Carotid artery stenting with cerebral protection in 100 consecutive patients: immediate and two-year follow-up results

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Background. **Carotid artery stenting is emerging as an alternative to surgical endarterectomy for the treatment of extracranial carotid artery disease. However, few data are available on the long-term clinical efficacy of carotid artery stenting and on the incidence of restenosis.**

Methods. **Stent implantation with the routine use of cerebral protection devices was attempted in a single center experience including 100 consecutive patients (104 lesions) with significant stenosis of the internal carotid artery (mean stenosis 82.8 ± 9%). The mean age of the patients was 70.8 ± 14 years, 27 lesions were symptomatic (26.0%) with a lesion related to a previous stroke or transient ischemic attack.**

Results. **Procedural success was achieved in 103 lesions (99%) and the cerebral protection was successfully applied in 102 procedures (98%). The 30-day incidence of stroke and death was 4% (4 patients). Complications consisted of one major stroke (1%) with persistent ipsilateral amaurosis, two minor strokes (2%), and one (1%) fatal myocardial infarction occurring 4 days after the stent procedure. During follow-up (minimum 24 months; mean 31 ± 6 months) no further neurological events occurred, 6 patients died of non-neurological causes (6%) and 2 (2%) presented with a non-fatal myocardial infarction. Echo color Doppler scan control (minimum 24 months) was carried out in all surviving patients showing a restenosis classified as moderate (50-69%) in 2 cases and as critical (≥ 70%) in another 2 cases (1.8%). Both critical restenotic lesions were successfully treated by repeating balloon angioplasty.**

Conclusions. **The present study demonstrates that carotid artery stenting with routine cerebral protection can be performed with an acceptable procedural complication rate. At the 2-year follow-up carotid artery stenting appeared effective in stroke prevention and durable with a low incidence of restenosis.**

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Introduction

Stent placement has been proposed for the treatment of extracranial carotid artery disease as an alternative to carotid endarterectomy (CEA)[1-3]. Compared to the surgical approach, carotid artery stenting (CAS) is a less invasive approach but has been associated with an increased dislocation of microemboli[4], a potential cause of periprocedural stroke[5-7]. The use of cerebral protection devices during carotid stent implantation prevents intracranial embolization of debris and is thought to reduce the incidence of periprocedural complications[8-13].

With regard to the clinical efficacy in terms of stroke prevention, the superiority of CEA compared to medical therapy when treating carotid artery stenoses ≥ 80% in asymptomatic patients and ≥ 50% in symptomatic patients has clearly been shown[14-16].

We report on a prospective, single center study which was designed to evaluate the procedural outcome of CAS with the routine use of cerebral protection. The purpose of this study was to evaluate the incidence of restenosis after stenting and the initial clinical efficacy of CAS in terms of stroke prevention during a follow-up of 2 years.

Methods

Patients and lesions. Between November 1999 and March 2001 elective carotid artery stent implantation using a distal emboli protection filter was attempted in 104 consecutive lesions diagnosed in 100 patients. The patients were referred to our center with a diagnosis of severe (≥ 70%) stenosis of the internal carotid artery detected at echo color Doppler, magnetic res-

onance, or digital angiography. At selective angiography performed at our center all patients presented a ≥ 70% diameter stenosis (mean 82.8 ± 9%) of the internal carotid artery. The angiographic diameter stenosis was measured according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria using the distal, non-tapering segment of the internal carotid artery as reference[16]. One hundred were *de novo* lesions, 2 were restenotic lesions occurring after endarterectomy, and 2 were restenotic lesions occurring after stent placement.

Twenty-seven lesions (26.0%) were classified as symptomatic since they were correlated with a transient ischemic attack or a stroke within 6 months prior to the stenting procedure. In symptomatic patients a cerebral computed tomographic scan was performed before the stent procedure. The clinical and angiographic characteristics are listed in tables I and II.

Drug protocol. All patients were taking aspirin (100-325 mg/day). Therapy using ticlopidine (500 mg/day) or clopidogrel (75 mg/day) was started at least 48 hours before the procedure. Heparin (70-100 IU/kg) was given preprocedurally. Following the procedure, patients received aspirin indefinitely and ticlopidine or clopidogrel for 1 month.

Stenting procedure. All procedures were performed in the hemodynamic cath-lab without procedural-specific stand-by of a vascular surgery team. Percutaneous access was gained through the femoral or brachial (2 lesions) artery. Long sheaths (6 or 7F) or coronary guiding catheters (8F) were advanced into the common carotid artery on 0.035" support wires positioned in the external carotid artery. Having deployed the filter, in 66 (63%) of the lesions predilation was performed using coronary balloons. Appropriately sized self-expandable stents were implanted covering in all cases the origin of the external carotid artery (Fig. 1). Two types of stents were used. These were mesh-wire stents (Carotid Wallstent, Boston Scientific, Natwick, MA, USA) in 50 cases and nitinol stents (0.018" Smart; Cordis, Warren, NJ, USA) in 52 cases. All stents were post-dilated with non-compliant balloons. The arterial sheaths were removed the same day. After the procedure, the patients were transferred to the cardiology ward for continuous ECG monitoring for 24 hours and for non-invasive blood pressure measurements every 2 hours for at least 12 hours.

Protection device description. The filter device used in this study consists of a nitinol skeleton, the distal part of which is covered by a polyurethane membrane with 80 μm diameter pores (Angioguard, Cordis). The diameter of the filters used ranges from 5.0 to 8.0 mm. The filter is connected to a proximal, floppy wire tip and to a distal 0.014" wire shaft which is used as a guidewire during the procedure. The closed filter is contained in a delivery sheath and is advanced through the lesion. In case the filter does not cross the lesion a gentle predilation with a coronary 1.5 or 2.0 mm diameter balloon is performed. The filter is opened in the internal carotid artery distally to the lesion by removing the delivery sheath. At the end of the procedure a retrieval sheath is advanced to close the filter and the protection system is removed *en bloc* from the artery (Fig. 2).

A neurological examination including the NIH stroke scale was performed before and after stent implantation by an independent neurologist. Neurological

Table I. Baseline clinical characteristics (100 patients).

Age (years)	70.8 ± 14
> 80 years	12 (11.5%)
Male gender	74 (71%)
Diabetes	22 (22%)
Hypercholesterolemia	74 (74%)
Hypertension	85 (85%)
Coronary artery disease	62 (62%)

Table II. Baseline lesion characteristics (104 lesions).

De novo lesions	100 (96%)
Previous endarterectomy	2 (1.9%)
Previous stent	2 (1.9%)
Symptomatic lesion*	27 (26%)
Contralateral occlusion	7 (6.7%)
Diameter stenosis (%)	
Pre	82.8 ± 9
Post	14 ± 5

* lesion related to a stroke/transient ischemic attack within 6 months before the procedure.

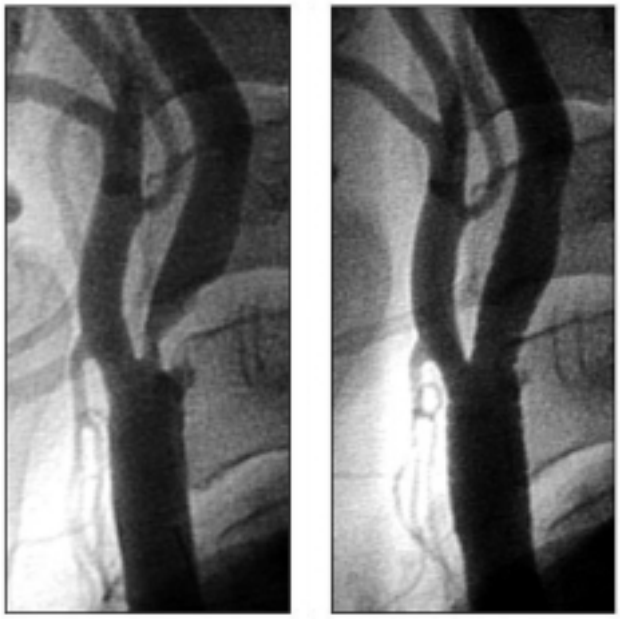

Figure 1. *The* left panel *shows a severe ulcerated stenosis at the origin of the right internal carotid artery. The* right panel *shows the final result after stent implantation.*

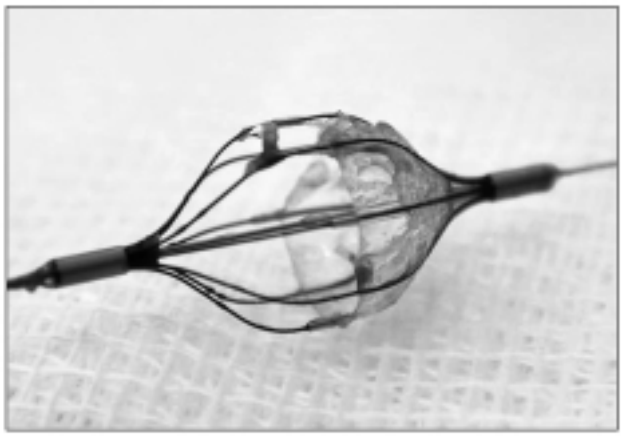

Figure 2. *The filter used during carotid artery stent implantation shown in figure 1. Note the debris trapped in the polyurethane membrane and in the nitinol skeleton of the filter.*

complications were defined as by Roubin et al.[1]. A transient ischemic attack was defined as a focal retinal or hemispheric event from which the patient recovers completely within 24 hours. A minor stroke was defined as a new neurological deficit that either resolves completely within 30 days or increases the NIH stroke scale by ≤ 3. A major stroke was defined as a new neurological deficit that persists for 30 days and increases the NIH stroke scale by ≥ 4. All procedures were performed in the hemodynamic cath-lab without procedural-specific stand-by of a vascular surgery team.

Clinical follow-up was performed at 30 days, at 6 and 12 months, and subsequently every 6 months. When necessary a neurological evaluation was carried out.

Ultrasonic evaluation was performed before the procedure, after 6 and 12 months, and subsequently every 12 months. The ultrasonographic examination was performed using a 7.5 MHz linear array scanner (Agilent 5500, Agilent Technologies, Andover, MA, USA). The degree of stenosis after stent implantation was assessed using color and power Doppler assisted duplex imaging and the angle corrected systolic peak flow velocity ratio of the internal carotid artery on the peak systolic flow velocity of the common artery (a stenosis was considered significant when the ratio was ≥ 4 and a new angiographic study was performed).

Statistical analysis. Data are expressed as mean ± SD. To display the post-interventional clinical course of the study patients, Kaplan-Meier curves were drawn. The censor points were transient ischemic attack, any stroke, death, and myocardial infarction.

Results

Stent procedure. In 1 patient (1%) we were unable to position a stent at the lesion site due to the impossibility of gaining a stable catheter access to the common carotid artery. In 2 other patients (2%) the filter could not be positioned and the procedure was performed without protection. The mean duration of the intervention was 38 ± 16 min. Short (< 10 s) seizures were observed in 2 patients (2%) during balloon post-dilation. Spasm of the distal internal carotid artery, resolving after the administration of nitrates, was observed in 3 cases (2.8%). Flow impairment resistant to nitrates, without angiographic signs of vessel spasm and which resolved after removal of the filter occurred in 6 procedures (5.8%). Angiographically evident vessel alterations of the segment of the internal carotid artery where the filter was positioned were not observed.

Difficult retrieval of the closed filter through the stent requiring a repeated rotation of the device or movement of the patient's head occurred in 4 cases (3.8%). At macroscopic evaluation particles could be seen in 75 filters (72%). Histological analysis revealed that the captured particles prevalently consisted of acellular material characterized by macrophages and cholesterol clefts. A more specific histopathological analysis of the debris has been published previously[17]. The procedural results are shown in table I.

Procedural and 30-day outcome. Four neurological complications (4.0%) occurred in hospital and included 1 intraprocedural major stroke (ipsilateral, persistent amaurosis with 80% loss of vision probably due to retinal artery embolization) and 2 minor strokes (1 intraprocedural and 1 occurring after 72 hours, both fully recovering within 1 week) and 1 (0.9%) transient ischemic attack. The 3 patients who experienced a stroke underwent repeat selective angiography of the intracranial circulation without angiographic evidence of vessel occlusion. Fifty milligrams of recombinant tissue-type plasminogen activator were administered intravenously to the patient who experienced a major stroke without any clinical benefit. Four patients (4.0%) required prolonged intravenous dopamine infusion for persistent hypotension. There were no procedural deaths and no major vascular access complications. During the 30-day follow-up no additional neurological events were observed and only 1 major adverse cardiac event occurred (0.9%). This patient, with an uneventful stent procedure, was affected by three-vessel coronary artery disease and had a massive anterior myocardial infarction 4 days after the procedure. He died 3 days later. Therefore the 30-day stroke/death rate was 4% and the 30-day major stroke/death rate was 2%. The 30-day stroke and death rates for symptomatic and asymptomatic lesions were respectively 7.4% (1 major and 1 minor stroke) and 2.6% (1 minor stroke and 1 cardiac death). The procedural and 30-day outcomes are shown in table III.

Late outcome. Clinical follow-up lasting at least 24 months (mean 31 ± 6 months) was completed for all patients. The results are reported in table IV. With the ex-

Table III. Procedural and 30-day outcome (100 patients).

Successful procedure*	103 (99%)
Cerebral protection successfully positioned*	101 (97%)
30-day neurological complications	4 (4%)
Transient ischemic attack	1 (1%)
Minor stroke	2 (2%)
Major stroke	1 (1%)
Acute myocardial infarction	1 (1%)
Death	1 (1%)
Stroke/death rate	4 (4%)

* values and percentages refer to 104 lesions.

Table IV. Follow-up outcome* (mean 31 ± 6 months, minimum 24 months).

Neurologic events > 30 days**	0
Acute myocardial infarction	4 (4%)
Fatal	2 (2%)
Non-fatal	2 (2%)
Death	6 (6%)
Cardiac death	4 (4%)
Cancer death	1 (1%)
Car accident§	1 (1%)
Echo color Doppler scan§§	
Moderate restenosis (50-69%)	2 (1.9%)
Critical restenosis (≥ 70%)	2 (1.9%)

* excluding first 30 days; ** all strokes and transient ischemic attacks; § patient did not drive; §§ available at 6, 12 and 24 months for all 93 surviving patients.

ception of the first 30 days no neurological events occurred (Fig. 3). During follow-up 6 patients (6%) died. Among these, 2 died of an acute myocardial infarction, 1 of congestive heart failure, 1 after coronary artery bypass surgery, 1 died of lung cancer, and 1 in a car accident. Two further patients (2%) had a non-fatal myocardial infarction (Figs. 4 and 5).

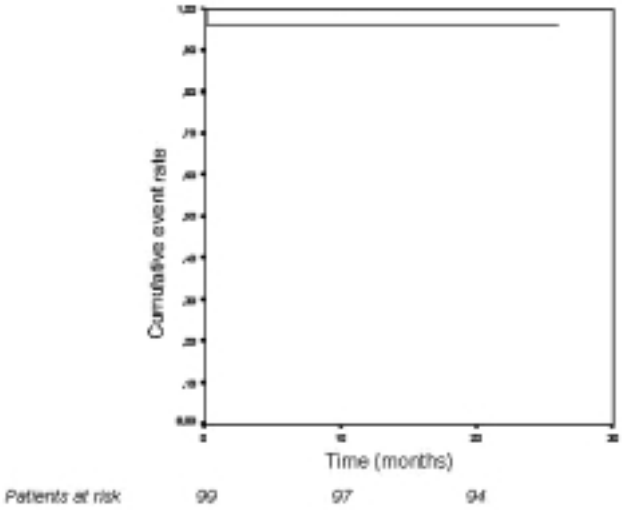

Figure 3. *Kaplan-Meier cumulative event rate for all neurological events.*

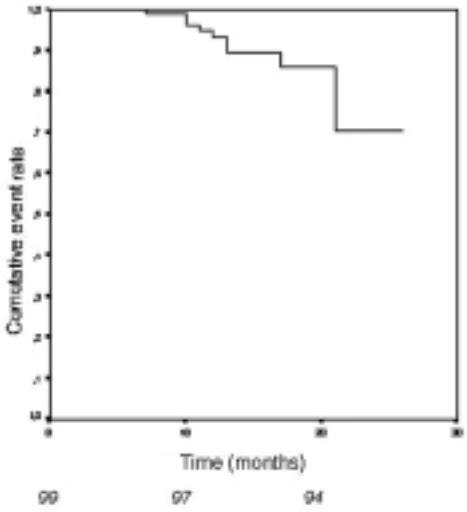

Figure 4. *Kaplan-Meier cumulative event rate for all deaths and myocardial infarctions.*

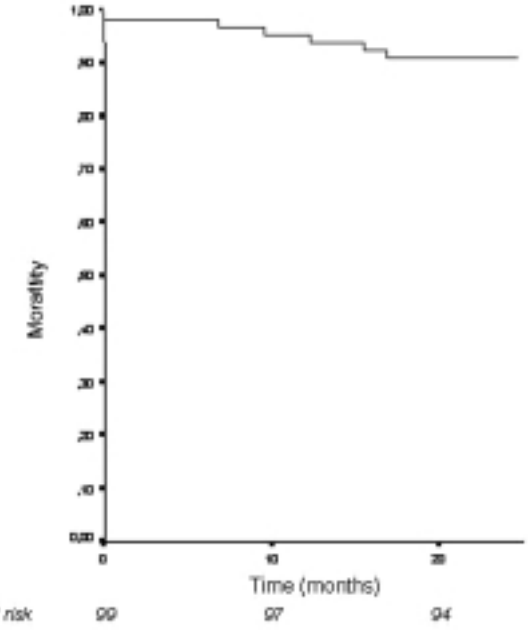

Figure 5. *Kaplan-Meier cumulative event rate for all deaths.*

Echo color Doppler ultrasound at 24 months was available for all the 93 surviving patients (93%). This procedure revealed recurrent stenosis of the treated vessel classified as moderate (50-69%) in 2 cases and as critical (≥ 70%) in another 2 cases (1.9%). Both critically restenotic lesions were successfully treated at repeat balloon angioplasty.

Discussion

In the present study CAS was performed in a laboratory of interventional cardiology mainly using coronary angioplasty equipment and with the routine appli-

cation of cerebral protection. The procedural success rate was high and the incidence of stroke/death was only 4%. In a recent paper Roubin et al.[1] report on the important reduction of the periprocedural complication rate over a 5-year learning experience. This was probably due to a refinement of the stenting technique. Furthermore, it is our opinion that the utilization of low profile equipment routinely used for coronary interventions and the development of lower profile, dedicated carotid artery stents markedly influence the clinical outcome of the procedures.

Procedural outcome and cerebral protection. The low incidence of procedural neurological complications and the presence of particulate matter detected in a high percentage of filters show that the protection device was able to collect debris which otherwise could have caused cerebral vessel embolization. The histological findings confirm that material is dislocated from the atheromatous plaque during the intravascular procedure[17]. The impossibility of resorting to cerebral protection in 2 cases is probably related to the fact that first-generation protection devices were used. More recent devices, in particular those with filters that can be advanced on the wire already positioned in the internal carotid artery, should reduce the incidence of impossible protection. Flow impairment due to debris occlusion of the filter pores was observed in 5.8% of cases. This was not related to any adverse event and was well tolerated by the patients. It is impossible to predict the clinical impact that the debris collected in the filters might have had but during surgical endarterectomy the majority of the complications could be related to the occurrence of distal embolism[5,6]. Previously published series of cerebral protection with occlusive balloon systems report similar favorable results in terms of a low incidence of neurological complications[10,11,18-20]. In order to achieve periprocedural complication rates ≤ 3% for carotid artery interventions as recommended by the American Heart Association guidelines[21] the routine use of protection devices is highly supported by these studies. However, it needs to be mentioned that the incidence of stroke/death after treating symptomatic lesions was 7.4%, which is above the 6% limit of the American Heart Association guidelines[21]. This underscores the importance of further improvements in the technique. The stroke/death rate after treating asymptomatic lesions was 2.6%, which is well within the 3% limit.

Long-term results. Comparison of the efficacy in reducing the incidence of stroke after CAS and CEA is difficult because of the limited long-term data available for patients treated with stents. In the only available randomized trial with a long follow-up (CAVATAS)[22], the incidence of stroke at 3 years after CAS and CEA was similar. In the NASCET trial[14] the incidence of stroke/death was 15.8% at 2 years and in the ACAS trial[15] it was 20.7% at 5 years. In the registry published by Roubin et al.[1] the incidence of stroke in symptomatic patients was 11 and 14% in asymptomatic patients. Other randomized studies of CAS vs CEA do not yet report long-term results[23] (and Yadav J., SAPPHIRE study, unpublished data). The results of the present study with a stroke/death rate at 2 years of 10% (stroke 3%, death 7%) compare well with the previous experiences. The absence of strokes and transient ischemic attacks from 30 days to 2 years can be considered as being strongly indicative of a high clinical efficacy of CAS in reducing the incidence of stroke. The > 30 day follow-up incidence of death/myocardial infarction rate of 8% includes 4% cardiac deaths and 2% infarctions (Table IV, Fig. 4) and is strongly related to the high (62%) prevalence of patients with coronary artery disease.

Restenosis. The incidence of restenosis (1.9%) is very low and compares favorably with the 6.7%[24] or 8 to 19%[25] presented for CEA. In the present study both cases of restenosis occurred at 4 months after the stent procedure (Fig. 6). This time interval from stent implantation to the occurrence of restenosis appears to be similar to that of other vascular stent procedures where the process of intimal proliferation is generally completed within 4 to 6 months. Compared to other vascular districts the carotid artery appears particularly adapt for stent implantation with a singularly low incidence of significant restenosis. The rare cases of restenosis were easily treated by repeat cerebral protected balloon angioplasty and good results were obtained.

Study limitations. The major limitation of this study is that it does not include a randomized comparison of CAS and CEA. Furthermore, the length of follow-up (2

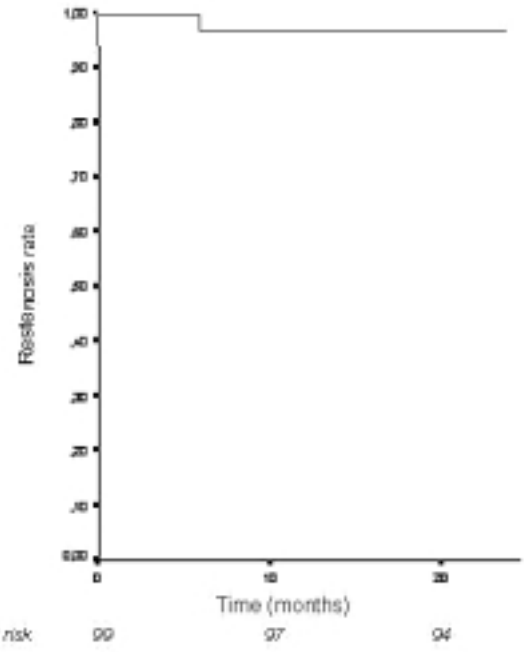

Figure 6. *Kaplan-Meier cumulative event rate for restenosis.*

years) is shorter than that available for CEA. For the evaluation of restenosis, mostly occurring within 6 months, a follow-up of 2 years can be considered adequate but longer observations are probably needed to determine the real clinical efficacy of CAS in reducing the incidence of stroke. However, the complete absence of neurologic events from 1 month to 2 years appears very promising. A further limitation of the study is that a morphologic echo color Doppler evaluation of the plaque was not performed.

In conclusion, the present registry demonstrates that CAS with routine cerebral protection can be performed with an acceptable procedural complication rate.

At 2 years of follow-up CAS appears durable with a low incidence of restenosis. It also seems to be effective in preventing stroke.

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