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Restenosis After Carotid Surgery

The Importance of Clinical Presentation and Preoperative Timing

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Background and Purpose—Carotid endarterectomy (CEA) of stable atherosclerotic plaques is associated with an increased risk for restenosis. Patients with transient ischemic attack and patients with and stroke have relatively unstable atherosclerotic plaques. However, carotid plaques stabilize over time after a cerebrovascular event due to plaque repair after rupture. These findings raised 2 questions: (1) Is preoperative clinical presentation related to restenosis after CEA? (2) Does delayed revascularization result in a higher risk for restenosis compared with CEA in the short term after a cerebrovascular event?

Methods—Between 2002 and 2009, 1203 patients undergoing CEA were included. The impact of clinical presentation on the occurrence of restenosis 1 year after CEA was investigated and corrected for cardiovascular risk factors, medication use, and type of arteriotomy closure. Patency was assessed with standardized duplex ultrasound imaging at 1 year after CEA. Restenosis was defined as recurrent luminal narrowing $\geq 50\%$ at the endarterectomy site.

Results—At 1 year of follow-up, restenosis was observed more frequently in asymptomatic patients than in patients with transient ischemic attack and patients with stroke. The adjusted odds ratio (95% CI) for restenosis was 0.56 (0.35 to 0.89) for patients with transient ischemic attack and 0.49 (0.27 to 0.87) for patients with stroke compared with asymptomatic patients. Subgroup analysis showed an increased risk for restenosis if CEA was performed >30 days after stroke (adjusted OR, 2.23; 1.02 to 5.73).

Conclusions—Asymptomatic patients have an increased risk for restenosis at 1 year after CEA compared with patients with transient ischemic stroke and patients with stroke. CEA within 30 days after stroke is associated with a decreased risk of restenosis, which supports the current strategy for early surgical intervention after stroke. (*Stroke*. 2011;42:965-971.)

Key Words: asymptomatic carotid stenosis ■ carotid endarterectomy ■ restenosis ■ stroke risk factors
■ timing of surgery ■ transient ischemic attack

Carotid endarterectomy (CEA) is the gold standard for the treatment of patients with a symptomatic internal carotid artery stenosis and for selected subgroups of patients with an asymptomatic stenosis.^{1–5} Restenosis at the site of surgery is a drawback of CEA that can eventually lead to relapse or de novo cerebrovascular events, thereby limiting the long-term benefit of revascularization in the prevention of stroke. Restenosis resulting in a $>50\%$ diameter reduction, as detected on duplex ultrasound, has been reported to occur in 6% to 36% during long-term follow-up.^{6,7} The risk for restenosis has been described to be the highest in the first 2 years after surgery.⁸ Smoking, age, diabetes mellitus, female sex, and a history of ipsilateral carotid surgery have been reported as clinical risk factors for restenosis.^{9–12} In addition,

stable atherosclerotic plaque characteristics with low macrophage content and small lipid core size are associated with an increased incidence of restenosis compared with unstable inflammatory lesions.¹³ Carotid plaques from patients who have had a stroke or transient ischemic attack (TIA) contain more unstable inflammatory properties and a larger lipid core than plaques from asymptomatic patients who are considered eligible for carotid surgery.¹⁴ Combining these observations, the question arises whether asymptomatic patients with relatively stable carotid plaques are more at risk for restenosis after CEA than patients with TIA and patients with stroke.

Plaques from patients operated on after a relatively long interval between their ischemic event and CEA revealed more smooth muscle cells, less macrophages, and a decrease in

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local carotid plaque inflammation, suggesting that carotid atherosclerotic plaques stabilize over time after a cerebrovascular event.¹⁵ Therefore, we consecutively hypothesized that early surgical intervention after an ischemic cerebral event could be associated with a decreased restenosis rate. The timing of carotid surgery in symptomatic patients is an ongoing subject of discussion but mainly focuses on the incidence of secondary events due to delayed surgery versus a believed higher operative risk due to early surgery.^{16,17} For clinical perspectives, the outcome of the current study could be helpful in the identification of patients who are at increased risk for restenosis 1 year after surgery based on initial clinical presentation and supports the growing evidence in favor of early revascularization.

Methods

Athero-Express Biobank

Athero-Express is an ongoing translational carotid biobank with a longitudinal study design that has been reported previously.¹⁸ Carotid plaques from patients undergoing CEA were collected and subjected to histological examination. Patients are prospectively monitored for 3 consecutive years after surgery. All patients who underwent CEA in 1 of the participating hospitals were considered eligible for inclusion in this study. Medical ethics boards of both participating hospitals approved the study, and all included patients provided written informed consent.

Study Population

Between April 1, 2002, and May 1, 2009, 1251 consecutive patients underwent CEA at the University Medical Center Utrecht or the St Antonius Hospital Nieuwegein, The Netherlands. Criteria to perform CEA were based on recommendations by the Asymptomatic Carotid Atherosclerosis Study and Asymptomatic Carotid Surgery Trial for asymptomatic patients and the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial for symptomatic patients.^{1–3} All indications were reviewed in a multidisciplinary vascular team, and all patients were evaluated by a neurologist before CEA to assess their neurological status and document the preoperative symptoms.

To investigate the association between restenosis and clinical presentation, we stratified among asymptomatic patients, patients with TIA, and patients with stroke. Asymptomatic presentation was defined as no ipsilateral symptoms for at least 6 months before neurological assessment.⁴ TIA was defined as a brief episode of neurological dysfunction caused by focal brain ischemia with clinical symptoms typically lasting <24 hours and without evidence of acute infarction.^{1,3} Repetition of imaging at a later stage was left to the decision of the neurologist in charge. In case of multiple TIAs, the last event was used to calculate the time between symptoms and surgery. Amaurosis fugax was included in the TIA group and was defined as ipsilateral partial or complete visual field loss in 1 eye that was of ischemic origin and was followed by complete recovery.¹⁹ Stroke was defined as focal neurological dysfunction of sudden onset caused by brain ischemia lasting ≥ 24 hours confirmed by imaging.

Clinical studies have shown that the benefit from CEA is highest in the first 30 days after an event, especially in the first 14 days.^{16,17,20} Furthermore, histopathologic observations have shown a significant decrease in local plaque inflammation, especially 30 days after stroke.¹⁵ Combining these clinical and histopathologic findings, a cutoff of 30 days was chosen to differentiate between early and delayed surgery.

All CEAs were performed by an open, noneversion technique. A policy of selective patching was applied, preferably with venous patches. If no venous patch could be harvested, closure was performed with Dacron or bovine patches.

Baseline characteristics and cardiovascular risk factors were gathered from questionnaires and patient medical records preopera-

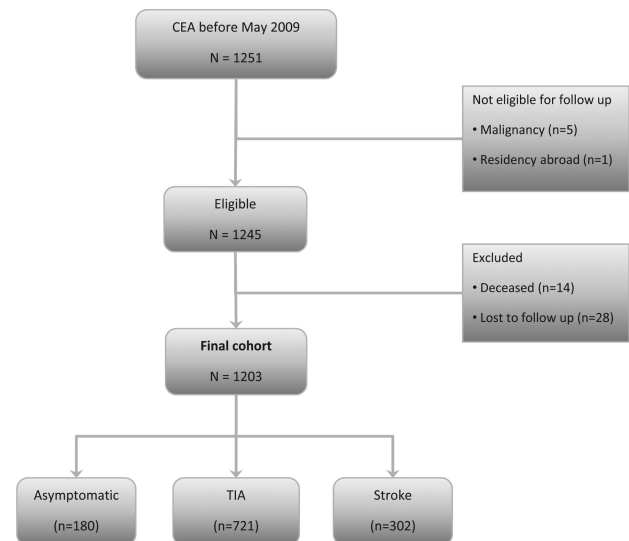


Figure 1. Patient inclusion flow chart of patients who underwent carotid endarterectomy between April 1, 2002, and May 1, 2009.

tively. Patients were classified as “current smokers” if they reported current smoking or did not quit smoking until the year of CEA. The definition of hypertension and diabetes mellitus was restricted to those patients receiving medical treatment. Medical history, including previous vascular interventions, contralateral stenoses, and medication use, was gathered from admission records before surgery.

Atherosclerotic Plaque Characterization

After endarterectomy of the atherosclerotic plaque, the specimen was directly taken to the laboratory. The segment with the greatest plaque burden was subjected to histological examination. We quantitatively examined the presence of macrophages (CD68), smooth muscle cells (α -actin), and neovessels (CD34). In addition, the following parameters were scored semiquantitatively: calcifications (hematoxylin and eosin), collagen (picrosirius red), large lipid cores ($\geq 40\%$ of total plaque), and the presence of intraplaque hemorrhage. Interobserver and intraobserver reproducibility have been reported previously and were excellent (κ , 0.6 to 0.9).²¹

Follow-Up

Patency of the ipsilateral carotid artery was assessed by means of duplex ultrasound (Philips Medical Systems, Eindhoven, The Netherlands) 1 year after CEA. Restenosis was defined as recurrent luminal narrowing of $>50\%$ at the site of the endarterectomy. The occurrence of $\geq 50\%$ restenosis at the ipsilateral side was defined as a peak systolic velocity of at least 125 cm/s.²² If the end point of restenosis $\geq 50\%$ was observed, 3-month duplex data were gathered to investigate whether residual stenosis could already be observed at that time. Duplex ultrasound measurements were performed by fully qualified and certified radiologists and clinical neurophysiologists. All investigators were blinded for data regarding the type of presentation and the time between the event and surgery. Patients who lacked complete 1-year duplex ultrasound follow-up data were excluded from this study (Figure 1).

To investigate the effect of preoperative timing in subgroups of symptomatic patients, 61 patients were excluded because the exact time between their last symptomatic event and CEA could not be obtained.

Patients were routinely examined by a neurologist after CEA, and cerebrovascular complications during hospitalization were registered by the neurologist in charge. A perioperative stroke was considered to have occurred if it manifested within 30 days of CEA and was defined as neurological dysfunction, as documented by a neurologist, caused by brain ischemia lasting ≥ 24 hours confirmed by imaging.

After discharge, a strict follow-up protocol was implemented for all patients with visits to the neurologist and vascular surgeon at 6 weeks, 3 months, and 1 year. The occurrence of stroke during follow-up was prospectively registered and defined identically as stated previously.

Statistical Analysis

For data analysis, SPSS 15.0 (SPSS Inc, Chicago, IL) was used. Univariate analysis was performed with nonparametric tests for continuous variables or the Pearson χ^2 test for dichotomous variables, where appropriate. To test the influence and independent effect of clinical characteristics on restenosis, multiple correction through binary logistic regression was performed and outcome was reported in adjusted ORs with 95% CIs. All clinical factors that showed an association with restenosis in univariate logistic regression analyses with a probability value <0.20 were included in the multivariable model. For the 3 categories of clinical presentation, asymptomatic patients were chosen as the reference category. For different types of closure after endarterectomy, venous patch closure was considered as the reference category. A probability value <0.05 or a 95% CI not including 1 was considered statistically significant.

Results

Patients

Between April 1, 2002, and May 1, 2009, 1251 patients underwent CEA at 1 of our institutions (Figure 1). Five patients were discharged from follow-up due to malignant disease and 1 patient due to residency abroad. Within the first year after CEA, 14 patients died of ischemic stroke ($n=4$), hemorrhagic stroke ($n=5$), myocardial infarction ($n=2$), or a noncardiovascular ($n=3$) cause. Another 28 patients (2.2%) lacked 1-year duplex ultrasound data and were considered lost to follow-up. The final cohort consisted of 1203 patients, 822 men (68.3%), mean age 68.1 ± 9.1 years. There were 180 asymptomatic patients (15.0%), 721 (59.9%) with TIA and 302 (25.1%) with stroke. Baseline characteristics are provided in Table 1.

Atherosclerotic Plaque Composition

Histological plaque characteristics are listed in Table 2. Carotid atherosclerotic plaques from asymptomatic patients contained relatively more smooth muscle cells compared with plaques from patients with TIA or patients with stroke: 2.13 (0 to 18.68) versus 1.58 (0 to 17.60) and 1.46 (0 to 20.85), respectively ($P=0.014$). A large lipid core, covering $>40\%$ of the plaque surface, was most frequently observed in the plaques from patients with stroke (35.9% [106 of 295]) and patients with TIA (30.5% [217 of 712]) than in the plaques of asymptomatic patients (23.6% [42 of 178]). Moderate or heavy calcifications were more frequently observed in asymptomatic patients (67.2% [199 of 177]) compared with patients with TIA (56.5% [402 of 712]) and patients with stroke (55.6% [164 of 295]; $P=0.023$). No differences were observed for amounts of macrophages or vessels or for collagen content.

Follow-Up: Restenosis 1 Year After CEA

Overall of 1203 patients, restenosis $\geq 50\%$ developed in 178 (14.7%) after a mean follow-up of 365 ± 80 days. Of all patients with restenosis $\geq 50\%$ at 1 year after CEA, 159 (89.3%) did not have signs of residual stenoses at 3 months, 13 (7.3%) did show signs of residual stenosis, and for 6

Table 1. Baseline Characteristics of the Total Cohort of Patients That Underwent CEA

	Total Cohort
No. of patients	1203
Risk factors	
Age, mean \pm SD, years	68.1 ± 9.1
Male gender	68.3% (822/1203)
Current smoker	35.5% (393/1108)
Diabetes	20.5% (219/1068)
Hypertension	86.2% (941/1092)
Body mass index, mean \pm SD, kg/m ²	26.4 ± 3.7
History of coronary intervention	20.7% (249/1203)
History of peripheral intervention	17.2% (198/1150)
Days between surgery and duplex, mean \pm SD	365 ± 80
Symptoms	
Asymptomatic	15.0% (180/1203)
TIA	59.9% (721/1203)
Stroke	25.1% (302/1203)
Contralateral stenosis	
None	56.5% (614/1087)
Stenosis 50%–99%	28.5% (310/1087)
Occlusion	15.0% (163/1087)
Lesion	
De novo stenosis	96.1% (1129/1175)
Restenosis after CEA	3.9% (46/1157)
Medication use	
Statin	74.8% (856/1144)
Aspirin	85.1% (973/1144)
Oral anticoagulants	13.0% (149/1144)
Clopidogrel	12.8% (146/1144)
Closure	
Venous patch	51.9% (618/1190)
Dacron patch	34.2% (407/1190)
Bovine patch	1.5% (18/1190)
Primary closure	12.4% (147/1190)

patients (3.4%), no 3-month duplex imaging could be retrieved. There was no difference in clinical presentation between patients with and without residual stenosis. Of the 178 patients with restenosis $\geq 50\%$, 13 (7.3%) had a stroke during mean follow-up of $269 (\pm 161)$ days. These 13 patients included 1 fatal stroke, 4 major invalidating strokes, and 8 strokes for which a secondary carotid revascularization was performed. In 15 patients (8.4%) with restenosis $\geq 50\%$, secondary ipsilateral carotid interventions were performed after a mean follow-up of $345 (\pm 158)$ days. Secondary interventions in these 15 patients were performed in 8 patients because of stroke, in 4 patients because of TIA, and in 3 asymptomatic patients with rapidly increasing restenosis.

The incidence of restenosis was significantly higher among asymptomatic patients (23.3% [42 of 180]) compared with patients with TIA (13.7% [99 of 721]; adjusted $P=0.017$) and patients with stroke (12.3% [37 of 302]; adjusted $P=0.014$; Figure 2A). Adjusted ORs for restenosis $\geq 50\%$ for patients

Table 2. Histological Plaque Characteristics for Different Groups of Clinical Presentation

Histological Parameters	Asymptomatic (n=177)	TIA (n=712)	Stroke (n=295)	P
Macrophages, median (range)	0.50 (0–6.88)	0.59 (0–15.10)	0.55 (0–8.12)	0.322
Smooth muscle cells, median (range)	2.13 (0–18.68)	1.58 (0–17.60)	1.46 (0–20.85)	0.014*
Moderate/heavy calcifications	67.2% (199/177)	56.5% (402/712)	55.6% (164/295)	0.023*
Moderate/heavy collagen	84.2% (149/177)	80.0% (569/711)	80.7% (238/295)	0.454
Lipid core >40%	23.6% (42/178)	30.5% (217/712)	35.9% (106/295)	0.018*
Vessels per hotspot, median (range)	7.8 (0–27.3)	7.7 (0–35.7)	8.0 (0–47.0)	0.872

* $P<0.05$.

with TIA and patients with stroke were 0.56 (0.35 to 0.89) and 0.49 (0.27 to 0.87), respectively, compared with asymptomatic patients (Table 3).

Dacron path closure resulted in an adjusted OR of 2.33 (1.52 to 3.58) for restenosis $\geq 50\%$ compared with venous patch closure. Primary arterial closure revealed an adjusted OR of 2.32 (1.33 to 4.04).

Patient characteristics, including age, gender, and smoking, did not contribute additionally to the development of restenosis $\geq 50\%$ in our cohort.

To assess the influence of preoperative timing, subgroup analyses were performed for patients with TIA and patients with stroke. The timing of surgery after TIA did not affect restenosis rates after 1 year. Restenosis after TIA developed in 27 of the 238 patients (11.3%) who underwent CEA within 30 days of TIA and in 57 of the 422 patients (13.5%) operated on after >30 days after TIA ($P=0.423$; Figure 2B). Perioperative stroke was observed in 5 patients with TIA (2.1%) operated on within 30 days and in 12 patients with TIA (2.8%) operated on after 30 days ($P=0.563$).

Significantly less restenosis developed in patients who underwent CEA within 30 days after stroke compared with patients who underwent CEA >30 days after stroke. Restenosis was observed in 6 of 91 patients (6.6%) operated on within 30 days versus 30 of 194 patients (15.5%) who underwent surgery more than 30 days after stroke ($P=0.043$; Figure 2B). After correction for general cardiovascular risk factors, multiple regression analysis revealed that a delay between stroke and CEA exceeding 30 days resulted in an adjusted OR of 2.23 (1.02 to 5.73) for restenosis $\geq 50\%$. Perioperative stroke was observed in 2 of 91 patients with

stroke (2.2%) operated on within 30 days and in 5 of 194 patients with stroke (2.6%) operated on after 30 days ($P=0.847$). Of all the perioperative strokes in these subgroups, 5 (71.4%) were ipsilateral and 2 (28.6%) were contralateral. The median time between surgery and perioperative stroke for these patients was 1 day (range, 0 to 7 days).

Discussion

The present study shows that asymptomatic patients have an increased risk for restenosis within 1 year after CEA compared with patients with TIA or patients with stroke. Subgroup analysis showed that delayed CEA after stroke is independently associated with an increased risk for restenosis. These clinical characteristics might help to stratify between patients at risk for development of restenosis. To the best of our knowledge, this is the first report considering a large cohort of >1200 patients undergoing CEA that links clinical presentation to restenosis rates. The association between asymptomatic presentation and restenosis is likely to be based on the underlying relatively stable plaque type. It is generally accepted that asymptomatic lesions have a more stable plaque composition characterized by less inflammation and lower lipid content.¹⁴ Stable plaque characteristics have been reported to be associated with increased risk of restenosis.^{13,23} The present study also confirmed the presence of a relatively stable plaque composition in asymptomatic patients and thereby supports previous findings and our hypothesis.

The underlying mechanism to explain the association between plaque phenotype and restenosis is believed to be lipid- and inflammation-driven and therefore has dual components. First, endarterectomy of lipid-rich plaques is be-

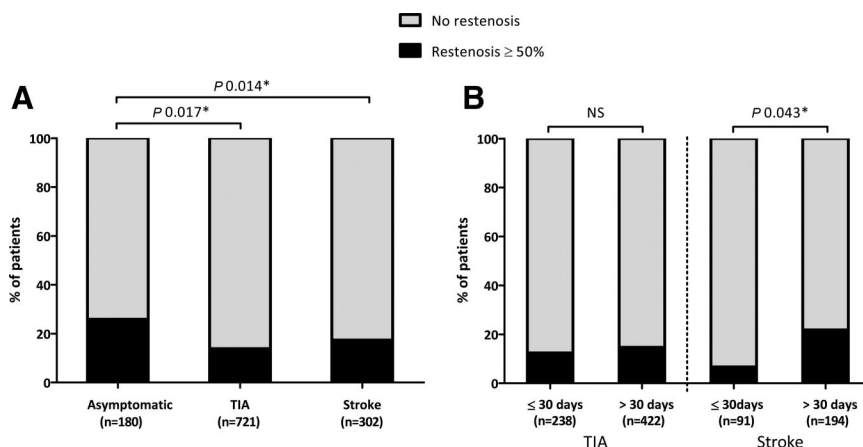


Figure 2. A, Restenosis $\geq 50\%$ 1 year after CEA in relation to clinical presentation before carotid endarterectomy. B, Restenosis $\geq 50\%$ 1 year after CEA and the time between last event and carotid endarterectomy.

Table 3. Effect of Clinical Parameters on Restenosis $\geq 50\%$, Expressed in ORs With 95% CI, Calculated With Binary Logistic Regression

	No Restenosis	Restenosis $\geq 50\%$	Univariate OR (95% CI)	<i>P</i>	Multivariate OR (95% CI)	<i>P</i>
No. of patients	1025	178				
Risk factors						
Age, mean \pm SD, years	67.9 \pm 9.2	66.8 \pm 8.2	0.99 (0.97–1.01)	0.166	1.00 (0.98–1.02)	0.769
Male gender	69.6% (713/1025)	61.2% (109/178)	0.69 (0.49–0.96)	0.028*	0.70 (0.46–1.06)	0.092
Current smoker	35.6% (337/946)	34.6% (56/162)	0.96 (0.67–1.36)	0.795		
Diabetes	20.5% (187/914)	20.8% (32/154)	1.02 (0.67–1.55)	0.928		
Hypertension	85.9% (804/936)	87.7% (137/156)	1.18 (0.71–1.98)	0.520		
Body mass index, mean \pm SD, kg/m ²	26.3 \pm 3.7	26.8 \pm 3.9	1.04 (0.99–1.09)	0.099	1.02 (0.97–1.07)	0.526
History of coronary intervention	20.4% (209/1025)	22.5% (40/178)	1.13 (0.77–1.66)	0.527		
History of peripheral intervention	17.1% (167/979)	18.1% (31/171)	1.07 (0.71–1.64)	0.732		
Symptoms						
Asymptomatic	13.5% (138/1025)	23.6% (42/178)	Reference	Reference	Reference	Reference
TIA	60.7% (622/1025)	55.6% (99/178)	0.53 (0.35–0.78)	0.002*	0.56 (0.35–0.89)	0.017*
Stroke	25.9% (265/1025)	20.8% (37/178)	0.46 (0.28–0.75)	0.002*	0.49 (0.27–0.87)	0.014*
Contralateral stenosis						
No	59.3% (549/926)	40.4% (65/161)	Reference	Reference	Reference	Reference
Stenosis 50%–99%	26.8% (248/926)	38.5% (62/161)	2.11 (1.45–3.08)	<0.001*	1.80 (1.17–2.79)	0.008*
Occlusion	13.9% (129/926)	21.1% (34/161)	2.23 (1.41–3.52)	0.001*	2.38 (1.41–4.03)	0.001*
Lesion						
De novo stenosis	96.3% (964/1001)	94.8% (165/174)	Reference	Reference		
Restenosis after CEA	3.7% (37/1001)	5.2% (9/174)	1.42 (0.67–2.99)	0.356		
Medication use						
Statin	73.5% (717/975)	82.2% (139/169)	1.67 (1.10–2.54)	0.017*	1.73 (1.04–2.87)	0.034*
Aspirin	84.2% (821/975)	89.9% (152/169)	1.67 (0.99–2.85)	0.056	1.54 (1.04–2.30)	0.033*
Oral anticoagulants	13.8% (135/975)	8.3% (14/169)	0.56 (0.32–1.00)	0.050	0.54 (0.27–1.09)	0.086
Closure						
Venous patch	55.1% (559/1015)	33.7% (59/175)	Reference	Reference	Reference	Reference
Dacron patch	31.9% (324/1015)	47.4% (83/175)	2.43 (1.69–3.84)	<0.001*	2.33 (1.52–3.58)	<0.001*
Bovine patch	1.3% (13/1015)	2.9% (5/175)	3.64 (1.26–10.58)	0.017*	1.14 (0.13–9.92)	0.904
Primary closure	11.7% (119/1015)	16.0% (28/175)	2.23 (1.36–3.64)	0.001*	2.32 (1.33–4.04)	0.003*

**P*<0.05.

lieved to cause less vascular trauma than dissection of fibrous plaques. This results in decreased inflammatory response and intimal hyperplasia in the operation area. Second, it is believed that patients with many inflammatory cells in their plaques also have a large amount of leukocytes in the vessel wall that remains in situ after endarterectomy. Leukocytes give rise to production of matrix metalloproteinases, which results in thinning of the media and outward remodeling. The proof of this concept has been shown in a previous study from our group.¹³

The process of plaque repair in symptomatic lesions starts after plaque rupture, which contributes to stabilization over time and results in a less inflammatory atherosclerotic carotid lesion.^{15,24} Therefore, we hypothesized that the timing of carotid surgery after the initial event would affect the rate of restenosis. For patients with stroke, carotid surgery within 30 days significantly decreased the rate of restenosis. These observations might be explained by plaque stabilization over time after the initial event and thereby support the concept

from previously published work.^{13,15} These findings suggest that the longer the delay from stroke until revascularization, the more the lesion stabilizes and the higher the risk for restenosis. The timing of surgical revascularization was not associated with the incidence of restenosis in patients with TIA. This can be explained by the less pronounced process of plaque repair and stabilization in plaques from patients with TIA compared with patients with stroke.¹⁵

Early CEA for symptomatic lesions to prevent recurrent ischemic events is a current subject of discussion.^{16,25,26} Delay in surgery has been reported to be associated with an increased incidence of recurrent adverse cerebrovascular ischemic events.²⁷ On the other hand, a relationship was shown with early surgery and increased procedurally related complications, including stroke and death.²⁸ Nevertheless, other studies showed that early carotid interventions after TIA or stroke significantly decreased the risk for recurrent clinical events without an increased periprocedural risk of stroke and death.^{16,25} We did not observe increased risks for

periprocedural stroke for patients who underwent early revascularization, and the 2.1% to 2.8% incidence of adverse events in our cohort is lower than the 4.6% to 5.6% risk for stroke and death after CEA that a large pooled data analysis reported.¹⁶ The outcomes of the present study therefore support and strengthen the principle of early carotid surgery after stroke.

The importance of patch angioplasty after CEA has been widely accepted, and venous patch closure is still considered to be the gold standard.^{29,30} We observed an increased risk for restenosis after Dacron patch and primary closure compared with the reference group with venous patch closure with adjusted ORs of 2.33 (1.52 to 3.58) and 2.32 (1.33 to 4.04), respectively. Naylor et al observed that the freedom from restenosis during a 3-year follow-up period was significantly lower in the venous-patched group compared with the Dacron-patched group,³¹ which is in line with our data.

Limitations

The current study has some limitations. The analysis of subgroups of patients with TIA and patients with stroke resulted in a slightly significant beneficial effect of early revascularization in patients with stroke. We therefore stress that it is a subgroup analysis and naturally hypothesis-generating. Our findings will have to be confirmed by data from large trials with randomization between early and delayed surgery.

The group of patients with stroke operated on within 30 days is relatively small. This is probably due to the growing amount of evidence in favor of early surgery over time. Patients operated on early were included more recently, whereas delayed surgery was more common in the early years of this study. Nevertheless, we believe that this study has enough power for statistical analyses, resulting in reliable observations.

The estimated time between stroke and surgery is generally well defined due to hospitalization, neurological examination, and diagnostic imaging. The estimated time between TIA and CEA is mainly dependent on patient anamnesis and might therefore be less accurate.

Patients with clinically symptomatic significant carotid stenosis without signs of fresh ischemia on imaging and symptoms <24 hours were classified as TIA. Repetition of imaging at a later stage was left to the decision of the neurologist in charge. Patients who were classified as TIA could have developed ischemia that was not detected on the initial scan. This might have caused some overlap between the TIA and stroke groups. Nevertheless, independent from the diagnosis of TIA or minor stroke, symptomatic patients with a significant carotid stenosis have an indication for revascularization. It is therefore unethical to wait for the results of repeated imaging, also due to the high risk of a secondary cerebrovascular event. This overlap is therefore an inevitable limitation, but we feel that the number of patients in the 3 groups provides sufficient power to minimize possible confounding.

A small part of the patients that had 1-year restenosis $\geq 50\%$ also showed residual stenosis at 3 months. There were no differences in clinical presentation between patients with

and without residual stenosis. We therefore expect that it will not be a confounding factor for the research question of the current study.

Overestimation of the degree of restenosis can be caused by several factors. First, primary closure has been reported to cause increased peak systolic velocity compared with patch closure.³² This might have resulted in an overestimation of the risk of restenosis in patients who underwent primary closure after CEA. On the other hand, primary closure has been reported as a common risk factor for restenosis compared with patch angioplasty, which shows our data are in line with the currently available literature.²⁹ Second, contralateral stenosis or occlusion can result in overestimation of the degree of stenosis. Hence, we also corrected for the presence of contralateral stenosis or occlusion in multiple regression models. Finally, a certain amount of overestimation is present in our series due to the use of European Carotid Surgery Trial (ECST) criteria. It is commonly accepted that ECST criteria result in a relatively high degree of stenosis in comparison with North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.³³ Nevertheless, the goal of the current study was to describe the occurrence of restenosis in relation to patient characteristics and timing of CEA rather than in relation to the degree of stenosis.

Conclusions

The main finding of the current study is that asymptomatic patients have an increased risk for restenosis $\geq 50\%$ compared with patients with TIA and patients with stroke. Furthermore, we show that early surgical revascularization resulted in a decreased risk for restenosis $\geq 50\%$ for patients with stroke without a significantly increased perioperative risk. These observations can be explained by the underlying stable plaque phenotype in asymptomatic patients and plaque stabilization over time after stroke. These findings might help to identify patients who are at risk for restenosis and additionally indicate that early CEA is favorable after stroke. We therefore emphasize the importance of early referral of patients with stroke for carotid surgery.

Disclosures

The following authors are consultants for Cavadis, a start-up company for diagnostic plaque biomarker kits: D.P.V.d.K., F.L.M., and G.P. However, the content of this article is not related with the activities of the company.

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