# Percutaneous Transluminal Angioplasty and Stenting for Carotid Bifurcation Stenosis

Jan Albert Vos


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# Percutaneous Transluminal Angioplasty and Stenting for Carotid Bifurcation Stenosis

Percutane Transluminale Angioplastiek met Stentplaatsing voor Vernauwingen ter Plaatse van de Splitsing van de Halsslagader

(Met een samenvatting in het Nederlands)

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in het openbaar te verdedigen
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door

**Jan Albert Vos**
geboren op 30 juni 1967 te Hoogezand-Sappemeer

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**Co-promotor:**
Dr. R.G.A. Ackerstaff

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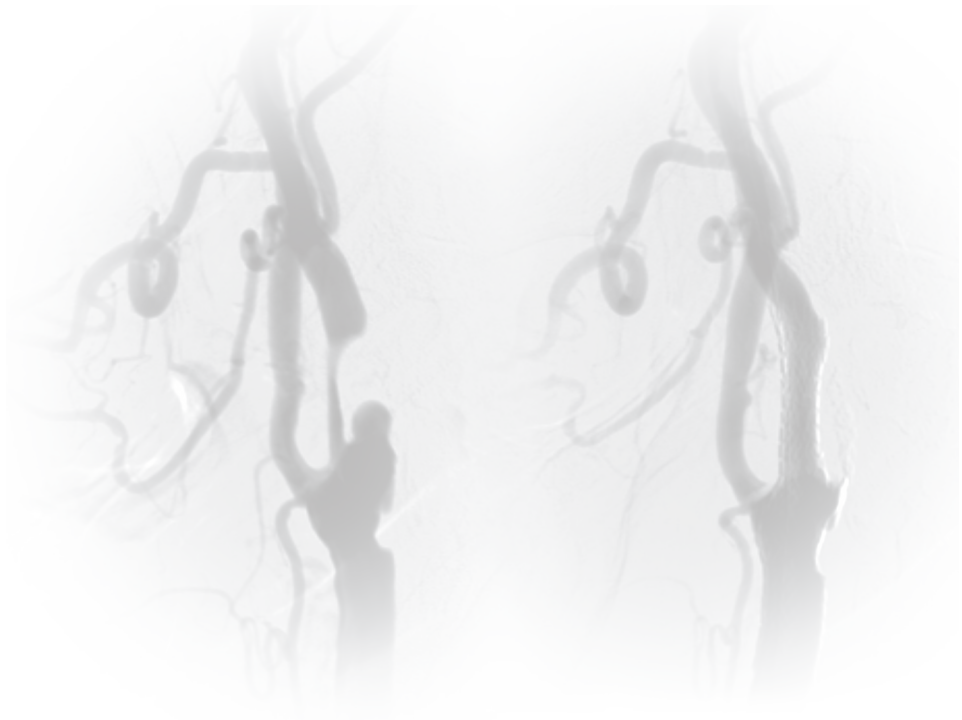
## General Introduction



# Chapter 1

# Part I

# Chapter 1

# General Introduction and outline of this thesis

# Chapter 1

## Introduction

Stroke is the most common cause of permanent disability and the third cause of death in developed countries. About 700 000 people annually suffer a stroke in the USA[1] and some 41 000 in the Netherlands[2]. Stroke survival is associated with profound impact on quality of life leading to great personal tragedy for the patient and his loved ones. Many stroke survivors lose the function of an arm, leg or both. Furthermore, if the stroke occurs in the dominant cerebral hemisphere, loss of phatic or language skills, both sensory and motory often ensues. In laymen's terms this means that the patient is both unable to understand what is being said to him and unable to speak himself, in effect virtually cutting off all normal interpersonal communication.

Apart from the personal consequences for the patient and his family, stroke, with its high prevalence and high costs associated with chronic care for permanent disability is also one of the most costly diseases in monetary terms. The estimated mean lifetime costs from an ischemic stroke are $140,000 per patient in the USA, amounting to a staggering $ 65 billion of annual costs for the USA alone[3].

Most strokes are ischemic in nature and most of those are thrombo-embologenic, rather than hemodynamic in origin. An embolus is dislodged into a blood vessel of the brain from elsewhere in the body, causing a blockage of this vessel and depriving the area of the brain it normally supplies from oxygen and other nutrients. This causes a loss of function, resulting in neurological deficit, which will likely be permanent if the occlusion persists. The most common sites of origin of the emboli found in ischemic stroke are the heart, especially in patients suffering from (bouts of) cardiac arrhythmia, and the carotid artery, mainly in cases of carotid bifurcation stenosis. About 30% of patients with newly occurring strokes have extracranial obstructive disease of the ipsilateral carotid artery, usually located around the carotid bifurcation[4]. The high velocity of the blood being pressed through a cervical carotid stenosis is thought to be the cause of fragments in the stenotic segment detaching from the vessel wall and being propelled into the cerebral circulation. This may result in either temporary (Transient Ischemic Attack, TIA) or permanent (stroke) cerebral deficit. Fortunately, in most cases the first symptoms are TIA's. There is a powerful association between TIA's and the subsequent occurrence of a stroke in the same vascular territory. Therefore TIA's are considered to be a warning sign and an indication for treatment.

In the nineteen fifties a surgical procedure was introduced to revascularize the carotid bifurcation[5] and consequently remove the source of cerebral emboli and hence

reduce the risk of cerebral ischemic stroke. This surgical procedure is nowadays known as Carotid EndArterctomy (CEA).

Two large randomized controlled trials, the North American Symptomatic Carotid Endarterectomy Trial[6] (NASCET) and the European Carotid Surgery Trial[7] (ECST) performed during the nineteen eighties have established the superiority of CEA to best medical treatment (BMT) in selected symptomatic patients. A further study, the Asymptomatic Carotid Atherosclerosis Study[8] (ACAS) established CEA to be superior to BMT in asymptomatic people with high grade carotid stenosis, but the number of people that needed to be treated (NNT) to prevent one stroke was significantly higher.

A disadvantage of CEA is that, by definition, it can only be performed in patients fit for surgery. Many patients with carotid obstructive disease simultaneously suffer from atherosclerotic disease elsewhere, for instance in the coronary arteries. Many have pulmonary co-morbidity, or other conditions that render them poor candidates, or indeed blandly unfit, for surgery. Local, cervical conditions may also make CEA a less appealing procedure: previous surgery or cervical irradiation may cause extensive scar tissue formation compromising surgical options. A high cervical location of the carotid bifurcation, or significant anatomical abnormalities, e.g. in patients with ankylosing spondylitis may also prove problematic for surgical approach of the carotid bifurcation.

For patients with extracranial carotid stenosis who are unfit for surgery, an alternative revascularization strategy was developed during the nineteen eighties: percutaneous carotid angioplasty, at first used only in patients with fibromuscular dysplasia[9], later also in the much more common setting of atherosclerotic disease[10]. However, as balloon angioplasty carries the risk of per-procedural embolization of dislodged plaque material, use of this treatment modality remained largely anecdotal. In the nineteen nineties the first reports on primary stenting of the carotid arteries, Carotid Angioplasty and Stenting (CAS) were published[11-13]. The concept of primary stenting is that plaque material is trapped between the stent and the vessel wall, thereby reducing the risk of embolic complications during the procedure.

In view of the inherent differences between CEA and CAS, both have their particular properties. Before CAS can be considered for general use, a more in-depth knowledge of the particular properties of CAS is necessary.

The St. Antonius Hospital in Nieuwegein was the first institute in The Netherlands to adopt CAS as treatment modality for carotid stenosis and remains the centre with the

most extensive CAS experience nationally, having performed over 1000 procedures to date. In this thesis several aspects of CAS are evaluated, stemming from the prospective database of all CAS procedures in our institution performed since 1996.

In **Part II** of this thesis per-procedural Trans Cranial Doppler (TCD) detected micro-emboli in the ipilateral Middle Cerebral Artery (MCA) are evaluated. They are correlated to clinical and MRI-detected cerebral embolic events in Chapter 2A and to clinical and fundoscopically detected retinal embolic events in Chapter 2B. Additionally, in Chapter 2C, TCD and outcome are evaluated comparing patients treated with and without filter type cerebral protection devices.

In **Part III** several of the inherent differences between CAS and CEA are highlighted. One of these differences is the potentially increased stiffness of the ICA after CAS, as compared to CEA. As this might manifest itself after head movements, MRA images in several different head positions are compared between patients treated with CAS, compared to CEA. In Chapter 3A the morphology of the ICA is examined. In Chapter 3B, with new sets of subjects, the evaluation is expanded to include MR flow measurements in the distal ICA, to establish any reduction in volumetric flow caused by kinking of the ICA. Another inherent difference between CAS and CEA is that the stent is frequently placed from the internal carotid artery to the common carotid artery, thereby covering the origin of the external carotid artery. As this might have consequences for the flow in the external carotid artery, Chapter 3C evaluates if the overstenting of the external carotid artery results in hemodynamic changes, both during the procedure and at follow up.

**Part IV** specifically describes subsets of patients undergoing CAS because the local, cervical situation rendered them unsuitable candidates for surgery. Restenosis after previous ipsilateral CEA is discussed in Chapters 4A and 4B. Chapter 4A reports the peri procedural clinical and TCD data comparing post CEA restenoses to primary stenoses. Chapter 4B describes the long term follow up of patients treated for post CEA restenoses. Chapter 4C focuses on post-irradiation restenosis.

In **Part V** contents of the preceding chapters are summarized and general conclusions are drawn (Chapter 5A). A summary in Dutch is included (Chapter 5B), as

well as a list of publications (Chapter 5C), the resume of the author (Chapters 5D and E) and finally a word of appreciation and gratitude to those who have contributed to making this thesis possible is included as Chapter 5F.

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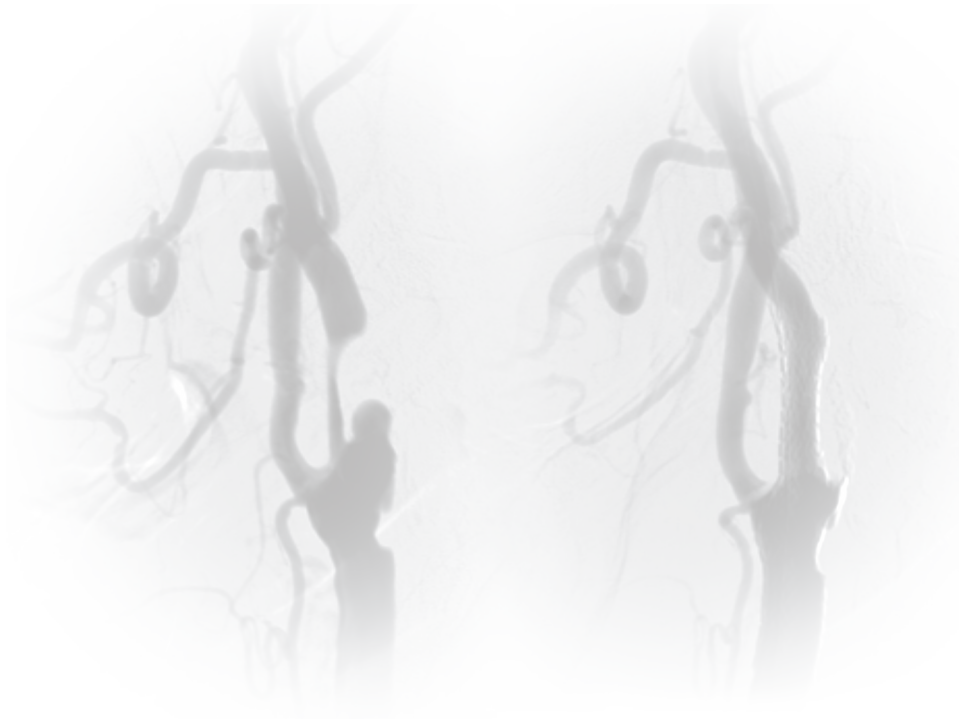
# Part II

## Embolic complications during Carotid Angioplasty and Stenting; Correlation with Transcranial Doppler data



# PART II
# CHAPTER 2A

# New Brain Lesions at MR Imaging after Carotid Angioplasty and Stent Placement

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*Radiology. 2002 Aug;224(2):361-5.*

## Abstract

**Purpose***:* To assess, with magnetic resonance (MR) imaging, the number and size of new brain lesions after carotid angioplasty and stent placement (CAS) and to evaluate the association of these new lesions with neurologic deficits and transcranial Doppler ultrasonographic (US) data.

**Material and Methods***:* Seventy-two consecutive CAS procedures were performed in 72 patients. Patients underwent neurologic examination before, during, immediately after, and 1 day, 3 months, and 1 year after CAS. MR imaging was used before and after CAS to assess the number of symptomatic and silent new infarctions. Two radiologists reviewed all pre- and postintervention MR images. The radiologists were blinded to the clinical data.

**Results***:* Postprocedural MR images showed new lesions on the side of stent placement in 11 patients. In six patients, the new lesions were clinically silent. Two patients had a major stroke, one had a minor stroke, and two had transient ischemic attack. In patients who had had transient ischemic attack or stroke before CAS, the frequency of new lesions at postprocedural MR imaging was higher (23%) than in asymptomatic patients (12%); this difference was not statistically significant ($P = .29$). There was no statistically significant correlation between embolic load as detected with transcranial Doppler US monitoring and the occurrence of either clinical symptoms or new lesions seen at MR imaging.

**Conclusion***:* CAS is associated with embolic events. The majority of new lesions seen on postintervention MR images are not detected at neurologic examination.


**Index terms:** Carotid arteries, MR, 1722.121411, 178.121411 • Carotid arteries, stenosis or obstruction, 1722.721, 178.721 • Carotid arteries, transluminal angioplasty, 1722.1269, 178.1269 • Carotid arteries, US, 1722.12989, 178.12989

## Introduction

Carotid endarterectomy (CEA) has been proved to be a beneficial treatment in patients with high-grade carotid artery stenosis. The efficacy and safety of CEA have been carefully evaluated in large randomized clinical trials[1,2]. CEA has a mortality rate of about 1% and a combined mortality and morbidity rate that is lower than 6% in symptomatic patients and lower than 3% in asymptomatic patients. A potential alternative to CEA is an endovascular technique, percutaneous transluminal carotid angioplasty and stent placement (CAS).

Authors of some studies have documented the frequency of new lesions, presumably infarctions, at magnetic resonance (MR) imaging of patients after CEA[3,4]. More recently, similar studies have been reported in the literature in which diffusion-weighted MR imaging was used[5-9]. Enthusiasm for CAS has led to increasingly widespread clinical application of this endovascular technique[10]. Although there are several studies in the literature of the incidence of cerebral lesions detected at MR imaging after manipulation of angiographic catheters in the carotid arteries[11,12], until now, to our knowledge, only one study of a small series of patients has been published that specifically assessed the safety of CAS by means of an evaluation of MR imaging findings after CAS[13]. The purpose of our study was to assess, with MR imaging, the number and size of new brain lesions after CAS and to evaluate the association of these new lesions with neurologic deficits and transcranial Doppler (TCD) ultrasonographic (US) data.

## Material and Methods

### *Study Design*

In an ongoing, prospective, phase II, open-safety study in the vascular center of our institution to investigate whether CAS is feasible, especially in patients with high risk of complications if they were to undergo surgery, MR imaging of the brain was performed before and 3 days after the intervention in 72 consecutive patients. Results of neurologic and memory testing were available for all patients.

### *Study Population*

Fifty-six men (median age, 69 years) and 16 women (median age, 71.5 years) were included in the study. Fifty patients (69%) had experienced no symptoms. Twenty-two patients (31%) had experienced symptoms in the 12 months prior to CAS–eight patients had had a minor stroke, five patients had had transient ischemic attack (TIA), and nine

patients had had ocular symptoms (eg, transient monocular blindness). The majority of patients had relatively high risk of complications if they were to undergo surgery due to cardiac and pulmonary comorbidity.

All patients had 90%–99% stenosis of the internal carotid artery. The degree of stenosis had been assessed with both intraarterial digital subtraction angiography and duplex US scanning before therapy. Furthermore, all patients had either documented progressive stenosis or severe four-vessel disease with insufficient collateral vasculature at color Doppler US and had to undergo major cardiac or vascular surgery. The majority of the asymptomatic patients had undergone placement of a carotid stent during the work-up for coronary artery bypass surgery.

The hospital human research committee approved this study, and informed consent was obtained from each patient.

***Stent Placement***

All patients were treated for stenosis of either the carotid bifurcation or the proximal internal carotid artery. In all patients, the stent in the internal carotid artery extended into the common carotid artery so that a portion of the stent covered the external carotid artery (a technique we call "overstenting"). Endovascular treatment was performed by two experienced board-certified interventional radiologists (J.C.v.d.B. and T.T.C.O.) and one interventional cardiologist (S.M.P.G.E). The technique used is described amply in the literature[14,15]. A femoral approach was used in all patients. In all cases predilation of the stenosis was performed with a balloon of 2.5–3.5 mm in diameter. After routine predilation, the stent was introduced, positioned, placed, and, finally, tailored. The postdilation diameter of the balloon was 5–9 mm, depending on the diameter of the artery as determined with duplex US prior to the procedure. In all cases a flexible, self-expandable stent (Easy Wall; Schneider, Minneapolis, Minn) was used. All 72 patients underwent angioplasty and stent placement without the use of cerebral protection devices.

***Medication***

All patients in our study received antiplatelet and antithrombotic drugs, including 250 mg/d of aspirin, 250 mg/d of ticlopidine (Ticlid; Sanofi-Winthrop, Maassluis, the Netherlands), or 75 mg/d of clopidogrel (Plavix; Sanofi-Winthrop), starting the day before the procedure. In addition, all patients received 6,000–8,000 IU of heparin (Heparine Leo; Leo Pharma, Breda, the Netherlands) intravenously during the intervention. Twenty-

five patients also used anticoagulants. One milligram of atropine sulfate (Antonius Hospital, Nieuwegein, the Netherlands) was administered to reduce bradycardia and/or hypotension induced by compression of the carotid body before inflation of the angioplasty balloon.

***Monitoring during Intervention***

During the interventions, patients were continuously monitored by an independent neurologist and with TCD US of the ipsilateral middle cerebral artery so that any neurologic complications could be directly related to the phase of the intervention, brain perfusion, and embolic load. Systemic blood pressure, heart rate, and peripheral arterial oxygen saturation were routinely monitored as well.

***MR Imaging***

MR imaging examinations of the brain were performed 1 day before and 3 days after the intervention. MR imaging was performed with a 0.5-T system (T5 II; Philips Medical Systems, Best, the Netherlands) and a mirror head coil. The imaging protocol included a transverse T2-weighted spin-echo sequence (repetition time msec/echo times msec, 2,200/30, 90) and a fluid-attenuated inversion recovery (FLAIR) turbo spin-echo sequence (repetition time msec/echo time msec/inversion time msec, 6,500/120/2,000). The angulation of sections was bicommissural, with a section thickness of 6 mm, a gap of zero, a field of view of 230 mm, and a matrix size of 205 x 256 pixels. The sections used in the MR imaging sequences performed after the intervention were at the same levels as those used in the MR imaging sequences performed before the intervention.

Two neuroradiologists (H.P.M.v.H. and J.A.V.) simultaneously reviewed all MR images obtained before and after the interventions. Disagreement occurred in none of the cases. The radiologists were blinded to the clinical data, TCD US data, and examination date. The number, location, and size of the lesions were recorded. Lesions that had signal intensity characteristics equivalent to those of cerebrospinal fluid on T2-weighted images and were larger than 3 mm in diameter and lesions that were wedge shaped and cortico-subcortical were regarded as brain infarctions.

***Evaluations before Intervention and during Follow-up***

Patients were examined by an independent neurologist according to a standardized protocol that included neurologic examination, functional rating scales (Barthel Index, Rankin Scale), a memory test (the Mini–Mental State Examination), the National Institutes of Health Stroke Scale, and carotid duplex US scanning. These examinations

were conducted before and directly after the intervention, during each of the first 3 days after the intervention, and 3 and 12 months thereafter. Signs and symptoms of any new neurologic deficit were recorded. Dependency in daily life was assessed with the Modified Rankin Scale. Stroke was defined as the occurrence of an acute focal neurologic deficit persisting for more than 24 hours. Strokes were considered major if patients had a Rankin score of 3 or higher at 3 months. A minor stroke resulted in a score of 0–2 on the Rankin scale.

### *Statistical Analysis*

The Fisher exact test was used to analyze the clinical symptoms and the MR imaging findings. For data not normally distributed (eg, TCD US data) we used median and interquartile ranges for descriptive purposes and the Wilcoxon rank sum test for comparisons between groups. A value of $P < .05$ was considered to indicate a statistically significant difference.

## Results

### *Clinical Symptoms*

Eleven of 72 patients showed clinical signs of neurologic complications after angioplasty and stent placement. Two patients had a major stroke (both had new lesions at postprocedural MR imaging), two patients had a minor stroke (one had a new lesion at MR imaging), four patients had TIA (two had a new lesion at MR imaging), and three patients had transient monocular blindness (none had new lesions at MR imaging). If we divide our study population into two groups—patients with asymptomatic carotid artery stenosis ($n = 50$) and patients with recently symptomatic carotid artery stenosis ($n = 22$)—the neurologic complication rate was lower in the group of asymptomatic patients (six patients [12%]; 95% CI: 4.5, 24.3) than in the group of symptomatic patients (five patients [23%]; 95% CI: 7.8, 45.4). This difference was not statistically significant ($P = .3$).

### *MR Imaging Findings*

In 11 of 72 patients (15%; 95% CI: 7.9, 25.7) postprocedural MR imaging revealed a total of 19 new lesions. All new lesions were located on the side of the brain where a stent had been placed. In six patients these new lesions were clinically silent; the size of the lesions in this subgroup varied from 3 mm to 3 cm. Five patients who had new lesions on postprocedural MR images experienced adverse neurologic events during or

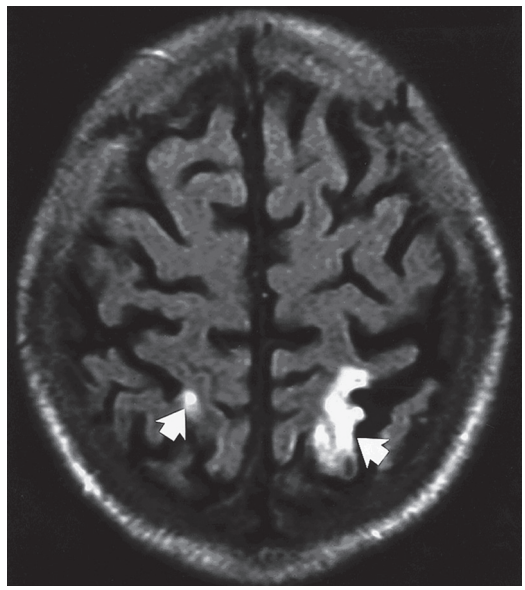

**Figure 1A** Transverse MR image before carotid angioplasty and stenting (FLAIR image, TR 6500, TE 120 ms, inversion delay 2000 ms)

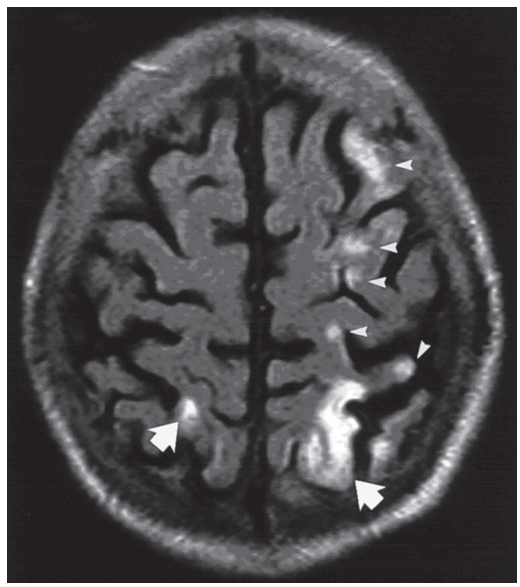

**Figure 1B** Transverse MR image after left-sided carotid angioplasty and stenting (FLAIR image, TR 6500, TE 120 ms, inversion delay 2000 ms) demonstrates new and enlargement of preexisting hyperintense lesions on the side of stenting

**Table 1**: New MRI lesions and new post-procedural clinical signs

| Number of patients | | | |
|---|---|---|---|
| **Clinical signs** | **no new MRI lesions** | **new MRI lesions** | **Total** |
| - No clinical signs | 55 | 6 | 61 |
| - TMB | 3 | | 3 |
| - TIA | 2 | 2 | 4 |
| - Major stroke | | 2 | 2 |
| - Minor stroke | 1 | 1 | 2 |
| - Total | 61 | 11 | 72 |

TIA= Transient Ischemic Attack
TMB= Transient Monocular Blindness

immediately after the intervention; the size of the lesions in this subgroup varied from 3 mm to 7 cm. Two patients had a major stroke, one patient had a minor stroke (Figure 1A and B), and two patients had TIA. In patients who had had TIA or stroke before undergoing CAS, the frequency of new lesions detected at MR imaging was higher (five patients [23%]; 95% CI: 7.8, 45.4) than in asymptomatic patients (six patients [12%]; 95% CI = 4.5, 24.3). This difference was statistically not significant ($P$ = .29). Postprocedural clinical signs and MR imaging findings are summarized in the Table 1.

***TCD US Findings***

In 64 of the 72 patients (89%) an acoustic window was available for TCD US monitoring of the ipsilateral middle cerebral artery. During the CAS procedure the number of isolated emboli in the middle cerebral artery was recorded, as well as the number of embolic showers. An embolic shower was defined as the occurrence of too many emboli to be counted separately in one cardiac cycle.

Of the 11 patients with new lesions at postprocedural MR imaging, 10 had an acoustic window for TCD US monitoring. In these 10 patients, the median number of isolated emboli was 164.5 (interquartile range [IQR], 42–215), and the median number of embolic showers was 11 (IQR, 1–26). In the 54 patients without new lesions at MR imaging for whom TCD US data were available, the median number of isolated emboli was 103 (IQR, 69–155), and the median number of embolic showers was nine (IQR, 2–16). These differences were not statistically significant ($P$ = .32 for isolated emboli and $P$ = .90 for embolic showers).

In the group of patients that had new neurologic symptoms, 10 of 11 had an acoustic window. In this group, the median number of isolated emboli was 76.5 (IQR, 42–155), and the median number of embolic showers was 8.5 (IQR, 3–15). In the group of patients without new neurologic symptoms, 54 had an acoustic window for TCD US examination. The median number of isolated emboli in this group was 109 (IQR, 71–172), and the median number of embolic showers was 9.5 (IQR, 1–18). These differences were not statistically significant ($P$ = .24 for isolated emboli and $P$ = .88 for embolic showers).

## Discussion

The endovascular management of carotid disease is a rapidly developing area. The percutaneous revascularization technique of CAS offers advantages in the treatment of carotid stenosis. It requires no anesthesia, enabling continuous neurologic monitoring of the patient. Lesions that are difficult to access surgically (eg, high cervical lesions) may be treated with this technique. Because it is a less invasive procedure and does not involve cervical dissection, the patient may experience less periprocedural discomfort and a lower risk of cardiac and pulmonary complications. This in turn may result in a shorter hospital stay and lower health care costs. However, the procedure also has disadvantages. The major risk of CAS is the possibility that it will result in dislodgment and distal embolization of plaque and thrombotic debris into the brain or eye. This may result in a stroke, the very event we want to prevent. Several risks are that the balloon may obstruct carotid blood flow long enough to cause a low-flow ischemic stroke, cerebral vasospasms may occur, and balloon dilation and continuous pressure from the stent may cause systemic hypotension and bradycardia due to carotid body stimulation.

Noninvasive monitoring methods are desirable to establish the efficacy and safety of these endovascular procedures[13]. During the interventional procedure, cerebral perfusion and embolism can be continuously monitored with TCD US of the ipsilateral middle cerebral artery. The embolic load during CAS, as documented with TCD US monitoring, is much higher in comparison with the embolic load during carotid endarterectomy[16]. However, the neurologic complication rate is relatively low in view of this high embolic load. A possible cause of the relatively low number of neurologic deficits may be the extensive treatment of the patients with antiplatelet and antithrombotic drugs during stent placement.

On the basis of combined embolic and neurologic findings at TCD US, critical

phases during the intervention have been identified. They include predilation of the carotid stenosis (especially after balloon deflation), stent placement, and tailoring of the stent.

In this study there was no statistically significant difference in the embolic load, as detected with TCD US monitoring, between the group with and the group without new lesions detected at MR imaging or between the group with and the group without new neurologic symptoms. Nevertheless, it seems reasonable to attribute these occurrences to embolic material.

It is difficult to compare the neurologic deficits in our group of patients treated with CAS with those occurring in patients treated with CEA. TIAs, which occurred in four patients in our group, and transient monocular blindness, which occurred in three patients in our group, are seldom diagnosed in patients treated with CEA because in most patients CEA is performed with general anesthesia.

Like the results of carotid surgery trials[17], the results of our study show that patients with symptomatic carotid artery stenosis seem to be at higher risk than asymptomatic patients of experiencing neurologic complications due to the intervention. In our group of 72 patients treated with CAS, 50 were asymptomatic. At our institution, asymptomatic patients are treated during the work-up for coronary artery bypass surgery. In patients with coexisting severe carotid and coronary disease, there is an increased rate of stroke during coronary artery bypass grafting[18,19].

In a large randomized trial[20], carotid endarterectomy was compared with medical therapy in patients with asymptomatic carotid stenosis. In patients with asymptomatic carotid stenosis of 60% or greater, this Asymptomatic Carotid Atherosclerosis Study reported an actuarially estimated 5-year risk of ipsilateral stroke or any perioperative stroke or death of 5.1% for patients who underwent surgery versus 11% (annual event rate of 2.2%) for patients who were treated medically. This results in an absolute risk reduction of 5.9% (1.2% per year) for patients who are treated with endarterectomy. In addition to the conclusions of the Asymptomatic Carotid Atherosclerosis Study, Norris et al.[21] have reported that patients with asymptomatic carotid stenosis greater than 75% have a combined rate of TIA and stroke of 10.5% per year. These studies support the treatment of asymptomatic patients, although controversy on this subject certainly remains.

We used conventional MR imaging in the evaluation of our patients. The frequency and size of new lesions in our study may have been different if we had used diffusion-weighted MR imaging. As reported by Bendszus et al[11], findings from diffusion-weighted MR imaging show new brain lesions after angiography in 23% of

patients with no apparent neurologic deficit. In their study, angiography was associated with a higher lesion rate in patients with a history of vasculopathy than in patients with no vascular risk factors. Our experience seems to support these findings.

The sensitivity of conventional MR imaging is relatively low in the early stages of cerebral ischemia. In the first 24 hours of the occurrence of cerebral ischemia, only 80% of conventional MR images show abnormalities[22]. Because we were examining instances of both clinically apparent and clinically silent cerebral ischemia in which the time of occurrence was well defined, we decided to perform our postprocedural MR imaging examinations 3 days after CAS to ensure that the new lesions were as conspicuous as possible. Diffusion-weighted MR imaging, a more sensitive modality in early brain ischemia, was used by Lövblad et al[13] to evaluate 19 patients before and after CAS. They found new hyperintense lesions in five patients (26%).

Cantelmo et al[3] evaluated 76 patients who underwent CEA, performing an MR imaging examination before and after surgery. They found small areas of ipsilateral ischemic change on seven postoperative MR imaging studies (9%). Jansen et al[4] compared pre- and postoperative MR images obtained in 40 patients treated with CEA to detect intraoperative infarcts. Four patients (10%) developed new lesions that were seen at MR imaging; all of these lesions were clinically silent. Percutaneous angioplasty with stent placement is associated with a rate of microemboli that is more than eight times higher than that seen during carotid endarterectomy when percutaneous angiography with stent placement and carotid endarterectomy are evaluated with TCD US monitoring[16]. In our study we saw new lesions at MR imaging in 11 (15%) of 72 patients; in six patients (8%)—the majority of those affected—these new lesions were clinically silent.

In comparing the neurologic complications seen in our study with those seen in a recent study conducted by Henry et al[23], some differences can be observed. Henry et al analyzed the results of 315 CAS procedures in 290 patients. Cerebral protection devices were used in 150 procedures. They observed the following periprocedural neurologic complications due to ischemia in 13 patients (4.2%): four TIAs (1.3%); four minor strokes (1.3%); and five major strokes (1.6%), including one death. In our study, four patients (5.6%) had TIA, two (2.8%) had minor strokes, and two (2.8%) had major strokes but no mortality. It should be noted that, unlike Henry et al, we did not use cerebral protection devices in any of our patients. In a group of 28 high-risk symptomatic patients with carotid artery stenosis evaluated by Malek et al[24], there were no minor strokes, one major stroke (3.6%), and three TIA (10.7%). The percentage of TIA and the percentage of stroke are both lower in our study.

It is difficult to make exact comparisons between the data of the current study and those of previously mentioned investigations. To our knowledge, few studies of the incidence of new lesions seen at MR imaging and neurologic deficits in patients after CEA and CAS have been published. Furthermore, the selection of patients (patients with serious cardiovascular comorbidity were substantially overrepresented) and the relatively small population in our study do not allow for a comprehensive comparison. More research into the safety and efficacy of CAS, as well as its long-term results, is certainly necessary before this procedure can be considered an alternative to CEA.

In conclusion, our data suggest that CAS is associated with a number of new hyperintense (ischemic) lesions at cerebral MR imaging, of which the majority are clinically silent; there does not appear to be a correlation between the occurrence of these lesions and the embolic load as evidenced with TCD US. In the future, the role of cerebral protection devices during CAS should be examined. These devices might lower the number of emboli.

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# PART II
# CHAPTER 2B

# Retinal Embolization during Carotid Angioplasty and Stenting: peri-procedural data and follow up

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* The members of the group are listed in the appendix

*Pending revision for publication*

## Abstract

**Objectives**:To prospectively evaluate the incidence of retinal emboli during Carotid Angioplasty and Stenting (CAS) and to correlate emboli with clinical findings and Trans Cranial Doppler (TCD) detected cerebral embolic load.

**Materials and Methods**: Between 2001 and 2005, 33 CAS procedures in 32 patients (23 [72%] male, 19 [58%] symptomatic, mean age 72.5 years, range 54.6-83.9) scheduled for CAS were included in this study. Bilateral fundoscopy, with retinal photography was performed by an experienced ophthalmologist immediately before, immediately after (fundoscopy only) and one day after the procedure and at long term follow up (mean 37 months). Visual field testing was performed before CAS and at long-term follow up. TCD detected cerebral emboli were stratified to five procedural phases: wiring, predilation, stent placement, postdilation, and cerebral protection device (CPD) use (if applicable). To establish correlation between TCD data and retinal embolization the Mann-Whitney test was used. $P<0.05$ was regarded as statistically significant.

**Results**: All procedures were performed successfully. In 5 of 33 procedures (15%) new retinal emboli were found. Two of the procedures with emboli had small retinal infarcts. Three out of 5 were performed using CPDs, vs. 7 out of 28 who had no retinal emboli (P= not significant). Two of 4 patients (50%) with prior radiation therapy to the neck had new retinal emboli, versus 3 of 29 patients (10%) who had no prior radiation therapy (P=0.038). None of the other patient characteristics was associated with retinal embolization. In 30 (91%) of patients with an adequate acoustic temporal window for TCD monitoring there was no statistically significant correlation between TCD-data and the incidence of retinal emboli. No visual field defects were found. On long-term follow-up all retinal emboli and retinal infarcts had resolved.

**Conclusions**: Retinal embolization during CAS is not uncommon, occurring both in protected and unprotected procedures. Most retinal emboli are clinically silent.


**Key words**:
Carotid arteries, Stenting, Retina, Emboli, Fundoscopy, Trans Cranial Doppler

## Introduction

Carotid Endarterectomy (CEA) has been well established as treatment for both symptomatic and asymptomatic carotid bifurcation stenosis[1-4]. Increasingly Carotid Angioplasty and Stenting (CAS) is considered as an alternative to CEA in selected cases, especially in patients with hostile neck after surgery, tracheostomy or irradiation therapy or in anatomically high lesions[5]. In both procedures distal embolization of plaque material is recognized as a potential cause of procedural complications, which may occur in the brain as well as in the retina. To date the vast majority of publications on CAS have concentrated solely on cerebral emboli. Only one previous study has specifically addressed retinal embolization during CAS[6]. The retinal circulation has the unique potential of direct visualization by using fundoscopy or retinal photography, making it ideally suitable for direct detection of emboli. The cerebral embolic load can not be directly visualized, but may be estimated using peri-procedural Trans Cranial Doppler (TCD)[7] and post-procedural Magnetic Resonance Imaging[8,9].

In this study we used fundoscopy and retinal photography before and after CAS to establish the incidence of peri-procedural retinal embolization. Findings are correlated to Trans Cranial Doppler (TCD) data, to establish any correlation between retinal embolization and TCD detected cerebral embolic load. Furthermore, in cases where retinal emboli were detected, a follow up retinal examination and a visual field examination was performed to establish any permanent sequelae.

The purpose of this study was to establish the incidence of retinal embolization during CAS and to correlate this to cerebral embolic load and to evaluate the clinical consequences of this occurrence.

## Material and methods

Between October 2001 and May 2005, 33 CAS procedures in 32 patients were included in this study. Twenty-three patients (72%) were male, median age was 72.5 years (Range 54.6- 83.9). Seventeen procedures were on the right carotid bifurcation, 14 on the left; one female patient had staged bilateral procedures. Patient characteristics are detailed in table 1.

One hour before the procedure mydriatic medication (tropicamide 0,5% and fenylefrine 5%) was administered in both eyes. An experienced ophthalmologist then performed a full retinal examination and a digital retinal photograph was made of both

retinae, using a dedicated digital fundoscopic camera (FF450plus, Zeiss Inc., Jena, Germany). Subsequently patients were transferred to the department of interventional radiology for the CAS procedure.

CAS was performed using a standard protocol described in detail in several previous publications[7,10]. In all procedures a groin approach was used. All patients received platelet aggregation inhibitors: aspirin (250 mg daily) and clopidogrel (75 mg daily). During the procedure 5000 to 10000 IU of heparin were administered intravenously. After positioning of a guiding catheter in the common carotid artery, the stenosis was navigated with a guidewire. Before balloon inflation, 1 mg of atropine sulphate was given intravenously to reduce bradycardia and/or hypotension induced by carotid body compression. If necessary predilation with an undersized balloon was performed and subsequently a dedicated self expandable stent was placed. The types of stents used are summarized in Table 2.

If a stenosis persisted, post dilation, using a larger balloon, was performed. In the early part of this study the use of filtering Cerebral Protection Devices (CPD's) was routine. However, when a negative correlation between the use of these devices and cerebral embolic load was established[11], their use was discontinued. Ten out of 33 procedures (30%) were performed using a CPD.

In all patients with an acoustic temporal window (30/33, 91%), TCD of the ipsilateral Middle Cerebral Artery (MCA) was performed during the interventional procedure. The technique has been described in detail previously[10]. During the various stages of the procedure isolated microembolic signals were recorded according to the criteria described by the consensus committee[12]. If the number of microembolic signals was too high to be counted separately, heartbeats with microemboli were counted as microembolic showers. For the evaluation of the relative risk of several procedural phases, the intervention was subdivided into 5 distinct phases: 1) wiring/passing the stenosis, 2) predilation, 3) stent placement, 4) postdilation and 5) protection device use (if applicable).

Immediately after conclusion of the procedure, a repeat fundoscopy was performed while the patient was still on the angiography table. No retinal photograph was made at this moment, as patients need to be seated for this examination and this was not possible directly after closing the arterial access site in the groin. Subsequently the patient was transferred to the recovery room for intensive observation for six hours, before being discharged to the ward. The next morning a further dose of mydriatics

**Table 1**. Baseline patient characteristics

| **Patient characteristics** | **N (%)** |
|---|---|
| **Sex** Male / Female (%) | 23 (72%) / 9 (28%) |
| **Age** Mean (Range) | 72.5 Yrs (54.6-83.9 Yrs) |
| **Ipsilateral symptoms** Yes / No (%) | 19 (58%) / 14 (42%) |
| **Side of stenting** Left / Right / Bilateral (%) | 17 (53%) / 14 (44%) / 1 (3%) |
| **Prior ipsilateral CEA** Yes / No (%) | 19 (58%) / 14 (42%) |
| **Prior radiation therapy** Yes / No (%) | 4 (12%) / 29 (88%) |
| **Contralateral occlusion** Yes / No (%) | 1 (3%) / 32 (97%) |
| **Acoustic window MCA** Yes / No (%) | 30 (91%) / 3 (9%) |

was administered and the patient was re-examined using both fundoscopy and retinal photography. Any new retinal emboli were recorded, as well as any visual symptoms. When embolization occurred, patients were submitted to visual field examination and entered in an ophthalmologic follow-up schedule.

All data were recorded prospectively and all patients were included on intention-to-treat basis. The study was approved by the institutional human research committee and prior written informed consent was obtained from all patients.

For the statistic analysis of the incidence of retinal embolization the two-tailed Mann-Whitney test was used. $P<0.05$ was regarded as statistically significant.

## Results

In all procedures the CAS procedure was technically successful and no major or minor strokes, TIA's or deaths occurred. Correlation between retinal findings and baseline patient characteristics are presented in table 3. New retinal embolizations were found in 5 procedures, including 3 retinal infarcts. Three out of 10 patients treated with CPD (33%) had new retinal emboli, versus 2 out of 23 unprotected procedures (9%), this difference was not statistically significant. Two of 4 patients (50%) treated for a stenosis after prior radiation therapy to the neck had new retinal emboli, versus 3 of 29 patients (10%) who had no prior radiation therapy ($P=0.038$). There was no statistically

**Table 2**. Types and numbers of stents used

| Stent type | Manufacturer | N |
|---|---|---|
| **Precise** | Cordis J&J, Miami Lakes, FL | 19 |
| **Carotid Wallstent** | Boston Scientific, Natick, MA | 6 |
| **Acculink** | Abbot Laboratories, Abbott Park, IL | 4 |
| **Carotid SE** | Medtronic, Minneapolis, MN | 3 |
| **Nex** | Boston Scientific, Natick, MA | 1 |
| | | 33 |

significant difference in any of the other patient characteristics between patients with and those without retinal embolization. Details of the patients with new retinal emboli are described below.

In patient 1 fundoscopy and retinal photography showed an ipsilateral cholesterol embolus in the distal superior temporal artery, without signs of infarction . The visual field examination showed no defects due to embolization. At long term follow-up (50 months) the embolus had resolved.

Patient 2 had a cholesterol embolus in a branch of the inferior temporal artery and a small retinal infarction distally. The visual field examination showed no defects due to infarction or embolization. Unfortunately this patient was lost to follow-up.

Fundoscopy and retinal photography in patient 3 showed two small ipsilateral retinal infarcts in side branches of the superior temporal artery (figure 1). Visual field examinations peri-procedurally and at long-term follow up showed no new defects. At follow-up (43 months) the 2 infarcts had resolved.

Patient 4 had a new cholesterol embolus in an ipsilateral foveal sidebranch of the superior temporal artery, without signs of infarction (Figure 2). Visual field examination showed no defects peri-procedurally or at long-term follow-up (31 months).

In patient 5, fundoscopy immediately after the procedure revealed no new emboli or infarctions. Retinal photography the next day however, showed 2 new emboli situated in the inferior temporal artery. No visual field defects were found the day after the procedure or at follow-up (23 months).

The 5 patients who had retinal emboli were treated with a variety of self-expandable stents: 2 procedures with a Precise stent (Cordis J&J, Miami Lakes, FL)

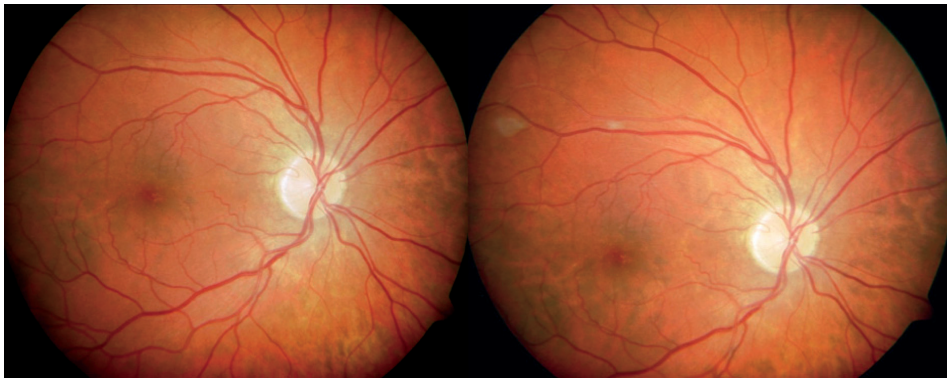

**Figure 1 A and B**: Retinal photographs of the right eye prior to ipsilateral CAS (1A) and 24 hours after CAS (1B). Two new small retinal infarcts are seen in the territory of the superior temporal artery.

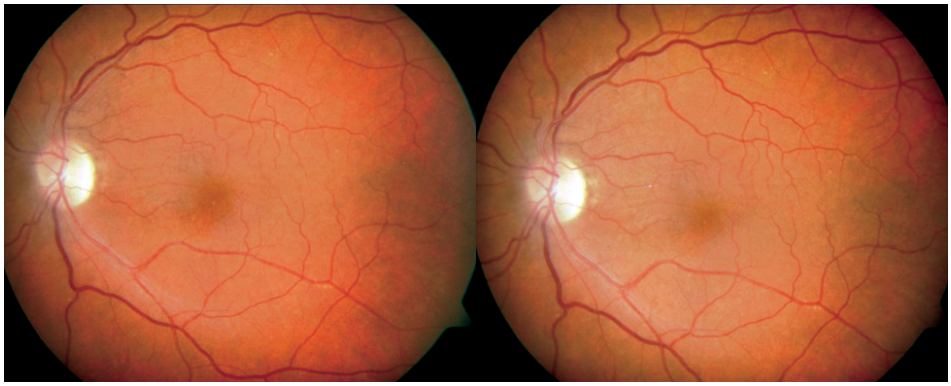

**Figure 2 A and B**: Retinal photographs of the left eye prior to ipsilateral CAS (2A) and 24 hours after CAS (2 B). A small cholesterol embolus in a foveal side branch is seen without signs of infarction.

and one each with the Carotid Wallstent (Boston Scientific, Natick, MA), Carotid SE (Medtronic, Minneapolis, MN) and Acculink (Abbot Laboratories, Abbott Park, IL).

## Discussion

In this study on carotid angioplasty and stenting, peri-procedural retinal embolization was investigated. We found new retinal emboli after CAS in 5 out of 33

procedures (15%). Fortunately, none of the emboli caused symptoms and all emboli and even associated silent retinal infarctions had resolved at long-term follow up. No correlation between the occurrence of retinal emboli and the TCD-detected cerebral microembolic load was found. The only patient characteristic that was statistically associated with retinal embolization during CAS was prior radiation therapy to the neck.

Only one previous study has been published on retinal embolization during CAS[6]. Wilentz et al. used one of two types of distal balloon protection systems in all cases. Overall, retinal embolization occurred in 4% of procedures; 5 out of 38 (13.2%) using the Théron protection system versus 1 in 80 (1.3%) when the Percusurge® distal balloon protection system was used. We have used the latter system on a limited number of cases, not included in this study, but discontinued its use after some patients did not tolerate the occlusion of the ICA, as has been described before[13]. The number of emboli found by Wilentz et al. when using the Théron system is quite comparable to our results in a combination of unprotected procedures and procedures using distal filter devices.

The retinal circulation is normally derived from the ophthalmic artery, which in turn is a side branch of the internal carotid artery. As cerebral protection filters are positioned in the internal carotid artery, below the level of the ophthalmic artery, they should provide protection for the retinal, as well as the intracranial circulation. Our findings in the retina confirm that these distal filters do allow passage of emboli to the distal circulation, as has been shown before pertaining to the cerebral circulation[5].

There is a well-established association between retinal symptoms and carotid stenosis. Wijman et al.[14] found an association between spontaneous symptomatic retinal emboli, carotid stenosis and an increased risk of cerebral ischemia, whereas the significance of asymptomatic spontaneous retinal emboli in their study was limited. No data are available, however, on the clinical significance of silent retinal emboli that do not occur spontaneously, but are the consequence of CAS. Only one study, from the nineteen nineties, describes retinal embolization during Carotid Endarterectomy[15], correlating findings with peri-procedural TCD. In 100 endarterectomies only one new retinal embolus was found. Interestingly, there was deterioration in visual field scores after the procedure for the ipsilateral eye, even in the absence of retinal emboli. There was no association between visual field disturbances and the TCD detected cerebral embolic load, paralleling our findings of TCD and fundoscopic data in CAS. Although we found more retinal emboli in our CAS series, we did not find visual field defects in any of the affected patients.

**Table 3.** Grouped patient characteristics. Group1:cases with new retinal emboli. Group 2: cases without new retinal emboli. * One female patient had staged bilateral procedures, both did not result in retinal emboli.** Statistically significant

| Patient characteristics | Group 1<br>N = 5 | Group 2<br>N = 28 | P-value |
|---|---|---|---|
| **Sex** Male/Female | 4(80%) /1 (20%) | 19(70%)/8* (30%) | .59 |
| **Age** Median (Range) | 71 years (59-75) | 74 years (59-83) | .34 |
| **Ipsilateral Symptoms** Yes / No | 4 (80%) / 1 (20%) | 12 (43%) / 16 (57%) | .13 |
| **Side of Stenting** Left / Right | 3 (60%) / 2 (40%) | 12 (43%) / 16 (57%) | .48 |
| **Prior ipsilateral CEA** Yes / No | 3 (60%) / 2 (40%) | 17 (61%) / 11 (39%) | .92 |
| **Prior Radiation Therapy** Yes / No | 2 (40%) / 3 (60%) | 2 (7%) / 26 (93%) | .038** |
| **Contralateral occlusion** Yes / No | 0 (0%) / 5 (100%) | 1 (4%) / 27 (96%) | .83 |
| **Protection Device use** Yes / No | 3 (60%) / 2 (40%) | 7 (25%) / 21 (75%) | .12 |

**Table 4**. Number of isolated emboli during the various stages of the procedure. Mean and [Standard Deviation of Mean]. Group 1 patients with new retinal emboli. Group 2 patients without new retinal emboli. NS= Not Significant.

| | Group1 | Group 2 | P-value |
|---|---|---|---|
| **Wiring** | 50 [26.6]<br>N=5 | 80.8 [102.0]<br>N=25 | .83 (NS) |
| **Predilation** | 11 [8.0]<br>N=3 | 21.1 [18.5]<br>N=15 | .36 (NS) |
| **Stent placement** | 48.8 [16.0]<br>N=5 | 62.2 [25.3]<br>N=25 | .15 (NS) |
| **Postdilation** | 42.8 [41.6]<br>N=5 | 28.3 [24.3]<br>N=25 | .39 (NS) |
| **Protection device** | 53.7 [39.8]<br>N=3 | 33.1 [24.5]<br>N=7 | .63 (NS) |
| **Total** | 180.4 [79.0]<br>N=5 | 193.7 [128.1]<br>N=25 | .87 (NS) |

**Table 5**. Number of embolic showers during the various stages of the procedure. Mean and [Standard Deviation of Mean]. Group 1 patients with new retinal emboli. Group 2 patients without new retinal emboli. NS= Not Significant.

| | Group1 | Group 2 | P-value |
|---|---|---|---|
| **Wiring** | 0.4 [0.5]<br>N=5 | 1.24 [2.5]<br>N=25 | .99 (NS) |
| **Predilation** | 0.7 [0.9]<br>N=3 | 4 [6.3]<br>N=15 | .57 (NS) |
| **Stent placement** | 16.0 [18.5]<br>N=5 | 21.1 [14.1]<br>N=25 | .30 (NS) |
| **Postdilation** | 3.2 [2.3]<br>N=5 | 3.6 [6.8]<br>N=25 | .33 (NS) |
| **Protection device** | 1.7 [2.4]<br>N=3 | 4.6 [3.7]<br>N=7 | .27 (NS) |
| **Total** | 21.0 [17.1]<br>N=5 | 29.7 [19.6]<br>N=25 | .48 (NS) |

Of the 5 patients with retinal emboli, four had emboli detected by fundoscopy immediately after the procedure. In one patient however, the retinal emboli were detected the day after the CAS procedure with fundoscopy and retinal photography. This might be caused by a lower sensitivity of fundoscopy immediately after the procedure, with the patient supine on the angiography table, but may also reflect the fact that stented carotid arteries do have some embologenic potential during the first hours to days after completion of the procedure, as has been established before for the cerebral circulation[9].

We used TCD to correlate retinal embolization with cerebral embolic load during five distinct procedural phases of CAS. Isolated emboli were most common during wiring and stent deployment, whereas embolic showers were mostly detected during stent deployment and postdilation. There was no statistically significant difference in embolic load (isolated emboli or embolic showers) between the group with and those without retinal emboli, in any of the procedural phases.

One of the limitations of this study is the relatively small size of the cohort and especially of the group of patients with retinal emboli. Perhaps a larger number of patients might have shown a difference in cerebral embolic load between groups. A further limitation may be the fact that several different types of stents were used. There

is extensive debate in the literature about a possible association between stent design and embolic potential. Retinal emboli in our series were distributed between several stent types used, with both open and closed cell design, so we do not feel this influenced results, but rather reflects real world experience.

In conclusion, our study shows that retinal embolization during CAS is not uncommon, regardless of the use of protection devices; it can occur during, but also in the first 24 hours after the procedure. Most retinal emboli are clinically silent.

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## Appendix

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# PART II
# CHAPTER 2C

# Carotid angioplasty and stenting in 509 cases: comparison of Trans Cranial Doppler data and clinical outcome with and without the use of filtering cerebral protection devices

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## Abstract

**Purpose**. To prospectively compare Trans Cranial Doppler (TCD) detected emboli and outcome in patients treated with Carotid Angioplasty and Stenting (CAS), with and without Filtering Cerebral Protection Devices (FCPD´s).

**Material and Methods**. 509 CAS procedures were divided into 3 groups: 1) 161 patients treated before FCPD availability; 2) 151 patients treated with an FCPD; 3) 197 patients treated after FCPD´s had become available, but treated without protection. The choice of which type of FCPD to use, if any, depended on availability and operator preference. Clinical end-points were cerebral ischemic events and death. TCD end-points were numbers of isolated microemboli, microembolic showers and cases with macroembolus or distal thrombus. Microemboli were stratified to 5 procedural phases. Group 2 was compared to group 3 and group 1 to the combination of groups 2 and 3. Not normally distributed data were analysed with the Mann-Whitney U test. For binomial data the $\chi^2$-test was used, $p < .05$ was regarded as statistically significant

**Results**. 427 patients (84%) had an acoustic window for TCD monitoring. Median and [Interquartile Range] numbers of isolated microemboli in group 2 compared to 3 were: wiring 51 [31-69]: 27 [15-48], predilation 19 [13-33]: 13 [8-19], stent placement 64 [46-82]: 48.5 [33.25-66], postdilation 24 [14-39]: 16 [11-27.5] ($p<0.001$ for each phase). For microembolic showers: wiring 0 [0-3]: 0 [0-0], predilation 1.5 [0-4]: 0 [0-2], stent placement 22 [11-36]: 11 [6-17], postdilation 3 [0-9]: 1 [0-4] ($p= 0.001$ for postdilation, $p<0.001$ for all other phases).

Comparing group 1 to the combination of groups 2 and 3 for isolated microemboli: predilation 10 [5-22.75]: 16 [9-25] ($p=0.001$), stent deployment 32 [15-58]: 54 [40.5-74] ($p<0.001$) and postdilation 11 [6-19]: 18 [12-33] ($p<0.001$) and for microembolic showers: stent deployment: 6 [1-14]: 13 [7-26] ($p<0.001$).

Five patients died (0.98%) and 5 major strokes (0.98%) and 14 minor strokes (2.8%) occurred. All 8 macroemboli occurred in unprotected procedures, all 6 distal thrombi in protected procedures.

**Conclusions**: CAS using FCPD´s yielded more microemboli compared to patients treated without protection. The infrequent occurrence of cerebral sequelae did not allow comprehensive statistical comparison between groups.



**Key words**

Carotid arteries; Stents; Embolism; Transcranial Doppler; Protection devices

## Introduction

Several controlled clinical trials [1-3] have proven Carotid EndArterectomy (CEA) to be superior to medical treatment alone for carotid bifurcation stenoses. For patients at high risk for surgery however, the optimal treatment strategy is unresolved. Traditionally these patients were managed medically, without treating the underlying carotid stenosis.

Over the last few years an alternative treatment for carotid stenoses has emerged: Carotid Angioplasty and Stenting (CAS)[4-7]. This procedure obviates the need of anesthesia and surgical approach and may, therefore, be employed in surgically high-risk patients. It does have its drawbacks, however. The major hazard of CAS is dislodgement and distal embolization of plaque material, which may result in a stroke. Several options for prevention of distal embolization have been proposed[8-11]. These Cerebral Protection Devices (CPD's) can be divided into three categories: filtering cerebral protection devices (FCPD´s), obstructing protection devices and flow reversal devices.

So far few studies have been published comparing the different categories of protection devices[10, 11] or comparing patients treated with cerebral protection to those treated without[12-16]. Only one of these publications[12], on a small series of patients using distal occluding balloons, compared Trans Cranial Doppler (TCD) data, as a tool to assess the efficacy of the protection device. No series have been published so far comparing TCD data in patients treated with and without the use of filtering CPD's.

The intended advantage of FCPD use during CAS is prevention of cerebral embolic complications. Potential disadvantages include a more cumbersome procedure, filling of the filter with embolic material and subsequent stasis in the Internal Carotid Artery (ICA), thrombus formation on the filter, damage to the vascular wall, and costs.

Thus the purpose of our study was to prospectively compare TCD detected emboli and outcome in patients treated with CAS, with and without the use of FCPD´s.

## Material and methods

### *Study design*

Between December 1997 and November 2003, a total of 509 patients were treated with CAS in our institute. Initially all procedures were performed without the use of an FCPD. When FCPD's had become available the choice of which type of device to use, if any, depended on their availability and the personal preference of the interventionalist performing the procedure. 151 patients (30 %) were treated with an FCPD. All data were

recorded prospectively and all patients were included on intention-to-treat basis. The study was approved by the institutional human research committee and prior written informed consent was obtained from all patients.

The study population was divided into three groups: group 1 containing all patients treated before FCPD's had become available, group 2 consisted of all patients treated with an FCPD and group 3 contained all patients treated after the advent of FCPD's, but treated without cerebral protection. Two separate statistical analyses were conducted. In the first analysis group 2 was compared to group 3, i.e. patients treated in the same period, either with or without cerebral protection. In the second analysis all patients treated before the advent of FCPD's (group 1) were compared to all patients treated after FCPD's had become available (groups 2 and 3 combined).

***Study population***

Included in the study were 360 males (71%, median age 70 years) and 149 females (29%, median age 73 years). All patients had a stenosis at the carotid bifurcation of more than 70% according to the NASCET[1] criteria. The degree of stenosis had been assessed by duplex ultrasound scanning and intra-arterial digital subtraction angiography prior to therapy. Prior ipsilateral symptoms (Amaurosis Fugax, Transient Ischemic Attack [TIA] or minor stroke) were present in 166 patients (33%).

***Stenting***

All procedures were performed by an experienced, board-certified endovascular specialist, from a pool of 2 interventional radiologists and 2 interventional cardiologists, with experience in endovascular procedures ranging from 8 to 30 years. A femoral approach was used in all patients. If necessary a predilation was performed using a 2.5 to 3.5 mm balloon, followed by introduction of a self-expandable stent. Finally postdilation was performed with a balloon size between 5 and 8 mm, depending on the diameter of the ICA as determined by preprocedural duplex scanning. Several types of self-expandable stents were used: Easy Wallstent® (Boston Scientific, Natick, MA) 84, Carotid Wallstent® (Boston Scientific, Natick, MA) 332, Peripheral Wallstent® (Boston Scientific, Natick, MA) 4, Acculink® (Guidant, Indianapolis, IN) 23, Carotid SE® (Medtronic, Minneapolis, MN) 13, Protege® (EV3, Plymouth, MN) 1 and Precise® (Cordis J&J, Miami Lakes, FL) 37. In 15 patients (2.9%) no angioplasty or stent placement was performed. In 11 cases because of technical or anatomical impediments, in 2 cases because the stenosis was less severe than anticipated and in one case the procedure was discontinued because the ICA had asymptomatically become occluded in the 3 days between the last

preprocedural duplex examination and the procedure. Finally in one case the procedure was discontinued because a major stroke occurred during angiography, prior to stent placement. This was one of the major strokes in patient group 3.

***Filtering Cerebral Protection Devices***

In 151 cases an FCPD was used. The first FCPD was used in July 2000, after an experience of 2.5 years and 161 patients treated without cerebral protection. During the procedure the FCPD was introduced before stent placement and if possible before predilation. The FCPD was removed at the end of the procedure, after postdilation and postprocedural angiography. In 2 cases (1.3%) placement of the FCPD was unsuccessful. As the actual stenting procedure was done without cerebral protection in these cases, they were regarded as unprotected procedures for statistical analysis. The various types of FCPD's used are listed in table 1.

***Trans Cranial Doppler***

In all patients with an acoustic temporal window (427/509, 84 %), TCD of the ipsilateral Middle Cerebral Artery (MCA) was performed during the interventional procedure. The technique is described in detail in a recent publication[17]. For the evaluation of the relative risk of several procedural phases, the intervention was initially subdivided into 4 distinct phases: 1) wiring/passing the stenosis, 2) predilation, 3) stent deployment and 4) postdilation. Later when FCPD's had become available an additional phase was recognized, if applicable: 5) FCPD handling. This included both the deployment of the FCPD and its retrieval at the end of the procedure.

For each phase of the procedure the number of TCD-detected isolated microembolic signals in the MCA was registered as well as all microembolic showers (i.e. a cardiac cycle with too many microembolic signals to be counted separately). The microemboli were identified according to the criteria described in the literature[18]. A macroembolus was defined as an embolus partially or completely obstructing flow in the MCA, as evidenced by decreased flow on TCD and confirmed by angiography. If a macroembolus was found, this was recorded separately. Also any angiographically demonstrated thrombus formation on the guidewire or protection device distal to the site of stenting, was recorded.

***Medication***

All patients received platelet aggregation inhibitors: aspirin (250 mg daily) and clopidogrel (75 mg daily), starting the day before the procedure. During the procedure

5000 to 10000 IU of heparin were administered intravenously. Before balloon inflation 1 mg of atropine sulfate was given intravenously to reduce bradycardia and/or hypotension induced by carotid body compression.

***Monitoring***

The neurological status of the patient was monitored throughout the procedure by an independent neurologist, from a pool of 2 neurologists with more than 10 years of experience in cerebrovascular diseases.. Systemic blood pressure, heart rate and peripheral arterial oxygen saturation were continuously monitored as well.

***Evaluations before the intervention and during follow-up***

Patients were examined according to a standardized protocol, which included neurological examination using the modified Rankin Scale[19] and carotid duplex scanning. These examinations were done before and directly after the intervention, the day after the intervention and subsequently at day 7. Any neurological deficit persisting for more than 24 hours was regarded as a stroke. A deterioration in clinical situation of 3 or more categories on the Rankin Scale[19] was regarded as a major stroke.

***Statistical analysis***

Group 1 contained 161 patients. In this group 141 patients (88%) had an adequate temporal window for TCD monitoring. There were 151 patients in group 2, of whom 125 (83%) had an acoustic window. Group 3 contained 197 patients. In this group TCD monitoring was possible in 161 patients (82%).

Data that were not normally distributed are presented with median and Inter Quartile Range (IQR) and differences were tested using the Mann-Whitney U test. For binomial data the $\chi^2$-test was used. In all cases $p < .05$ was regarded as statistically significant. Statistical analyses were performed using SPSS® 11.5 /2003 (SPSS Inc, Chicago, IL).

## Results

***Baseline patient characteristics***

Baseline patient characteristics are presented in table 2. There was no statically significant difference in patient characteristics between groups 2 and 3, nor between group 1 as compared to groups 2 and 3 combined.

***TCD detected emboli***

The numbers of isolated microemboli and microembolic showers detected during the different phases of the procedure are presented in tables 3 and 4, respectively. As microembolic showers occurred less frequently than isolated emboli, table 4 also shows the total number of showers and the average number of showers per procedure for each group.

There is a statistically significant difference between groups 2 and 3 for all phases of the procedure, both for the number of isolated microemboli ($p<0.001$ in all phases) and for microembolic showers ($p=0.001$ for postdilation and $p<0.001$ for all other phases). In all instances the microembolic load is higher for patients in group 2, the patients treated with an FCPD. Also the total number of both isolated microemboli and of microembolic showers during the entire procedure is higher in group 2 ($p<0.001$).

When group 1 is compared to the combination of groups 2 and 3, there is a statistically significant difference for isolated microemboli during predilation ($p=0.001$), stent deployment ($p<0.001$) and postdilation ($p<0.001$). For microembolic showers there is a statistically significant difference only during stent deployment ($p<0.001$). There is also a statistically significant difference in the total number of microembolic showers during the entire procedure ($p<0.001$). In all instances the microembolic load is higher in groups 2 and 3 combined, as compared to group 1.

***Adverse events***

The comparison between the two groups for the non-clinical adverse events during the procedure is presented in table 5. There were 6 particulate macroemboli in group 1, none in group 2 and 2 in group 3. Of 8 patients with a macroembolus 3 had a TIA during the procedure (2 in group 1, 1 in group 3) and a further 2 had a major stroke (one each in groups 1 and 3), the remaining 3 patients did not have cerebral symptoms. Remarkably all cases of macro-embolism occurred in the first 186 cases. In more than 300 cases performed since, no macro-emboli were found, regardless of whether or not an FCPD was used.

There were 6 cases of thrombus and stasis in the ICA distal to the diseased segment. All occurred in patients treated with an FCPD. Two of these 6 patients had a TIA during the procedure and the other 4 were asymptomatic.

***Complications***

Cerebral outcome at one week is presented in table 6. In group1 there were 2

deaths (1.2%), 2 major strokes (1.2%) and 3 minor strokes (1.9%). In group 2 there were no fatalities, 2 major strokes (1.3%) and 5 minor strokes (3.3%). In group 3 there were 3 deaths (1.5%), one major stroke (0.5%) and 6 minor strokes (3.0%).

## Discussion

Although the concept of cerebral protection during CAS is in itself appealing, our results show a higher number of TCD-detected microemboli during filter protected CAS, compared to non-protected CAS. The number of particulate macroemboli was higher in the non-protected group, but distal thrombus formation occurred only in FCPD cases. Our findings do not provide support for the consensus view of a panel of world opinion leaders published in 2001[20], that the use of CPD's is mandatory in all CAS cases.

The higher microembolic load in the FCPD group is counterintuitive and puzzling. A very small randomized series recently presented[21], also showed more microemboli in protected, compared to unprotected procedures, paralleling our findings. A theoretical explanation might be that a macroembolus may be propelled into the filter and subsequently disintegrates into smaller particles which can pass through the micropores, leading to an increase in the number of microemboli. This could also account for the lower number of macroemboli found. A different theory would be that FCPD's do not adequately cover the entire ICA, allowing some emboli to pass by. An in vitro study[22] proved that embolic material can be found distal to all 4 types of FCPD's studied. One of the devices used in that study was the Filterwire EX®, which is the most frequently used FCPD in our series. The investigators found a gap between this device and the vascular wall during deployment according to the manufacturer's specification and had to manually adjust its position to optimally cover the ICA in their model. The higher microembolic load might also be explained by a more cumbersome procedure as a result of FCPD use. Another theoretical explanation might be thrombus formation on the distal filter surface or the tip of the FCPD wire, with the possibility of subsequent embolization. We found a thrombus large enough to be seen angiographically in 6 FCPD cases. Smaller thrombi may be present in more cases, leading to an increased embolic load. Yet another explanation for the increased embolic load in protected procedures might be the considerable movement of the FCPD in the distal ICA, observed during the procedure. This has been described before[11] and might be the cause of microtrauma to the vascular wall, which in turn might lead to increased embolic load.

Two studies[23, 24] have been published using Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) to assess filter protected CAS. New ipsilateral lesions were found on postprocedural DW-MRI in 3 of 16 patients[23] and in 10 out of 42 patients[24] respectively, apparently confirming that an FCPD does not prevent all emboli from reaching the cerebral circulation during CAS.

A limitation of our study is the gradual introduction of FCPD's in our patient population and the fact that their use depended both on availability and operator preference. Some selection bias for FCPD use may therefore have been introduced. At first we analyzed all patients treated after FCPD's had been introduced in our series, comparing patients treated with cerebral protection (group2), to those treated without (group 3); comparing two groups of patients, treated in the same time frame. As shown we found more microemboli in the FCPD group, a difference which was statistically significant.

This analysis might contain the possible selection bias mentioned before. To preclude this possible bias we then analyzed the data comparing the entire group treated before the advent of FCPD's (group 1) to all patients starting with the first protected procedure (groups 2 and 3 combined), in effect comparing patients treated without choice of cerebral protection to patients treated with a choice for the operator to use an FCPD. We thereby considerably 'diluted' the FCPD-group. Nevertheless the significantly higher microembolic load in the group containing the FCPD patients remained.

More important than the TCD data is clinical outcome. Fortunately the complication rate of CAS is low in all three patient groups. This low event rate however, precludes comprehensive statistical conclusions about clinical outcome. A non-randomized study[13] compared clinical outcome in 75 patients treated without cerebral protection to 75 procedures with Neuroshield® filter protection. No statistically significant difference in cerebral outcome was observed. In a different study[14], comparing early outcome in 125 non-protected CAS procedures to 150 CAS procedures with cerebral protection (147 filters), no deaths or major strokes were found. There were three minor strokes, 1 TIA and 1 subarachnoid hemorrhage in the non-protected group compared to one minor stroke and 1 subarachnoid hemorrhage in the protected group. Although this difference is described as a 79% reduction in 'the acute neurological event rate' in the group treated with CPD's, this difference can easily be calculated not to be statistically significant. The same group more recently published the results of protected CAS in 442 patients[25], again with a very low complications rate, concluding that the use of cerebral protection

is feasible and effective in preventing distal embolization. As they did not use TCD, or pre- and postprocedural CT or MRI examination, they do concede that their study does not provide objective information on the degree of embolization during the procedure. The editorial comment[26] on this publication puts its findings in a broader perspective and concludes that, to date, real evidence either for or against using cerebral protection during CAS is still lacking.

The low event rate in CAS means that only a trial with a very large number of cases could potentially yield a statistically significant difference in cerebral outcome between patients treated with cerebral protection and those treated without. An attempt at this was made in two recent publications[15,16], one reviewing all CAS series reported in the literature to date[15], in which the authors conclude that 'the use of protection devices appears to reduce thromboembolic complications during CAS'. The other publication[16] is based upon a survey from the global carotid artery stent registry. The authors found a reduction in stroke and procedure-related death from 5.29 % in unprotected procedures, to 2.23 % in protected CAS. Although both studies are based on a very large number of cases, both are hampered by a difference in time-frame. The unprotected procedures in both studies have on average been performed earlier, than the protected procedures. Other significant improvements, such as dedicated catheters, sheaths and stents and a more dedicated medication regimen have been introduced meanwhile, which may have contributed to the steady decline in event-rate during CAS. Furthermore, the nature of both publications probably means that there is significant overlap in patient populations. One of the studies[16] however, did find that 8 of 28 centers had worse results with protected procedures than with unprotected procedures.

We used TCD as a tool to assess the efficacy of FCPD's in preventing embolic material to pass through to the cerebral circulation during CAS. The applicability of TCD to assess microembolic load is limited by its inability to differentiate between the sizes of various detected microemboli. There is a correlation between increase in particle size and increased likelihood of adverse outcome[27]. It is therefore possible that, although the total number of microemboli in our FCPD group is higher, the number of clinically relevant emboli is not. The occurrence of particulate macroemboli is also correlated to adverse outcome[17]. In the current study we found more microemboli in protected patients, but fewer particulate macroemboli. Conversely thrombus formation distal to the site of stenting was found only in patients treated with an FCPD and this finding may also be correlated with adverse outcome.

Our study population contains a significant number of asymptomatic patients. The high number of asymptomatic patients in our series is caused by the fact that many CAS procedures were performed in the workup before major cardiothoracic surgery. A combined surgical procedure for Coronary Artery Bypass Grafting (CABG) and CEA has been employed in our institution for several years. Over the last few years CEA has progressively been replaced by CAS in these patients. Although controversy remains regarding the optimal management of the multisystem disease in these patients, this strategy of staged CAS and CABG has successfully been employed elsewhere[28,29]. Consequently the majority of patients in our series were relatively high surgical risk patients due to cardiac and pulmonary co-morbidity. The high number of asymptomatic patients and the large fraction of patients with significant co-morbidity may have influenced results in our series.

In our study only filtering CPD's were analyzed. In a TCD controlled study[12] of CAS using distal occlusion balloon protection, significantly less microemboli were found during protected procedures, compared to non-protected CAS. The third category of CPD's are the flow reversal devices. A small study[10] compared all three different categories of CPD's (6 filters, 10 distal occlusion balloons and 9 flow reversal devices) to 25 patients treated without CPD. The investigators used TCD whenever an acoustic window was available (75%), but the results are mentioned non-quantitatively. However with the use of flow reversal devices 'no embolic signals were detected'. The use of occluding CPD's or flow reversal CPD's may consequently yield an embolic load quite different from our findings and indeed a different cerebral outcome.

In conclusion, our study with filtering cerebral protection devices does not provide support for the commonly held view that cerebral protection is required in all CAS cases; in our series more microemboli were found in protected, compared to unprotected cases. The FCPD group also had more cases with distal thrombus formation, whereas the number of particulate macroemboli was higher in the non-protected group. Only a large multicenter randomized trial can resolve the issue of cerebral protection during CAS. Such a trial may also provide insight into the question of which patients might benefit from cerebral protection and which type of CPD provides the most adequate protection for the brain.

**Table 1**. Types of FCPD's used.

| CPD type | Manufacturer | n |
|---|---|---|
| Filterwire EX® | Boston Scientific, Natick, MA | 98 |
| Filterwire EZ® | Boston Scientific, Natick, MA | 4 |
| Angioguard® | Cordis J&J, Minneapolis, MN | 14 |
| Angioguard XP® | Cordis J&J, Minneapolis, MN | 13 |
| RX Accunet® | Guidant, Indianapolis, IN | 9 |
| TRAP® | Microvena, White Bear Lake, MN | 4 |
| Spiderwire® | EV3, Plymouth, MN | 4 |
| Emboshield® | Abbott, Chicago, IL | 4 |
| Neuroshield® | MedNova Inc, Galway, Ireland | 1 |

**Table 2**. Patient characteristics.

| | **Group 1** (n=161) | **Group 2** (n=151) | **Group 3** (n=197) | **Groups 2+3** (n=348) |
|---|---|---|---|---|
| Gender (Male/Female) | 120/41 | 111/40 | 129/68 | 240/108 |
| Age (median[IQR]) | 70 [64.5-75] | 72 [67-75] | 71 [66-76] | 71 [66-76] |
| Ipsilateral symptoms (Yes/No) | 55/106 | 52/99 | 58/139 | 110/238 |
| Side of stenting (Left/Right) | 89/72 | 85/66 | 109/88 | 194/154 |
| Prior ipsilateral CEA (Yes/No) | 11/150 | 12/139 | 27/170 | 39/309 |

Group1: before FCPD introduction, Group 2 patients treated with an FCPD. Group 3 patients treated after FCPD introduction, but treated without FCPD.

**Table 3**. Isolated microemboli. Median number of isolated microemboli in the different stages of the CAS procedure [Interquartile range].

| | **Group 1** (n=141) | **Group 2** (n=125) | **Group 3** (n=161) | **Group 2+3** (n=286) | **p** 2 vs 3 | **p** 1 vs 2+3 |
|---|---|---|---|---|---|---|
| Wiring | 28 [15-59] | 51 [31-69] | 27 [15-48] | 37 [21-61.75] | <0.001* | 0.1 |
| Predilation | 10 [5-22.75] | 19 [13-33] | 13 [8-19] | 16 [9-25] | <0.001* | 0.001* |
| Stent deployment | 32 [15-58] | 64 [46-82] | 48.5 [33.25-66] | 54 [40.5-74] | <0.001* | <0.001* |
| Postdilation | 11 [6-19] | 24 [14-39] | 16 [11-27.5] | 18 [12-33] | <0.001* | <0.001* |
| FCPD handling | NA | 33 [23-48] | NA | NA | NA | NA |
| **Total** | **94.5 [58.25-145]** | **209 [171-260]** | **111 [84-158]** | **156.5 [103-218.75]** | **<0.001*** | **<0.001*** |

NA= Not Applicable. *Statistically significant. Group1: before FCPD introduction, Group 2 patients treated with an FCPD. Group 3 patients treated after FCPD introduction, but treated without FCPD.

**Table 4**. Microembolic showers. Median number of microembolic showers in the different stages of the CAS procedure [Interquartile range].

| | **Group 1** (n=141) | **Group 2** (n=125) | **Group 3** (n=161) | **Group 2+3** (n=286) | **p** 2 vs 3 | **p** 1 vs 2+3 |
|---|---|---|---|---|---|---|
| Wiring | 0 [0-2] | 0 [0-3] | 0 [0-0] | 0 [0-1] | <0.001* | 0.5 |
| Predilation | 0 [0-3] | 1.5 [0-4] | 0 [0-2] | 0 [0-3] | <0.001* | 0.8 |
| Stent deployment | 6 [1-14] | 22 [11-36] | 11 [6-17] | 13 [7-26] | <0.001* | <0.001* |
| Post-dilation | 0 [1-6] | 3 [0-9] | 1 [0-4] | 2 [0-6] | 0.001* | 0.4 |
| FCPD handling | NA | 3 [0-8] | NA | NA | NA | NA |
| **Total** | **11 [4.25-23.75]** | **38 [19-63]** | **13 [8-25]** | **21 [10-40.25]** | **<0.001*** | **<0.001*** |
| Total number of microembolic showers in all cases. [average] | 2503 [17.8] | 5501 [44.0] | 3012 [18.7] | 8513 [29.8] | | |

NA= Not Applicable. *Statistically significant. Group1: before FCPD introduction, Group 2 patients treated with an FCPD. Group 3 patients treated after FCPD introduction, but treated without FCPD.

**Table 5**. Non-clinical adverse events during CAS. *Statistically significant.

| | **Group 1** (n=141) | **Group 2** (n=125) | **Group 3** (n=161) | **Group 2+3** (n=286) |
|---|---|---|---|---|
| Particulate macroembolus | 6 (4.2%) | 0 (0%) | 2 (1.2%) | 2 (0.70%) |
| Distal thrombus formation | 0 (0%) | 6 (4.8%) | 0 (0%) | 6 (2.1%) |

Group 1: before FCPD introduction, Group 2 patients treated with an FCPD. Group 3 patients treated after FCPD introduction, but treated without FCPD.

**Table 6**. Procedural complications.

| | **Group 1** (n=161) | **Group 2** (n=151) | **Group 3** (n=197) | **Group 2+3** (n=348) |
|---|---|---|---|---|
| Death | 2 (1.2%) | 0 (0%) | 3 (1.5%) | 3 (0.86%) |
| Major stroke or death | 4 (2.5%) | 2 (1.3%) | 4 (2.0%) | 6 (1.7%) |
| Any stroke or death | 7 (4.3%) | 7 (4.6%) | 10 (5.1%) | 17 (4.9%) |

Group 1: before FCPD introduction, Group 2 patients treated with an FCPD. Group 3 patients treated after FCPD introduction, but treated without FCPD.

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## Appendix A

List of abbreviations used

| | |
|---|---|
| CABG | Coronary Artery Bypass Graft |
| CAS | Carotid Angioplasty and Stenting |
| CEA | Carotid EndArterectomy |
| CPD | Cerebral Protection Device |
| DW-MRI | Diffusion Weighted Magnetic Resonance Imaging |
| FCPD | Filtering Cerebral Protection Device |
| ICA | Internal Carotid Artery |
| IQR | Inter Quartile Range |
| MCA | Middle Cerebral Artery |
| NASCET | North American Symptomatic Carotid Endarterectomy Trial |
| TCD | Trans Cranial Doppler |
| TIA | Transient Ischemic Attack |

# Part III

## Inherent differences between Carotid Angioplasty and Stenting and Carotid Endarterectomy, which may influence clinical results

# PART III
# CHAPTER 3A

# Carotid Artery Dynamics during Head Movements: A Reason for Concern with regard to Carotid Stenting?

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## Abstract

**Purpose**: To evaluate carotid artery mobility patterns during head movements following carotid angioplasty-stenting (CAS).

**Methods**: In 7 patients who had undergone unilateral CAS, 3D time-of-flight MR angiography was performed, visualizing both carotid arteries in five different head positions (neutral, turned left, right, bent forward and backward). Maximum intensity projection (MIP) reconstructions were obtained to measure angulation at the proximal and distal stent junction. Configuration changes of the stented section of the carotid artery and the unstented contralateral artery were judged. Secondly, transverse sections at the level of the carotid bifurcation and at the skull base were used to calculate torsion shear in the common and internal carotid artery (CCA, ICA) during turned left and right head position. Results were expressed as median (range).

**Results**: In neutral head position, maximal angulation at the distal stent junction was 34.3° (32.3-55.6). In bent forward this angulation changed to 47.6° (42.6-85.2, p=0.028) and in bent backward to 26.5° (25.0-48.7, p=0.027). In all patients, configuration changes of the stented sections were absent. The contralateral unstented side showed diffuse configuration changes without specific angulation at one location. At the stented side in turned left and turned right head positions, CCA was subjected to 28.6° (13.6-53.7) and 24.9° (2.0-50.6) of torsion shear. Torsion of the ICA was subsequently 18.1° (12.7-40.5) and 15.2° (2.9-69.4).

**Conclusions**: Following carotid stenting, sharp ICA angulations occur at the distal stent junction that are aggravated by forward bending of the head. The stented section of the carotid artery shows complete lack of flexibility despite highly flexible features of the stents ex vivo. Both CCA and ICA, in turned left and right head position, are subjected to considerable torsion shear that is not accommodated by the current stent designs.


**Keywords**: stent, magnetic resonance imaging, mobility, torsion, angulation

## Introduction

Carotid angioplasty-stenting (CAS) is currently being widely embraced due to the perceived advantages of a less invasive treatment for carotid artery occlusive disease. Several studies suggest that early complication rates may be comparable to those of carotid endarterectomy.[1,2] However, long-term durability of CAS in preventing stroke and long-term patency rates of carotid stents are being questioned for various reasons.[3] Interestingly, to date, very little attention has been directed towards the mobile features of the carotid artery, whereas repetitive motions of lower extremity vessels such as the external iliac and popliteal arteries have been widely implicated in long term stent failure.[4-6] The purpose of this study is to describe the geometrical changes of the carotid artery during head movements in patients following CAS. A thorough understanding of these geometrical changes might lead to improved device design as this is the key feature to successful long term CAS.

## Methods

### *Patients*

Between November 2001 and September 2002, seven patients were treated with CAS for high grade stenosis of the left carotid artery. All patients, underwent a high resolution magnetic resonance imaging (MRI) scan postoperatively. Scans were made after a mean period of 154 days (50-229). Patients were all men, with a mean age of 69 years (65-76). In all subjects stents specifically designed for the carotid artery have been used containing low-artefact nitinol metallic components: Carotid SE (Medtronic, Minneapolis, MN, USA), Acculink (Guidant, Indianapolis, IN, USA) or Precise (Cordis, Miami, FL, USA) (Table 1). Patients who underwent CAS with a Carotid Wallstent (Boston scientific, Natick, MA, USA) were excluded, because of the well-known artefacts appearing in MR images caused by this stainless-steel containing stent. Informed consent was obtained from all subjects in accordance with the requirements of the institutional ethical committee.

### *MRI*

A 1.5 T MRI whole body system (Siemens Sonata, Erlangen, Germany) was used. First, the carotid artery was localized by 2-dimensional (2D) true-FISP (Fast Imaging with Steady State Precession with balancing gradients in all spatial orientations) acquisition in transversal, sagittal and coronal planes. Then, a 3-dimensional (3D) ‘time of

**Table 1**. Summary of patient and stent data

| Patient no. | Age (y), (Sex) | Degree of stenosis | Stented side | Location | Stent type/brand | Stent length x diam. |
|---|---|---|---|---|---|---|
| 1. | 65, (M) | 80-90% | Left | BIF | Carotid SE Medtronic ® | 20 x 6 mm |
| 2. | 70, (M) | 90-99% | Left | ICA | Carotid SE Medtronic ® | 20 x 6 mm |
| 3. | 69, (M) | 80-90% | Left | ICA | Carotid SE Medtronic ® | 30 x 8 mm |
| 4. | 67, (M) | 90-99% | Left | BIF | Precise Cordis ® | 30 x 9 mm |
| 5. | 66, (M) | 90-99% | Left | ICA | Acculink Guidant ® | 30 x 9 mm |
| 6. | 76, (M) | 90% | Left | BIF | Acculink Guidant ® | 30 x 7 mm |
| 7. | 73, (M) | 80-90% | Left | CCA | Precise Cordis ® | 40 x 9 mm |

ICA = Internal carotid artery; CCA = Common carotid artery; BIF = Bifurcation.

flight angiography' acquisition was performed in transverse slabs covering the full range of both carotid arteries from the aortic arch up to the skull base. This 3D time of flight sequence was a Fast Low Angle Shot (FLASH) gradient echo sequence. This acquisition was obtained in neutral head position, with the head turned left, turned right, bent forward and bent backward. The in-plane spatial resolution was 1 x 0.8 mm, obtained with a matrix size of 168 x 256 pixels and a field of view of 175 x 200 mm. Slice thickness was 1.4 mm (for more technical details: see Appendix MRI acquisition). Transverse and sagittal planes are defined as fixed planes related to the position of the MR field uninfluenced by the position of the head. Additional sagittal localizing images were acquired in the bent forward and bent backward conditions, in order to measure the exact bending angle in each patient. Finally, from the 3D acquisition a maximum intensity projection (MIP) was

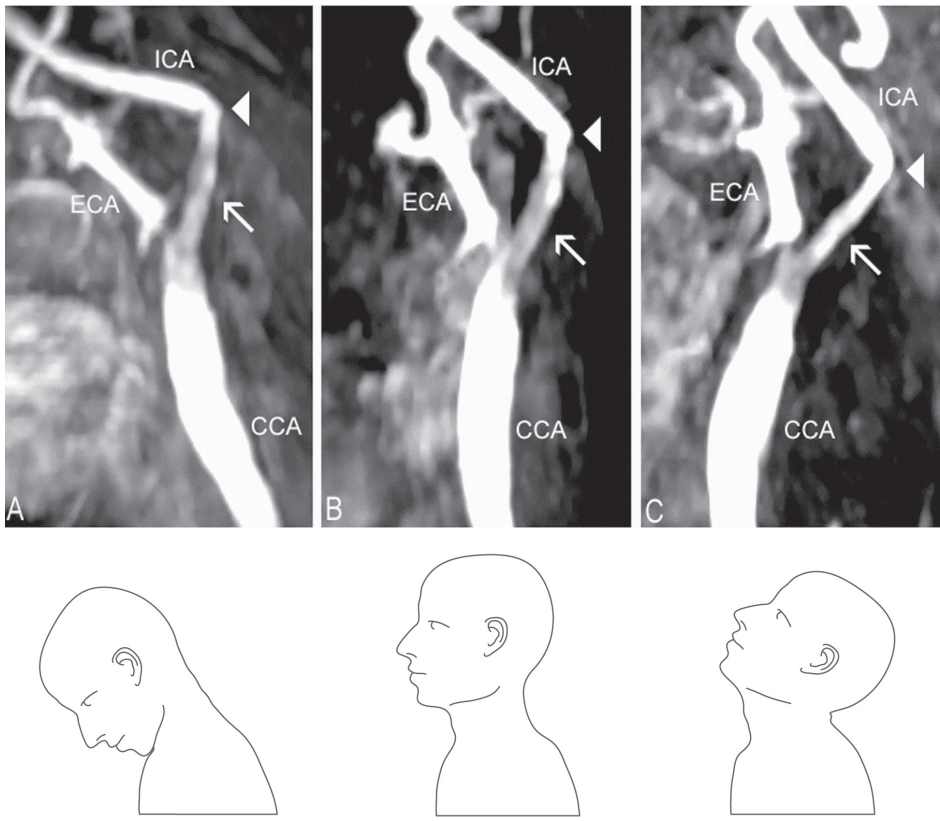


**Figure 1**. MR images of a 66-year-old man following stent (arrows) placement. Images showing the carotid artery from the same viewpoint, during three different head positions. In the Neutral head position (B) there is an angulation of the distal stent junction (arrowheads) of 56°. Note the increase in this angulation, up to 85° when the head is bent Forward (A). In the bent Backward head position (C) the same angulation is decreased to 49°.
ICA: internal carotid artery, CCA: common carotid artery, ECA: external carotid artery

reconstructed of the full range of the carotid arteries in all head positions. This MIP was constructed in such a way that the observer's viewpoint rotated from the left, via anterior, to the right in steps of 6 degrees.

***Data Collection***

Patients were asked to place their head in all head positions in a maximal possible way. Head positions were defined by measuring the angle between bony structures of the

**Table 2**. Summary of angulation results (stented side)

| Stent junction | Head position | | | | |
|---|---|---|---|---|---|
| | **N** | **F** | **B** | **L** | **R** |
| **Distal** | 34.3° (32.3-55.6) | 47.6° * (42.6-85.2) | 26.5° * (25.0-48.7) | 34.8° (30.7-59.5) | 34.7° (32.6-55.4) |
| **Proximal** | 24.1° (15.9-32.3) | 23.5° (16.4-40.2) | 24.8° (16.1-30.9) | 27.5° * (16.9-38.2) | 21.5° (13.0-32.9) |

Values are expressed as median (range). N = Neutral; F = bent Forward; B = bent Backward; L = turned Left; R = turned Right; * P < 0,05.

**Table 3**. Summary of torsion results.

| | | Head position | |
|---|---|---|---|
| | | **L** | **R** |
| **Stented side** | ICA | 18.1° (12.7-40.5) | 15.2° (2.9-69.4) |
| | CCA | 28.6° (13.6-53.7) | 24.9° (2.0-50.6) |
| **Contralateral side** | ICA | 15.4° (13.6-53.7) | 28.6° (5.2-65.4) |
| | CCA | 34.3° (20.4-82.5) | 26.9° (14.3-38.1) |

Values are expressed as median (range). ICA = Internal carotid artery; CCA = Common carotid artery; L = turned Left; R = turned Right

head and the thorax. The neutral position was considered to be 0° in both transverse and sagittal plane. The median angle of the head positions was 54.1° (40.0-74.8) in turned left, 51.5° (32.1-67.4) in turned right, 22.2° (18.3-25.6) in bent forward and 26.4° (21.4-36.0) in bent backward head position. Maximal angulations at the proximal and distal carotid stent junction in neutral head position were selected by measuring all angulations in every viewpoint of the 3D MIP reconstructions. These maximal angulations were compared

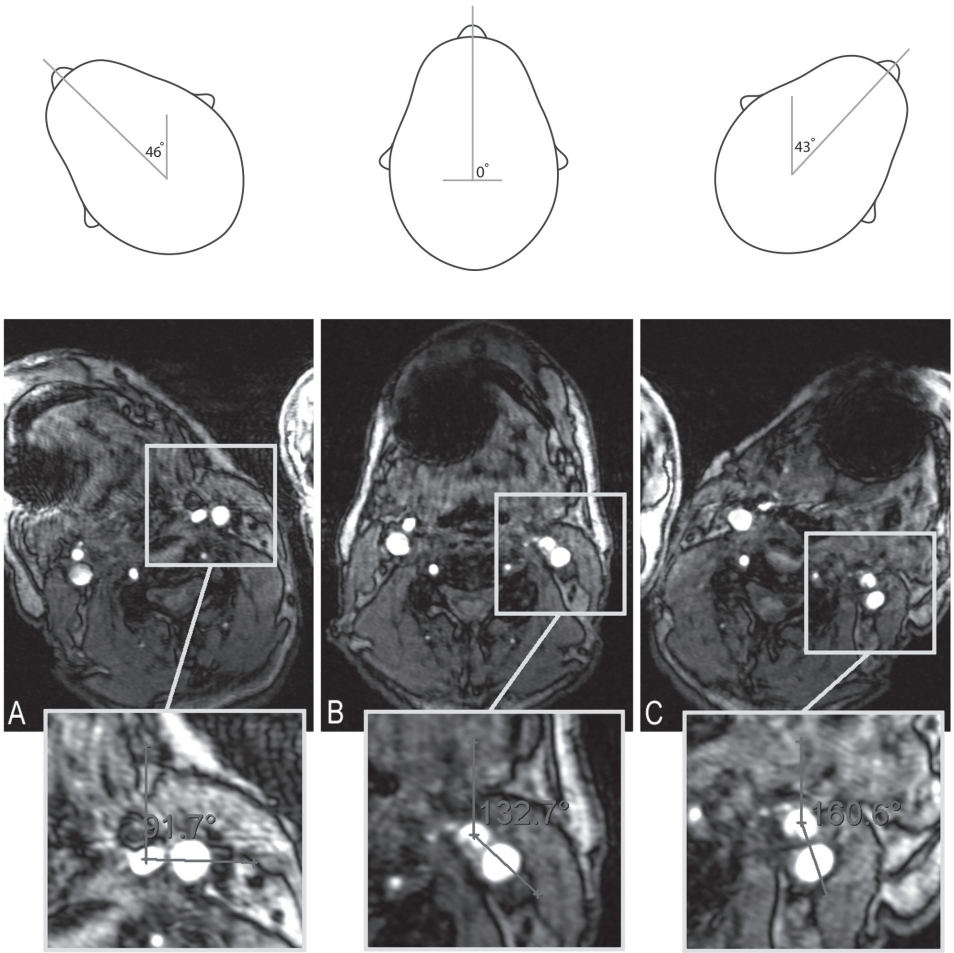


**Figure 2**. MR images of a 69-year-old man following stent placement in the left internal carotid artery. Transverse sections at the level of the bifurcation in different head positions: turned Right (A), Neutral (B) and turned Left (C), were used to measure torsion of the carotid artery.
Common carotid artery torsion = rotation of the bifurcation.
Internal carotid artery torsion = head rotation minus rotation of the bifurcation.

with angulations at the same viewpoint in the other head positions (Figure 1). Shape changes of the stented section of the carotid artery were evaluated.

For torsion shear measurements of both carotid arteries, transverse sections at the level of the carotid bifurcation and the carotid artery at the skull base were used to

calculate torsion shear in the common and internal carotid artery (CCA, ICA) during turned left and turned right head positions. The assumption was made that at the level of the skull base there is no rotation of the ICA relative to the bone (i.e. the ICA is "fixed" in the carotid foramen). By measuring both rotation of the skull, as well as rotation of the carotid bifurcation we were able to differentiate degrees of torsion shear of the CCA and ICA respectively (Figure 2). Measurements of the stented and the contralateral side were compared, where possible.

All measurements were done by two independent observers blinded for the aim of the study. The images were processed on a RadWorks 5.1 diagnostic radiology workstation (IBM Corp, White Plains, NY).

***Statistical Analysis***

Statistical analysis was performed with SPSS version 9.0 software. Maximal angulations and torsion shear of each patient were calculated as the mean of the measurement results of the two observers. For the entire group of patients, measurements were expressed as the median (range). Maximal angulations in neutral head position were compared with angulations at the same viewpoint in the other head positions using the Wilcoxon rank sum paired nonparametric test to evaluate statistical significance. The same test was used to compare torsion shear of the carotid artery at the stented and contralateral side. A p value $<0.05$ was considered statistically significant. The coefficient of variance for repetitive measurements of the two observers for angulation and torsion shear was calculated using the paired samples t test to clarify the degree of data homogeneity within the study group.

## Results

In neutral head position, maximal angulation at the proximal stent junction was 24.1° (15.9-32.3) and 34.3° (32.3-55.6) at the distal junction. From the same viewpoint angulation at the distal stent junction in bent forward and bent backward head positions changed significantly up to 47.6° (42.6-85.2, p=0.028) in bent forward and 26.5° (25.0-48.7, p=0.027) in bent backward head position. In turned left head position angulation at the proximal stent junction showed a significant change, 27.5° (16.9-38.2, p=0.028). All other compared angulations showed no significant change (Table 2). In all patients configuration changes of the stented section of the carotid artery were absent. No differences were seen between the respective stent brands used. In one patient the

contralateral unstented side was occluded and could not be visualized, the remaining six patients showed diffuse configuration changes of the carotid artery during head movements without specific angulation at one location. Of all angulation data, the mean difference between both observers was 0.16±3.49°.

At the stented side in turned left and turned right head positions, the CCA was subjected to 28.6° (13.6-53.7) and 24.9° (2.0-50.6) of torsion shear. Torsion shear of the ICA at the stented side was subsequently 18.1° (12.7-40.5) and 15.2° (2.9-69.4). At the contralateral side values were not significantly different compared to the stented side, CCA 34.3° (20.4-82.5, p=0.46) and 26.9° (14.3-38.1,p=0.60) and ICA 15.4° (13.6-53.7,p=0.35) and 28.6° (5.2-65.4,p=0.46) (Table 3). Of all torsion shear data, the mean difference between both observers was 0.82±5.25°.

## Discussion

Percutaneous carotid balloon angioplasty with stent placement has been branded as potentially safer, less traumatic and more cost-effective than carotid endarterectomy. It is usable in high risk patients and is not limited to the cervical carotid artery.[7-9] However, broad variations in success and complication rates have been reported.[1,10-13] Despite promising early results, long-term performances may theoretically be hampered by the mobile features of the carotid artery. Stent failure in arteries that are subject to repetitive motion has been broadly described. Van Lankeren et al, observed stent remodelling leading to early onset neointimal hyperplasia and continued plaque and thrombus formation in mobile arteries of the knee region.[14] Edelman et al, postulated that dynamic arteries oppose the strain caused by the stent struts through increased collagen deposition, marked destruction of elastin and persistent inflammation.[15] Moreover, stent implantation has been shown to cause changes in 3-D vessel geometry in such a way that regions with decreased and increased shear stress may occur close to the stent edges.[16] Alterations in shear stress, in turn, have been commonly implicated to play a role in recurrent plaque and thrombus formation.[17,18] Even the occurrence of stent fracture is described in an otherwise flexible artery as the superficial femoral artery.[19]

Our results show major changes in 3-D carotid artery geometry especially at the distal junction site in bent forward and bent backward head position. In this study, the flexible properties of the stents were demonstrated to be absent following deployment in the carotid artery. Despite claims of manufactures that nitinol stents are more flexible

and conformable than the commonly used wall stent, the stented segment of the artery appears as a stiff, unflexible unit in all head positions. This leaves the unstented segments to accommodate head movements by increased flexion and torsion, inevitably leading to friction at both ends of the stent. For example, the sharply angled carotid artery shown in Figure 1 represents the fairly common position of a patient asleep in a chair with the head bent forward. In comparison, the carotid artery of the opposite side showed a diffuse shape change throughout the complete artery causing a far more subtle change in 3-D geometry.

Furthermore, our results showed the carotid artery to be subject to considerable torsion shear with turning of the head whereas most currently used carotid stents have negligible ability of torsion shear. This leaves the unstented parts of the artery to accommodate all torsion shear movements and this is likely to cause friction at the stent limits. For example, by turning the head 46.9° to the left, we measured 18.1° of torsion shear in the ICA, normally executed by the entire length of the ICA.

MRI is non-invasive and provides high-resolution images of the carotid artery without use of ionizing radiation or nephrotoxic contrast media. In our institution, extensive experience has been obtained with various MRI techniques, which have been proved to be excellent tools to measure motions of the heart and great vessels.[20-23] MRI can provide morphologic information about caliber and course of the arteries as well as functional information about velocity and flow.[24-26] A possible limitation of MRI techniques are the artefacts produced by the endovascular implants in the magnetic field. Previously published studies showed that the image quality around and within the stents is very much dependent on the magnetic properties of the stent material and the imaging sequence used.[27-29] In this study, the 3D MIP in combination with the high-resolution transverse plane images showed sufficient data to objectify major angulation changes and torsion shear of the carotid artery including the stented part and its junction sites (Figure 1).

In our opinion, based on these findings CAS should be reserved for selected series of patients who are either poor candidates for carotid endarterectomy because of previous neck surgery or radiation therapy to the neck or candidates who have limited survival expectancy because of co morbid disease. Our findings might strengthen the theoretical rationale for drug eluting stents in future practice to overcome the hyperplastic reaction to the frictional forces described.[30] With regard to follow-up examinations, attention should be given on the distal internal carotid artery at the level of the distal stent junction as, this location might be prone to restenosis after CAS.

In conclusion, the carotid artery is a highly mobile artery and by stenting a major part of it, its flexible and rotational capacities are lost leading to sharp angles that are aggravated by head movement at the end of the stent as well as rotational friction. Based on this study and the similarity to what has been described following stent placement in the mobile arteries of the lower extremity, we speculate that long-term results of CAS may well be hampered by the highly mobile features of the carotid artery. Effort should be put into development of carotid stents with *in vivo* flexible and torsional capacities.

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## Appendix MRI acquisition

Coils: Circularly Polarized (CP) Neck array, CP head array, CP spine array
Pulse sequence: 3-dimensional 'time of flight angiography' Fast Low Angle Shot acquisition Specifications:

**3D slabs:**
3 slabs in a transverse plane; a tracking saturation band (gap 10 mm, thickness 40 mm) was applied at the cranial side, in order to suppress venous blood.

**TONE pulse**:
In the 3D TOF angiography we applied a TONE RF pulse. TONE is an acronym for Tilted Optimized Non-saturating Excitation, which is achieved with a ramped RF pulse. We have selected a 1-3 ramped RF pulse. This 1-3 ramped TONE pulse was empirically determined in volunteers to be the optimal pulse in our conditions.

| | |
|---|---|
| distance factor | -36.54%, the 3 slabs are partially overlapping |
| gap | -26.6 mm |
| phase enc. direction | R>>L |
| slice over sampling | 8% |
| slice thickness | 1.4 mm |
| # slices per slab | 52 |

**Pixel size**:

| | |
|---|---|
| FoV in read direction: | 200 mm |
| in phase encoding direction: | 175 mm |
| Matrix | 168x256 pixels |
| Voxel | 1 x 0.8 x 1.4 mm |
| Slice resolution: | 64% |
| Phase partial Fourier: | 6/8 |
| Slice partial Fourier: | 6/8 |

**Timing**

| | |
|---|---|
| tr = | 25 ms |
| te = | 6.90 ms |
| bandwidth = | 81 Hz/pixel |
| flip angle = | 25 deg |

# Part III
# Chapter 3B

# Impact of head movements on morphology and flow in the Internal Carotid artery after Carotid Angioplasty and Stenting versus Endarterectomy

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## Abstract

**Purpose**. Because stents can cause vessel angulation during movement, we hypothesized that Internal Carotid Artery (ICA) stents might lead to alteration of cerebropetal blood flow. This study aims to assess 3 dimensional anatomy and Volumetric Flow Rate (VFR) in the ICA in various head positions, comparing patients treated with Carotid Angioplasty and Stenting (CAS) to patients treated with Carotid Endarterectomy (CEA).

**Material and methods**. 3-D Time-of-flight Magnetic Resonance Angiography and Magnetic Resonance flow quantification were performed on 6 subjects after CAS (median age 70years) and 6 subjects after CEA (median age 67years). All investigations were performed in five head positions: Neutral (N), bent Forward (F), Backward (B), turned to the treated, Ipsilateral side (I) and to the Contralateral side (C). Maximum Intensity Projection reconstructions were obtained to measure maximal angulation of the ICA in F, B, I and C positions compared to N. Subsequently the plane perpendicular to the ICA, 1 cm distal to the stent or 4 cm distal to the carotid bifurcation (CEA patients) was established. The VFR through this plane was measured for each position and F, B, I and C were compared to N.

**Results**. In CAS patients there was a median change in ICA angulation of +10.2°( Inter Quartile Range +7.3° to +17.9°) in Forward position, compared to +0.2°(–1.0° to +2.4°) in CEA patients (P=.016). In all other head positions there was no statistically significant difference in angulation change. There was no statistically significant difference in VFR change between groups in any of the head positions tested.

**Conclusions**. There was a significant increase in ICA angulation in CAS patients if the head was bent forward; this was not observed in endarterectomy patients. This angulation change did not lead to significant changes in cerebropetal blood flow acutely, but might have chronic effects not yet tested.

## Introduction

Several large controlled trials [1-3] have proven Carotid Endarterectomy (CEA) to be superior to medical treatment alone for symptomatic stenoses of the carotid bifurcation. More recently an alternative treatment has emerged obviating the need of instrumentation of the neck, namely Carotid Angioplasty and Stenting (CAS) [4-7]. This treatment was initially used mainly in patients with an increased surgical risk. As initial results appeared promising the popularity of CAS has increased substantially over the last couple of years and currently CAS is more and more being advocated as an alternative to CEA. Several controlled trials comparing CAS to CEA are currently being conducted [8-10]. However long-term results of CAS are still sparse and several issues regarding the inherent differences between both treatment modalities have not been elucidated.

One of these is the increased stiffness of the internal carotid artery resulting from the introduction of a stent as compared to the situation following CEA[11-13]. The carotid bifurcation is located in a highly mobile part of the human anatomy and after the introduction of a stent it has been proven to be only partially able to accommodate the changes in geometry that result from physiologic movements of the head, which may lead to kinking at he distal end of the stent[14]. Although the clinical importance of carotid artery kinking remains controversial, significant flow changes during head movements have been found to be associated with ICA kinking many years ago[15]. Magnetic resonance (MR) phase-contrast flow quantification is a non-invasive technique able to measure the blood flow in separate arteries[16,17]. It can be used to evaluate the Volumetric Flow Rate (VFR) in the Internal Carotid Artery (ICA) distal to the stented or surgically treated segment. Furthermore in the same session a Magnetic Resonance Angiography (MRA) can depict the anatomy of the ICA in the same head position allowing assessment of correlation between its geometry and the VFR. The aim of this study is to use MRA and MR flow quantification to asses whether different head positions affect ICA geometry and flow in patients following CAS and CEA.

## Material and Methods

### *Study design and study population*

Six patients treated with CEA and six treated with CAS between January 2002 and September 2003 were asked to participate in this study. Only CAS patients treated with non-ferromagnetic self expandable stents were eligible. Patients treated with stainless

steel stents were excluded as the inherent properties of these stents may produce artifacts on MR imaging and MR flow measurements. Patients with significant pre-procedural carotid elongation were also excluded in both groups, as this might influence the results of this study. All patients had been treated for symptomatic stenoses at the carotid bifurcation of more than 70% according to the NASCET criteria. There were 4 males and 2 females in the CAS group; 3 were treated on the left and 3 on the right carotid bifurcation. Median age of this group was 70 years (Inter Quartile Range, IQR 67-71). Four patients were treated with a Precise® stent (Cordis J&J, Minneapolis, MN) (7x20 mm n=2, 8x20 mm n=1, 8x30 mm n=1), one with a 7x30 mm carotid SE® stent (Medtronic, Minneapolis, MN) and one with a 6-8x 40 mm Acculink® stent (Guidant, Indianapolis, IN). This last stent was placed across the carotid bifurcation, all others were placed in the ICA only. The CEA group consisted of 5 males and one female, median age of 67 years (IQR 63-72), 4 patients were treated on the right, 2 on the left side. In all cases a patch was used: 2 with autologous venous material, 4 Dacron®. After a median interval of 7 months (IQR 5-8) in CAS patients and 8 months (IQR 7-8) in CEA patients MR imaging and MR flow measurements were performed. The study was approved by the institutional human research committees and prior written informed consent was obtained from all subjects.

***Imaging***

All MR investigations were performed using a 1.5 T MR whole body system (Sonata, Siemens Medical Solutions, Erlangen, Germany). A circularly polarized head array coil, a circularly polarized neck array coil, and a spine coil were simultaneously used. First a 3D time-of-flight (3D-TOF) MR angiography was performed. Then sagittal and coronal maximum intensity projections (MIP's) were calculated. Using both these MIP's, the image plane for flow quantification was adjusted orthogonal to the treated internal carotid artery, at a distance of 1 cm downstream from the distal stent edge in CAS patients. In CEA patients, the plane was positioned 4 cm downstream from the carotid bifurcation. Subsequently an MR flow measurement was performed. The specifications of the MRA and MR flow quantification sequence used are summarized in appendices A and B respectively (Internet only). Both sequences were performed in five different head position: neutral (N), bent forward (F), bent backward (B), turned toward the treated side (ipsilateral, I) and turned away from the treated side (contralateral, C). N was always used as the starting position, the subsequent order of positions was randomized. Patients were asked to place their heads in F, B, I and C positions in the maximal possible way. Head positions were defined by measuring the angle between bony structures of the head and

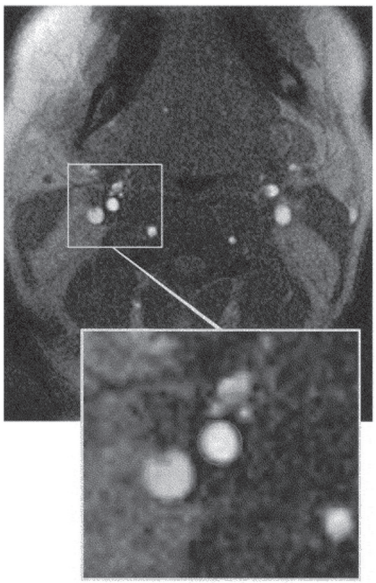

**Fig 1**. Magnetic flow magnitude image of a patient after stent placement in the right internal carotid artery. The cross section of the internal carotid artery was delineated by drawing contours on the magnitude images through the cardiac cycle.

the thorax, for the F and B positions. For the measurement of the I and C positions, the angle between the mid saggital plane of the head was compared to the antero-posterior axis. The neutral (N) position was considered to be 0° in both transverse and sagittal plane.

All angulation measurements were performed on a RadWorks 5.1 diagnostic radiology workstation (IBM Corp, White Plains, NY, USA).Flow measurements were performed on a Sun Sparcstation (Sun Micosystems, Mountain View, CA, U.S.A) using the software package 'FLOW' (Medis, Leiden, The Netherlands). The cross section of the internal carotid artery was delineated by drawing contours on the magnitude images through the cardiac cycle (see figure 1). Then, from the velocity and the cross sectional area the volumetric flow in ml/s was derived. Subsequently, integrating flow over the cardiac cycle yielded the stroke volume in ml per heart beat; which was equal to the area under curve (see figure 2). Finally, multiplying the volumetric flow per heart beat with the heart rate yielded the Volumetric Flow Rate (VFR) in ml/min.

***Statistical analysis***

In each individual N was considered to be the standard for both ICA angulation and VFR. In all head positions other than N the angulation and VFR were compared

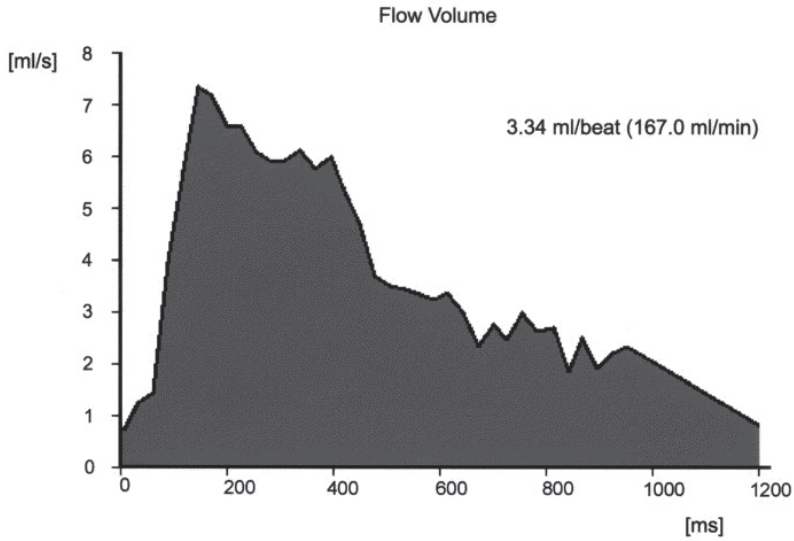


**Fig 2**. Example of flow curve across the cardiac cycle. The area under the curve (shaded) represents the total cerebropetal volumetric flow rate through this internal carotid artery during one cardiac cycle.

to N and the difference was recorded. This then excluded baseline data and allowed comparison between groups of the effect of the head movements.

Data that were not normally distributed are presented with median and Inter Quartile Range (IQR). For this type of data differences between groups were tested using the Mann-Whitney U test. $P < .05$ was regarded as statistically significant.

Statistical analyses were performed using SPSS® 11.5/2002 (SPSS Inc. Chicago,IL)

## Results

The median degree of forward angulation of the head was 15.8° in CAS patients, 18.9° in CEA patients. The median backward angulations were 19.1° and 20.0° respectively. The median ipsilateral rotation of the head was 46.9° in CAS patients, 48.3° in CEA patients. The median contralateral rotations were 46.7° and 54.6° respectively.

The degree of head movement and the concomitant angulation change of the ICA as observed on the MRA-images in the individual subjects is shown in table 1 for

CAS patients and in table 2 for CEA patients. In CAS patients the median increase of angulation at the distal stent end during forward (F) motion of the head was 10.2° (IQR 7.3°/17.9°). In CEA patients this was 0.2° (–1.0°/2.4°), a difference which was statistically significant (p=0.016), see figure 3. In all other head positions there was no statistically significant difference in angulation change between groups.

The corresponding VFR data are presented in tables 3 and 4 for CAS and CEA patients respectively. There was no statistically significant difference between the two groups in VFR change in any of the head positions tested. The case with the most profound kinking of the ICA (F position in CAS case #6) where the angulation of the ICA increased from 37.4° to 84.7° showed an increase rather than a decrease of VFR in the ipsilateral ICA.

## Discussion

The fact that head movements can cause changes in carotid blood flow in healthy subjects is well known and was described as early as 1964[18]. These changes may be aggravated by the increased kinking of the internal carotid artery that is observed in some patients after CAS and might be the cause of cerebral hypoperfusion in these head positions. In this study the increased stiffness of the ICA after CAS was confirmed as a potential cause of increased angulation at the distal stent end during forward bending of the head. This phenomenon was not observed in CEA patients, where there was a much more global curvature of the entire ICA as a result of changes in head position. Conceptually this increased angulation in CAS patients might lead to a decrease in volumetric flow through the ICA during flexion of the neck, a head position that may very well occur physiologically in daily life, for instance when a patient falls asleep while sitting in a chair. There was however no statistically significant decrease in VFR associated with the increased angulation in our series.

The wide range of normal cerebropetal VFR is reflected in the results, which show a substantial variation, between head positions and between subjects. As mentioned before, the subject with the most profound increase in angulation at the distal stent edge showed an increase rather than a decrease of VFR in this head position. A significant reduction of VFR, which we had hypothesized might occur, was not found in any of our subjects. In a TCD controlled study by Malek et al [19] patients with known internal carotid elongation were examined, using Trans Cranial Doppler (TCD). In the 8 head positions tested in their series, no reduction of Middle Cerebral Artery (MCA) flow was found.

Apparently the ICA is able to conform to geometric changes in physiologic situations even in the presence of significant tortuosity.

Berkefeld et al [13] propose a method of measuring the Common Carotid Artery (CCA) to ICA angle and the ICA offset before and after carotid stenting. They found a significant reduction in both CCA-ICA angulation and ICA offset after CAS, compared to baseline, in their patients. The measurements in their series were all performed in Neutral head position with the patient supine on the angiography table. Kinking at the distal stent end was observed in several cases, even in this neutral position, but not structurally evaluated.

Although no acute reduction in cerebropetal blood flow was found to be associated with the increased angulation of the ICA caused by neck flexion in our series, the repetitive changes in morphology may very well be associated with more chronic detrimental effects. The increased stiffness caused by the introduction of stents has previously been implicated as the cause of recurrent stenosis in arteries subject to physiological flexion[20,21]. The mechanism of this re-stenosis formation has been hypothesized to entail primarily the deposition of collagen as a reaction of the vessel to oppose the strain caused by the stent struts[22]. This same mechanism may very well lead to similar effects in the stented carotid artery. Angles at stent edges are instrumental in the velocity of overgrowth of endothelial cells, to cover the stent struts[23]. Delayed overgrowth is associated with an increased risk of neo-intimal hyperplasia and restenosis[24].

Even fracturing of stents placed in highly mobile parts of the human anatomy has been reported [25,26]. So far these reports have been confined to arteries of the extremities. No reports on fractured carotid stents have been published as yet, but this may change and the clinical consequences of this eventuality remain to be awaited.

Our study has been limited to patients treated with segmented nitinol stents. The most frequently used carotid stent to date, both in our series as worldwide, is the Wallstent® (Boston Scientific, Natick, MA), which is a stainless steel stent with continuous filaments. This type of stent was not included in our current study, on account of the artifacts it might induce on MR imaging. The geometry changes of this type of stent could conceivably be quite different from our current findings. In an in vitro study by Tanaka and co-workers[27] the conformity of 5 different types of self-expandable carotid stents was tested. They found better wall apposition and less straitening and kinking of their carotid bifurcation model when segmented nitinol stents were used as compared to stents with continuous filaments. Even these segmented nitinol stents however show considerable angulation in

our in vivo study, when the position of the head changes.

We used MR imaging and MR phase-contrast flow quantification to examine patients in our study. With these techniques no ionizing radiation is used. Increasing evidence suggests that Gadolinium-enhanced MRA may be superior to 3D-TOF MRA for grading of carotid bifurcation stenoses. We nevertheless decided to use 3D-TOF because it was the morphology of the internal carotid artery we were trying to depict rather than a possible stenosis and this method does not require the administration of intravenous contrast agents. For the flow quantification sequence we used prospective cardiac triggering. This implies that flow was measured from the ECG R-wave to late diastole. The end diastolic phase coincides with the refractory period of the sequence when a new R-wave of the ECG is awaited. This does not appear to influence the results of our study, as the same sequence was used in all head position and in all patients, as suggested by Ho et al.[28]. Furthermore this part of the cardiac cycle plays only a minor role in the total cerebropetal blood flow.

The choice of the location of the plane for VFR measurement may seem rather arbitrary. Four cm distal to the bifurcation and 1 cm distal to the stent both equate to roughly the same segment of the vessel. This segment did not contain significant tortuosity in any of the subjects tested, which allowed accurate measurement. As volumetric flow was measured rather than velocity and there are no side branches in this segment, a variation in location along this segment will not lead to a difference in flow.

In conclusion our present study confirmed significant increases in ICA angulation in patients treated with CAS if the head was bent forward; this was not observed in patients treated with CEA. Although this increased angulation did not lead to acute changes in cerebropetal bloodflow, it is possible that such angulation might result in chronic changes, such as restenosis. This however remains to be tested in future studies.

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# PART III
# CHAPTER 3C

# The Fate of the external carotid artery after carotid artery stenting

## *A follow-up study with duplex ultrasonography*

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On behalf of the Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group. The members are listed in the appendix*.

*Eur J Vasc Endovasc Surg. 2007 Jun;33(6):657-63.*

## Abstract

**Objective**. To evaluate the long-term effect of carotid angioplasty and stenting (CAS) of the internal carotid artery (ICA) on the ipsilateral external carotid artery (ECA).

**Subjects and Methods**. We prospectively registered the pre- and post-interventional duplex scans obtained from 312 patients (mean age 70 years) who underwent CAS. Duplex scans were scheduled the day before CAS, 3 and 12 months post-procedurally and yearly thereafter, to study progression of obstructive disease in the ipsilateral ECA compared to the contralateral ECA. The duplex ultrasound criteria used to identify ECA stenosis ≥ 50% were Peak Systolic Velocities of ≥125 cm/s.

**Results**. Preprocedural evaluation of the ipsilateral ECA demonstrated ≥ 50% stenosis in 32.7% of cases vs 30% contralateral. Both ipsilateral and contralateral 3 (1%) ECA occlusions were noted. After stenting 5 (1.8%) occlusions were seen vs 1% contralateral. No additional ipsilateral occlusions and 2 additional contralateral oclusions were noted at extended follow-up. The prevalence of ≥ 50% stenosis of the ipsilateral ECA (Kaplan-Meier estimates) progressed from 49.1% at 3, to 56.4%, 64.7%, 78.2%, 72.3%, and 74% at 12, 24, 36, 48, and 60 months respectively. Contralateral prevalences were 31.3%, 37.7%, 41.7%, 43.1%, 46.0%, and 47.2% respectively ($p < 0.001$). Progression of stenosis was more pronounced in 234 patients (75%) with overstenting of the carotid bifurcation ($p = 0.004$).

**Conclusion**. Our results show that significant progression of ≥ 50% stenosis in the ipsilateral ECA occurs after CAS. There was greater progression of disease in the ipsilateral compared with the contralateral ECA. Progression of disease in the ECA did not lead to the occurrence of occlusion during follow up.

## Introduction

Carotid Angioplasty and Stenting (CAS) has emerged as an alternative to carotid endarterectomy (CEA) in treatment of carotid artery occlusive disease[1]. Despite promising early results, recurrent stenosis and its management are reported disadvantages of the method. Another possible disadvantage of CAS might be the covering of the external carotid artery (ECA) orifice. This might be a further argument against carotid stenting.

Most high-grade arteriosclerotic lesions are located at the carotid bifurcation, usually at the distal common carotid artery (CCA) and the proximal internal carotid artery (ICA), and frequently the ECA is also involved. In many cases stents are placed from the ICA, extending into the CCA thereby covering the ECA origin.

The ipsilateral ECA can potentially provide an important collateral pathway for retinal and cerebral blood flow in the presence of occlusion or severe stenosis of the ICA, especially in patients with an incomplete circle of Willis. In contrast to the ICA, evaluations of development of ECA stenosis have been rarely described[2-4]. The fate of the ipsilateral ECA has been investigated with[2] and without[3] additional external endarterectomy. A comparison of the development of obstructive disease between the ipsilateral ECA and the contralateral ECA after CEA has, to our knowledge, never been performed. In most studies on ECA patency, duplex-scan-based flow criteria were used to grade ECA stenosis[2-5].

As far as we know, only one study has been published so far with data concerning the effect of carotid stent placement on the ipsilateral ECA immediately after the procedure and during a limited 2 years of follow-up[5]. Furthermore, this study did not differentiate between overstented en non-overstented bifurcations.

Therefore, in the present study the following four questions were addressed: 1) What is the prevalence of primary stenosis and occlusion of the ipsilateral and contralateral ECA before carotid stent placement? 2) Is there further development of obstructive disease in the ipsilateral ECA immediately after stenting and during follow-up compared with the contralateral side? 3) Is there a difference in the development of ECA stenosis between overstented and non-overstented bifurcations? 4) Is there a relationship between development of ECA stenosis and development of in-stent restenosis?

To answer these questions, we performed a follow up study with annual duplex US of both the ipsi- and contralateral carotid arteries, in patients treated with CAS.

## Methods

### *Patients*

Between December 1998 and 2002 all patients scheduled for CAS in our institution were prospectively entered in a computerized database. Patients had their CAS performed for either primary carotid bifurcation stenosis or restenosis after previous CEA. Patients with preceding contralateral CAS were excluded from this study, as were patients in which no stent was placed during the procedure. A total of 312 patients were included in this study. Median age was 70 years (range 47-89), 221 (70.6%) were male. In 173 patients (55.4%) the left carotid artery was treated. The study was approved by the local ethics committee, and written informed consent was obtained from all patients in accordance with institutional guidelines.

Seventy (22.4%) had been symptomatic of the ipsilateral carotid artery stenosis (Transient Ischemic Attack, Transient Monocular Blindness or minor stroke) in the 4 months preceding CAS. In 242 patients (77.6%) CAS was performed in the work-up before coronary artery bypass grafting (CABG), or other cardiothoracic reconstructive surgery. These patients were treated to prevent perioperative complications and most had not been symptomatic of the ipsilateral carotid bifurcation stenosis.

The degree of stenosis was assessed by duplex ultrasound scanning and intra-arterial digital subtraction angiography prior to endovascular treatment. Symptomatic patients were treated if the degree of stenosis at the carotid bifurcation exceeded 70%, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria[6]. For asymptomatic patients the cut-off point for treatment was a diameter reduction of 80%. Preoperative and postoperative carotid artery duplex examination that specifically evaluated the degree of ECA stenosis were available for review on all 312 CAS procedures performed during this period. Patients were monitored at the recovery room and, barring any complication, discharged the following day.

### *Carotid angioplasty and stenting procedure*

In all patients CAS was performed in accordance with our previously described CAS protocol[7,8]. All procedures were performed under local anesthesia, from a groin approach. All procedures were performed by either an experienced interventional cardiologist or an experienced interventional radiologist. The choice of stent type, and the decision whether or not to use a cerebral protection device (CPD) were at the discretion of the treating interventionalist. As most procedures were performed before CPD's had become available, no protection device was used in 267 cases (85.3%). Several different

types of appropriately sized self expandable stents were used (Table 1). Overstenting of the carotid bifurcation was defined as covering of the ECA origin by stent placement from the ICA extending into the CCA. Aspirin (80-100 mg/day) was given prior to CAS and continued indefinitely. Clopidogrel (75 mg/day) was started 72h before the procedure and continued for at least 4 weeks. Patients re-entered the carotid surveillance programme, with duplex US at 3 and 12 months and yearly thereafter.

***Duplex Ultrasound Scanning***

All patients were evaluated initially preprocedurally and during follow-up with duplex ultrasonography of the ipsi- and contralateral CCA, ICA, and ECA. The duplex criteria used in our vascular laboratory (HP/Agilent, Sonos 2500 or 4500, Andover, USA) are based on the Strandness criteria (20-49% / 50-70% / 70-90% / 90-99% / occlusion). In terms of classification of the degree of ICA and ECA stenosis with duplex ultrasound, we used the same velocity criteria in the post-stenting as for the pre- stenting situation.

***Endpoints***

Endpoints in the analyses were development of ECA occlusion or > 50% ECA stenosis during follow-up assessed by Duplex US scanning.

***Statistics***

Statistical analysis was performed using the statistical software package SPSS (SPSS, Inc., Chicago, Il). Actuarial survival analysis was performed by using Kaplan-Meier life tables. A p-value of $< 0.05$ (log-rank) was considered statistically significant for all analyses.

## Results

Preprocedural evaluation of the ipsilateral ECA demonstrated ≥ 50% stenosis in 32.7% of cases vs 30% contralateral. Three ipsilateral and 3 contralateral ECA occlusions (1%) were noted (p = NS). After stenting 2 new ECA occlusions (0.8%) were seen vs 0 contralateral. These 2 additional ipsilateral and asymptomatic occlusions occurred immediately after the procedure, both in patients in which the carotid bifurcation was overstented. Contralaterally, no new occlusion was noted immediately after the procedure. No additional ipsilateral ECA occlusions and two additional contralateral ECA occlusions (at 24 and 36 months respectively) were noted at extended follow-up.

A comparison of progression of disease of the ipsilateral ECA (n= 312) and

contralateral ECA, as demonstrated by duplex US, is shown in figure 1. On the day preceding stenting the ipsilateral and contralateral ECA did not differ significantly. The prevalence of ≥ 50% stenosis of the ipsilateral ECA progressed from 49.1% at 3 months, to 56.4%, 64.7%, 68.2%, 72.3%, and 74% at 12, 24, 36, 48, and 60 months respectively. The contralateral prevalences were 31.2%, 37.6%, 41.5%, 43.1%, 45.8%, and 47.1% respectively. Compared with preprocedural data, the pronounced increase in stenosis rate of the ipsilateral ECA and the moderate increase in the contralateral ECA was statistically significant ($p < 0.001$).

In 234 patients (75%) the carotid bifurcation was overstented. Prevalence of ≥ 50% ECA stenosis in non-overstented cases was 20.4% pre-CAS and 25%, 29.9%, 37.1%, 42.9%, 53.6%, and 53.6% at 3, 12, 24, 36, 48 and 60 months follow-up respectively. In patients with overstented bifurcations the prevalence was 35.4% pre-CAS, and 53.4%, 61.4%, 70.2%, 73.2%, 75.9%, and 77.9% at 3, 12, 24, 36, 48 and 60 months follow-up respectively (Figure 2). This difference, with the overstented bifurcations showing more disease progression of the ipsilateral ECA was statistically significant ($p = 0.004$).

So far we looked at the complete patient group including those with a more than 50% ECA stenosis at baseline. In fact it would be more fair to look at the development of truly new stenoses. If patients with a preprocedural ≥ 50% ECA stenosis were excluded from analysis, 176 patients remained (Figure 3). In these 176 patients with no ≥ 50% ECA stenosis at baseline, the prevalence of ≥ 50% stenosis of the ipsilateral ECA progressed from 0% pre-CAS to 24.6% at 3 months, 35.3 %, 47.3%, 52.8%, 58.9%, and 61.5% at 12, 24, 36, 48, and 60 months respectively.

In 37 of 176 patients with no overstenting of the bifurcation prevalence of ≥ 50% stenosis of the ipsilateral ECA progressed from 0% at baseline to 5.9%, 11.9%, 21.1%, 28.2%, 41.7%, 41.7% at 3, 12, 24, 36, 48, and 60 months respectively (Figure 4). In patients with overstented bifurcations prevalence of ≥ 50% stenosis of the ipsilateral ECA progressed from 0% at baseline to 29.9%, 41.1%, 53.8%, 58.5%, 62.7%, 65.8% at 3, 12, 24, 36, 48, and 60 months respectively (N=139).

During follow-up in 48 patients (15.5%) an in-stent stenosis ≥ 50% of the ipsilateral ICA occurred (Figure 5). Comparison of ECA and ICA stenosis progression demonstrated a correlation between the two. There were more ECA stenoses in patients who developed an in-stent ICA stenosis (38/48; 79%), compared to those who did not (94/264; 36%) ($\rho = 0.026$).

In separate analyses no statistically significant correlation was found between

ECA stenosis development in symptomatic versus asymptomatic patients, or in primary versus post-CEA restenosis, nor was there a statistically significant correlation between ECA stenosis development and CPD use, or the type of stent used.

## Discussion

This study reports the long term fate of the ECA after carotid stenting. Our results show that significant progression of disease in the ipsilateral ECA occurs after overstenting. Furthermore, there was greater progression of disease in the ipsilateral stented ECA compared with the untreated contralateral ECA. However, this did not have an adverse impact on either the patency of the ECA or the clinical outcome of the patient.

The role of the ECA as a collateral to the brain is worthy of discussion. The ipsilateral ECA is thought by many to be an important source of cerebral blood flow in the presence of occlusion or severe stenosis of the ICA, that might also serve as significant conduit for vascular reconstruction[9]. As the severity of ICA disease increases, the contribution from the extracranial collateral circulation is expected to become greater up to 10 to 15% of middle cerebral artery blood flow[10]. Others doubt if the contribution of the ECA collaterals to cerebral perfusion is substantial[11,12]. Still, many surgeons routinely perform some kind of ECA endarterectomy during standard CEA[2], to preserve ECA patency and hereby collateral supply in cerebral perfusion in the event of recurrent ICA stenosis. Management of ECA stenosis during routine CEA is however controversial, in part because of high residual stenosis rate as well as early and late recurrent stenosis rate[2]. Thus some surgeons have recommended leaving the diseased ECA intact during CEA[3]. According to the guidelines of an international consensus meeting[13] CAS is also recommended without intervention at the ECA.

The prevalence of ECA stenosis depends on definition and measurement tool. ECA stenosis (>50%) was found in 22% of patients indicated for CEA[3]. Willfort found 17.5% of patients with >70% ECA stenosis in patients preceding CAS[5]. The preprocedural ipsi- and contralateral prevalence of ECA stenosis in our study group was 32.7% vs 30% respectively using duplex with a cut-off point of ≥ 50% stenosis (PSV > 125 cm/s).

Ascer et al.[3], being the first to compare pre- and post-operative duplex evaluation of the ECA, found no significant early or late influence of CEA on disease progression in the ipsilateral ECA. Postoperative occlusion of the ECA following CEA showed to be rare, and even in the presence of significant preoperative ECA stenosis, postoperative

occlusion did not occur despite intentionally leaving plaque within the ECA. ECA stenoses showed relatively stable and only a minority progressed to severe stenosis. More importantly, those that did progress to severe stenosis did not appear to confer additional risk of neurologic complication in their series. In Willforts study, the clinical significance of disease progression in the ipsilateral ECA during the first year after CAS was limited [5]. Only one patient with presumed embolic ECA occlusion immediately after stent placement had transient jaw claudication. Similarly we found 2 patients with occlusion postprocedurally also without symptoms. No other ipsilateral occlusions occurred during follow-up.

Both in Willfort's and in our study a significantly higher progression of disease in the ipsilateral versus the contralateral ECA after CAS was found[5]. We also showed that progression was more significant with overstenting of the carotid bifurcation. During stent placement atheromatous material might be pushed from the CCA/ICA into the origin of the ECA. Furthermore, it is assumed that flow turbulence caused by passage through the meshes of the stent wall to the ECA might be a plausible explanation for the increased narrowing of the ECA. Although prospective with a follow-up of 121 carotid arteries, the duration of Willforts study was limited to 24 months. After 1 year, based on Wallstents only, some kind of steady state seemed to be achieved. Our results however, with longer follow-up, clearly show that development of ECA stenosis is an ongoing process and therefore probably not only caused by early flow turbulence, but by true disease progression.

Comparison of ECA and ICA stenosis progression post-endarterectomy demonstrated no correlation between the two[3]. In Ascers study only 8% of cases showed ≥70% stenosis of both the ICA and ECA. Moreover, progression of disease within the ECA after CEA did not lead to restenosis of the ICA, suggesting the independence of disease within these two vessels. Interestingly, for the post-stenting situation we found a correlation between ECA and ICA stenosis progression [Figure 5]. In-stent restenosis, reported 3.5% using only Wallstents with overstenting of the bifurcation[14] reduces the impact of the ECA as a source of collateral supply to the brain. In case of higher incidence of carotid stent recurrent stenosis, as published in CAVATAS or our own experience[1,15,16] the dynamics of ECA disease and the importance of the ECA as a collateral seem even more limited. On the other hand, in-stent restenosis of nitinol stents that are being used increasingly and can be placed selectively in the ICA, does probably not affect the origin of the ECA, and will subsequently lead to increased flow through the ECA which emphasizes the importance of the ECA as a collateral.

Two characteristics that make the carotid bifurcation somewhat unique are the different blood flow requirements and waveforms of the ICA and the ECA[17,18]. Probably both phenomena are induced by the different resistances found in the runoff beds for each artery, high in the case of the ECA and low in the case of the ICA. In case of significant ICA stenosis and thus high resistance in the ICA, an increasing percentage of ECA flow is speculated to be diverted through collateral paths into the bed normally supplied by the ICA. When endarterectomy relieves bifurcation stenosis, CCA blood flow is redistributed preferentially to the ICA[19]. The proportionate change in total flow has a positive increase in the ICA, whereas flow in the ECA is likely to decrease. Duplex ultrasonography is the primary non-invasive screening procedure for evaluation of ICA stenosis to select patients for angiography[20]. In contrast to the ICA, evaluations of degree of ECA stenosis have been rarely described[2-4]. The duplex US findings concerning ECA stenosis have been handled in the same manner as ICA stenoses and the same Doppler criteria have been used to evaluate them[4]. Ascer and Archie used PSV of the ECA to grade ECA stenosis. Paivansalo found the peak systolic flow ratio ECA/CCA to be superior for grading ECA stenosis, which was also used by Willfort. In terms of classification of the degree of ICA and ECA stenosis with ultrasound, we used the same velocity criteria in the post-stenting as for the pre- and post-endarterectomy situation. However, measurement of external carotid stenosis is more complicated and less accurate as a result of its smaller transverse diameter, as compared with ICA lesions[3]. Furthermore, ipsilateral ICA stenosis affects the flow parameters of the ECA. Thus, ECA flow values must be considered carefully[21].

Our study has several limitations. It was a non-randomized study using different types of stents. Our analysis did not show a relation between stenosis development and used type of stent. However, 96% of the stents used in this cohort were Wallstents, and analysis of a more balanced mix of stent types might discover such a relationship. Furthermore, in our analysis we used the PSV as the only measurement tool as discussed above. However, we believe that the clear trend shown by our results is independent of the measurement technique used.

## Conclusion

Our results show that significant progression of stenosis in the ipsilateral ECA occurs after CAS. Progression is more pronounced with bifurcation overstenting. In the opposite ECA non or mild progression was found. In other words, there was greater

progression of disease in the ipsilateral ECA compared with the contralateral ECA. Finally, progression of disease in the ECA did not have an adverse impact on the patency of the ECA. Even in the presence of preprocedural ECA stenosis, post-CAS occlusion did not occur.

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## Appendix

Members of the Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group:

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Department of Cardiothoracic Surgery – R.H. Heijmen, MD, PhD; W.J. Morshuis, MD, PhD; M.A.A.M. Schepens, MD, PhD.
Department of Clinical Neurophysiology – R.G.A. Ackerstaff, MD, PhD; L.L.Teunissen, MD, PhD; O.J.M. Vogels, MD, PhD.
Department of Neurology – H.W. Mauser, MD, PhD; W.J. Schonewille, MD; O.J.M. Vogels, MD, PhD.
Department of Radiology – J.P.M. van Heesewijk, MD, PhD; M. van Leersum, MD; T.Th.C. Overtoom, MD; J.A. Vos, MD.
Department of Vascular Surgery – J.P.P.M. de Vries, MD, PhD; H.D.W.M. van de Pavoordt, MD, PhD.

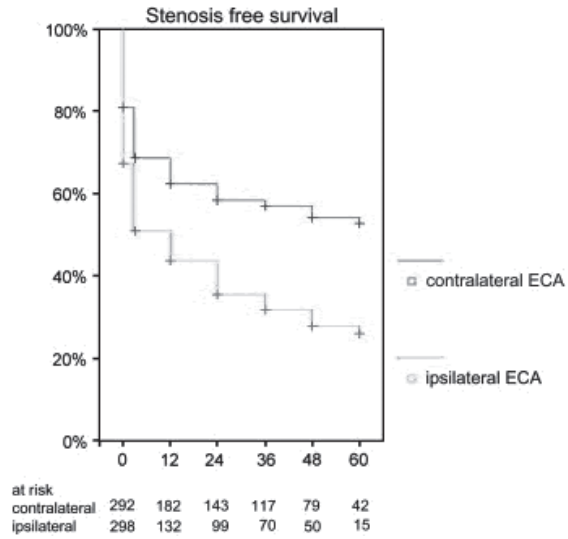



**Figure 1**. Kaplan Meier estimates of ECA stenosis free survival: ipsilateral ECA vs contralateral ECA (N=312) ($p<0.001$). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

*Ipsilateral:* 67.3% (baseline) - 50.9% - 43.6% - 35.3% - 31.8% - 27.7% - 26.0%
The Standard Error (SE) was 0.0296, 0.0297, 0.0296, 0.0294, 0.0301 and 0.0329 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 194 with a mean stenosis free follow-up of 23.3 months 95% CI (20.2 – 26.3) SE 1.56.

*Contralateral:* 70% (baseline) - 68.8% - 62.4% - 58.5% - 57% - 54.2% - 52.9%
The SE was 0.0274, 0.0289, 0.0299,0.0303, 0.0320, and 0.0336 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 124 with a mean stenosis free follow-up of 36.5 months 95% CI (33.3 – 39.7) SE 1.64.

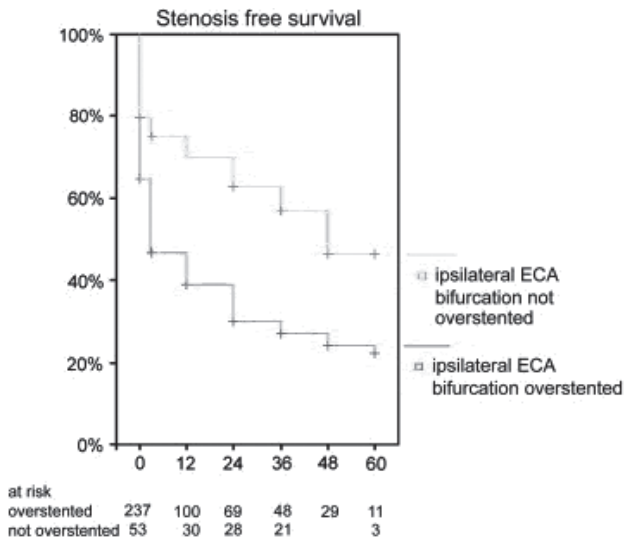



**Figure 2.** Kaplan Meier estimates of ECA stenosis free survival: ipsilateral non-overstented ECA (N=54) vs ipsilateral overstented ECA (N=238) (p=0.0004). Time schedule: BASELINE-3m-12m-24m-36m-48m-60m.

*Ipsilateral (All)*: 67.3% (baseline) - 50.9% - 43.6% - 35.3% - 31.8% - 27.7% - 26.0%
The Standard Error (SE) was 0.0296, 0.0297, 0.0296, 0.0294, 0.0301 and 0.0329 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 194 with a mean stenosis free follow-up of 23.3 months 95% CI (20.2 – 26.3) SE 1.56.

*Non-overstented*: 79.6% (baseline) - 75.0% - 70.1% - 62.9% - 57.1% - 46.4% - 46.4%
The SE was 0.0608, 0.0658, 0.0711, 0.0752, 0.0827 at 3 to 48 months respectively.
Number of events (stenosis ≥ 50%) was 23 with a mean stenosis free follow-up of 37.5 months 95% CI (30.3 –44.7) SE 3.67.

*Overstented*: 64.6% (baseline) - 46.6% - 38.6% - 29.8% - 26.8% - 24.1% - 22.1%
The SE was 0.0327, 0.0323, 0.0316, 0.0312, 0.0318, 0.0350 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 167 with a mean stenosis free follow-up of 20.6 months 95% CI (17.3 –23.9) SE 1.68.

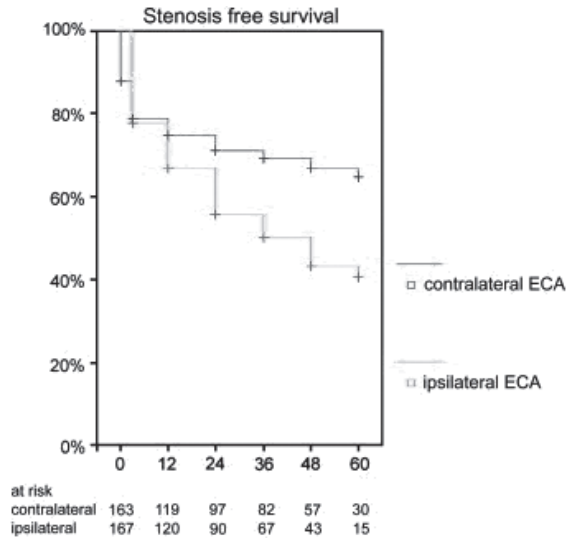



**Figure 3**. Kaplan Meier estimates of ECA stenosis free survival in selected patients with no stenosis at baseline: ipsilateral ECA vs contralateral ECA (N=167) (p=0.0043). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

*Ipsilateral*: 0% (baseline) - 75.4% - 64.7% - 52.4% - 47.2% - 41.1% - 38.5%.
The Standard Error (SE) was 0.0327, 0.0373, 0.0406, 0.0418, 0.0444 and 0.0492 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 82 with a mean stenosis free follow-up of 36 months 95% CI (32.1 – 39.8) SE 1.97.

*Contralateral*: 0% (baseline)- 90.1% - 82.6% - 76.8% - 74.0% - 69.6% - 67.3%
The SE was 0.0323, 0.0345, 0.0367, 0.0377, 0.0401 and 0.0442 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 50 with a mean stenosis free follow-up of 43.6 months 95% CI (39.7–47.5) SE 2.0.

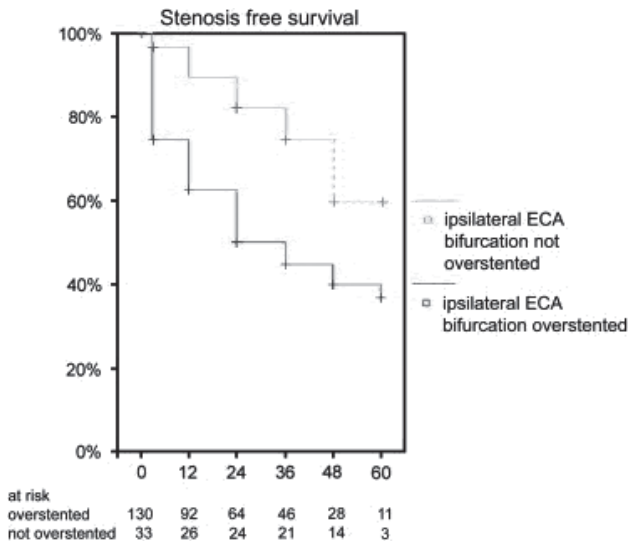



**Figure 4**. Kaplan Meier estimates of ECA stenosis free survival in patients with no ECA stenosis at baseline: ipsilateral non-overstented ECA (N=37 ) vs ipsilateral overstented ECA (N=139) (p=0.004). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

*Ipsilateral (All N=167)*: % (baseline) - 75.4% - 64.7% - 52.4% - 47.2% - 41.1% - 38.5%. The Standard Error (SE) was 0.0327, 0.0373, 0.0406, 0.0418, 0.0444 and 0.0492 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 82 with a mean stenosis free follow-up of 36 months 95% CI (32.1 – 39.8) SE 1.97.

*Non-overstented*: 0% (baseline) - 94.1% - 88.1% - 78.9% - 71.8% - 58.3% - 58.3%. The SE was 0.0339, 0.0579, 0.0720, 0.0838 and 0.102 at 3 to 48 months respectively.
Number of events (stenosis ≥ 50%) was 10 with a mean stenosis free follow-up of 48 months 95% CI (41.8 – 54.8) SE 3.32.

*Overstented*: 0% (baseline) - 71.1% - 58.9% - 46.2% - 41.5% - 37.3% - 34.2% The SE was 0.0382, 0.0428, 0.0462, 0.0471, 0.0492, and 0.0553 at 3 to 60 months respectively.
Number of events (stenosis ≥ 50%) was 70 with a mean stenosis free follow-up of 33.4 months 95% CI (29.0 – 37.8) SE 2.24.

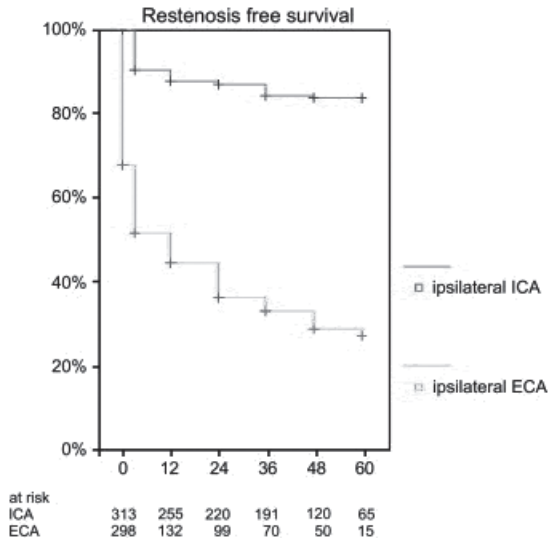



**Figure 5**. During follow-up in 48 patients stenosis ≥ 50% of the ipsilateral Internal Carotid Artery occurred.

The incidence of in-stent recurrent stenosis (≥50%) therefore was 15,5% in the present study after a mean follow-up of 44 months.

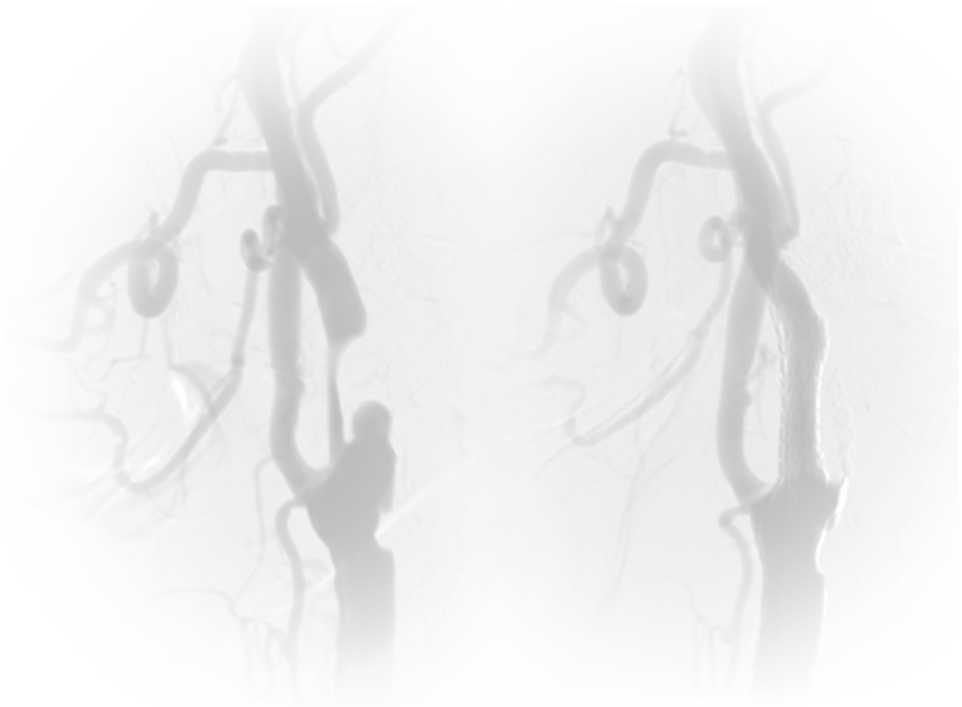
The correlation between ICA and ECA reached significance when patients with ECA stenosis at baseline were included (Chi-Square test; $\rho = 0.026$). If patients with a preprocedural ≥ 50% ACE stenosis were abandoned from analysis the correlation was non significant ($\rho = 0.09$).

**Table 1**. Types of stents (and their manufacturers) as used in the present study (N = 312).

| **Stent type** | **Manufacturer** | ***N* (%)** |
|---|---|---|
| Carotid Wallstent | Boston Scientific, Natick, MA | 219 (70) |
| Easy Wallstent | Boston Scientific, Natick, MA | 82 (26) |
| Peripheral Wallstent | Boston Scientific, Natick, MA | 1 (0.3) |
| Acculink | Guidant, Indianapolis, IN | 2 (0.6) |
| Carotid SE | Medtronic, Minneapolis, MN | 7 (2.2) |
| Precise | Cordis J&J, Miami Lakes, FL | 1 (0.3) |
| **Total** | | **312** |

# Part IV

## Carotid Angioplasty and Stenting for specific subsets of patients, deemed unfavourable candidates for surgery



# Part IV
# Chapter 4A

# Carotid angioplasty and stenting: treatment of post CEA restenosis is at least as safe as primary stenosis treatment

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## Abstract

**Objectives** To compare Transcranial Doppler (TCD) and outcome of Carotid Angioplasty and Stenting (CAS) in post Carotid Endarterectomy (CEA) restenoses versus primary atherosclerotic stenoses.

**Design** Retrospective analysis of prospectively accumulated database.

**Material and Methods** 812 CAS procedures were divided into two groups: group 1: 72 restenoses, mean 71 months [range5-245] after initial CEA; group 2: 740 primary stenoses. Clinical endpoints: cerebral ischemic events and death. TCD endpoints: numbers of isolated micro emboli and micro embolic showers, during five procedural phases. Mann-Whitney U test and $\chi^2$-test were used. To test for independence of variables the Mantel-Haentzel test and univariate regression analysis were performed. $P<.05$ was regarded as statistically significant.

**Results** Groups were evenly matched for demographic data (median age: 70 vs. 71 years, male: 44/72 [61%] vs. 525/740 [71%], symptomatic 14/72 [19%] vs. 147/740 [20%]). There were 7 fatalities (0.9%), 10 major (1.2%) and 21 minor (2.6%) strokes, all occurred in group 2 (P=0.049), which was independent from CPD use. Mean (Standard Deviation) numbers of isolated micro-emboli for Groups 1 vs. 2 were: wiring 37.0 (31.1)/ 50.4 (52.6), predilation 14.8 (18.7)/ 21.7 (21.8), stent-placement 58.6 (31.1)/ 64.7 (38.8), post-dilation 20.4 (16.5)/ 27.2 (34.9), CPD use 44.2 (30.2)/ 37.5 (36.8), total 134.8 (68.7)/ 175.3 (113.8) and micro-embolic showers: wiring 1.7 (4.5)/ 2.2 (6.4), predilation 2.1 (4.1)/ 3.3 (5.8), stent-placement 21.5 (22.0)/ 26.9 (25.1), post-dilation 5.3 (15.7)/ 5.0 (8.1), CPD use 5.8 (6.9)/ 6.2 (8.9), total 30.4 (36.0)/ 39.6 (35.0). TCD data for patients treated with vs. without CPD: isolated emboli: wiring 53.2 (45.1)/ 44.3 (51.7), predilation 24.7 (20.2)/ 18.2 (22.5), stent placement 77.5 (34.8)/ 53.5 (37.3), post-dilation 33.6 (36.6)/ 20.7 (21.8), CPD use 38.3 (36.6)/ 0 total 222.5 (113.8)/ 132.3 (89.1); showers: wiring 2.4 (6.6)/ 1.9 (5.8), predilation 4.2 (6.4)/ 2.4 (5.0), stent placement 38.9 (25.8)/ 16.2 (18.7), post-dilation 7.0 (11.2)/ 3.4 (6.4), CPD use 6.3 (8.9)/ 0 total 58.4 (37.7)/ 23.3 (23.1). P=0.01 for showers during wiring and $P<0.001$ for all other variables. After correction for the difference in CPD use between groups 1 and 2 (17/72 [24%] vs. 369/740 [50%]), no statistically significant differences remained between groups 1 and 2, in numbers of isolated emboli and embolic showers in any of the procedural phases, nor for the entire procedure.

To establish any correlation between the rapidity of restenosis occurrence and procedural embolic potential, TCD detected microembolic load for early (<3 years between CEA and CAS) and late (>5 years) restenoses were compared. No statistically significant differences were found.

**Conclusions** CAS for restenosis after CEA has a complication rate lower than primary CAS; time interval between CEA and CAS did not influence micro embolic load.

**Key words:** Carotid arteries, Stents, Endarterectomy, Restenosis, Transcranial Doppler Ultrasonography

## Introduction

Based on the results of several large randomised trials, Carotid Endarterectomy (CEA) is currently the accepted standard treatment for patients with severe symptomatic and asymptomatic carotid artery stenosis [1-4]. Carotid Angioplasty and Stenting (CAS) has been evaluated as a potential alternative to CEA[5]. Compared with the surgical approach, the endovascular procedure is associated with a significant cerebral embolic burden, as shown by transcranial Doppler (TCD) of the ipsilateral Middle Cerebral Artery (MCA) [6,7] and Magnetic Resonance Imaging (MRI) of the brain [8,9]. Post-operative restenosis after CEA, defined as a greater than 50% diameter reduction, has been reported with incidences varying from 6% to 36%[10], partly depending on follow up length. On account of scar tissue in the cervical region and the loss of tissue planes, redo operations are generally considered to be technically more challenging and a higher complication rate is cited in most reports[11]. Since CAS is not hampered by previous neck dissection, it has been considered as an alternative to redo surgery in these cases and encouraging results have been published over the last decade[12-16]. The main culprit in early restenosis after CEA is hypothesised to be myointimal hyperplasia (MIH), whereas late restenosis is generally considered to result from progression of the underlying atherosclerotic disease[17]. As MIH is supposed to be more stable and less embologenic[18], the procedural risk of emboli might be lower in CAS after prior ipsilateral CEA, as compared to primary CAS, especially in early restenoses.

We have previously reported our experience with TCD monitoring and its usefulness with regard to emboli detection and the prediction of early cerebral outcome in CAS[7,19]. In the present study we compare the TCD detected embolic load and clinical outcome in patients who underwent stent placement for restenosis after prior ipsilateral CEA to CAS performed for primary carotid artery stenosis. In addition we stratified redo cases in early and late restenoses, to establish any correlation between the time of onset of restenosis and periprocedural embolic load.

## Material and methods

### *Patients*

Between December 1997 and June 2006 all 812 patients scheduled for CAS in our tertiary referral centre for vascular disease were prospectively entered in a computerised database and included in this study. Median age was 71 years (InterQuartile Range [IQR] 66-76), 569 (70%) were male. In a subgroup of 72 patients (Group 1), CAS was performed

for recurrent stenosis at a mean of 71 months (range 5 to 245, standard deviation 57 months) after previous ipsilateral CEA. Median age in this subgroup was 70 (IQR 65-75), 44 (61%) were male. Fourteen (19%) had been symptomatic of the ipsilateral carotid artery stenosis (Transient Ischemic Attack [TIA], Transient Monocular Blindness [TMB] or minor stroke) in the 4 months preceding CAS. Four of these 14 (29%) had their symptoms within 36 months after the initial ipsilateral CEA. The majority of CEA's had also been performed in our institution. The remaining 740 patients (Group 2) had their CAS performed for primary carotid bifurcation stenosis. In this group 525 (71%) were male, median age was 71 years (IQR 66-76), 147 patients in this group (20%) had recently been symptomatic. Baseline patient characteristics are summarised in table 1.

In 588 patients (72%) CAS was performed before coronary artery bypass grafting, cardiac valve replacement, or reconstructive surgery of the thoracic aorta. These patients were treated to prevent perioperative complications[20] and most (505/588, 86%) had not been symptomatic of the ipsilateral carotid bifurcation stenosis.

Symptomatic patients were treated if the degree of stenosis at the carotid bifurcation exceeded 70%, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria[2]. For asymptomatic patients the cut-off point for treatment was a diameter reduction of 80%. The degree of stenosis was assessed by duplex ultrasound scanning and intra-arterial digital subtraction angiography prior to endovascular treatment.

Written informed consent was obtained from all patients in accordance with institutional guidelines.

***Carotid angioplasty and stenting procedure***

In all patients CAS was performed using a standard protocol described in detail previously[7,19]. All procedures were performed under local anaesthesia, from a groin approach. Several different types of appropriately sized self-expandable stents were used (see table 2). As we started performing CAS in our institution, before cerebral protection devices (CPD's) had been developed, 426 cases (52%), mainly in the early part of our experience, were treated without these devices. CPD's used are listed in table 3. To prevent any potential hypotension and bradycardia resulting from carotid body compression, 0.5 mg of atropine sulphate was administered in the primary stenting cases. As the ipsilateral carotid body generally is dysfunctional after prior CEA, atropine was not routinely administered in post CEA restenosis cases. All procedures were performed by either an experienced interventional cardiologist or an experienced interventional radiologist.

***Transcranial Doppler monitoring***

The technique of TCD monitoring during CAS has been described in detail in previous publications[7]. During the various stages of the procedure isolated micro embolic signals were recorded according to the criteria described by the consensus committee [21]. If the number of micro embolic signals was too high to be counted separately, heartbeats with micro emboli were counted as micro embolic showers. Micro embolic signals were stratified to five procedural stages: 1) wiring/ passing of the stenosis, 2) predilation, 3) stent deployment, 4) postdilation and 5), if applicable, protection device use (including placement and retrieval of the device).

***Clinical outcome***

All patients were formally assessed before and after the procedure by a neurologist who was not involved in the intervention. During CAS, a different neurologist was present in the angiography suite.

New cerebral deficits persisting for > 24 hours were regarded as stroke, the severity of which was graded according to the modified Rankin scale[22]. Major strokes exceeded 3 on the Rankin scale, while minor strokes did not. In patients with adverse cerebral outcome, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain were performed.

Endpoints in the analyses were minor and major strokes (ischemic and hemorrhagic), death, TIA and TMB during or within seven days after the procedure.

Surrogate endpoints were the number of TCD-detected cerebral micro emboli during the various stages of the procedure.

***Statistics***

TCD data are presented with mean and Standard Deviation of mean (SD). For the analysis of this type of data the Mann-Whitney U test was used. For binomial data the $\chi^2$-test was used. To test interdependence of variables the Mantel-Haentzel test was used for binomial data and univariate analysis for numeric variables. In all cases $p < .05$ was regarded as statistically significant.

## Results

***Clinical results***

Out of 72 patients in Group1, 17 (24%) were treated with a filtering type distal CPD. In Group 2 CPD's were used in 369 of 740 patients (50%), a difference which was statistically significant ($p<.001$)

In 22 of 812 arteries in the entire cohort (2.7%) no stent was placed. Two of these cases occurred in group 1 (2.8%), both procedures did not lead to complications. Twenty procedures (2.7%) in group 2 were terminated without placement of a stent. In two of these cases a major stroke occurred during the initial angiography and the procedure was terminated. Therefore overall procedural success was achieved in 790 of 812 arteries (97.3%).

Clinical outcome is represented in Table 4. In 812 CAS procedures, seven patients (0.9%) died. Ten additional patients (1.2%) suffered a major stroke (including the two discontinued cases) and a further 21 (2.6%) suffered a minor stroke. All strokes were confirmed with either CT or MRI, or both. The combined stroke and death rate in the entire cohort therefore was 38 out of 812 (4.7%).

All fatalities and all strokes occurred in the primary CAS treatment group, giving a combined stroke and death rate in this group of 38 out of 740 cases (5.1%). No strokes and no deaths occurred among the 72 cases in the CEA after CAS group (P=.049). The Mantel-Haentzel test established that this difference was independent of CPD use.

There were five TIA's in group 1, versus 46 in group 2 (P= 0.8). One patient in group 1 suffered TMB, versus nine in group 2 (P= 0.9)

***TCD data***

In 678 of 812 cases (83%) an adequate temporal window was available for TCD monitoring, 65 of 72 (90%) in group1 and 613 of 740 (83%) in group 2. The number of isolated micro emboli was lower in Group 1 compared to Group 2 in all phases of the procedure except the phase of protection device use (See Table 5). This difference was influenced however by the use of CPD's, which was much more prevalent in Group 2. The influence of CPD's on micro embolic load is presented in Table 6. After correction for this difference, using linear regression analysis, the difference was no longer statistically significant. The TCD data with correction for CPD use are summarised in tables 7 and 8, both for isolated emboli and for embolic showers respectively.

***Subgroup analyses***

To establish any correlation between the rapidity of restenosis formation and the cerebral embolic load during CAS, an additional analysis was performed within group 1, comparing patients treated with CAS within 36 months after CEA to those treated more than 60 months after CEA. Twenty-one patients were treated within 36 months and 35 after more than 60months of the initial CEA procedure. TCD data of this comparison

are shown in tables 9 and 10. There was no statistically significant difference in TCD detected cerebral embolic load between early and late restenoses in any of the phases.

## Discussion

In this study we analysed results of CAS comparing treatment of restenosis after prior ipsilateral CEA to that of primary carotid stenosis. No strokes or deaths occurred in the post-CEA group, compared to a total of 38 strokes or deaths in the much larger group of primary CAS cases (P=.049). At first analysis the TCD-detected cerebral micro-embolic load was significantly lower in post-CEA restenoses, compared to primary cases. Multivariate regression analysis however showed that this difference was caused by a higher rate of CPD use in primary cases, compared to restenosis cases. CPD's, designed to protect the brain from clinically significant *macro*-emboli have previously paradoxically been shown to be associated with an increase in TCD detected cerebral *micro*-embolic load during CAS[23,24].

The low event rate establishes that CAS is a safe procedure for restenosis after prior CEA. In a sub group analysis we tried to ascertain whether the embolic load is affected by the rapidity of restenosis occurrence. No statistically significant differences were found between patients treated for early versus late restenosis.

Endarterectomy for restenosis after prior CEA is generally considered to be more challenging than primary CEA[11]. In 1989 the American Heart Association (AHA) issued guidelines for CEA[25]. These guidelines allow a <3% perioperative risk of complications during CEA for asymptomatic stenosis, <5% for patients with recent ipsilateral TIA's, <7% for recent ipsilateral stroke and up to 10% periprocedural risk of complications for patients with recurrent stenosis after CEA. In several revisions of these guidelines, we have not been able to find a revocation of the last figure and we therefore assume that the maximum of 10% complications during CEA for restenosis is still prevalent according to the AHA. Clearly in view of the results in this series as well as previous research by other authors, a revision is indicated. In our opinion CAS in experienced hands should be considered the primary treatment option for restenosis after prior CEA.

Earlier series of CAS after CEA[13-16,26] have also shown a low periprocedural event rate, comparable to our results. Only three previous studies [27-29] have specifically compared CAS for restenosis after CEA to CAS for primary stenosis. None of these have used TCD to establish periprocedural microembolic load. Neither did any study find a

significant difference in outcome between groups for periprocedural stroke and death. Cuadra et al.[28] conclude that CAS for restenosis should not be considered to be a low-risk procedure, useful for training purposes. Although we did find a difference, favourable for restenotic lesions, we agree that CAS should never be considered to be an easy procedure, but should always be performed by a highly experienced team. Our study is the first to compare TCD results in restenotic versus primary lesions and the fact that no difference in microembolic load was established, underscores the fact that even in restenotic lesions a significant embolic burden to the brain is present.

Many authors suggest an association between the time of onset of restenosis formation and the likelihood of cerebral sequelae, suggesting that early restenoses are less embologenic, compared to late restenoses [17,30,31], however only one author actually reports a difference[11].

The cut-off point for early versus late restenosis after prior ipsilateral CEA varies between reports from two[17,18,32,33] to three[32,34,35] years. To avoid any possible overlap in mechanism of restenosis formation, we compared cases with an interval between CEA and CAS of less than 3 years, presumably MIH, to cases with an interval of more than 5 years, presumably renewed atherosclerotic lesions. No statistically significant difference in cerebral embolic load was found. This appears to imply that the risk of cerebral embolisation during CAS for post CEA restenosis is independent from the time interval.

Limitations of this study include 1) the design, which, by nature, is non-randomised, 2) the relatively limited number of patients in the restenosis group and particularly in the sub groups, 3) the use of TCD, with its inherent limitations, as surrogate end-point and 4) the fact that clinical outcome is presented for the first week only. 1) Consequence of the non-randomised design was for instance that the primary stenting group contained significantly more CPD cases, than the redo group. Univariate analysis and Mantel-Haentzel testing were used to correct for this difference in baseline data and the difference in clinical outcome proved to be independent from CPD use. 2) The relatively small sample size has its limitations: we reported non-significant differences between the early and late restenosis groups and we acknowledge that such may be due to the sample size. Increasing the sample size lowers the probability of a type II error and of the magnitude of the difference detectable. 3) TCD has a number of limitations in monitoring cerebrovascular interventions, including the fact that it cannot distinguish the size of micro-emboli. CPD's have pores of up to 100 micrometers, to allow passage of blood, whilst capturing potentially significant larger particles. This may be one of the

contributing factors to the paradoxical increase in micro embolic load in CPD protected cases. 4) A further limitation of this study, when compared to other studies, is that most authors report all cerebral events in the first 30 days as the peri-procedural event rate. Many patients in our series had their CAS performed in the work-up before major cardio-thoracic surgery, scheduled more than one week, but within one month after the CAS procedure. The data of the second procedure might then have influenced the peri-procedural data on the CAS procedure. Accordingly, in this study cerebral complications are represented for the first week only. The vast majority of cerebral sequelae after CAS occur during, or in the first few hours after the procedure, so we feel this did not significantly influence our results.

In conclusion, this study indicates that CAS for restenosis after CEA can be performed safely, with a complication rate and cerebral embolic load as least as good as primary CAS. The time interval between CEA and the occurrence of the restenosis does not appear to influence these results. We propose that CAS in experienced hands is an appropriate treatment for post CEA restenosis.

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**Table 1**. Patient characteristics.

| | **Group 1** (n=72) | **Group 2** (n=740) | **Total** (n=812) | **P-value** Group 1 vs. 2 |
|---|---|---|---|---|
| Male Gender (%) | 44 (61%) | 525 (71%) | 569 (70%) | NS |
| Median Age (IQR) | 70 (65-75) | 71 (66-76) | 71 (66-76) | NS |
| Recent ipsilateral symptoms (%) | 14 (19%) | 147 (20%) | 161 (20%) | NS |
| Side of stenting (Left/Right) | 38/34 | 391/349 | 429/383 | NS |
| Protection Device use Yes/No (Yes%) | 17/55 (24%) | 369/371 (50%) | 386/426 (48%) | <.0001* |

IQR= Inter Quartile Range. Recent ipsilateral symptoms: Transient ischemic attack, transient monocular blindness or minor stroke < 4 months prior to procedure. NS= Non Significant.
* Statistically significant.

**Table 2**. Types and numbers of stents used.

| **Stent type** | **Manufacturer** | **N (%)** |
|---|---|---|
| Carotid Wallstent | Boston Scientific, Natick, MA | 355 (54.1) |
| Acculink | Guidant, Indianapolis, IN | 210 (25.9) |
| Precise | Cordis J&J, Miami Lakes, FL | 103 (12.7) |
| Easy Wallstent | Boston Scientific, Natick, MA | 84 (10.3) |
| Nex | Boston Scientific, Natick, MA | 15 (1.8) |
| Carotid SE | Medtronic, Minneapolis, MN | 13 (1.6) |
| Peripheral Wallstent | Boston Scientific, Natick, MA | 4 (0.5) |
| Protegé | EV3, Plymouth, MN | 3 (0.4) |
| Sinus Carotid | Optimed, Ettlingen, Germany | 2 (0.2) |
| Bridge | Medtronic, Minneapolis, MN | 1 (0.1) |
| Not stented | | 22 (2.7) |
| **Total** | | 812 (100) |

**Table 3**. Types and numbers of protection devices used.

| Type | Manufacturer | N (%) |
|---|---|---|
| Epifilter EZ | Boston Scientific, Natick, MA | 181 (22.3) |
| Epifilter | Boston Scientific, Natick ,MA | 98 (12.1) |
| Spider filter | eV3, Plymouth, MN | 28 (3.4) |
| Angioguard XP | Cordis J&J, Miami Lakes, FL | 18 (2.2) |
| Angioguard | Cordis J&J, Miami Lakes, FL | 14 (1.7) |
| Accunet RX | Guidant, Indianapolis, IN | 12 (1.5) |
| Trap filter | eV3, Plymouth, MN | 4 (0.5) |
| Emboshield | Abbott, Santa Rosa, CA, | 4 (0.5) |
| Percusurge | Medtronic, Minneapolis, MN | 3 (0.4) |
| Neuroshield | Abbott, Santa Rosa, CA | 1 (0.1) |
| Interceptor | Medtronic, Minneapolis, MN | 1 (0.1) |
| Failed protection | | 5 (0.6) |
| No protection | | 421 (51.8) |
| Not stented | | 22 (2.7) |
| **Total** | | 812 |

**Table 4**. Number of permanent cerebral deficits during or within one week of CAS. Group 1 CAS for restenosis after CEA. Group 2 CAS for primary carotid stenosis. TIA= Transient Ischemic Attack, TMB= Transient Monocular Blindness. * Statistically significant.

| | **Group1** n=72 | **Group 2** n=740 | **P-value** |
|---|---|---|---|
| TIA | 5 | 46 | 0.81 |
| TMB | 1 | 9 | 0.90 |
| Minor Stroke | 0 | 20 | 0.15 |
| Major Stroke | 0 | 10 | 0.28 |
| Death | 0 | 8 | 0.38 |
| Any stroke/death | 0 | 38 | 0.049* |

**Table 5**. Number of isolated emboli and embolic showers during the various stages of the procedure.

| | Group1 | | | | Group 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | With CPD | | Without CPD | | With CPD | | Without CPD | |
| | Isolated emboli | Embolic showers | Isolated emboli | Embolic showers | Isolated emboli | Embolic showers | Isolated emboli | Embolic showers |
| Wiring | 43.4 [24.0] n=16 | 3.0 [4.6] n=16 | 35.0 [33.8] n=47 | 1.4 [4.5] n=47 | 53.6 [46.1] n=280 | 2.3 [6.7] n=280 | 45.7 [53.8] n=310 | 2.0 [6.0] n=310 |
| Predilation | 17.4 [14.8] n=12 | 4.1 [6.3] n=12 | 13.6 [20.5] n=28 | 1.2 [2.5] n=28 | 25.0 [20.5] n=251 | 4.2 [6.4] n=251 | 18.7 [22.7] n=272 | 2.5 [5.1] n=272 |
| Stent placement | 78.4 [36.3] n=16 | 30.8 [28.4] n=16 | 51.8 [26.7] n=47 | 18.4 [19.1] n=47 | 77.3 [34.8] n=280 | 39.4 [25.6] n=280 | 53.8 [38.7] n=310 | 15.9 [18.7] n=310 |
| Post dilation | 25.4 [14.3] n=16 | 10.4 [27.3] n=16 | 18.6 [17.1] n=45 | 3.5 [8.6] n=45 | 33.9 [43.6] n=280 | 6.8 [9.5] n=280 | 21.0 [22.5] n=293 | 3.4 [6.0] n=293 |
| CPD use | 44.2 [31.2] n=16 | 5.8 [7.1] n=16 | NA | NA | 37.9 [36.9] n=280 | 6.3 [9.0] n=280 | NA | NA |
| **Total** | 203.9 [68.8] n=16 | 51.8 [55.3] n=16 | 111.3 [51.8] n=47 | 24.4 [24.5] n=47 | 216.1 [95.1] n=280 | 58.8 [36.6] n=280 | 135.5 [93.2] n=310 | 23.2 [23.0] n=310 |

Mean and [Standard Deviation of Mean]. Group 1 CAS for restenosis after CEA. Group 2 CAS for primary carotid stenosis. CPD=Cerebral Protection Device

**Table 6**. Mean [Standard deviation] numbers of isolated micro-emboli and embolic showers during various phases of the procedure, comparing patients treated with and without filtering Cerebral Protection Devices (CPD).

| | **Isolated emboli** | | | **Micro embolic showers** | | |
|---|---|---|---|---|---|---|
| | CPD | No CPD | P | CPD | No CPD | P |
| Wiring | 53.2 [45.1] n=295 | 44.3 [51.7] n=357 | <0.0001* | 2.4 [6.6] n=295 | 1.9 [5.8] n=357 | 0.01* |
| Predilation | 24.7 [20.2] n=262 | 18.2 [22.5] n=300 | <0.0001* | 4.2 [6.4] n=262 | 2.4 [5.0] n=300 | <0.0001* |
| Stent placement | 77.5 [34.8] n=295 | 53.5 [37.3] n=357 | <0.0001* | 38.9 [25.8] n=295 | 16.2 [18.7] n=357 | <0.0001* |
| Postdilation | 33.6 [42.5] n=295 | 20.7 [21.8] n=338 | <0.0001* | 7.0 [11.2] n=295 | 3.4 [6.4] n=338 | <0.0001* |
| CPD use | 38.3 [36.6] n=295 | NA | | 6.3 [8.9] n=295 | NA | |
| Total | 222.5 [113.8] n=295 | 132.3 [89.1] n=357 | <0.0001* | 58.4 [37.7] n=295 | 23.3 [23.1] n=357 | <0.0001* |

NA=Not Applicable. *Statistically significant

**Table 7**. Mean and [Standard Deviation of Mean] of isolated microemboli stratified to procedural stage. Group 1 CAS for restenosis after CEA. Group 2 CAS for primary carotid stenosis. CPD=Cerebral Protection Device. Left side of table denotes gross numbers of micro emboli. The right side shows the numbers after correction for protection device use, using multivariate regression analysis.

| | Group1 | Group 2 | P-value | Group1 | Group 2 | P-value |
|---|---|---|---|---|---|---|
| Wiring | 37.0 [31.1] n=65 | 50.5 [52.6] n=599 | 0.017* | 39.3 [6.2] n=65 | 49.8 [2.0] n=599 | 0.11 |
| Predilation | 14.8 [18.7] n=40 | 21.7 [21.8] n=523 | <0.001* | 16.1 [3.4] n=40 | 21.9 [0.9] n=523 | 0.10 |
| Stent placement | 58.6 [31.1] n=64 | 64.7 [38.8] n=592 | 0.119 | 64.3 [4.6] n=64 | 65.8 [1.5] n=592 | 0.77 |
| Postdilation | 20.4 [16.5] n=61 | 27.2 [34.9] n=575 | 0.085 | 23.5 [4.3] n=61 | 27.6 [1.4] n=575 | 0.36 |
| Protection device | 44.2 [30.2] n=16 | 37.5 [36.9] n=282 | 0.218 | 43.4 [12.4] n=16 | 37.2 [8.3] n=282 | 0.51 |
| Total | 134.8 [68.7] n=65 | 175.4 [113.8] n=599 | 0.004* | 156.6 [12.9] n=65 | 180.3 [4.2] n=599 | 0.08 |

**Table 8**. Mean and [Standard Deviation of Mean] of microembolic showers stratified to procedural stage.

| | Group1 | Group 2 | P-value | Group1 | Group 2 | P-value |
|---|---|---|---|---|---|---|
| Wiring | 1.7 [4.5] n=65 | 2.2 [6.4] n=599 | 0.66 | 3.7 [38.8] n=65 | 14.5 [12.6] n=599 | 0.66 |
| Predilation | 2.0 [4.1] n=40 | 3.3 [5.8] n=523 | 0.13 | 2.4 [0.9] n=40 | 3.4 [0.248] n=523 | 0.32 |
| Stent placement | 21.5 [22.0] n=64 | 26.9 [25.2] n=593 | 0.25 | 26.9 [2.9] n=63 | 27.8 [0.9] n=593 | 0.77 |
| Postdilation | 5.3 [15.7] n=61 | 5.0 [8.1] n=575 | 0.22 | 6.2 [1.2] n=61 | 5.1 [0.4] n=575 | 0.37 |
| Protection device | 5.8 [6.9] n=16 | 6.2 [9.0] n=282 | 0.82 | 9.2 [3.0] n=16 | 9.6 [2.0] n=282 | 0.87 |
| Total | 30.4 [36.0] n=65 | 39.6 [35.1] n=599 | 0.028* | 39.7 [3.9] n=65 | 41.3 [1.3] n=599 | 0.71 |

Group 1 CAS for restenosis after CEA. Group 2 CAS for primary carotid stenosis. CPD=Cerebral Protection Device. Left side of table denotes gross numbers of embolic showers. The right side shows the numbers after correction for protection device use, using multivariate regression analysis.

**Table 9**. Isolated micro emboli in the various phases of the procedure in post CEA cases.

| | Early restenoses | Late restenoses | P-Value |
|---|---|---|---|
| Wiring | 29.5 [12.0] n=20 | 47.0 [38.9] n=30 | 0.13 |
| Predilation | 11.6 [13.2] n=10 | 19.6 [23.0] n=21 | 0.36 |
| Stent placement | 63.0 [30.8] n=20 | 59.6 [25.2] n=30 | 0.59 |
| Postdilation | 26.2 [21.3] n=20 | 17.5 [12.2] n=30 | 0.31 |
| CPD use | 40.0 [16.5] n=4 | 43.8 [34.4] n=11 | 0.65 |
| Total | 125.0 [64.3] n=20 | 152.6 [67.1] n=30 | 0.26 |

Mean and [Standard Deviation]. Early restenosis: interval CEA to CAS <36 months, late restenosis: interval > 60 months. * Statistically significant.

**Table 10**. Showers of micro emboli in the various phases of the procedure in post CEA cases.

| | Early restenoses | Late restenoses | P-Value |
|---|---|---|---|
| Wiring | 0.7 [1.4]<br>n=20 | 3.2 [6.2]<br>n=30 | 0.28 |
| Predilation | 2.0 [2.8]<br>n=10 | 2.6 [5.2]<br>n=21 | 0.88 |
| Stent placement | 23.0 [23.1]<br>n=20 | 24.8 [23.5]<br>n=30 | 0.55 |
| Postdilation | 5.1[11.7]<br>n=20 | 6.6 [20.0]<br>n=30 | 0.73 |
| CPD use | 4.8 [3.3]<br>n=4 | 6.6 [7.9]<br>n=11 | 0.90 |
| Total | 29.1 [32.7]<br>n=20 | 39.0 [42.2]<br>n=30 | 0.22 |

Mean and [Standard Deviation]. Early restenosis: interval CEA to CAS <36 months, late restenosis: interval > 60 months. * Statistically significant.

# PART IV
# CHAPTER 4B

# Carotid angioplasty and stenting for post-endarterectomy stenosis: long-term follow-up

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## Abstract

**Background and purpose** Carotid angioplasty and stenting (CAS) for recurrent stenosis after carotid endarterectomy (CEA) has been proposed as an alternative to redo-CEA. Although early results are encouraging the extended durability remains unknown. We present the long-term surveillance results of CAS for post-CEA restenosis.

**Methods** Between 1998 and 2004, 57 CAS procedures were performed in 55 patients (36 men, mean age 70). Mean interval between CEA and CAS was 83 months (range 6 to 245). Nine patients (16%) were symptomatic.

**Results** CAS was performed successfully in all patients. No deaths or strokes occurred. Two patients suffered a periprocedural TIA. During a mean follow-up of 36 months (range 12 to 72) two patients exhibited ipsilateral cerebral symptoms (1 TIA, 1 minor stroke). In 11 patients (19%) in-stent restenosis (≥ 50%) was detected at 3 (3), 12 (3), 24 (2), 36 (1), 48 (1) and 60 (1) months post-CAS respectively. The cumulative rates of in-stent restenosis free survival at 1,2,3 and 4 years were 93, 85, 82 and 76% respectively. Redo procedures were performed in six patients: repeat angioplasty (n=3) and re-CEA with stent-removal (n=3). The cumulative rates of freedom from re-intervention at 1,2,3, and 4 years were 96, 94, 90, and 84% respectively.

**Conclusion** Carotid angioplasty and stenting for recurrent stenosis after CEA can be performed with a low incidence of periprocedural complications with durable protection for stroke. However, the rate of in-stent recurrent stenosis is high and does not only occur early after CAS but is an ongoing process.

## Introduction

Restenosis of the carotid artery after previous ipsilateral carotid endarterectomy (CEA) has been detected with increasing frequency because of the use of non-invasive testing[1]. Symptomatic recurrent carotid stenosis has been reported to range from 0.6% to 3.6%, and asymptomatic recurrent stenosis, based on these noninvasive studies, from 8.8% to up to 19%[1-3]. Most authors agree that symptomatic restenosis warrants intervention but the issue of treatment of asymptomatic restenoses remains controversial[4]. Justification of renewed surgical exploration requires that the intervention has a low periprocedural risk and provides long-term freedom from stroke. Although reoperative CEA is an accepted treatment for recurrent stenosis, morbidity rates relating to surgery for restenosis of the internal carotid artery are higher than those of endarterectomy for primary lesions[5-7]. This has led some authors to advocate the use of endovascular techniques in the management of this condition [5,8]. In the treatment of recurrent ipsilateral carotid artery stenosis after CEA, case reports and small series dedicated to angioplasty (PTA) alone[9-13] as well as angioplasty with stenting (CAS)[5,8,14-23] have accumulated since 1993 [Table 1]. Evaluation of outcome after angioplasty alone versus CAS demonstrated a higher recurrence rate in the group treated with angioplasty alone[10]. As in treatment of primary stenosis[24] it is therefore currently recommended that standard stenting is the endovascular technique of choice for carotid restenosis.

The reports of CAS for post-CEA restenosis published so far [Table 1] are mostly single center series that have shown good feasibility and encouraging early results. Durability was not an end point in the majority of these studies resulting in limited follow-up duration. The growth of indications for CAS however will require a basis not only in feasibility but also in long-term outcomes. The current study was undertaken to prospectively determine the safety and durability with long-term surveillance of CAS for ipsilateral restenosis following CEA.

## Materials and Methods

From our single center Carotid Artery Registry (St.Antonius Hospital, Nieuwegein, The Netherlands) all patients with a history of CAS for restenosis after previous ipsilateral CEA were selected. Inclusion criteria were: 1) complete peri-operative data on primary CEA and peri-procedural data of CAS, 2) complete clinical and duplex ultrasound (US) follow-up between primary CEA and CAS, 3) clinical and duplex US

follow-up of at least 1 year after CAS. Patients with primary surgery in another vascular center were included pending inclusion criteria 1 and 2. Bilateral procedures were counted separately and evaluated as two entries.

Between 1998 and August 2004, 55 patients received 57 CAS procedures. Five patients with primary CEA in another vascular center were included. Two women had a staged bilateral procedure. There were 36 men and 19 women with a mean age of 70 years at time of CAS. Mean elapsed time for restenosis (> 50%) to occur since endarterectomy was 74 months (6 to 245). In 9 patients restenosis was detected within 24 months. Mean elapsed time between primary endarterectomy and repeat intervention (CAS) was 83 months (6 to 247). Nine patients (16%) had a symptomatic recurrent stenosis (non-hemispheric 2, TIA 6 [20, 42, 44, 48, 96, and 156 months post CEA respectively] or minor stroke 1 [10 years post CEA]). The remaining 48 arteries in 46 patients (84%) showed an asymptomatic high grade recurrent carotid stenosis after CEA on repeated duplex US examination.

Symptomatic patients were treated if the degree of stenosis at the carotid bifurcation exceeded 70%, according to the NASCET criteria. For asymptomatic patients the cut-off point for treatment was 80%. The degree of stenosis was assessed by duplex US scanning and intra-arterial digital subtraction angiography (iaDSA) prior to endovascular treatment. In the present series no discrepancies were noted between estimated duplex stenosis grade and angiographic measurements. The decision to treat asymptomatic lesions was based on clinician judgment. Treatment was offered to symptomatic patients and to asymptomatic patients with three or four diseased (> 50% stenosis) extracranial cerebropetal vessels. All patients had a high-grade internal carotid artery (ICA) stenosis at time of CAS (Table 2). The decision to offer CAS over standard operative therapy was based on a higher than usual risk of operative complications or high anesthetic risk. The procedure was offered only after consensus was established about the appropriateness of therapy in a joint vascular surgery, neurology, clinical neurophysiology, and interventional radiology forum. The choice of stent type, and the decision whether or not to use a Cerebral Protection Device (CPD) were at the discretion of the treating interventional radiologist or cardiologist. Various types of stents used were: Carotid Wall (Boston Scientific, Natick MA, USA) 30, Easy Wall (Boston Scientific) 4, Peripheral Wall (Boston Scientific) 1, Carotid SE (Medtronic, Minneapolis, Minn, USA) 2, Precise Cordis (Cordis J&J, Miami Lakes FL, USA) 17, Acculink (Guidant, Indianapolis In, USA) 3. CPDs were used in 12 procedures [Angioguard (Cordis J&J) 8, Neuroshield (Mednova Galway, Ireland)

1, Epifilter EZ (Boston Scientific) 1, Accunet (Guidant) 2]. In 20 arteries the carotid bifurcation and origin of the external carotid artery was overstented. Twelve of 55 patients had a contralateral occlusion at time of CAS.

The technical details of CAS in our institution have been published elsewhere in detail[25]. Technical success of CAS procedure was defined as residual-stenosis < 30% on post-procedural angiography. Heparin (5-10.000 IU) and atropine sulphate (0.5 – 1.0 mg) was given during the procedure. Aspirin (80-100 mg/day) was given prior to CAS and continued indefinitely. Clopidogrel (75 mg/day) was started 72h before the procedure and continued for 4 weeks. Patients re-entered the carotid surveillance program, with both duplex US and clinical evaluation by a vascular surgeon and an independent neurologist at 3 and 12 months and yearly thereafter. For duplex US classification of the degree of in-stent restenosis, we used the same velocity criteria in the post-stenting as for the post-endarterectomy situation. Specific endpoints analyzed were periprocedural death and/or stroke, the occurrence of late stroke and/or death, and in-stent restenosis (> 50%). Statistical analysis was performed using statistical software package SPSS (SPSS, Inc., Chicago, Il). Actuarial survival analysis was performed by using Kaplan-Meier life tables.

## Results

### *Procedural results*

All 57 procedures were technically successful (100%). There were no peri-operative deaths or strokes as a consequence of undergoing CAS. Two patients (3.4%) had periprocedural neurologic complaints. One patient had a transient ischemic attack (TIA), manifesting as contralateral limb weakness during the procedure, which completely resolved within minutes. During this procedure an Angioguard (Cordis J&J) CPD was used. Another patient had a TIA within 48 hours following stenting. In this patient no CPD was used. Both patients completely recovered before discharge. Perioperative myocardial infarction or cranial nerve injury did not occur in these 57 procedures. Therefore, the total 30 days stroke/mortality was 0%. One patient was found to have a groin hematoma which was treated conservatively. In one patient an aneurysma spurium of the femoral artery was discovered during follow-up which resolved spontaneously. The length of stay for an uncomplicated CAS procedure was 24 hours. Only five patients had a longer stay (range 48 – 96 hours).

***Late outcome***

The mean clinical and duplex follow-up after CAS was 36 months (12 to 72). During follow-up two patients had neurological symptoms ipsilateral of the treated ICA: one TIA at 30 months, and one minor stroke at 60 months after CAS. Asymptomatic ICA occlusion was demonstrated in 1 patient 48 months after CAS. All other ICA's remained patent. During follow-up 3 patients died (all of cardiac causes). In 11 patients (19%) in-stent restenosis (≥ 50%) was detected. In-stent restenosis was detected at 3 (3), 12 (3), 24 (2), 36 (1), 48 (1), and 60 months (1) post CAS. The cumulative rates of in-stent restenosis free survival at 1, 2, 3, and 4 years were 93, 85, 82, and 76% respectively (Figure 1). There was no difference in restenosis free survival between different types of stents.

During follow-up 6 patients with high-grade in-stent restenosis (≥ 70% for symptomatic, and ≥ 80% for asymptomatic lesions) underwent a further re-intervention. The patient that suffered one episode of TIA 30 months after the endovascular procedure underwent successful redo-CEA with removal of the stent. Two additional patients (both asymptomatic) underwent redo-CEA with removal of the stent at 6 and 33 months after CAS. Three patients at 12, 42 and 54 months following of the original intervention, all asymptomatic, required repeat angioplasty for restenosis, one of whom needed a third angioplasty. All six patients remained free from cerebral symptoms during further follow-up. The remaining 5 of 11 patients with restenosis were followed up conservatively because their (asymptomatic) stenosis was not severe enough, or because of comorbidity (2 patients; bronchogenic- and pancreatic-carcinoma respectively). The cumulative rates of freedom from re-intervention at 1,2,3, and 4 years were 96, 94, 90, and 84% respectively (Figure 2).

## Discussion

In our present series of CAS after prior ipsilateral CEA we successfully treated 57 arteries in 55 patients with no major neurological complications over a mean follow-up of 36 months. Despite, two patients suffered a periprocedural TIA, and during follow-up one TIA and 1 minor stroke were noted. There was only 1 groin complication (1.7%) which compares favorably with the 4 to 10% risk of wound hematoma or infection and cranial nerve injury associated with repeated endarterectomy[26]. In evaluating the results of CAS it is important to consider that these procedures are often performed in high-risk patients with severe coexistent disease. Despite this, the non-neurological morbidity rate

in our study was very low, and no perioperative cardiac events were encountered.

Previously published series of CAS for recurrent stenosis after CEA seemed to support the short-term safety and feasibility of the procedure, with a low cerebral complication rate (Table 1). In a study by Hobson et al., CAS was successful in all 17 cases and produced no periprocedural neurological deficits or deaths[5]. Leger et al. found 1 periprocedural TIA and no deaths in 8 patients[12]. Similar favorable results were reported by Yadav with only one minor stroke in 25 procedures in 22 mainly symptomatic patients; a complication rate of 4% per treated artery[14]. On the other hand, in a comparative study by Aburahma et al., a higher 30-day stroke rate for CAS than for redo surgery (16% vs. 3.4%) was reported[18]. The apparent discrepancies among series can in part be explained by the differences in access (carotid artery puncture vs. femoral access)[16], primarily stenting versus stent placement on demand (i.e. occlusion or dissection)[11], and differences in type of stenosis (primarily myointimal hyperplasia (MIH) lesions versus mixed pathology)[5,18]. They also might reflect a difference in operator experience, or be the result of small study size.

Despite the satisfactory early results, concern remains regarding long-term outcome of CAS after ipsilateral CEA. Documentation of long-term outcome is relatively scarce because durability of the repair has not been the specific outcome being investigated [Table 1]. Rockman found a 13% restenosis rate at a mean follow-up of 14 months[22]. In a series of 25 procedures Aburahma found 24% restenosis rate at 20 months[18]. Most studies had a relatively short follow-up and reported absolute recurrence rates, counting each procedure equally, regardless of duration of follow-up. The main issue however in comparing repeated surgery with CAS for recurrent stenosis has now become durability[17]. Our study shows a cumulative rate of in-stent restenosis free survival at 4 years of 76%. These data show the importance of life table assessment, and demonstrate that in-stent restenosis is an ongoing process that requires long-term follow-up.

Most patients with in-stent restenosis of the carotid artery remain asymptomatic, although occasionally ipsilateral cerebral symptoms occur[27]. The CAVATAS trial showed that at 1 year after endovascular treatment the proportion of patients experiencing recurrent ischemic symptoms is significantly increased with ipsilateral $\geq$ 70% restenosis[24]. However, most of these recurrent symptoms were TIA's; no disabling or fatal stroke occurred during follow-up. In the present study major complications during follow-up were avoided but there was one minor stroke. This complication occurred 60 months after CAS and confirms the need for long-term follow-up.

We found no difference in restenosis free survival observed between different types of stents. This must be interpreted with caution, because a larger cohort may be required to unmask minor differences in long-term durability of various stent types. The introduction of drug-eluting stents has already revolutionized the management of coronary artery disease by significantly reducing the incidence of restenosis[28]. The application of these stents to the carotid artery territory will likely improve long-term outcomes. Plaque debris has been demonstrated in the CPD of over 50% of patients undergoing carotid angioplasty with stenting for primary stenosis, lending weight to the argument for routine cerebral protection[29]. On the other hand, in our own experience CAS yielded more microemboli in patients treated with CPDs than in unprotected procedures[30]. Clearly, during the time frame of the present study no consensus existed on the use of these devices. Therefore, in this study CPDs were used at discretion of the treating interventional radiologist.

The characteristics and the morbidity of recurrent lesions may vary depending on the histology of the lesion. Usually, the literature differentiates between early restenosis, attributed to MIH, occurring within 6 to 24 months after arterial intervention, and delayed restenosis that develops 2 years after endarterectomy, which is presumed to be caused by progression of atherosclerosis[18,31]. Although we cannot be certain of the histological substrate of the restenoses of our patients, 9 of 57 restenotic arteries (16%) underwent CAS within 24 months after CEA, while the other 48 underwent CAS more than 24 months after surgery. MIH lesions tend to be smooth lesions with little embolic potential[18,31]. When symptoms occur, they are more likely to be flow-related hemodynamic TIA's[32]. In general, recurrent atherosclerotic disease tends to produce more delicate, friable lesions that are more likely to show intraplaque hemorrhage, ulcerate, or form emboli[31,33].

Most published series on the use of CAS for treatment of restenosis after CEA included both symptomatic patients and patients with asymptomatic but hemodynamically significant stenoses, making our series comparable from this point of view[15,21,22]. In our hospital, post-endarterectomy patients were entered into a duplex surveillance program, which undoubtedly detected a greater proportion of asymptomatic high-grade stenoses. Criteria for quantifying in-stent recurrent stenosis remain a challenge and duplex ultrasound scan criteria for evaluation of in-stent restenosis are in evolution[34,35]. In terms of classification of the degree of stenosis with ultrasound, we used the same velocity criteria in the post-stenting as for the post-endarterectomy situation[25].

In our institution no standard policy or protocol dictates treatment strategy for

recurrent carotid artery stenosis after endarterectomy. Our criteria are conform the criteria used to justify treatment of primary lesions. At this time, given the results of our and other groups, it is difficult to support the use of CAS as a routine alternative to open endarterectomy. Arguments in favor of endovascular or operative management should be based on the clinician's experience. In general, the decision to operate on an asymptomatic patient with a recurrent carotid stenosis should be individualized and based on several factors including the degree and rate of progression of the stenosis, the condition of the remainder of the cerebral circulation, and the age, gender, and overall medical condition of the patient. A randomized clinical trial ultimately will be necessary to determine the role of CAS, as compared with operative management of post-CEA restenosis.

## Conclusion

The results of this study suggest that carotid angioplasty and stenting for recurrent stenosis after CEA can be performed with a low incidence of periprocedural complications with durable protection from stroke. However, the rate of in-stent recurrent stenosis is high and does not only occur early after CAS but is an ongoing process according to life-table analysis. At this stage, the exact role of endovascular intervention in the management of carotid artery restenosis remains open for discussion.

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# Part IV
# Chapter 4C

# Outcome of Carotid Artery Stenting for Radiation-Induced Stenosis

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## Abstract

**Purpose**: Patients who have been irradiated at the neck have an increased risk of symptomatic stenosis of the carotid artery during follow-up. Carotid Angioplasty and Stenting (CAS) can be a preferable alternative treatment to carotid endarterectomy which is associated with increased operative risks in these patients.

**Methods and Materials**: We performed a prospective cohort study of 24 previously irradiated patients who underwent CAS for symptomatic carotid stenosis. We assessed periprocedural and non-procedural events composed of TIA, non-disabling stroke, disabling stoke and death. Patency rates were evaluated on duplex ultrasound scans. Restenosis was defined as a stenosis of > 50% at the stent location.

**Results**: Periprocedural TIA-rate was 8% and periprocedural stroke (non-disabling) occurred in 4% of patients. After a mean follow-up of 3.3 years (range 0.3-11.0 years) only one ipsilateral incident event (TIA) had occurred (4%). In 12% of patients a contralateral incident event was present: one TIA (4 %) and 2 strokes (12%, 2 disabling strokes). Restenosis was apparent in 17%, 33% and 42% at respectively 3, 12 and 24 months, although none of the patients with restenosed vessels became symptomatic. The length of the irradiation to CAS interval proved the only significant risk factor for restenosis.

**Conclusions**: The results of CAS for radiation induced carotid stenosis are favourable in terms of recurrence of cerebrovascular events at the CAS-side.

**Keywords**: carotid angioplasty and stenting, stroke, radiotherapy, head and neck cancer, carotid artery stenosis

## Introduction

External neck irradiation is a risk factor for transient ischemic attack (TIA) and stroke, probably mediated by the development of carotid artery stenosis.[1-4] The occurrence of clinical symptoms may be long (range 1 to > 20 years) after radiotherapy (RT).[5] With the therapeutic advancement of primary head and neck malignancies and the attendant increased long-term survival after RT, these patients are at high risk for the development of RT induced carotid artery stenosis; hence the need for evaluating its treatment.

Although RT-induced carotid stenosis can surgically be treated by carotid endarterectomy (CEA)[6], this technique is challenging due to diminished healing capacities, scar tissue due to former radical neck dissection and /or the irradiation itself, compared with stenosis based on atherosclerosis. In addition, the surgical access is considered more difficult because of a often, more proximally located stenosis in the common carotid artery.[7] Therefore, the American Stroke Association guidelines state that Carotid Angioplasty and Stenting (CAS) can be considered for patients under specific conditions such as radiation induced stenosis.[8] Although theoretically CAS could possibly overcome some of these limitations that exist for CEA, reliable empirical data on incident stroke and patency rates of CAS after RT induced carotid artery stenosis are sparse.[9,10] We therefore performed a prospective study to investigate incident cerebrovascular events and the occurrence of restenosis among 24 patients who were treated with CAS after RT.

## Methods and Materials

### *Patients and possible risk factors*

We assembled a cohort of patients who underwent CAS for symptomatic RT-induced carotid stenosis between the years 1998 and 2006 at the Neurointerventional Radiology department of two institutes (St Antonius Hospital, Nieuwegein and the University Medical Center Utrecht). Inclusion criteria were prior RT of the neck before CAS, complete periprocedural data of CAS and complete clinical follow-up.

By medical record review, we collected baseline data including age, sex, neurological symptoms prior to stenting, vascular risk factors according to clinical guidelines (hypertension (defined as either treatment for high blood pressure or a blood pressure that exceeded twice the limit of 95 mm Hg), diabetes mellitus, dyslipidemia/ statin treatment, smoking (current, former and never), cardiovascular morbidity) and previous CEA. We also took tumour type and oncological treatment regimen into account

including: RT-dose, RT–CAS interval and previous neck surgery (radical neck dissection and/or laryngectomy). Symptomatic carotid disease prior to stenting was diagnosed if the patient had experienced a TIA or stroke referable to the carotid lesion.

***Procedure***

Diagnosis of carotid stenosis was made by duplex ultrasound (DUS), in combination with either computed tomographic (CT) angiography or magnetic resonance (MR) angiography. Pre-stent stenosis of the carotid artery was further graded on digital subtraction angiography according to the NASCET criteria.[11] All patients were treated with CAS for symptomatic stenosis of their carotid artery, at either the common carotid artery (CCA), the internal carotid artery (ICA) or both, depending on the location of the stenosis. In all patients, CAS was performed in accordance with our previously described protocol.[12,13] All procedures were performed under local anaesthesia, from a groin approach. Procedures were performed by an experienced interventionalist. Technical failure was defined as residual stenosis of 30% graded on the digital subtraction angiography after the procedure.

***Follow-up***

The whole cohort was followed for the occurrence of the following primary end points; TIA and (non) disabling stroke (either ipsilateral –or contralateral of the CAS procedure) and death. TIA was classified as any neurological deficit (either ocular or cerebral) that resolved completely within 24 hours, non-disabling stroke if the modified Rankin score was $\leq 2$ (on a scale of 0-5, with higher score indicating more disability), a disabling stroke if the modified Rankin score was 3 points of more.[14] Death was categorized as death from stroke, death from vascular cause or death from other cause.

Follow-up evaluations were performed by an independent stroke neurologist. In addition DUS were performed at 48 hr, 30 days, 3 and 12 months post-CAS and thereafter annually. If patients were not followed anymore in our tertiary centres, information on outcome events was collected by the general practitioner. Peri-procedural complications were classified as events that occurred within 30 days after CAS. Non-procedural events were collected from 30 days after the procedure until the end of follow-up, i.e. the last surveillance by the neurologist or the general practitioner.

DUS was performed by an independent rater and consisted of the ipsi -and contralateral CCA (proximal and distal), ICA (proximal, middle and distal) and external carotid artery (ECA). The DUS criteria used in our vascular laboratory are based on the

Strandness criteria.[15] In terms of classification of the degree of ICA or CCA stenosis, we used the same velocity criteria in the post-stenting as for the pre-stenting situation. We measured the highest peak systolic and enddiastolic velocities in the stented artery for grading the restenosis. Restenosis was defined as a stenosis of > 50%. Contralateral stenosis was graded as 50% or more.

***Endpoints***

The primary endpoint was the occurrence of non-procedural incident cerebrovascular events (TIA, non-disabling, disabling stroke) and death during follow-up.

The secondary endpoint was the occurrence of restenosis of the stented carotid artery during follow-up. Restenosis was defined as a stenosis of > 50% at the CCA or ICA at the treated side.

***Statistics***

Statistical analyses were performed using the statistical software package SPSS 14.0 (SPSS, Inc., Chicago, Il). Actuarial survival analysis was performed by Kaplan Meier life tables in order to analyze the occurrence of incident cerebrovascular events.

Multivariate Cox proportional hazard models were used to assess the risk of the primary end points, adjusted for possible confounding factors including hypertension, diabetes mellitus, smoking, oncologic treatment (time interval between RT-CAS) and procedure related factors (previous neck operation, contralateral carotid disease).

The relationship between restenosis at specific time points and potential risk factors (hypertension, diabetes mellitus, smoking, contralateral stenosis, previous neck operation and time-interval between RT and CAS) was assessed by means of sex and age adjusted logistic regression analysis.

## Results

***Patient characteristics***

We identified 24 patients who underwent CAS for symptomatic radiation induced carotid stenosis. The demographic characteristics, tumour en RT-status are presented in table 1. The mean time elapsed between RT and CAS was 13.1 years (SD 8.1). The contralateral carotid artery was occluded in 6 patients (25%), while 8 patients (33%) had a contralateral ACI stenosis of > 50%. In 12 patients (50%) a stenosis of more than 50% was observed at the ipsilateral external carotid artery (ECA).

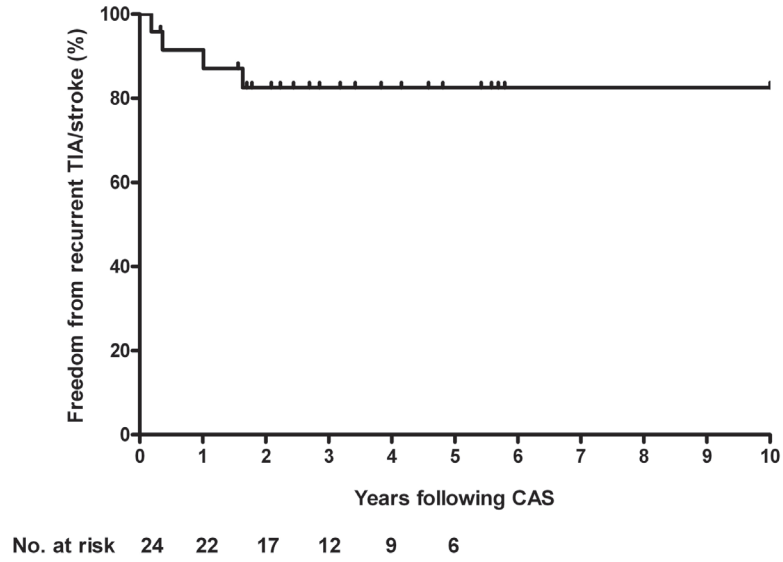


**Figure 1**. Kaplan-Meier analysis showing the cumulative freedom from cerebrovascular events (TIA and stroke) at the ispilateral and contralateral side of CAS.

***Outcomes***

Technical and perprocedural angiographical success (i.e. a residual stenosis of less than 30%) was achieved in 100 % of patients. Within 30 days, 2 patients (8%) had a TIA and one patient suffered (4%) a non-disabling stroke that resolved completely within 2 days. The 30-day-all-cause-mortality was 0%. The mean clinical follow-up time after CAS was 3.3 years (SD 2.3, range 0.3-11.0 years). Non-procedural cerebrovascular events occurred in four patients: one patient had an ipsilateral TIA (4%) and in 3 patients a contralateral event (12%) occurred (table 2). The proportion without any cerebrovascular events during follow-up is shown in figure 1. Multivariate Cox- proportional hazard analysis showed no risk factor for ipsi -and contralateral icident cerebrovascular events.

Rates and degrees of restenosis are presented in table 3. No in-stent occlusion occurred. None of the restenosed vessels were symptomatic. In only one patient a restenting procedure was performed because of a rapid occurring instent restenosis of 90-99% with good post-procedural results (free from rerestenosis after 2 years).

The length of the RT- CAS interval proved to be the most significant risk factor for

restenosis at 3 months (RR; 1.14, 95% CI 1.0-1.3), meaning that each year elapsed since RT, the risk of restenosis increases with 14%.

## Discussion

We report the long-term outcome for patients with Carotid Angioplasty and Stenting (CAS) for symptomatic carotid stenosis after RT on the neck. These patients are at increased operative risk during carotid endarterectomy (CEA) and are excluded by large randomized intervention trials. In this high risk population we found that periprocedural CAS risks appear to be comparable to CAS in non-irradiated patients.[16] Disabling stroke or death within 30 days was 0%. Overall, the non-procedural proportion of ipsilateral incident cerebrovascular events in our study was low (4%) and only transient (one patient with TIA). The actuarial risk of any incident TIA and stroke was 16% after a median follow-up of 3.3 years. At 3 years follow-up this is comparable to other high-risk surgical patients (those with coexisting conditions, such cardiac morbidity and a destructed neck anatomy). The recently completed SAPPHIRE study reported an overall stroke occurrence in 9% of patients at 3 years which is comparable to the 8% stroke occurrence in our cohort.[17] The observed incident cerebrovascular events cannot be attributed to failure of the CAS procedure, since 3 out of 4 events occurred at the non-CAS side. The occurrence of new cerebrovascular events is most likely a reflection of high incidence of bilateral carotid disease after RT rather than a result of restenosis: almost 60% of our patients had a contralateral stenosis or occlusion of the carotid artery.

Restenosis was apparent in 17%, 33% and 42% of patients at 3 months, 1 and 2 years following CAS. None of these patients became symptomatic. These results are comparable to two cohort studies of CAS after irradiation: both studies show high restenosis rates of respectively 21% and 43% after a mean follow-up of 28 months (n=16 patients) and 14.4 months (n=23 patients).[18,19] This high percentage of restenosis can be a result of overrating.[20] DUS velocity criteria, e.g. PSV, correlate with angiographic percentages of stenosis in non-stented carotids. In CAS patients, DUS velocity criteria are not yet well established. One recent cohort study proposed new criteria for grading percentage of stenosis after CAS by ultrasound after comparison with the gold standard: angiography.[21] In this study it was found that compliance and flow characteristics are much different when compared to non-stented arteries. New thresholds of velocity criteria for different degrees of intrastent stenosis were found much higher. It is conceivable that in our patient cohort, with fibrous and scarred necks, duplex application is even more

difficult than in non-irradiated patient. Also, a contralateral occlusion (present in 25% of our patients) is known to overrate the degree of ipsilateral stenosis.[22] We therefore advise to perform (CT- or MR-) angiography to confirm restenosis in case of symptomatic disease. In case of restenosis without symptoms it is warranted to carefully survey these patients by frequent DUS at intervals of 3 months to detect any progression of restenosis.

The study has limitations. First, we performed an observational study. Ideally comparison of CAS versus CEA is warranted to define the best treatment; however, such randomized trial is not feasible for this specific, relatively small cohort of patients. Second, DUS follow-up is not complete. This is due to the fact that our centres serve as tertiary referral hospitals and most patients will be followed by their referral physician.

Despite of this we consider strong elements of our study being a double-centre, cohort study with 100% response rate and complete clinical follow-up.

The final decision how to treat a patient with radiation induced carotid stenosis should be individualized and based on several factors, including e.g. former neck operation and cardiovascular risk factors. Also the time elapsed between RT and the primary cerebrovascular symptoms should be weighted, as in our study a longer time interval since RT proved to be negatively correlated with patency rates. Although we found a high rate of restenosis on DUS only 2 patients (4%) progressed to high grade (90-99%) stenosis. The long-term clinical follow-up results in our cohort are favourable i.e. no new strokes occurred at the ipsilateral stented carotid artery. Close surveillance of patency is necessary also for detection of contralateral stenosis that remains a risk factor for new cerebrovascular events.

## Acknowledgements

We thank L.J. Kappelle and C. Haaring for supplying data on CAS-patients after RT at the University Medical Centre Utrecht, the Netherlands. We are indebted to several physicians who provided follow-up data for the study.

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**Table 1**. Demographics of 24 patients undergoing CAS for symptomatic radiation induced stenosis.

| **Characteristics** | **N = 24 (%)** |
|---|---|
| Age (year, mean +/- SD) | 68 (+/-8.1) |
| Male | 18 (75) |
| Tumour type | |
| Larynxcarcinoma | 11 (46) |
| Oropharynxcarcinoma | 6 (25) |
| Lymphoma | 2 (8) |
| Other | 5 (21) |
| Radiotherapy | |
| < 40 Gy | 2 (8) |
| 40-60 Gy | 5 (21) |
| > 60 Gy | 17 (71) |
| Time elapsed between RT-CAS (years, SD) | 13.1 (+/- 8.1) |
| Previous operation | 13 (54) |
| Lymph node dissection or laryngectomy | |
| Carotid endarterectomy (ipsilateral) | 2 (8) |
| Concomitant vascular risk factors | |
| Hypertension | 13 (54) |
| Smoking (current) | 5 (21) |
| Diabetes mellitus | 3 (13) |
| Hypercholesterolemia/ Statin treatment | 11 (46) |
| Cardiovascular disease | 5 (21) |
| Qualifying symptoms | |
| TIA | 14 (59) |
| Ischemic Stroke | 10 (42) |
| Preprocedural stenosis | |
| 50-69% | 1 (4) |
| 70-89% | 8 (33) |
| 90-99% | 15 (63) |
| Lesion location of stenosis | |
| Common carotid artery | 4 (17) |
| Internal carotid artery | 18 (75) |
| Both internal and common carotid artery | 2 (8) |
| Contralateral carotid patency | |
| Stenosis (50-99%) | 8 (33) |
| Occlusion | 6 (25) |

**Table 2**. Clinical outcome of CAS for radiation induced stenosis.

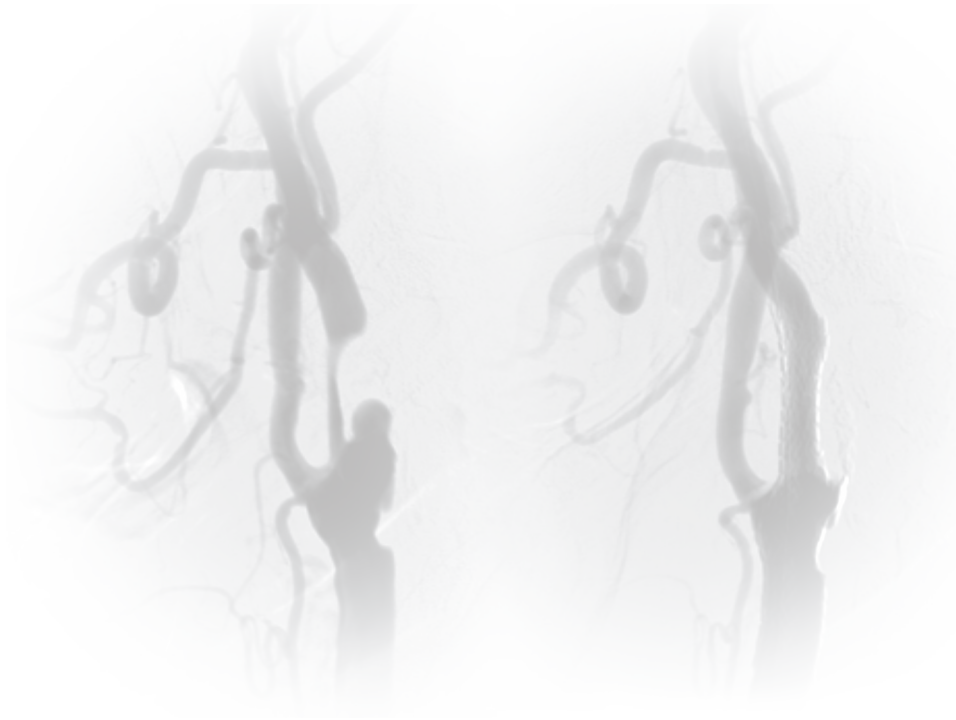
| **Clinical outcomes** | **N= 24 (%)** |
|---|---|
| Technical failure | 0 |
| Any periprocedural TIA, stroke or death | |
| TIA | 2 (8) |
| Non-disabling Stroke | 1 (4) |
| Death | 0 |
| Any non-procedural TIA & strokes (disabling and non-disabling) | 4(16%) |
| **Ipsilateral** | |
| TIA | 1 (4) |
| **Contralateral** | |
| TIA | 1 (4) |
| Disabling stroke | 2 (8) |
| Any non-procedural deaths | 7 (29) |
| Contralateral stroke* | 1 (4) |
| Other vascular death ** | 2 (8) |
| Non-vascular death † | 4 (16) |

**Table 3**. Stent patency measured by duplex ultrasound at 3 months, 1 and 2 years follow-up.

| **Stent patency** | **N (%)** |
|---|---|
| Restenosis 3 months (n= 23) | |
| 0-49% | 19 (83) |
| 50-69% | 4 (17) |
| 70-89% | 0 |
| 90-99% | 0 |
| Occlusion | 0 |
| Restenosis 1 year (n=21) | |
| 0-49% | 14 (67) |
| 50-69% | 3 (14) |
| 70-89% | 3 (14) |
| 90-99% | 1 (5) |
| Occlusion | 0 |
| Restenosis 2 year (n= 17) | |
| 0-49% | 10 (59) |
| 50-69% | 4 (24) |
| 70-89% | 1 (6) |
| 90-99% | 2 (12) |
| Occlusion | 0 |

# Part V

## General Discussion, Conclusions and Summaries



# Part V

# Chapter 5A

# Summary, General Discussion and Conclusions

Carotid Endarterectomy (CEA) was the first causative treatment for carotid stenosis, conceived to prevent stroke[1]. After more than thirty years of using CEA for carotid bifurcation stenosis, it was finally established to be superior to best medical treatment for intermediate and high-grade symptomatic and high-grade asymptomatic carotid stenosis, through a series of large Randomised Controlled Trials[2-4] (RCT's) during the nineteen nineties. CEA, in experienced hands, has a low complication rate and provides good long term protection against stroke.

By nature however, this procedure is restricted to patients fit to undergo surgery. Whilst the RCT's on CEA were underway, a novel and less invasive treatment modality for carotid stenosis was developed, namely Carotid Angioplasty and Stenting (CAS)[5]. The only invasive part of this procedure is a puncture of an artery, typically in the groin. No dissection of any kind is necessary, obviating the need for anaesthesia. It can therefore be used in patients with significant co-morbidity. Furthermore it is not hampered by local cervical impediments that may render CEA a less appealing option, such as previous neck dissection or irradiation, or a high cephalad carotid stenosis.

In the fifteen years since introduction of CAS several important improvements in materials and peri-procedural medication have been introduced and CAS has found a place in the spectrum of treatment options for carotid artery stenosis. Encouraging early reports[5-7] have even prompted the initiation of several RCT's comparing CAS and CEA. Some of these trials have already met their conclusion and their results have been published[8-10]. These results however are conflicting and the debate about the preferential treatment for carotid stenosis has by no means been resolved. The most obvious conclusion one can draw when reviewing the results of these trials, is the very logical fact that the outcome depends very much on the input. Trials randomising poor surgical candidates have a better outcome for CAS as compared to CEA[8]. If, on the other hand, patients are selected who are excellent candidates for CEA, while poor candidates for CAS are included, the former treatment performs better[9,10]. Furthermore, in general, CEA's in these trials have been performed by very experienced vascular surgeons, whereas the experience of specialists performing CAS tended to be quite limited. This will inevitably have influenced results as well[11,12].

In this thesis several aspects of CAS are described.

In Part II Trans Cranial Doppler (TCD) detected cerebral micro embolic load during CAS was investigated. In **Chapter 2A**[13] a possible correlation between cerebral

micro emboli and new MRI detected lesions after CAS was investigated. In 11 of 72 patients (15%) new ischemic lesions were found on the post-procedural MRI. Most of these lesions were clinically silent. No correlation was found in this relatively small group of patients between cerebral micro embolic load and either clinical or MRI detected asymptomatic ischemic lesions. In **Chapter 2B**[14] retinal emboli were investigated. The retinal circulation has the unique feature of direct visualisation by fundoscopy. In 15% of 33 cases included in this study, new retinal emboli were found after CAS. All retinal emboli were clinically silent and all had resolved at long-term follow up. No correlation between retinal embolisation and TCD detected micro-emboli was established. Interestingly, three of the patients with new retinal emboli had been treated using filtering cerebral protection devices (CPD's). These devices were positioned between the carotid stenosis and the origin of the ophthalmic artery and should therefore have provided protection for the retinal as well as the cerebral circulation.

These CPD's have been developed to prevent emboli from reaching the brain during CAS. The types that have gained the most widespread use are the filtering type of CPD. When we started with CAS in our institution, CPD's had not been developed. They were gradually introduced in our patient series. After more than 150 patients had been treated using these devices, we evaluated their performance. The results are shown in **Chapter 2C**[15], which describes the first 509 CAS procedures in our institution. No difference in clinical outcome was found between patients treated with and those treated without CPD's. There was, however, a very significant difference in cerebral micrembolic load between groups. Paradoxically the microembolic load was higher in patients treated with CPD's, compared to patients treated without. Several possible explanations for this finding are coined, but the true cause remains unknown. This finding however did prompt us to rethink our protocol for CAS. Contrary to the situation in most CAS centres worldwide, the use of filtering CPD's has virtually been abolished in the department of Interventional Radiology in our institution. The use of (filtering type) CPD's, has never been proven to be beneficial in a controlled trial[16]. It is nevertheless unlikely that an RCT of protected vs. unprotected CAS will ever be performed in a highly industry driven field such as this, as their universal use is strongly advocated by a number of experienced and vociferous CAS specialists. In view of these strong views, rather than in view of strong evidence, many specialists performing CAS will probably feel quite apprehensive about the concept of an RCT.

Part III of this thesis focuses on several inherent differences between CAS and CEA. An important difference is that the introduction of a stent, no matter how flexible it is ex vivo, will inevitably lead to stiffening of the vessel in which it is implanted. This increased stiffness might lead to problems in a highly mobile part of the human anatomy, such as the neck. In **Chapter 3A**[17] seven patients treated with nitinol self-expandable carotid stents were evaluated with Magnetic Resonance Angiography (MRA). Images were obtained with the head in several different positions. On the not-stented side a gentle curving of the entire region of the carotid bifurcation was seen after head movement. On the stented side however, the stented segment itself did not show any movement and consequently all configuration change was transferred to the edges of the stented segment. This lead to an increased angulation of the Internal Carotid Artery (ICA) at the distal end of the stent, when the neck was flexed. Although an increased angulation was seen, no kinking, with luminal narrowing was observed. To evaluate if this configurational change lead to impeded volumetric flow a further study was performed, which is presented in **Chapter 3 B**[18]. Six different patients treated with CAS and six treated with CEA were compared. MRA's were made according to the protocol in Chapter 3A. In this study non-invasive MR volumetric flow measurements were added to establish any flow disturbance resulting from the change in configuration of the ICA. Although the same angulation was found as in **Chapter 3A**, this did not lead to a reduction of volumetric flow through the ICA.

In **Chapter 3C**[19] another difference between CAS and CEA is highlighted. As the stenosis in the carotid bifurcation is mostly located at the origin of ICA and frequently even involves the distal Common Carotid Artery (CCA), it is often necessary to place the stent from the ICA, extending into the CCA, thereby covering the origin of the External Carotid Artery (ECA). In the cohort of 312 patients in this study, 3 patients had pre-existing occlusions on the side of stenting and 3 different patients on the contra lateral side. During the procedure 2 additional ipsilateral ECA occlusions occurred. At extended follow up of up to 5 years, no further ECA occlusions occurred, but the fraction of patients with significant stenosis in the ECA increased to about 75% on the treated side, whereas it stabilised at 50% on the contra lateral side. This increase in ECA stenosis was more pronounced in, but not restricted to, patients with overstenting of the ECA.

Part IV of this thesis describes specific subsets of patients that are deemed unfavourable candidates for CEA. **Chapter 4A**[20] compares procedural details of patients

treated with CAS for post CEA restenosis (n= 72) versus primary (n=740) atherosclerotic stenosis. The clinical results were better for patients undergoing CAS for restenosis: no strokes or deaths occurred in this group, compared to 30 strokes and 8 fatalities in the much larger primary stenosis group. The TCD data were not significantly different between groups. As redo CEA carries a significantly increased risk of complications compared to the primary procedure, CAS is proposed as the treatment modality of choice for post-CEA restenosis. In **Chapter 4B**[21] the same category of patients is investigated at long term follow up. Results show that CAS post CEA provides adequate protection against stroke. However the rate of re-restenosis, 19% in 5 years, is considerable. These re-restenoses did not always lead to re-re-intervention.

**Chapter 4C**[22] describes results in 24 patients undergoing CAS for post-irradiation stenosis. This condition too is associated with an increased risk of peri-procedural complications, if treated with CEA. Results of CAS are good, with only one minor stroke occurring in this group of patients. During 3.3 years of follow up an adequate, but not perfect, protection against ipsilateral stroke was found.

Several challenges remain for endovascular management of carotid stenosis. During the last decade numerous improvements have been made in the procedure, materials and medication regimen. Stent types have been improved, but room for further improvement remains. The increased angulation that is observed in **Chapters 3A and B** might play a role in restenosis formation. Stents that have variable flexibility have meanwhile been introduced, which may aid in overcoming this problem. These stents have a closed cell design in their mid-segment, where the most tight stenosis is situated, but have open cells towards the stent edges, providing increased flexibility. Results of these newer stent types are subject of ongoing research.

Cerebral protection is an appealing concept, but, as has been shown in **Chapter 2C**, the types of CPD's that are currently most frequently used have significant drawbacks. Different types of CPD's may help to further reduce cerebral embolic load during CAS. Some of these devices are already on the market and favourable results have already been published[23,24]. Further research in this field is also warranted.

In short: CAS is a treatment modality that is still very much developing. A further improvement of results may therefore be expected. CEA on the other hand is a treatment modality, which after five decades of advances in technique, monitoring and medication regimen, is currently probably at its optimum, as is reflected in a stabilisation or even slight increase in complication rate over recent years[25].

In the opinion of the author of this thesis, CAS should not be considered to be a competitor for CEA, but rather a useful complementary treatment modality for patients with carotid bifurcation stenosis. Not all results of randomised CAS vs. CEA trials have, as yet, been published. Nevertheless some conclusion can probably be drawn from the existing literature. It appears fair to assume that the short term results of CAS and CEA, when performed by highly experienced teams, are quite comparable. There may be specific subsets of patients that would benefit more from one or the other. For instance, heavily calcified lesions are most likely best treated with CEA. Octogenarians may also be better off with CEA than with CAS[26], as the progressive elongation of the arch vessels poses a challenge to endovascular therapy, whereas CEA is not influenced by this condition. On the other hand patients with prior neck surgery or cervical irradiation will probably benefit more from CAS than from CEA. Naturally CAS is the preferred treatment for patients who are poor surgical candidates on account of co-morbidity. Some patients are very reluctant toward neck dissection or even surgery in general. For these patients CAS can be a very appealing alternative to CEA. After assigning the afore mentioned subgroups to their appropriate therapies, a large cohort of patients with carotid stenosis remains, for whom both therapies would likely be equally beneficial in the short run. Long term results of CAS are not as well known as they are for CEA, but what little evidence there is appears to be slightly in favour of CEA. This should be discussed with all patients when carotid treatment is contemplated.

More research especially into the long term results of CAS is necessary and additional improvements of dedicated materials are eagerly awaited. Close cooperation and exchange of data between high volume centres are instrumental in further development of CAS for carotid bifurcation stenosis.

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# PART V

# CHAPTER 5B

## Samenvatting in het Nederlands [Summary in Dutch]

Carotis EndArteriectomie (CEA) was de eerste causale behandeling voor vernauwingen in de halsslagader, ter voorkoming van herseninfarcten[1]. Nadat deze behandelmethode al 30 jaar lang gebruikt was werd uiteindelijk in een aantal gerandomiseerde onderzoeken tijdens de jaren ’90 bewezen dat zij betere resultaten oplevert dan medicamenteuze behandeling. CEA is superieur bij matige en ernstige symptomatische en bij ernstige asymptomatische vernauwingen[2-4]. In ervaren handen heeft CEA een laag complicatie risico en biedt een adequate langdurige bescherming tegen het optreden van herseninfarcten.

Uiteraard kan CEA alleen worden toegepast bij patiënten die überhaupt geopereerd kunnen worden. Terwijl de onderzoeken naar CEA liepen, werd een nieuwe en minder invasieve behandelmethode voor carotisstenosen ontwikkeld, namelijk Carotis Angioplastiek met Stentplaatsing (CAS)[5]. Het enige invasieve aan deze procedure is een punctie in een arterie, meestal in de lies. Aangezien er in het geheel geen dissectie nodig is, kan de procedure onder locale verdoving, zonder algehele anesthesie worden verricht. Dit betekent dat CAS kan worden toegepast bij patiënten met ernstige co-morbiditeit. Bovendien wordt CAS niet gehinderd door locale problemen die CEA minder aantrekkelijk maken, zoals eerdere chirurgie of bestraling in de hals, of een anatomisch hoog gelegen vernauwing.

In de vijftien jaar die er sinds de introductie CAS zijn verstreken, zijn er diverse belangrijke verbeteringen aangebracht in de gebruikte materialen en de medicatie, die tijdens de procedure wordt toegediend en heeft CAS een plaats gevonden in het spectrum van behandelopties voor carotisstenosen. Veelbelovende initiële ervaringen[5-7] hebben zelfs geleid tot het uitvoeren van enkele onderzoeken, waarbij gerandomiseerd wordt tussen CEA en CAS. Enkele van deze trials zijn al afgerond en de resultaten zijn gepubliceerd[8-10]. Deze resultaten zijn helaas niet eensluidend en de discussie over de beste behandeling voor carotisstenosen is zeker nog niet beëindigd. De meest voor de hand liggende conclusie die getrokken kan worden uit deze trials, is het logische feit dat de uitkomst sterk afhangt van de input. Indien patiënten met een verhoogd risico-profiel voor chirurgie worden gerandomiseerd, dan heeft CAS betere resultaten, dan CEA[8]. Indien juist patiënten worden geselecteerd die uitstekende kandidaten zijn voor chirurgie, terwijl slechte CAS kandidaten ook worden geïncludeerd, dan komt CEA er beter uit[9,10]. Bovendien zijn bij deze trials in het algemeen de operaties uitgevoerd door zeer ervaren vaatchirurgen, terwijl CAS vaak werd verricht door relatief onervaren medisch specialisten. Dit zal ongetwijfeld de resultaten ook hebben beïnvloed[11,12].

Het St. Antonius Ziekenhuis in Nieuwegein was in 1996 het eerste ziekenhuis in Nederland dat CAS toepaste voor carotisstenosen en is nog steeds het ziekenhuis met de meeste evaring op dit gebied, met een totaal aantal procedures dat op het moment van schrijven van dit proefschrift ruim boven de 1000 ligt. In dit proefschrift worden verscheidene aspecten van CAS beschreven, afkomstig van de prospectieve CAS database, die in ons ziekenhuis vanaf de allereerst procedure is bijgehouden.

In deel II worden de resultaten van Trans Craniële Doppler (TCD) tijdens CAS beschreven. In **Hoofdstuk 2A**[13] werd een correlatie onderzocht tussen TCD gedetecteerde micro-emboliën en nieuwe laesies te zien op een post-procedurele MRI. Bij 11 van de 72 patiënten (15%) werden nieuwe afwijkingen gevonden op de MRI na CAS. De meeste van deze afwijkingen leverden geen symptomen op. Er werd in deze relatief kleine groep patiënten geen correlatie gevonden tussen de TCD afwijkingen en klinische of MR gedocumenteerde afwijkingen. In **Hoofdstuk 2B**[14] werden emboliën in de retina onderzocht. De retina heeft de unieke eigenschap dat de bloedvaten middels fundoscopie direct zichtbaar zijn. Bij 15% van de 33 procedures in deze studie werden nieuwe emboliën in de retina gevonden. Geen van deze emboliën leidde tot (visuele) symptomen en allen waren bij lange termijn follow-up verdwenen. Geen relatie tussen de TCD gegevens en het optreden van retinale emboliën kon worden aangetoond. Drie van de patiënten die retinale emboliën kregen tijdens CAS, werden behandeld met Cerebrale Protectie Devices (CPD's). Deze filters werden geplaatst tussen de carotisstenose en de origo van de a. ophthalmica en zouden dus zowel de retina als de hersenen tegen emboliën hebben moeten beschermen.

CPD's zijn ontwikkeld om te voorkomen dat emboliën in de hersenvaten terecht komen tijdens CAS. Het type dat het meest gebruikt wordt is het filter. Toen wij in ons ziekenhuis met CAS begonnen, waren ze nog niet ontwikkeld en werden patiënten dus zonder filter behandeld. De filters werden geleidelijk in onze serie geïntroduceerd. Toen we meer dan 150 patiënten met deze filters hadden behandeld hebben we hun werking onderzocht. De resultaten zijn vermeld in **Hoofdstuk 2C**[15], waarin de resultaten van de eerste 509 CAS procedures in ons ziekenhuis zijn beschreven. Er was geen verschil in klinische uitkomst tussen patiënten die mèt en hen die zónder CPD waren behandeld. Er was daarentegen wel een zeer significant verschil in cerebrale micro emboliën tussen deze groepen. Paradoxaal genoeg waren er méér emboliën in de groep die met CPD waren behandeld. Diverse oorzaken van dit verschil worden geopperd, maar de ware oorzaak is

vooralsnog onduidelijk. Deze bevinding heeft er echter wel toe geleid dat we ons protocol hebben herzien. In tegenstelling tot de meeste CAS centra in de wereld, is het gebruik van filter type CPD's vrijwel volledig afgeschaft op de afdeling Interventieradiologie van ons ziekenhuis. Nog nooit is in een gerandomiseerde trial een positief effect van CPD's bewezen[16]. Het is echter onwaarschijnlijk dat zo'n trial er ooit zal komen, in een vakgebied dat zo in de belangstelling van de industrie staat. Vele ervaren en luidruchtige CAS specialisten bevelen het universele gebruik van deze devices aan. Gezien deze sterke opinies en niet zo zeer door sterk klinisch bewijs, zullen weinig specialisten die CAS uitvoeren bereid zijn aan zo'n trial mee te doen.

Deel III van dit proefschrift richt zich op enkele inherente verschillen tussen CAS en CEA. Een belangrijk verschil is dat een stent, hoe flexibel deze ex-vivo ook is, altijd leidt tot een vermindering van de flexibiliteit van het vat waarin hij geplaatst is. Deze toegenomen rigiditeit kan leiden tot problemen in een zeer mobiel deel van de mensenlijke anatomie, zoals de hals. In **Hoofdstuk 3A**[17], werden zeven patiënten die behandeld waren met een nitinol self-expandable stent onderzocht met Magnetische Resonantie Angiografie (MRA). Opnames werden gemaakt in verscheidene hoofdposities. Aan de niet-gestente zijde trad een geleidelijke bocht op na buigen van het hoofd. Aan de gestente zijde echter, liet het gestente segment van het vat in het geheel geen beweging zien en werd de hele verandering van configuratie opgevangen door de gebieden aan de randen van de stent. Dit leverde een toegenomen hoek op in de a.carotis interna (ACI), m.n. bij het distale uiteinde van de stent. Hoewel de hoek toenam, vonden we geen 'afknikken' van de ACI. Om te bepalen of deze verandering in configuratie toch leidde tot een afname van doorstroming van de ACI werd een vervolgonderzoek gedaan, hetgeen gepresenteerd wordt in **Hoofdstuk 3B**[18]. Zes nieuwe CAS patiënten werden vergeleken met zes CEA patiënten. MRA's werden gemaakt volgens het protocol van de vorige studie. Nu werden er vervolgens in de diverse hoofdposities non-invasieve MR-flow metingen verricht. We vonden dezelfde toename van angulatie als in Hoofdstuk 3A, maar dit leidde niet tot afname van de hoeveelheid bloed die door de distale ACI stroomde.

In **Hoofdstuk 3C**[19], wordt een ander verschil tussen CAS en CEA belicht. Aangezien de vernauwing in de carotis bifurcatie zich meestal direct aan de origo van de ACI bevindt en vaak zelfs de distale a. carotis communis (ACC) erbij betrokken is, wordt de stent vaak vanuit de ICA doorlopend tot in de CCA geplaatst. Daarbij wordt dan de origo van de a. carotis externa (ACE) overstent. In deze studie van 312 patiënten

hadden er 3 pre-existent een occlusie van de ACE aan de behandelde zijde en ook 3 aan de andere zijde. Tijdens de procedure is bij 2 patiënten de ACE aan de behandelde zijde afgesloten geraakt. Tijdens langdurige follow up traden er verder geen occlusies van de ACE meer op, maar het aantal mensen met een stenose in de ACE nam wel meer toe aan de behandelde zijde in vergelijking met de niet-behandelde zijde.

Deel IV van dit proefschrift beschrijft een aantal categorieën patiënten, waarbij CEA minder aantrekkelijk is als behandeloptie. **Hoofdstuk 4A**[20] vergelijkt de procedurele gegevens van patiënten die middels CAS werden behandeld voor een restenose na eerdere CEA (n=72), met patiënten die CAS ondergingen voor een primaire atherosclerotische stenose (n=740). De klinische resultaten waren beter voor patiënten die voor een restenose werden behandeld: geen van de patiënten in de restenose groep kreeg een infarct of overleed, tegen 30 infarcten en 8 overleden patiënten in de veel grotere groep van primaire stenosen. De TCD gegevens waren niet significant verschillend tussen beide groepen. Aangezien een re-CEA een fors verhoogd complicatie risico heeft, moet CAS als de behandelmethode van eerste keuze voor restenoses worden beschouwd. **Hoofdstuk 4B**[21] beschrijft de lange termijn resultaten van deze zelfde groep patiënten. CAS voor restenose na CEA levert adequate bescherming tegen het optreden van herseninfarcten. Het aantal re-restenosen is wel aanzienlijk met 19% in 5 jaar.

**Hoofdstuk 4C**[22] beschrijft de resultaten van 24 patiënten die CAS ondergingen voor een carotis stenose na bestraling van de hals. Ook deze conditie is geassocieerd met een verhoogd risico op complicaties bij behandeling middels CEA. Resultaten van CAS voor deze groep patiënten zijn goed, met slechts één licht herseninfarct in deze groep. De behandeling leverde tijdens 3.3 jaar follow up een redelijke, maar niet perfecte, bescherming tegen herseninfarcten.

Er zijn nog verschillende uitdagingen voor de endovasculaire behandeling van carotis stenosen. Tijdens de afgelopen tien jaar zijn vele verbeteringen aangebracht in de procedure, de materialen en de medicatie. Stent types zijn verbeterd, maar ze kunnen nog verder verbeterd worden. De angulatie die wordt beschreven in **Hoofdtukken 3 A en B** zou een oorzaak kunnen vormen voor het optreden van restenosen. Stents met variabele flexibiliteit, die dit probleem mogelijk kunnen verminderen, zijn inmiddels op de markt. Deze stents hebben gesloten cellen in het mid-segment, waar de meest ernstige stenose zit, maar hebben open cellen aan de randen, waardoor daar een grotere flexibiliteit bestaat.

Naar de resultaten van dit stent type wordt op dit moment onderzoek gedaan.

Cerebrale protectie is op zich een aansprekend concept, maar zoals **Hoofdstuk 2C** beschrijft, hebben de meest frequent gebruikte soorten belangrijke nadelen. Andere types CPD kunnen wellicht een rol spelen bij de verdere reductie van het aantal emboliën tijdens CAS. Enkele van deze types zijn al ontwikkeld en goede resultaten zijn reeds gepubliceerd[23,24]. Verder onderzoek is ook op dit gebied aangewezen.

Kortom: CAS is een behandelmethode die nog volop in ontwikkeling is. Verdere verbetering van de resultaten is daarom te verwachten. CEA daarentegen is na vijf decennia van verbetering in techniek nu zo goed als uitontwikkeld. Dit lijkt bevestigd te worden door een lichte toename in het complicatierisico van CEA tijdens de laatste paar jaar[25].

Naar de mening van de auteur van dit proefschrift, zouden CAS en CEA niet beschouwd moeten worden als een concurrerende maar eerder als een complementaire behandeling. Niet alle resultaten van gerandomiseerde onderzoeken zijn op dit moment gepubliceerd, maar niettemin kunnen waarschijnlijk enkele conclusies worden getrokken uit de bestaande literatuur. Het lijkt redelijk om te concluderen dat de korte termijn resultaten van CAS en CEA, indien uitgevoerd door ervaren teams, vergelijkbaar zijn. Waarschijnlijk zijn er specifieke subgroepen van patiënten, waarbij de ene behandeling superieur is t.o.v. de ander. Sterk verkalkte laesies bijvoorbeeld kunnen waarschijnlijk het best met CEA behandeld worden. Ook bij patiënten van boven de tachtig jaar is CEA waarschijnlijk beter[26], aangezien de toenemende opkrulling van de boogvaten endovasculaire behandeling lastiger maakt. Aan de andere kant hebben patiënten met eerdere operaties of bestraling in de hals waarschijnlijk meer baat bij CAS. Vanzelfsprekend is CAS te prefereren bij patiënten bij wie CEA in verband met co-morbiditeit niet mogelijk is. Sommige patiënten hebben een sterke aversie tegen halschirurgie, of zelfs chirurgie in het algemeen. Voor hen kan CAS een aantrekkelijk alternatief zijn. Nadat de hiervoor genoemde patiënten aan de best passende behandeling zijn toegewezen, blijft er een grote groep patiënten over, voor wie beide therapieën op korte termijn waarschijnlijk even goed zouden werken. Over de lange termijn resultaten van CAS is veel minder bekend dan van CEA. Uit de beperkte gegevens lijken de lange termijn resultaten licht in het voordeel van CEA te zijn. Dit moet uiteraard besproken worden met alle patiënten bij wie endovasculaire behandeling wordt overwogen.

Meer onderzoek, met name naar de lange termijn resultaten van CAS is

noodzakelijk en naar nieuwe ontwikkelingen van materialen wordt reikhalzend uitgekeken. Nauwe samenwerking en uitwisseling van gegevens tussen centra met veel ervaring zullen een belangrijke rol blijven spelen bij de verdere ontwikkeling van CAS voor het behandelen van carotis stenosen.

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# PART V
# CHAPTER 5C

## List of publications

**2009**

J Vasc surg (in press)
**Carotid angioplasty and stenting: treatment of post CEA restenosis is at least as safe as primary stenosis treatment.**
Vos JA, de Borst GJ, Overtoom TTC, de Vries JPPM, van de Pavoordt HDWM, Zanen P, Ackerstaff RGA.

Eur J Vasc Endovasc Surg. 2009 Mar 30.
**The Association between Iliac Fixation and Proximal Stent-graft Migration during EVAR Follow-up: Mid-term Results of 154 Talent Devices.**
Waasdorp EJ, de Vries JP, Sterkenburg A, Vos JA, Kelder HJ, Moll FL, Zarins CK.

J Vasc Surg 2009; 49:214-6
**Renal artery pseudoaneurysm caused by a complete stent fracture: A case report**
Schuurman JP, deVreis JPM, Vos JA, Wille J

Nederlands Tijdschrift voor Neurologie en Neurochirurgie 2009 (110);1:13-21
**Vertebrobasilaire TIA's en herseninfarcten: nieuwe inzichten en ontwikkelingen.**
Compter A, Schonewille W, van der Worp HB, Vos JA, Lo TH, Kappelle LJ.

Nederlands Tijdschrift voor Geneeskunde 2009;153:B85
**Ernstige, symptomatische carotisstenose. Voorkeur voor percutane angioplastiek.**
Vos JA

**2008**

Trials 2008 Nov 24;9:65.
**VAST: Vertebral Artery Stenting Trial. Protocol for a randomised safety and feasibility trial.**
Compter A, van der Worp HB, Schonewille W, Vos JA, Algra A, Lo TH, Mali WP, Moll F, Kappelle LJ.

Nederlands Tijdschrift voor Dermatologie en Venereologie 2008 jun, vol. 18: 203
**Pijn in de lies bij de dermatoloog?**
Meijer BUGA, Vos JA

Injury Extra 2008 (39); 71-5
**Massive portal vein thrombosis and kidney trauma following blunt abdominal trauma: A diagnostic and therapeutic dilemma.**
van Riessen S, Wasowicz-Kemps DK. Besselink MGH, Bollen TL, Vos JA, Onaca MG

**2007**

Edurad 58
**Femoral Artery Closure devices**
Vos JA

J Endovasc Ther. 2007 Jun;14(3):307-17.
**Long-term single-center results with AneuRx endografts for endovascular abdominal aortic aneurysm repair.**

van Herwaarden JA, van de Pavoordt ED, Waasdorp EJ, Vos JA, Overtoom TT, Kelder JC, Moll FL, de Vries JP.

Eur J Vasc Endovasc Surg. 2007 Jun;33(6):657-63.
**The fate of the external carotid artery after carotid stenting: A follow-up study with duplex ultrasonography.**
De Borst GJ, Vos JA, Reichmann B, Hellings WE, de Vries JP, Suttorp MJ, Moll FL, Ackerstaff, RGA

Expert Rev Cardiovasc Ther. 2007 Mar;5(2):195-9.
**Carotid Artery Dynamics after Carotid Angioplasty and Stenting.**
Linsen MAM, Vos AWF, Vos JA, Wisselink W

J Vasc Surg. 2007 Jan;45(1):118-23.
**Carotid angioplasty and stenting for post-endarterectomy stenosis: long term follow-up.**
Borst GJ de, Ackerstaff RGA, Vos JA, Vries JP de, Moll FL

**2006**
Br J Anaesth, 2006; 97: 832-4.
**Early transection of a central venous catheter in a sedated ICU patient.**
de Graaff JC, Bras LJ, Vos JA.

Ann Thorac Surg. 2006 Aug;82(2):560-5.
**Thoracic stent grafting for acute aortic pathology.**
Kaya A, Heijmen RH, Overtoom TT, Vos JA, Morshuis WJ, Schepens MA.

Memorad 2006 (11)-2:5
**Prestatie-indicatoren.**
Vos JA

Eur J Vasc Endovasc Surg. 2006 Jul 25; [Epub ahead of print]
**Long-term Results of Percutaneous Transluminal Angioplasty for Symptomatic Iliac In-stent Stenosis.**
Kropman RH, Bemelman M, Vos JA, van den Berg JC, van de Pavoordt HD, van de Mortel RH, Moll FL, de Vries JP.

Ann Vasc Surg. 2006 Mar 20(2):278-81
**Acute Leg Ischemia: The Dark Side of a Percutaneous Femoral Artery Closure Device.**
Wille J, Vos JA, Overtoom TT, Suttorp MJ, van de Pavoordt ED, de Vries JP

**2005**
JBR-BTR. 2005 May-Jun;88(3):112-3.
**Bleeding stromal tumor in Meckel's diverticulum.**
Biemans JMA, Vos JA

Vascular. 2005 May-Jun;13(3):135-40.
**Clinical outcome and technical considerations of late removal of abdominal aortic endografts: 8-year single-center experience.**

de Vries JP, van Herwaarden JA, Overtoom TThC, Vos JA, Moll FL, van de Pavoordt HDWM

Memorad 2005 (10)-2:5
**Portefeuille 'Kwaliteit'.**
Vos JA

J Vasc Surg. 2005 Apr;41(4):618-24.
**Prediction of early cerebral outcome by transcranial Doppler monitoring in carotid bifurcation angioplasty and stenting.**
Ackerstaff RG, Suttorp MJ, van den Berg JC, Overtoom TT, Vos JA, Bal ET, Zanen P; Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group.

J Vasc Surg. 2005 Mar;41(3):469-75.
**Impact of head movements on morphology and flow in the Internal Carotid artery after Carotid Angioplasty and Stenting versus Endarterectomy.**
Vos JA, Vos AWF, Linsen MAM, Marcus JT, Overtoom TTC, van den Berg JC, Wisselink W.

Radiology. 2005 Feb;234(2):493-9. Epub 2004 Dec 22.
**Carotid Angioplasty and Stent Placement: Comparison of Transcranial Doppler US Data and Clinical Outcome with and without Filtering Cerebral Protection Devices in 509 Patients.**
Vos JA, van den Berg JC, Ernst SM, Suttorp MJ, Overtoom TT, Mauser HW, Vogels OJ, van Heesewijk HP, Moll FL, van der Graaf Y, Mali WP, Ackerstaff RG.

> Radiology. 2005 Oct;237(1):374-5; **Value of US in selecting patients for carotid angioplasty and stent placement.** Bluth IE. Radiology. 2005 Oct;237(1):author reply 375 Vos JA, Ackerstaff RGA

**2004**

Acta Chir Belg. 2004 Feb;104(1):55-9
**TCD-detected cerebral embolism in carotid endarterectomy versus angioplasty and stenting of the carotid bifurcation.**
Ackerstaff RG, Vos JA; Antonius Carotid Endarterectomy, Angioplasty, and Stenting Study Group.

Ned Tijdschr Geneeskd. 2004 Feb 28;148(9):433-7
**Het centraalveneuze-compressiesyndroom: zeldzaam, maar goed endovasculair te behandelen.**
van der Laan L, Vos JA, de Boer E, van den Berg JC, Moll FL.

J Vasc Surg. 2004 Feb;39(2):427-31
**Freedom from secondary interventions to treat stenotic disease after percutaneous transluminal angioplasty of infrarenal aorta: long-term results.**
de Vries JP, van Den Heuvel DA, Vos JA, van Den Berg JC, Moll FL.

**2003**

J Endovasc Ther. 2003 Oct;10(5):862-9
**Carotid artery dynamics during head movements: a reason for concern with regard to carotid stenting?**

Vos AW, Linsen MA, Marcus JT, van den Berg JC, Vos JA, Rauwerda JA, Wisselink W.

Pediatr Radiol. 2003 Dec;33(12):877-9. Epub 2003 Sep 13
**MRI findings in a child with sigmoid sinus thrombosis following mastoiditis.**
van den Bosch MA, Vos JA, de Letter MA, de Ru JA, van Diemen-Steenvoorde RA, Plotz FB.

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**Transcranial Doppler monitoring in angioplasty and stenting of the carotid bifurcation.**
Antonius Carotid Endaterectomy, Angioplasty, and Stenting Study Group.

**2002**
J Vasc Interv Radiol. 2002 Dec;13(12):1219-24.
**Repeated intervention for in-stent restenosis of the renal arteries.**
Bax L, Mali WP, Van De Ven PJ, Beek FJ, Vos JA, Beutler JJ.

Radiology. 2002 Aug;224(2):361-5.
**New brain lesions at MR imaging after carotid angioplasty and stent placement.**
van Heesewijk HP, Vos JA, Louwerse ES, Van Den Berg JC, Overtoom TT, Ernst SM, Mauser HW, Moll FL, Ackerstaff RG; Carotid PTA and Stenting Collaborative Research Group.

**Endovascular and other minimally invasive treatment modalities of aorto occlusive diseases.**
*In:* Critical lower limb ischemia : principles and practice. 2002: 165-173.
de Vries JPPM, Vos JA, van den Berg JC, Moll FL.

**2001**
Ned Tijdschr Geneeskd. 2001 Nov 10;145(45):2173.
**[Diagnostic image (63). Paraganglioma]**
Vos JA

**1997**
Invest Radiol. 1997 Jun;32(6):363-7.
**Digital chest imaging using a selenium detector. The impact of hard copy size on observer performance: a computed tomography-controlled study.**
van Heesewijk HP, van de Graaf Y, de Valois JC, Vos JA, Feldberg MA

**1996**
Radiology. 1996 Sep;200(3):687-90.
**Chest imaging with a selenium detector versus conventional film radiography a CT-controlled study.**
van Heesewijk HP, van de Graaf Y, de Valois JC, Vos JA, Feldberg MA

## Abstracts, Oral presentations and Lectures

**2009**
Society of Vascular Surgery, Denver, USA, June 2009
**Carotid angioplasty and stenting: treatment of post CEA restenosis is at least as safe as primary stenosis treatment.**
Vos JA, de Borst GJ, Overtoom TTC, de Vries JPPM, van de Pavoordt HDWM, Zanen P, Ackerstaff RGA.

Max Taks Vascular Meeting (MT Vaatsymposium), Doetinchem
**Intra arterial stroke treatment.** (Invited Lecture)
Vos JA

Dutch Interventional Radiology meeting (Radiologische Interventiedag Nederland), Ede
**Carotid stenting.** (Invited Lecture)
Vos JA

**2008**
EVAR Medtronic users meeting, Amerongen
**Embolisation of the Internal Iliac Artery pre-EVAR.** (Invited Lecture)
Vos JA

Cardiovascular and Interventional Radiology Society of Europe, Annual Scientific meeting, Copenhagen, Denmark
**Retinal embolization during carotid angioplasty and stenting.**
M.H. v Werkum, Vos JA

Dutch Society of Surgery, Annual Scientific Meeting, Veldhoven
**Endovascular management of complicated type B aortic dissections.** (Invited Lecture)
Vos JA

Dutch vascular meeting (Vaatdagen), Noordwijk
**Intra-arterial thrombolysis in acute cerebral ischemia.** (Invited Lecture)
Vos JA

Dutch Society of Gastroenterology, Refresher course, Veldhoven
**Endovascular management of gastro-intestinal haemorrhage.** (Invited Lecture)
Vos JA

'Max Taks' Vascular Symposium, Doetinchem
**Stenting of unstable plaques: Thrill-seeking?** (Invited Lecture)
Vos JA

**2007**
Dutch Radiological Society, annual Scientific meeting, Rotterdam, September 2007
**Real time 3D image guided intervention with soft tissue imaging on a flat panel detector system**

Strijen MJL van, Overtoom TThC, Vos JA, Leersum M van, Kraats E van der

Dutch Radiological Society, annual Scientific meeting, Rotterdam, September 2007
**Vroege post-EVAR CT-angiografie voor ontslag uit het ziekenhuis: noodzakelijk of niet? (Early post-EVAR CT angiography before discharge: necessary or not?)**
Waasdorp E, Hullemaar CDP van t, Herwaarden JA van, Vos JA, Leersum M van, Strijen MJL van, Vries JPPM de

Sandwich course Interventional Radiology, June 2007
**Closure Devices for femoral arterial access.** (Invited Lecture)
Vos JA

**2006**
Radboud University Medical Center, dept. of Neurology, Nijmegen, November 2006
**Carotid Angioplasty and Stenting, current standings.** (Invited Lecture)
Vos JA

Dutch Radiological Society, annual Scientific meeting, Kaatsheuvel, November 2006
**Results of endovascular recanalisations of chronic long segment occlusions of the inferior vena cava.**
Heuvel DAF vd, Vos JA, Riele WW te, Pavoordt HDWM vd, Vries JPPM de, Overtoom TThC

Dutch Radiological Society, annual Scientific meeting, Kaatsheuvel, November 2006
**The fate of the external carotid artery after carotid artery stenting. A follow-up study with duplex ultrasonography.**
Braak SJ, Borst GJ de, Vos JA, Reichmann B, Hellings WE, Vries JPPM de, Moll FL, Ackerstaff RGA

Dutch Radiological Society, annual Scientific meeting, Kaatsheuvel, November 2006
**Retinal embolization during carotid angioplasty and stenting**.
Werkum MH van, Vos JA, Bistervels JH

VEITH symposium, New York NY, November 2006
**Carotid Angioplasty and Stenting for Post Endarterectomy Stenosis: Long Term Follow-Up** (winning ISVS abstract)
Borst GJ de, Ackerstaff RGA, Vos JA, Vries JP de, Moll FL

Society of Vascular Surgery, Philadelphia, USA, June 2006
**Long-term results of PTA for focal iliac in-stent restenosis.**
Kropman R, Vries JPPM de, Vos JA, Overtoom TThC, Pavoordt HDWM vd

European Vascular Course (EVC), Amsterdam, May 2006
**Imaging derived treatment improvements in minimally invasive therapy** (Invited Lecture)
Vos JA

15th European Stroke Conference, Brussels Belgium, May 2006
**Percutaneous Transluminal Angioplasty and Stenting of Posterior Circulation Symptomatic Stenosis**

Schonewille WJ, Overtoom T, Vos JA, Suttorp MJ, de Vries JP, Ackerstaff RG

Dutch vascular meeting ('Vaatdagen'), Noordwijkerhout, March 2006
**Long-term results of PTA for focal iliac in-stent restenosis.**
Kropman R, Vries JPPM de, Vos JA, Overtoom TThC, Pavoordt HDWM vd

**2005**
Symposium 'Learning together', Ommen, December 2005
**Carotid Angioplasty and Stenting.** (Invited Lecture)
Vos JA

Dutch Radiological Society, annual Scientific meeting, Noordwijkerhout, September 2005
**Technical success rate and clinical outcome of intra-arterial treatment for basilar artery thrombosis.**
Vos JA, Schonewille W, Overtoom TThC

4th EACTS/ESTS Joint Meeting, Barcelona, Spain, September 2005
**Endovascular stent grafting for thoracic aortic Pathology: mid-term results in 105 consecutive patients**
Heijmen RH, Kaya A, Schepens MA, Morshuis WJ, Vos JA, Overtoom TThC

**2004**
Dutch Radiological Society, annual Scientific meeting, Noordwijkerhout, September 2004
**PTA and stenting for hemodynamically significant stenosis of the renal artery in patients with a single functioning kidney.**
Lely R, Vos JA, vd Berg JC, Overtoom TThC

Paris Course on Revascularisation, Paris, France, May 2004
**TCD during CEA and stenting, clinical need or scientific tool ?** (Invited lecture)
Vos JA, Ackerstaff RGA

**2003**
Dutch Radiological Society, annual Scientific meeting, Noordwijkerhout, October 2003
**Do cerebral protection devices change embolic load or outcome during CAS?**
Vos JA, Ackerstaff RGA

**2002**
Dutch Radiological Society, annual Scientific meeting, Noordwijkerhout, October 2002
**TCD evaluation during Carotid Angioplasty and stenting**
Vos JA, Ackerstaff RGA

**2000**
Dutch Radiological Society, annual Scientific meeting, Veldhoven, October 2000
**Repeated intervention for in-stent restenosis of the renal arteries.**
Vos JA, Bax L, Mali WP, Van De Ven PJ, Beek FJ, Beutler JJ.

# PART V
# CHAPTER 5D

## Resume of the author

The author of this thesis was born on June 30th 1967 in Hoogezand-Sappemeer in the north of the Netherlands. His secondary school education was spent in Zeist. He started medical school at Utrecht University in 1985. During his studies he participated in the development of a clinical trial for the pharmaceutical company Eli Lilly and he did his Obstetrics and Gynaecology rotation in St. Thomas' Hospital in London. After graduation in 1994 he did his military service as doctor in the Royal Dutch Army Medical Corps, for which he is still active as reserve officer (current rank lt-col). During this year he participated in research on the applicability of digital chest X-rays, with dr JPM v Heesewijk, radiologist in St. Antonius Hospital in Nieuwegein. In 1995 he started his Radiology residency in the Twenteborg hospital in Almelo (program chair J.W.Rethmeier). In 1997 he continued his Radiology residency in Utrecht University Medical Centre (chairs prof PFGM v Waes and dr FJA Beek). After finishing his residency in 2000 he started working as radiologist in St. Antonius Hospital in Nieuwegein, at first as fellow in Interventional Radiology and from 2002 as consultant Interventional Radiologist. This is where he started his research on carotid stenting, which eventually lead to this thesis. Since the formal confirmation of the Interventional Radiology fellowship by the Dutch Radiological Society, he serves as chair of the Interventional Radiology training program. He has served in numerous functions in the Dutch Radiological Society, among which was a four year period on the Board of the Society where he was responsible for Quality Assurance.

Through several humanitarian organisations he has done volunteer work teaching ultrasonography in Romania, Nicaragua and South Africa.

He and his girlfriend Annemarie Goud have a daughter Sophie Philiene, who was born on March 7th 2009.

# PART V

# CHAPTER 5E

## Curriculum Vitae
## [Resume in Dutch]

De schrijver van dit proefschrift werd geboren op 30 juni 1967 te Hoogezand-Sappemeer. Na het eindexamen gymnasium β (8 vakken) aan de Rijksscholengemeenschap 'Schoonoord' te Zeist begon hij in 1985 aan de studie Geneeskunde aan de Rijksuniversiteit Utrecht, alwaar hij in 1994 het artsexamen behaalde. Gedurende de studie werkte hij onder andere mee aan de voorbereiding van een klinische trial bij de farmaceutische firma Eli Lilly Benelux. Een deel van de co-assistentschappen deed hij in St. Thomas' Hospital in Londen. Na het artsexamen vervulde hij de militaire dienst als eerste luitenant-arts in Harderwijk en later Ede. Tijdens deze periode participeerde hij in een studie naar de toepasbaarheid van digitale thorax-opnames, het promotieonderzoek van J.P.M.van Heesewijk, radioloog in het St. Antonius Ziekenhuis in Nieuwegein. In 1995 begon hij met de specialisatie opleiding radiologie in het Twenteborg Ziekenhuis in Almelo (opleider J.W. Rethmeier). In 1997 zette hij de opleiding voort in het Academisch Ziekenhuis Utrecht (later Universitair Medisch Centrum Utrecht) met als opleiders Prof. dr. P.F.G.M. van Waes en dr. F.J.A. Beek. Sinds het beëindigen van de opleiding in november 2000 is hij als radioloog verbonden aan het St. Antonius Ziekenhuis in Nieuwegein, aanvankelijk als fellow interventieradiologie, later als interventieradioloog. Hier startte hij met het onderzoek naar endovasculaire behandeling van carotis stenosen, hetgeen uiteindelijk culmineerde in dit proefschrift. Sinds de formele introductie van de vervolgopleiding Interventieradiologie binnen de Nederlandse Vereniging voor Radiologie (NVvR), is hij opleider voor het fellowship in het St. Antonius Ziekenhuis.

Naast het klinische en wetenschappelijke werk heeft hij verschillende organisatorische functies vervuld binnen de NVvR, waaronder vier jaar in het Bestuur (portefeuille Kwaliteit). In deze periode heeft hij onder meer prestatie indicatoren geïntroduceerd in de NVvR. Via diverse hulporganisaties heeft hij daarnaast echografie onderwijs gegeven in Roemenië, Nicaragua en Zuid-Afrika.

Hij woont samen met Annemarie Goud. Op 7 maart 2009 is hun dochter Sophie Philiene geboren.

# Part V
# Chapter 5F

## Dankwoord
## [Acknowledgements in Dutch]

Wetenschappelijk onderzoek is per definitie teamwork. Dit geldt zeker ook voor dit proefschrift. Zonder de bijdragen van vele kanten en op vele vlakken was het nooit gelukt dit boekwerk te produceren. Enkele mensen wil ik met name bedanken voor hun bijdrage.

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