiac literature, which has shown statins to decrease the incidence of recurrent infarction and prolong life, it seems like you can't pick up a journal or go to a meeting these days without finding some new wonderful effect. The group from the Brigham has told us that it decreases leg vein graft stenosis. Last year at this meeting, Dr LaMuraglia of our group showed that they clearly decreased recurrent carotid stenosis and increased survival. So I wonder if we won't soon be having a sign in our offices that says you must be on this drug.

At any rate, I have two questions about your data. The first is that the important difference in your groups was the symptomatic status. So was the symptomatic status of the carotid entered into your multivariate model?

And the second is, with the higher incidence of stroke in the combined carotid and CABG patients, would the effect still hold if they were subtracted out?

Dr Brooke. To answer your first question, yes, patients who were symptomatic at the time of presentation were included in our multivariate analysis. Statin therapy was still found to be independently associated with the reduction in stroke and mortality, adjusting for that symptomatic status. But it was interesting to find that patients who were on statins presented less frequently with strokes.

To answer your second question, the decrease in stroke and mortality was still significantly lower when combined CABG/CEA patients were subtracted out.

Dr Phillip Puckridge (*Hamilton, New Zealand*). First, we know that statins are effective in stabilizing plaques; did you see a bigger difference in stroke rates between the symptomatic and the asymptomatic patients because of the effect of statins?

Second, the literature suggests that you have to be compliant with statin therapy for a long time before you get the reduction in stroke risk. Did you look at the timing of the patients who were on statins before they came to surgery and whether that made a difference?

Dr Brooke. To answer your first question, we looked at symptomatic status in the multivariate analysis and found that the benefit of statins was independent of the symptomatic status.

To answer your second question, one of the limitations of the study was not knowing exactly how long patients have been on the statin medication before their operation occurred. In medical patients, there have been several studies that have shown that patients need to be on statins for a longer period of time. Some people have said at least 3 months before you'd see an effect, at least in terms of lipid lowering. In terms of the pleiotropic or lipid-independent effects of statins, it's a little bit unclear, but this is certainly one of the issues that would need to be addressed in further studies.

Dr J. Fernandes (*Lisbon, Portugal*). We know statins stabilize carotid plaques, and I wonder if you could tell us if there was any difference in the echographic characteristics of the carotid plaques in those patients with statins and without statins and if there was any difference in the percentage of echolucent plaques in these two groups.

My second question would be related to the long-term effects of statins on the incidence of cardiovascular events. Please elaborate on this regarding your group of patients. Was there any difference in the incidence of cardiovascular events in those two groups of patients—the long-term results?

Dr Brooke. To answer your first question, we did look at the percentage of plaques that were assessed radiographically to be ulcerative plaques, and there was no significant difference between groups. Approximately 10% of plaques were assessed to be ulcerative.

In terms of your second question, you raise an excellent consideration. Unfortunately, our study examined only the perioperative impact of statin use, and we do not have the long-term follow-up of these patients.

Dr Michael Judd (*Spokane, Washington*). Was antiplatelet therapy employed equally in both cohorts of your patients?

Dr Brooke. Yes, it was.

Dr Judd. Can you elaborate on the type of therapy used? Did you use aspirin or Plavix?

Dr Brooke. Again, patient management was surgeon specific. However, the vast majority of the patients were treated with dextran postoperatively for 24 hours, and almost all patients were continued on aspirin postoperatively. Moreover, there was not a significant difference between the statin vs no-statin cohorts in terms of the percentage of patients taking antiplatelet medication preoperatively.

INVITED COMMENTARY

Thomas S. Huber, MD, PhD, *Gainesville, Fla*

McGirt et al have reviewed their collective experience with more than 1500 carotid endarterectomies spanning 11 years and have reported that the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (commonly referred to as *statins*) independently reduced the incidence of perioperative death and stroke. Despite the limitations of their nonrandomized, retrospective study, the results are fairly compelling and provide further justification for the use of the statin agents. In other studies, the statin agents have been shown to reduce perioperative mortality after coronary artery bypass grafting, percutaneous coronary revascularization, and noncardiac vascular surgery. Furthermore, they have been shown to reduce the incidence of cerebrovascular events in high-risk patients, reduce the progression of carotid atherosclerosis, and improve graft patency after infrainguinal bypass. The mechanisms responsible for these beneficial effects are likely multifactorial and include plaque stabilization and attenuation of inflammatory mediators, in addition to the reduction of the serum lipid levels. Although their use in many of these clinical settings