Statin Therapy at Carotid Angioplasty and Stent Placement: Effect on Procedure-related Stroke, Myocardial Infarction, and Death[1]

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Purpose: To retrospectively determine if preprocedural statin treatment is associated with a reduction of cardiovascular events after carotid angioplasty and stent placement (CAS) in patients with symptomatic carotid stenosis.

Materials and Methods: A study resulting in a prospective database was approved by the institutional ethics review board; written informed consent was obtained. The approval and informed consent included future retrospective analysis. Consecutive patients ($n = 180$) from the prospective database underwent CAS for high-grade symptomatic carotid disease. The frequency of cardiovascular complications (composite of stroke, myocardial infarction, and death within 30 days after CAS) between 127 patients without preprocedural statin treatment and that of 53 patients with preprocedural statin treatment at CAS were compared with χ^2 and multivariate logistic regression analysis.

Results: The overall 30-day myocardial infarction rate was two of 180 (1%) patients, the minor stroke rate was 16 of 180 (9%) patients, the major stroke rate was one of 180 (0.5%) patients, and the death rate was two of 180 (1%) patients. The incidence of cardiovascular events (composite of stroke, myocardial infarction, and death within 30 days after CAS) was significantly different between patients with preprocedural treatment (4%) and those without preprocedural statin treatment (15%) ($P < .05$). These higher complication rates among patients without preprocedural statin treatment were not mediated by adjustment for age, sex, other baseline characteristics, degree of carotid stenosis, use of cerebral protection devices, or the year in which CAS was performed.

Conclusion: Preprocedural statin therapy appears to reduce the incidence of stroke, myocardial infarction, and death within 30 days after CAS. Future prospective randomized trials are warranted to further assess this potential protective effect of statin drugs during carotid interventions.

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In the past few years, evidence has accumulated that cholesterol lowering with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the incidence of stroke and myocardial injury (1). In addition to the long-term benefit of statins associated with lipid lowering, results of several recent studies have indicated that preprocedural treatment with statins reduces the incidence of myocardial infarction after percutaneous coronary interventions (2,3). Because coronary angioplasty and stent placement induce platelet activation, thrombosis, and inflammation within the vessel wall, it has been speculated that the benefits of statin administration after percutaneous coronary intervention could be the result of favorable effects on platelet adhesion, thrombosis, plaque stability, and inflammation.

Similar to percutaneous coronary intervention, carotid angioplasty and stent placement (CAS) has been shown to induce vascular injury by mechanisms that are potentially amenable to statin therapy (4). Carotid endarterectomy is currently the established treatment for patients with high-grade symptomatic or asymptomatic carotid artery stenosis (5), and definite evidence about the equivalence of CAS and carotid endarterectomy remains to be clarified in ongoing trials. There is, however, an increasing enthusiasm for CAS, which is a minimally invasive revascularization technique, as an alternative to carotid endarterectomy. Therefore, the question arises if statins may also play a beneficial role after CAS. Thus, the purpose of our study was to retrospectively determine if preprocedural statin treatment is associated with a reduction of cardiovascular events after CAS in patients with symptomatic carotid stenosis.

Advances in Knowledge

- Preprocedural statin therapy appears to reduce the incidence of cardiovascular complications (composite of stroke, myocardial infarction, and death) within 30 days after carotid angioplasty and stent placement.
- Because serum concentrations of lipid parameters were similar in patients with and in those without preprocedural statin treatment, these beneficial effects seem to be mediated by various non–lipid-lowering effects of statins.

Materials and Methods

Study Patients

Approval of a prospective protocol by our institutional ethics review board was given, and informed consent was obtained. This institutional review board approval and informed consent included future retrospective analysis of the data.

From June 1999 to February 2005, 180 consecutive patients (129 men, 51 women) with high-grade (>70% assessed with ultrasonography and confirmed at angiography), symptomatic carotid artery stenosis were treated with CAS. The mean age of the population was 69 years ± 9 (standard deviation) (range, 45–90 years), and 25 of 180 (14%) patients were aged 80 years or older. A carotid stenosis was considered symptomatic if the patient had experienced an ipsilateral ocular or cerebral (transient or permanent) ischemic event within the 6 months prior to CAS. The outcomes of patients treated before August 2004 have been published previously (6). That study mainly assessed the effect of age and symptom status, as well as type of ischemic event, for the development of postprocedural complication after CAS.

A multidisciplinary team comprising a vascular surgeon, an interventional neuroradiologist (U.E., T.N.), and a stroke neurologist (A.K., K.G., J.B.S.) evaluated all patients. Initially, only patients with severe medical comorbidities and a high surgical risk were treated with CAS. On the basis of satisfactory preliminary results, patients suitable for either CAS or carotid endarterectomy were subsequently offered a choice of procedure after they had received detailed information about potential risks and benefits, as well as the investigational nature of CAS. With our increasing personal experience and in line with two recent publications (7,8), we excluded patients with long and multiple carotid artery stenoses, severe peripheral vascular disease precluding femoral artery access, or an extremely tortuous carotid artery anatomy from CAS during the course of the study.

Patients with known allergies to aspirin, clopidogrel, or contrast media, a total carotid occlusion, a disabling stroke, arteriovenous malformations, intracerebral tumors, a diagnosis of dementia (which limits informed consent), a cerebral hemorrhage in the past months, severe intracranial stenoses, a severe renal insufficiency, an evolving myocardial infarction, or an evolving stroke were excluded.

CAS Procedure

All CAS procedures were performed by one of three interventional neuroradiologists (U.E., T.N.), each with experience in endovascular procedures that ranged from 5 to 10 years. A standardized protocol recently described in detail was used in all patients (9). At least 3 days before the procedure, patients orally received aspirin (Aspirin; Bayer, Leverkusen, Germany) (100 mg daily) and clopidogrel (Iscover, Bristol-Myers Squibb, Munich, Germany; or Plavix, Sanofi-Aventis, Frankfurt, Germany) (75 mg daily). Patients taking hypertensive medications received their morning dose prior to CAS. Additional doses were withheld until after the procedure

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Abbreviation:
CAS = carotid angioplasty and stent placement

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Guarantor of integrity of entire study, A.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, K.G., J.B.S., A.K.; clinical studies, K.G., U.E., T.N.; statistical analysis, K.G., C.T., A.K.; and manuscript editing, K.G., J.B.S., C.T., A.K.

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and were then given if necessary. After performing a standard diagnostic cerebral angiography (Neurostar; Siemens, Germany) that was restricted to the preselected carotid artery, a loading dose of heparin (70–100 IU per kilogram of body weight) was administered intravenously in order to obtain an activated clotting time of 2.0–2.5 times baseline, which corresponded to more than 250 seconds. After stent placement, boluses of heparin (1000 units per bolus) were administered hourly. Glycoprotein IIb/IIIa antagonists were not used.

In this series, 110 patients were treated without cerebral protection devices and 70 patients were treated with filter-type cerebral protection devices during the CAS procedures. According to their preference and the commercial availability, physicians chose from two different filter-type cerebral protection devices (Neuroshield, MedNova, Horsham, England; Angioguard Filter, Johnson & Johnson–Cordis, Warren, NJ) and several appropriate-size self-expandable stents (Smart/Precise, Johnson & Johnson–Cordis; Wallstent, Boston Scientific, Maple Grove, Minn).

Percutaneous femoral access was obtained, and a 7-F guiding catheter was positioned into the distal common carotid artery. The stenosis was crossed with a 0.014-inch guidewire, and the tip of the guidewire was placed in the intracranial portion of the internal carotid artery, at least 4 cm above the lesion. With the guidewire across the stenosis, the filter-type cerebral protection system was advanced across the target lesion and deployed in the distal internal carotid artery. An angiogram was obtained to document the device placement distal to the target lesion and to document blood flow through the filter device. The guidewire was then used to deliver the balloon and the stent-delivery catheters. After opening the filter of the cerebral protection system, predilation with coronary angioplasty balloons was performed in most cases, and subsequently, appropriate-size self-expandable stents were implanted. After stent placement, a second dilation was performed. To establish whether the filter of the cerebral protection system had become occluded with a large embolic volume load and to confirm that the final dilation of the stenotic segment was adequate, follow-up angiography was performed. Intracranial vessels were also imaged to avoid undetected compromise of the intracranial circulation caused by thromboembolic events. At the end of the procedure, a retrieval sheath was advanced and the filter of the cerebral protection device was closed and removed from the artery. Visual inspection of the filter of the cerebral protection device was performed at the end of each procedure to evaluate the macroscopic presence of material. A formal histopathologic analysis of all filters with macroscopically visible plaque debris was not performed.

After CAS, administration of heparin was stopped and the patient was transferred to the neurointensive care unit for overnight observation. Heart rate and respiratory rate were monitored continuously. Blood pressure was monitored four times per hour at the left upper arm by using an automated cuff-inflation sphygmomanometer. A board-certified neurologist (A.K., J.B.S., K.G.) also evaluated any episode of neurologic change. In addition, routine neurologic examinations were performed by one of two board-certified neurologists (A.K., J.B.S.), one with 10 years of experience and one with 14 years of experience, the day after CAS and at day 30. Clopidogrel was continued for 6 weeks, and aspirin was given indefinitely. To document patency of the stent, an ultrasonographic follow-up examination was performed 1–2 days after CAS in all patients.

Data Collection

In each patient, a careful medical history was taken and a precise neurologic examination was performed by one of three stroke neurologists (A.K., K.G., J.B.S.) at least 7 days before CAS in our outpatient department. At that time, the presence of the following cerebrovascular risk factors was recorded: hypertension, diabetes mellitus, hyperlipidemia, tobacco use (current or within the previous year), peripheral vascular disease, and previous transient ischemic attacks and strokes. Hypertension was defined as systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 95 mm Hg or when the patient took antihypertensive drugs. Diabetes mellitus was defined as previously diagnosed insulin-dependent or non–insulin-dependent diabetes mellitus. Hyperlipidemia was defined as cholesterol level higher than 220 mg/dL (5.69 mmol/L) or when the patient took lipid-lowering drugs. Additionally, the presence of the following comorbidities was recorded for each patient: coronary artery disease, chronic obstructive pulmonary disease, and contralateral carotid disease. Moreover, the current medication (type and dosage) for each patient, which included the use of statins, was recorded on a predefined electronic data sheet. Because of the unknown potential effect of statins on postinterventional complication rates after CAS at the time our prospective database was designed, the length of statin pretreatment was not determined. Finally, routine laboratory investigations, including a complete blood cell count, blood chemistry, and lipid profile, were performed in all patients.

Definitions of Postinterventional Complications

The definitions of postinterventional complications that occurred within 30 days were based on a previous study by Mathur and colleagues (8). A minor stroke was defined as any new neurologic deficit (either ocular or cerebral) that persisted for more than 24 hours and that either resolved completely within 7 days or increased according to the National Institutes of Health Stroke Scale by fewer than 3 points. A major stroke was defined as any new neurologic deficit that persisted after 30 days and increased according to the National Institutes of Health Stroke Scale by more than 3 points. A myocardial infarction was defined as an occurrence of a new Q wave in two or more leads and the presence of elevated creatine kinase or creatine kinase–MB levels or occurrence of a creatine kinase elevation

more than two times the upper limit of the normal in the presence of an elevated creatin kinase-MB level.

Statistical Analysis

Continuous values are expressed as mean ± standard deviation, and nominal variables are expressed as number of patients and percentages. For comparisons of categorical data, two-tailed χ^2 statistics with a Yates correction and a univariate Fisher exact test were used. The Fisher exact test was used when the predicted contingency table cell values were less than five. Continuous variables were compared with the Student *t* test. A multiple logistic regression analysis was applied to assess the independent effect of statin treatment on postinterventional complication rates, and adjustment for the potentially confounding effects of other baseline variables was performed. Baseline variables were considered for inclusion in this analysis if they were imbalanced between both treatment groups, which was indicated with a *P* value of less than .2. Moreover, variables that were likely to influence the incidence of cardiovascular events, which included the degree of carotid stenosis, the use of cerebral protection devices during CAS, the type of stent, or the year in which the intervention was performed, were entered into this analysis. Interaction was assessed by using additive and multiplicative interaction terms. Results of the logistic regression model are presented as odds ratios and 95% confidence intervals. All statistical analyses were performed with computer software (SPSS version 12; SPSS, Chicago, Ill). A two-sided *P* value of less than .05 was considered to indicate a statistically significant difference.

Table 1

Baseline Characteristics of 180 Patients with or without Preprocedural Statin Therapy

Baseline Characteristics	With Preprocedural Statin Therapy ($n = 53$)	Without Preprocedural Statin Therapy ($n = 127$)	*P* Value
Demographics			
Mean age (y)	67 ± 10	70 ± 9	<.05
Men	40 (75)	89 (70)	
Women	13 (25)	38 (30)	
Event			
Minor stroke	18 (34)	37 (29)	
Hemispheric TIA	27 (51)	58 (46)	
Retinal TIA	8 (15)	32 (25)	
Medical risk factors			
Hypertension	47 (89)	92 (72)	<.05
Hyperlipidemia	53 (100)	43 (34)	<.05
Tobacco use (current or within previous year)	17 (32)	35 (28)	
Diabetes mellitus	14 (26)	33 (26)	
Coronary artery disease	20 (38)	23 (18)	<.01
Peripheral vascular disease	10 (19)	18 (14)	
Chronic obstructive pulmonary disease	5 (9)	4 (3)	
Serum parameters*			
Total cholesterol (mg/dL)	203 ± 47	202 ± 48	
Triglyceride (mg/dL)	185 ± 99	190 ± 110	
High-density lipoprotein (mg/dL)	43 ± 11	54 ± 17	
Low-density lipoprotein (mg/dL)	129 ± 42	115 ± 37	
Medications before CAS			
Aspirin	53 (100)	127 (100)	
Clopidogrel	53 (100)	127 (100)	
Angiotension converting enzyme inhibitors	23 (43)	43 (34)	
β-Blockers	19 (36)	31 (24)	
Diuretics	24 (45)	31 (24)	<.05

Note.—Unless otherwise indicated, values are mean ± standard deviation or number of patients with percentages in parentheses. TIA = transient ischemic attack.

* Data are serum levels ± standard deviation.

Results

All patients had symptoms attributed to the treated artery; 85 (47%) of 180 patients had hemispheric transient ischemic attacks, 55 (30%) had a minor stroke, and 40 (22%) had amaurosis fugax. Fifty-two (29%) patients had contralateral carotid disease (22% with a stenosis of at least 50% and 7% with carotid occlusion). While 127 (71%) patients were not taking any statins before CAS, 53 (29%) patients were taking the following statins for at least 1 week before the procedure: atorvastatin (Sortis; Pfizer, Karlsruhe, Germany) ($n = 40$, 10–40 mg/d), simvastatin (Zocor; MSD Sharp & Dohme, Haar, Germany) ($n = 6$, 40 mg/d), pravastatin (Pravasin; Bristol-Myers Squibb) ($n = 5$, 10–40 mg/d), cervistatin (Lipobay; Bayer) ($n = 1$, 0.3 mg/d), and lovastatin (Mevinacor; MSD Sharp & Dohme) ($n = 1$, 40 mg/d). Patients who used statin therapy before CAS were younger and more likely to have a history of hypertension, hyperlipidemia, or coronary artery disease. Serum concentrations for lipid parameters were similar in both groups (Table 1).

CAS Procedures

In each patient, only one CAS procedure was performed, and the procedural success rate was 100%. Two patients experienced transient bradycardia at balloon inflation or later in the intensive care unit. No patient, however, required a temporary pacemaker.

Cardiovascular Events

For the entire study population, the overall 30-day myocardial infarction rate was two of 180 (1%), the minor stroke rate was 16 of 180 (9%), the major stroke rate was one of 180

(0.5%), and the death rate was two of 180 (1%). The minor or major stroke rate within 30 days after CAS was seven of 70 (10%) patients treated without and 10 of 110 (9%) patients treated with cerebral protection devices (no significant difference). One death was due to pneumonia, which occurred 3 weeks after CAS in an 82-year-old patient. One patient developed an intracranial hemorrhage with left-sided hemiplegia 1 day after CAS. After initial recovery, this patient died in the course of a secondary traumatic intracranial hemorrhage after falling during rehabilitative therapy.

Both patients with myocardial ischemia had had a non–Q wave myocardial infarction, from which they recovered completely before being discharged. At 30 days, there were no residual sequelae in 10 of the 16 patients with minor stroke. The 30-day outcome for all major stroke and death was three of 180 (2%) patients.

The incidence of cardiovascular events (composite of stroke, myocardial infarction, and death within 30 days after CAS) was significantly different between patients with preprocedural statin treatment (two of 53 [4%]) and those without preprocedural statin treatment (19 of 127 [15%]) ($P < .05$) (Table 2). The mean length of stay in the intensive care unit was 1.13 days ± 0.5 in patients with and 1.75 days ± 2 in patients without preprocedural statin treatment ($P < .05$).

Multiple logistic regression analysis was applied to assess the independent effect of statin treatment on the incidence of cardiovascular events after CAS, to adjust for confounding factors, and to test for interactions between variables. Preprocedural statin therapy was identified as the only independent negative predictor (odds ratio, 0.2; 95% confidence interval: 0.02, 0.8; $P < .05$) of cardiovascular events after CAS.

Table 2

Frequency of Stroke, Myocardial Infarction, or Death within 30 Days after CAS in 180 Patients

Event	With Preprocedural Statin Therapy ($n = 53$)	Without Preprocedural Statin Therapy ($n = 127$)	*P* Value
Minor stroke	2 (4)	14 (11)	NS
Major stroke	0	1 (0.8)	NS
Myocardial infarction	0	2 (2)	NS
Death	0	2 (2)	NS
Total	2 (4)	19 (15)	<.05

Note.—Numbers in parentheses are percentages. NS = not significant.

Discussion

Our results suggest that preprocedural statin treatment is associated with a reduction of cardiovascular complications after CAS in patients with symptomatic carotid stenosis. Whereas several recent clinical studies have revealed a reduction in the extent of myocardial injury during percutaneous coronary interventions with statin treatment (2,3), our results support the notion that preprocedural statin treatment might also have a protective effect during carotid interventions. In conjunction with lowering total and low-density lipoprotein cholesterol, statins have been shown to stabilize plaques (10), improve endothelial function (11–13), decrease platelet aggregability and thrombus deposition (14), and reduce vascular inflammation (15,16). Theoretically, each of these mechanisms could have contributed to our favorable results during CAS, which has been shown to induce platelet activation, thrombosis, and inflammation within the vessel wall (4).

Of note, a recent report pointed out that preprocedural statin therapy abolished the negative prognostic effect of baseline C-reactive protein elevation after percutaneous coronary interventions (17). Therefore, the beneficial vascular effects of preprocedural statin during CAS in our study could also have been mediated by reducing circulating levels of C-reactive protein. This hypothesis is at least indirectly supported by results of a recent study of Schillinger and colleagues (18), who demonstrated a close association between the extent of the vascular inflammatory response measured with serum levels of C-reactive protein and the short-term restenosis rates after CAS. Because of serum concentrations of C-reactive protein were not available from our database, future studies need to address this important issue.

The overall 30-day stroke and death rates of approximately 10% for the entire study population and of up to 13% for patients without preprocedural statin treatment in our study are higher than the 6% limit that the American Heart Association has established as acceptable upper limit for combined postprocedural stroke and death for symptomatic patients who undergo carotid endarterectomy (5). On the other hand, 14% of patients were aged 80 years and older and 7% of patients had a contralateral carotid occlusion, so that our study included many patients with a high surgical risk (19). Especially advanced age has also been identified as an important risk factor for the development of neurologic complications after CAS (6,7,20,21). It should be stressed that despite the treatment of many surgical high-risk patients, the 30-day major stroke and death rate was only 2% in our study and the majority of patients with a minor stroke recovered completely within the 30-day observation period. Finally, all patients were evaluated by a neurologist, which could have contributed to the high detection rate especially of minor strokes (22).

Closer inspection of the literature reveals that 30-day stroke and death rates of approximately 10% after CAS exclusively for symptomatic patients have also been reported in several other case series (21,23–26) and trials (27,28). Roubin and colleagues (21), for instance, reported a 30-day stroke and death rate of 8.2% after CAS in a large series of symptomatic patients. Kirsch et al (23) reported a 30-day stroke and

death rate of 10.5% in a mixed population of symptomatic patients and asymptomatic patients. In the first patients of the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the stroke and death rate within 30 days of CAS was 10.3% despite the use of cerebral protection devices (28).

This study has several limitations. Serum C-reactive protein levels were not obtained systematically. Although we used the data from our prospective CAS series, the potential influence of preprocedural statin treatment on cardiovascular complications after CAS was analyzed in a retrospective fashion. Moreover, the nonrandomized sample sizes were relatively small compared with the large data sets obtained after coronary interventions (29,30). A potential interference with other drugs such as diuretics, even though it is rather unlikely, cannot be fully excluded. Finally, the length preprocedural statin treatment was not determined in this study. Therefore, the length of preprocedural statin treatment that would be required to produce the observed reductions in procedural complications during CAS remains unknown.

Despite these limitations, our observations clearly suggest that preprocedural statin therapy is associated with a reduction of cardiovascular complication rates after CAS. Thus, future prospective randomized trials are warranted to further assess this potentially protective effect of statin drugs during carotid interventions.

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