CAROTID ARTERY REVASCULARIZATION

Surgical and endovascular developments

G.J. de Borst

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Background on frontcover:
In 1849 the Great Trigonometrical Survey of India mapped the heights of peaks in the himalaya range. Three years later the results showed a peak, known as Peak XV, to be the highest mountain in the world (8848M). Peak XV was rather an ignominious name for the highest mountain in the world, and various local names were reported.
Devadhunga (Nepali for "Abode of Gods") and Chingopamari (Tibetan) did not make it. In 1862 the Royal Geographic Society opted for an Nepali name for the mountain: Gaurisanka. However, Gaurisanka turned out to be another peak, 50 km from Everest. Initiated by Andrew Waugh, surveyor-general of India, the peak then was named after the head of the Great Trigonometrical Survey, sir George Everest, despite much opposition (including from Everest himself). The true Tibetan name for the mountain however is Chomolungma (or Qomolangma as the Chinese have literated it). Chomolungma must be interpreted as "Goddess Mother of the Universe". Starting from Lukla (2899M) the Everest base camp (5620M) can be reached in 1 week trekking through the Khumbu valley. The frontcover shows a detail from the stunning view from Everest Base Camp on the Nepali side of Mount Everest of the Khumbu Icefall. The icefall is one of the key passages for expeditions between Base Camp to Everest Summit.

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Revascularisatie van de arteria carotis. Chirurgische en endovasculaire ontwikkelingen.
(met een samenvatting in het Nederlands)

Proefschrift

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"It is even conceivable that some day vascular surgery will find a way to bypass the occluded portion of the carotid artery during the period of ominous fleeting symptoms".

(Miller Fisher 1951)

CAROTID ARTERY REVASCULARIZATION

Surgical and endovascular developments

Chapter 10

CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In the era of established surgical techniques being challenged by endovascular alternatives it is justified to resumé the optimal treatment options for carotid artery revascularization. The collected chapters in this thesis are not the final word as to the discussion whether carotid endarterectomy (CEA) is better than carotid angioplasty and stenting (CAS), but far more try to find an answer to some single issues in the continuing controversy on treatment of carotid artery disease. This can not be done without respect and knowledge of the past.

1. Carotid artery disease; in historical perspective

Although the association of carotid artery disease and neurological dysfunction was understood by the Ancient Greeks, over 1700 years would pass before the relevant anatomy was described. In the 16th and 17th centuries, attempts at treatment of carotid injury and aneurysm by ligation were met with extremely high rates of stroke and death. It is not until the mid 20th century, with the introduction of carotid angiography and improved vascular surgical techniques, that the era of reconstructive carotid surgery begins [Table 1].

400 BC	Hippocrates : "apoplexy"
1552	Ambroise Paré : ligation of common carotid artery for trauma
1658	Wepfer describes cerebral vasculature
1809	Astley-Cooper : ligation of common carotid artery for aneurysm
1927	Moniz : performs carotid angiography
1938	Chao : excision of carotid occlusion
1951	Carrea, Molins, Murphy : reconstruction of occluded ICA.
1951	John Conley : carotid reconstruction with saphenous vein
1953	Michael DeBakey : first carotid endarterectomy
1954	Eastcott, Rob, Pickering : carotid reconstruction
1956	Cooley : shunt during endarterectomy
1977	Mathias : percutaneous carotid angioplasty
1991	NASCET, ECST
1994	Marks : carotid artery stent for dissection
1995	ACAS
1996	CAVATAS
2004	SAPPHIRE
2006	EVA-3S, SPACE
2007/08	ICSS

Table 1: Landmarks in carotid artery history

1.1 The early years

The carotid arteries derive their names from the ancient Greek verb "karoun", which means to stupify or plunge, and from "karos", which means heavy sleep [1]. Hippocrates, about the turn of the fourth century BC, already gave an accurate description of strokes, prodromal symptoms, and transient ischemic attacks [2] and knew that lesions of the carotid artery resulted in contralateral hemiplegia [3]. Ambroise Paré in the 16th century recounted this phenomenon as follows: "The two branches are called carotides or soporales, the sleepy arteries, because when being obstructed or any way stopped we presently fall asleep"[4]. The first meaningful description of the cerebral vessels, was given by the Swiss physician Wepfer. In 1658, he described the hemispheric supply of the brain by the carotid arteries, and made the first known reference to the association of pathological changes in the cerebral vessels and symptoms of cerebral ischemia [5]. Thomas Willis expanded on the work of Wepfer and in 1664 published his Cerebri Anatome [6]. Although he was not the first to describe the vascular ring which now bears his name, it was not until his treatise, that its true significance was understood [7].

1.2 The diseased carotid bifurcation & Nonreconstructive carotid surgery

The first report of operative ligation of the carotid artery was that of Ambroise Paré in 1552. His patient however, developed aphasia and hemiplegia [4]. Along with the performance of carotid artery surgery for trauma, in 1809 the noted British surgeon Sir Astley Cooper recognized and discussed the possibility of stroke after carotid ligation [8]. The relationship between extracranial cerebrovascular disease and stroke was further discussed by Gull[9] in 1855 who first suggested to restore blood supply to the brain [10]. And although the clinical picture of internal carotid thrombosis was fairly accurately described as early as 1881 by Penzoldt [11], the syndrome consisting of temporary hemiparesis, aphasia, and transient loss of consciousness was first tied conclusively to occlusive disease of the carotid arteries by Chiari [12], in Praque, in 1905. The next significant contribution was the report of Egas Moniz of Portugal who in 1927 described the technique of cerebral arteriography[13]. The first report of carotid thrombosis demonstrated by arteriography was that of Sjoqvist in 1936 [14]. Despite, throughout the 1940's, the treatment of choice for internal carotid occlusive disease remained excision and ligation to "prevent the propagation of the clot and release vasospasm" [15].

In June 1946 Jean Cid Dos Santos removed an acutely formed thrombus from the femoral artery. He discovered that he had inadvertently removed the intima and a portion of the media. The artery remained patent for many months. He concluded that in order to keep an artery patent, an uninjured intima is not absolutely necessary. As in many instances

of medical progress, the discovery of thrombendarterectomy came by chance. In 1951 Wylie introduced the procedure of thrombendarterectomy into the United States for the removal of atherosclerotic plaques in the aortailiac segment, but it was not used on the carotid artery [16].

Fisher published two important papers in 1951 and 1954 re-emphasizing the relationship between disease of the carotid artery and cerebrovascular symptoms and these publications revived Chiari's theory that ulcerative plaques of the carotid bifurcation were the source of cerebral embolism [17,18]. It was Fisher who stated that, in the future, surgical treatment of extracranial vascular disease might prevent stroke "during the period of ominous fleeting symptoms".

1.3 Reconstructive carotid surgery for occlusive disease

In January 1953, Strully, Hurwitt, and Blankenberg first attempted thromb-endarterectomy of the internal carotid artery but were unable to obtain retrograde flow [19]. The first successful true carotid endarterectomy was performed by DeBakey some months later on August 7, 1953 but published in 1975, in a 53 year old man with transient ischemic attacks [20]. The diagnosis was made without the benefit of angiography but based on that "published reports had indicated that such lesions may well be localized at the bifurcation of the common carotid artery". The left carotid bifurcation was explored, and a "well-localized atheromatous plaque which produced severe stenosis at the origin of the internal " was removed. An arteriogram performed postoperatively on the operating table showed the internal carotid artery to be patent. This patient lived for 19 years without further strokes.

However, the carotid reconstruction that truly gave great impetus to the development of carotid surgery was the resection of the carotid bifurcation and restoration of flow by anastomosis of the common to the internal carotid artery by Eastcott, Pickering, and Rob on May 19, 1954 and reported in the November issue of the Lancet in the same year [21].

The development of carotid duplex scanning further revolutionized the diagnosis of carotid artery disease. Duplex ultrasound scanning compared favourably with arteriography in quantifying carotid artery stenosis [22], and it allowed the performance of carotid surgery without the risks and expenses of arteriography [23].

The late 20th century saw a marked increase in the surgical treatment of the carotid artery occlusive disease not as a result of evolving technique, but rather due to the results of several large prospectively randomized trials in the US and Europe. The largest of these, the European Carotid Surgery Trial (ECST, 1991) [24] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET, 1991) [25] unequivocally showed the benefits of carotid endarterectomy for symptomatic patients with ≥ 70% internal carotid artery stenosis on the side of the symptomatic hemisphere, when compared to best medical treatment.

Treatment of carotid disease was given further impetus by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) in 1995, although gains were more modest and highly dependent on excellent surgical outcomes [26].

1.4 Alternative revascularization techniques: carotid angioplasty and stenting

In the late nineties, after finally being recognized by neurologists, the surgical treatment of carotid artery obstructive disease was challenged again, this time by an alternative revascularization technique. Claimed advantages of carotid angioplasty and stenting (CAS) include reduced morbidity rate, reduced cost, shortened hospitalization, and improved long-term patency rates. Given the presumed embolic nature of carotid territory neurological events, vascular surgeons did not consider the relief of a haemodynamic stenosis to be an appropriate treatment goal; CAS appeared to be an illogical treatment for a problem based on embolism rather than hypoperfusion. Carotid angioplasty was first described by Morris, Lechter and DeBakey in 1967, as a treatment for fibromuscular dysplasia. An open technique was utilized with gradual dilatation of the lesions using biliary dilators [27]. A percutaneous transluminal angioplasty technique of the carotid artery was reported by Mathias [28] in 1977. In 1994 Marks and associates at Stanford University published their experience using Palmaz stents in the internal carotid arteries of two patients who had failed medical treatment for spontaneous dissection. Based on the favorable outcomes, the authors suggested that stents might be used in conjunction with angioplasty in the cerebrovascular circulation to avoid the complications of prolonged balloon inflation [29]. Diethrich et al. [30] treated 110 patients with occlusive carotid artery disease with primary CAS between 1993 and 1995. However the authors found a rate of stroke (6.4%) and TIA (4.5%) that was too high to recommend the widespread application of this procedure. This risk was further demonstrated in a randomized trial between endarterectomy and CAS in the UK. After enrolling 17 patients, the trial was halted due to the occurrence of significant neurologic events in five of the seven patients (70%) undergoing angioplasty[31]. CEA has been well established as a proven operation with durable result. Vigorous scrutiny must therefore be applied to any new procedure that challenges CEA. At present, clinical trial results are at best showing equal or inferior results for CAS compared to CEA with regard to technical success and clinical outcome (See also Discussion). Refinement of patient selection criteria and standardization of techniques will continue to improve the results of CAS. Pending the outcome of upcoming trials, the consensus remains that CAS should be restricted to high-risk patients in experienced centers within randomized trials.

2. Clinical perspective

Stroke is among the most disabling chronic diseases and the third major cause of death in the Western world. In the Netherlands, with a population of 16 million inhabitants, around 12 per 1000 inhabitants suffers a stroke, and in 2005 over 10.000 people died as a result of stroke representing 7.6% of all deaths. Ischaemic stroke represents 66% of all strokes. In 10-20% of these patients with adverse ischaemic cerebral outcome, the stroke is heralded by transient monocular blindness (amaurosis fugax) or by transient ischaemic attack (TIA). These harbingers of stroke allow us a certain amount of time to search for the cause of the symptoms and, when atherosclerotic stenosis of the corresponding carotid artery bifurcation is demonstrated, to perform carotid endarterectomy (CEA) as the best treatment in patients with ≥ 70 linear diameter artery reduction. Carotid endarterectomy removes a source of emboli, increases the flow through the artery, restores the distal perfusion pressure, changes the distribution of ipsilateral cerebral blood flow, and delays the progression of stenosis to occlusion.

Although the benefit of CEA over best medical treatment has been clearly demonstrated, still, in these landmark trials the risk of stroke or death for symptomatic patients with severe stenosis within 30 days of CEA was 6.8% in ECST and 5.8% in NASCET [24,25]. For asymptomatic patients with stenosis exceeding 60% CEA is also superior to medical therapy alone, assuming a risk of perioperative stroke or death of less than 3% [32,33].
It therefore remains essential that the benefits of surgery in reducing the long-term risk of stroke are weighed against the immediate risk of death or stroke as a complication of the surgery, and the incidence of recurrent carotid disease. The durability of the operation is dependent not only on the incidence of restenosis but also on the frequency with which recurrent stenosis causes neurologic symptoms.

3. Outline of this thesis

This thesis consists of 8 studies. The central theme that connects the chapters in this thesis is the fate of the treated carotid artery. Some studies focus on immediate postprocedural outcome while others focus on durability and score the incidence of restenosis during follow-up.
In ***Chapter 2*** the underlying mechanism of perioperative stroke and the role of intraoperative monitoring is elucidated. Additional monitoring measures to further prevent stroke from CEA are proposed.

Chapter 3 studies the effect of different antiplatelet regimens on the rate of postoperative Transcranial Doppler registered micro-embolic signals following CEA in a prospectively randomized study group of 102 procedures.
Chapter 4 reviews a consecutive series of redo CEA to determine the safety, durability and long-term benefit associated with repeat surgical treatment for restenosis.
Carotid angioplasty and stenting (CAS) has been proposed as an alternative to redo-CEA in the treatment of recurrent stenosis after CEA. *Chapter 5* presents the long-term surveillance results of CAS for this condition.
Chapter 6 evaluates the long-term effect of CAS on the ipsilateral external carotid artery (ECA). In *Chapter 7* we compared rate of restenosis in patients who underwent both CAS and contralateral CEA. *Chapter 8* describes our first experiences with the surgical managment of restenosis after CAS. *Chapter 9* summarizes our animal experiment ; conducted to evaluate carotid diameter and velocity changes due to stent placement. Finally, general conclusions and practical recommendations are presented in *Chapter 10*. This chapter summarizes the current knowledge about the quality of the current revascularization techniques and questions how outcomes can be optimised in the future.

In this thesis, all reported carotid endarterectomies have been performed under general anaesthesia and continuous intraoperative monitoring of cerebral function with combined electroencephalography and transcranial Doppler ultrasonography, and selective shunting and patching.
The clinical research for this thesis has been done in the Department of surgery and Department of Clinical Neurophysiology of the St. Antonius Hospital in Nieuwegein, and Department of Vascular Surgery, University Medical Centre Utrecht, The Netherlands.

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CHAPTER 2

STROKE FROM CAROTID ENDARTERECTOMY: WHEN AND HOW ARE IMPROVEMENTS POSSIBLE ?

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ABSTRACT

Background: The short-term benefits of carotid endarterectomy (CEA) are dependent on the operation being performed with a low incidence of perioperative neurologic morbidity and mortality. In the present study, four years of CEA with respect to the underlying mechanism of perioperative stroke and the role of intraoperative monitoring were analysed.

Methods: From January 1996 through December 1999, 599 CEAs were performed in 404 men and 195 women; mean age 65 years (range 39-88). All operations were performed under general anaesthesia using computerized electroencephalography (EEG) and transcranial Doppler (TCD). Any new or any extension of an existing focal cerebral deficit, as well as stroke-related death were registered. Perioperative strokes were classified by time of onset (intraoperative or postoperative), outcome (minor or major stroke), and anatomical side (ipsilateral or contralateral). Stroke aetiology was assessed intraoperatively by means of EEG, TCD, completion arteriography or immediate re-exploration, and postoperatively by duplex ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI).

Results: The combined perioperative stroke and stroke-related death rate was 3.3% (20 patients). In 4 patients stroke was apparent immediately after surgery. Mechanisms of these 4 intraoperative strokes were ipsilateral carotid artery occlusion (1) and embolisation (3). In 16 patients stroke developed after a symptom-free interval (2-72 h, mean 18 h) due to occlusion of the internal carotid artery on the side of surgery in 9 out of 16. Other mechanisms were: contralateral occlusion of the internal carotid artery (1), postoperative hyperperfusion syndrome (1), contralateral ischaemia due to prolonged clamping (1), and intracerebral haemorrhage (1). In three procedures cause was unknwon.

Conclusions: In our experience most strokes from CEA developed after a symptom free interval and mainly due to thromboembolism of the operated artery. We suggest the introduction of additional TCD monitoring during the immediate postoperative phase.

INTRODUCTION

NASCET and ECST have demonstrated clear benefits of carotid endarterectomy (CEA) in patients with severe carotid artery stenosis in the prevention of stroke [1,2]. However, the absolute benefit of CEA is limited by the morbidity and mortality of the procedure itself, particularly the risks of stroke and death. Although a risk profile for cerebral complications has been published [3], the actual pathophysiological mechanisms of stroke from CEA often remain unclear. About 20 mechanisms of perioperative stroke have been proposed, mainly categorised into ischaemia from carotid artery clamping, intraoperative and postoperative thrombosis and embolism, and intracerebral haemorrhage [4]. In agreement with Radak et al. [5] we believe it is important to distinguish between intraoperative and postoperative stroke. The differentiation between stroke that is apparent in the recovery room and stroke that develops after a symptom-free interval can lead to a better understanding of the underlying mechanisms and, thus, may have important clinical implications.

In our institution, the use of intraoperative computerised electroencephalography (EEG) during CEA was evaluated in 1989 [6]. With regard to the detection of intraoperative major stroke the results were promising. However, the detection of intraoperative minor stroke was unreliable. In the study of Krul et al. [7] we showed that in 69% of these minor strokes embolism was the likely cause, but these embolic events were not detected by our EEG expert system. Transcranial Doppler (TCD) is the only modality that can provide direct information about the appearance of microemboli during CEA. Made audible in the operation theatre, the embolic signals can warn the surgeon in time as to which manipulation causes embolism and, thus, he or she can try to adopt a technique that avoids further embolisation. With respect to intraoperative haemodynamics, EEG and TCD give complementary information about metabolic state of the cerebral cortex and blood flow velocities in the ipsilateral middle cerebral artery, respectively. After the introduction and standardisation of TCD monitoring during CEA in our institution, the intraoperative stroke rate declined from 4.8% to 1% [8]. However, it was disappointing to observe that our monitoring programme had not altered our postoperative stroke rate.

A more profound understanding of the present causes of perioperative stroke might be the key in further prevention of stroke from CEA, possibly resulting in additional monitoring measures. Therefore, the purpose of the present study was to examine the pathogenesis of perioperative stroke and the role of monitoring in the prevention of these strokes.

MATERIALS AND METHODS

Patients

From a prospective computerized database the records of all patients undergoing endarterectomy of the internal carotid artery from January 1996 until December 1999 were analysed. Patients with a CEA in combination with coronary artery bypass surgery as well as patients undergoing operation of the carotid artery for nonatherosclerotic disorders were excluded. In patients with a second CEA (ipsilaterally or contralaterally), these operations were included and considered as independent procedures.

Preoperative patients characteristics

Age, gender, medical history and preoperative cerebral symptoms were documented. Symptomatic patients were classified according to the most severe symptom (amaurosis fugax < transient ischaemic attack < minor stroke). Preoperative evaluation included neurological examination and assessment of ipsilateral and contralateral internal artery stenosis by duplex ultrasonography and digital arteriography. Before surgery, a computerized tomography (CT) or magnetic resonance imaging (MRI) of the head was performed in all patients.

Carotid endarterectomy

All patients were operated under general anaesthesia, using nitrous oxide and halothane or isoflurane, and were mechanically ventilated. Carotid endarterectomy was performed in a standardised way. Surgery was executed by an experienced vascular surgeon or by a specialist vascular trainee under supervision. Before cross-clamping intravenous heparin (5000 IU) was administered; protamine reversal was not used. All patients were given 100 mg aspirin daily which was continued postoperatively. Duplex was performed 3 months after surgery.

Intraoperative monitoring

The methods of intraoperative brain function monitoring have been discussed elsewhere in detail [9,10]. In summary, all patients underwent EEG monitoring with fronto-parietal and temporo-occipital leads. In addition, TCD monitoring of the ipsilateral middle cerebral artery blood flow velocities was possible in 90% of the operations. Patients were selectively treated with intra-arterial shunting (Javid shunt) on the basis of EEG and TCD criteria mentioned in these reports. In patients at risk for a hyperperfusion syndrome, based on intraoperative TCD monitoring variables [11], blood pressure was closely monitored and controlled with medication intraoperatively after declamping and postoperatively on the medium care unit or the surgical ward.

Outcome

Pre- and postoperatively, all patients were assessed by the vascular surgeon. In the case of possible cerebral deficit the patient was examined by a neurologist. In the analysis, we focused on the occurrence of ischaemic and haemorrhagic stroke and stroke-related death within 7 days. Cerebral deficits persisting for more than 24 hours were regarded as stroke. Transient neurologic deficits were not included in this study. Perioperative strokes were classified by time of onset (intraoperative or postoperative), outcome (minor or major stroke), and side (ipsilateral or contralateral to the side of surgery). The severity of stroke was graded according to the modified Rankin scale [12].

Intraoperative stroke was defined as a persistent neurological deficit that became obvious at the conclusion of the operation, or at awakening from general anaesthesia in the recovery room. Postoperative stroke was defined as a persistent neurological deficit that developed within hours or days after the patient had awakened neurologically intact. Strokes that occurred on the side which was operated on were classified as ipsilateral strokes and those that occurred on the side which was not operated as contralateral strokes. Major stroke was defined as a persistent and disabling neurologic deficit that was present at the time of discharge from the hospital. Minor stroke was defined as a persistent but non-disabling neurologic deficit that was present at the time of discharge from the hospital.

We correlated the onset of cerebral symptoms with specific operative and monitoring events (carotid artery dissection, clamping and declamping, EEG asymmetry, TCD detected cerebral embolism and changes of MCA blood flow velocities). Furthermore, the pathogenesis of these strokes was assessed by completion arteriography or by means of intraoperative findings on immediate re-exploration of the carotid artery, and postoperatively by duplex ultrasonography, TCD, head CT or MRI. All these forms of quality control assessment were only performed in patients with possible stroke from CEA. We consider re-exploration an option when a CT-scan has ruled out cerebral haemorrhage and re-operation can be carried out within 3 hours after onset of symptoms. For logistic reasons this was not possible in all patients. Routine postoperative TCD monitoring to evaluate the possible impact of microemboli during the first hours after surgery on clinical outcome was not done.

Statistical analysis

Fisher's exact test and student t-test were used to test the differences of clinical and operative variables between the groups of patients with and without postoperative stroke. Probability values $p < 0.05$ were considered statistically significant.

RESULTS

A total of 599 consecutive carotid endarterectomies were studied. Clinical and surgical characteristics are outlined in Table 1. Three patients died from their stroke, resulting in a mortality-rate of 0.5%. Perioperative stroke occurred in 20 patients (3.3 %). Patients with a perioperative stroke showed more severe contralateral carotid artery disease; specifically, a subtotal stenosis (90-99%). Intraoperative stroke was assessed after 4 operations and postoperative stroke after 16 operations.

	Non-stroke n=579	Stroke n=20	p/value
Male gender	378 (65%)	17 (85%)	0.09
Mean age	65 (39-88)	68 (52-82)	0.27
Clinical presentation			
Ischaemic stroke	168 (29%)	7 (35%)	0.62
Asymptomatic	131 (23%)	8 (40%)	
Contralateral ICA (preop)			
Subtotal stenosis	39 (6.7%)	5 (25%)	0.01
Occlusion	103 (18%)	7 (35%)	0.07
Shunt used	174 (30%)	11 (55%)	0.03
Patch used	259 (45%)	11 (55%)	0.37

ICA = internal carotid artery.

Table 1. Clinical and operative characteristics of the non-stroke and stroke group

Intraoperative stroke

Four ipsilateral strokes (0.7%) were immediately apparent on waking from anaesthesia; two minor and two major strokes. In two operations, TCD detected multiple microembolism was the probable cause of cerebral deficit. In one operation a macroembolus blocked the MCA blood flow. In this patient, the postoperative CT scan showed a hyperdense artery sign in the MCA mainstem. In the fourth operation, there was ipsilateral thrombotic occlusion of the operated artery.

Postoperative stroke

In sixteen (2.7%) patients stroke appeared after a symptom-free interval of between 2 hours and three days following surgery (mean 18 h). Thirteen of these 16 strokes developed within the first 24 hours. Neurological outcome was a minor stroke in 7 patients

Onset	Contra	Shunt	Patch	Time onset (h)	Cause	Re-expl.	Outcome
I	90	N	Y	0	Embolisation	N	Minor
I	30	Y	N	0	Embolisation	Y	Minor
I	50	Y	N	0	Embolisation	Y	Major
I	100	Y	N	0	Occlusion	Y	Major
P	100	N	N	24	Occlusion	N	Minor
P	100	Y	Y	72	Occlusion	N	Minor
P	100	Y	Y	7	Occlusion	Y	Major #
P	0	N	Y	48	Occlusion	N	Major
P	40	N	Y	4	Occlusion	N	Major
P	80	N	N	9	Occlusion	N	Major #
P	100	Y	Y	3	Occlusion	Y	Major
P	100	Y	Y	2	Occlusion	Y	Major #
P	90	N	Y	19	Occlusion	N	Major
P	90	Y	N	2	HPS	N	Major
P	90	N	Y	32	Haemorrhage	N	Major
P	100	Y	N	6	Clamp time	N	Major *
P	90	Y	Y	18	Contralat occl.	N	Minor *
P	0	N	N	18	Unknown	N	Minor
P	90	Y	Y	24	Unknowm	N	Minor
P	0	N	N	24	Unknown	N	Minor

I = intraoperative, P = postoperative; Contra = degree of stenosis (%) of contralateral internal carotid artery; HPS = postoperative hyperperfusion syndrome; # = death due to stroke; Contralat occl = occlusion of the contralateral internal carotid artery; * = stroke contralaterally to the side of surgery.

Table 2. Preoperative and intraoperative characteristics, time of onset, causes of perioperative stroke, and outcome in 20 eventful CEAs.

and a major stroke in 9 patients. Except for 2 strokes (one minor and one major) that developed on the contralateral side, all postoperative strokes appeared on the ipsilateral side. In 13 of 16 cases it was possible to determine the specific or most probable cause: ipsilateral occlusion (9), contralateral internal carotid artery occlusion (1), intraoperative

hypoperfusion due to prolonged clamping (1), postoperative hyperperfusion syndrome (1), and intracerebral haemorrhage (1). In 3 patients (all minor strokes) it was not possible to pinpoint the cause of cerebral deficit.
Of the 20 CEA's that resulted in a stroke, Table 2 summarizes the most probable causes of cerebral deficit. Information about contralateral internal carotid artery stenosis, the use of a shunt or patch, and intraoperative findings at re-exploration are also shown.
In the group of 20 patients with intraoperative or postoperative cerebral deficit, a CT-scan of the head was performed in 19 cases. Postoperative angiography, duplex scanning or TCD monitoring were performed in 12 cases. Six patients were reoperated at the onset of neurological symptoms (3 intraoperative, 3 postoperative). In 4 patients reexploration confirmed an acutely thrombosed endarterectomy site and revision was performed. One of these 4 thrombotic occlusions was caused by a technical error and in three cases no evidence of technical error was found. In the remaining two patients re-exploration showed a mural thrombus in one, suggesting intraoperative embolisation as the cause. Unfortunately, in this patient TCD monitoring was not possible due to a poor acoustic window. In the last patient a patent vessel was found at re-exploration.
At three months, duplex follow-up of 579 non-stroke patients revealed an asymptomatic occlusion of the operated artery in 5 patients (0.9%). In the remaining patients all operated carotid arteries were found fully patent or with slight residual stenosis.

DISCUSSION

The present study evaluated the causes of perioperative stroke (intraoperative and postoperative) from CEA. We observed that during carotid surgery with intraoperative EEG and TCD monitoring intraoperative stroke only occurred in 4 out of 599 (0.7%) procedures. In contrast, a postoperative stroke was assessed in 16 operations (2.7%). In 9 out of the 16 (56%) postoperative strokes an occlusion of the operated artery was found. Moreover, in an additional 5 patients an asymptomatic occlusion of the operated artery was found with duplex ultrasonography. At three months after an uneventful CEA. Two patients (0.3%) developed symptoms of a postoperative hyperperfusion syndrome, one with and one without an intracerebral haemorrhage. Finally, 2 patients developed a stroke of the contralateral hemisphere. In one patient this was an intraoperative major stroke due to a difficult shunting procedure with prolonged clamping time. In the other patient, a tightly stenosed contralateral internal carotid artery completely occluded symptomatically one day after surgery.
Previous studies have shown that the introduction of standardised TCD monitoring during

CEA results in a decrease of the intraoperative stroke rate [13-15]. We share the opinion of these investigators that surgeons can be guided by the " embolic signals" and accordingly can adapt their technique to prevent a serious outcome. Moreover, in the course of TCD monitoring, it became apparent that microembolism occurring during dissection and wound closure showed a statistically significant association with perioperative stroke [16]. Since the introduction of intraoperative TCD monitoring in our institution in 1990, the intraoperative stroke rate from CEA declined from 4.8% in the late eighties [6,7] to 0.7% in this study.

With respect to postoperative stroke, probably the most devastating cerebral complication is the so-called postoperative hyperperfusion syndrome often resulting in intracerebral haemorrhage and death. Dalman et al. [11] have shown that TCD monitoring can reliably identify patients who are at risk. With strict postoperative control of hypertension the incidence of symptomatic hyperperfusion after CEA decreased from 2.1% in the early nineties [17] to 0.3% in this study.

Most (early) postoperative strokes are thought to be caused by technical errors made during CEA and are, therefore preventable and correctable within a certain time limit [15]. On the other hand, specific studies analysing the relative importance of technical errors in the development of postoperative stroke concluded differently, making technical errors responsible for less than 20% of postoperative strokes [18].

A frequent cause of postoperative stroke from CEA is thrombus formation at the endarterectomy and clamping sites coupled with an increasing cerebral embolic load. This often results in an occlusion of the operated artery [19-22]. Evidence suggests that platelets adhere to the exposed collagen of the endarterectomy site within minutes of restoring flow [19] and the maximal rate of adherence appears to be 1 hour after clamp release [20]. French et al. showed that a variable degree of adventitial acute inflammatory infiltration and medial necrosis is a consequence to any endarterectomy procedure in the acute phase [21]. It is at these sites of necrotic, inflamed media or direct adventitial exposure that mural thrombus is deposited. Clagett et al. hypothesized a process of ongoing thrombogenesis beginning immediately after blood flow is restored across the endarterectomized surface [22]. From this point of view even in the absence of technical failure every endarterectomised artery can embolize and subsequently thrombose.

Spencer et al. [23] first observed that TCD detected cerebral microemboli that occur during the first hours after CEA may be associated with postoperative cerebral deficit. More recently, several studies [24-26] revealed that a small proportion of patients (5-10%) who underwent CEA showed sustained cerebral embolisation, with a maximum rate of embolism during the first postoperative hours. Moreover, Cantelmo et al. [27] demonstrated that multiple cerebral microemboli during the immediate postoperative phase were

statistically significantly associated with new, clinically silent ischaemic lesions on MRI of the brain made after surgery. TCD monitoring in the early postoperative course of CEA has the potential to identify patients at high risk of postoperative embolic stroke. There is a strong association between embolic rates exceeding 50 microemboli per hour and focal postoperative ischaemic deficit [24-26] . Moreover, the administration of Dextran - 40 in the selected group of patients significantly reduced the risk of carotid thrombosis and cerebral embolic burden and, finally, resulted in a postoperative stroke rate of 0% [28].
The present study presents several limitations. Cerebral deficit was primarily assessed by a vascular surgeon and a neurologist was consulted only in patients with possible postoperative neurological complications. Therefore, it is reasonable to assume that some minor signs and symptoms of cerebral deficit were missed. Second, in 3 out of 20 CEA's that resulted in a postoperative minor stroke we were not able to find a plausible explanation for the underlying pathophysiological mechanisms. Third, postoperative TCD monitoring could not be of help because it was not routinely performed in our patients. Thus, there is only indirect evidence that postoperative thrombosis and occlusion resulted in a significant embolic burden and postoperative stroke.

In conclusion, intraoperative EEG and TCD monitoring has shown to be effective in the prevention of intraoperative ischaemic and haemorrhagic stroke. In contrast, postoperative thrombosis formation and occlusion still complicated CEA in a significant number of patients. In the present study of 599 CEA's, we found 10 symptomatic (1 intraoperative and 9 postoperative) and 5 asymptomatic occlusions of the operated artery, i.e. in 2.5% If TCD monitoring during the first hours after CEA has the ability to identify carotid thrombosis prior to the occurrence of carotid artery occlusion and cerebral deficit, this will be an important additional clinical application of this technique.

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CHAPTER 3

INFLUENCE OF ANTIPLATELET THERAPY ON CEREBRAL MICRO-EMBOLI AFTER CAROTID ENDARTERECTOMY USING POSTOPERATIVE TRANSCRANIAL DOPPLER MONITORING.

A prospective randomised trial

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ABSTRACT

Aim: To study the effect of different antiplatelet regimens (APT) on the rate of postoperative TCD registered micro-embolic signals (MES) following carotid endarterectomy (CEA).

Design: Prospective, randomised, double-blinded, pilot study.

Methods: The study group of 102 CEA patients (76 men, mean age 66.8 years) was randomised to routine Asasantin (Dipyridamole 200mg / Aspirin 25mg) twice daily (group I; n= 39), Asasantin plus 75mg Clopidogrel once daily (group II; n=33), or Asasantin plus Rheomacrodex (Dextran 40) 100g/L iv; 500ml (group III; n=30). TCD monitoring of the ipsilateral middle cerebral artery for the occurrence of MES was performed intraoperatively and during the second postoperative hour following CEA. Primary endpoints were the rate of postoperative emboli and the occurrence of cerebrovascular complications. Secondary endpoint was any adverse bleeding.

Results: There were no deaths or major strokes. We observed 2 intraoperative TIA's (group II and III) and 1 postoperative minor stroke (group I). In comparison with placebo, Clopidogrel or Rheomacrodex in addition to Asasantin produced no significant reduction in the number of postoperative MES. There was no significant difference between the number of postoperative MES and different antiplatelet regimens. The incidence of bleeding complications was not significantly different between the 3 APT groups.

Conclusion: In the present study, we could not show a significant influence of different antiplatelet regimens on TCD detected postoperative embolization following CEA.

INTRODUCTION

The in-hospital mortality of carotid endarterectomy (CEA) is 0-2% and the occurrence of ipsilateral minor or major stroke is reported 2-5% [1,2]. Intraoperative stroke, apparent on recovery from anaesthesia, has been virtually abolished by introducing a policy of intraoperative transcranial Doppler (TCD) monitoring [3,4]. However, this policy showed little effect on the prevention of early (<6 hours) postoperative stroke due to thrombosis of the endarterectomised zone, which continued to complicate 2.5% of CEA's [4-6]. It is well known that platelets begin to adhere to the endarterectomy zone within minutes of flow restoration [7] but it is still unknown why this becomes excessive in some patients, leading to new postoperative cerebral deficits.

Several centres have shown that patients destined to suffer an early postoperative stroke have a 1- to 2- hour period of increasing embolization before cerebral deficit becomes apparent [4,8-12]. The prevailing view is that, as the platelet thrombus accumulates, small particles are shed into the carotid circulation as micro-emboli. These micro-embolic signals (MES) can be detected by postoperative TCD monitoring of the ipsilateral middle cerebral artery (MCA). Overall, about 50% of patients with CEA will have one or more emboli detected in the postoperative period, but only about 5% will progress to high grade sustained embolization [4,5,13]. Of these, 30% to 60% will progress to thrombotic stroke [8,10]. Except for a meticulous surgical technique during endarterectomy the choice of antiplatelet therapy might be a powerful instrument to prevent these postoperative MES [14-16]. It is important to note that commonly used pretreatment regimens with antiplatelet agents, in most cases aspirin, do not abolish thrombo-embolization or embolic stroke in the early postoperative period [17]. Aspirin inhibits only 1 of the several pathways of platelet activation, and platelet activation through an aspirin insensitive pathway may be more important in the occurrence of thrombo-embolization [18]. Dual therapy with aspirin and Clopidogrel therefore may prove more effective in reducing thrombo-embolic complications [15,19].

Postoperative monitoring for MES is believed to be a proper quantative diagnostic tool that helps in deciding which patients could benefit from additional treatment. Selective TCD guided administration of Dextran has already been shown successful in reducing embolization and progression to stroke [13,20]. However, this policy is expensive and labour intensive and is unlikely to be adopted into routine clinical practice. It would be preferable to target appropriate antiplatelet pharmacotherapy from the outset.

In the present study we compared three different perioperative antiplatelet regimens and their influence on clinical outcome and postoperative TCD detected embolization in patients undergoing CEA.

METHODS

Study design

The present randomized and double blinded pilot study with 30 patients planned in each subgroup was performed between 2004 and 2006 in the St. Antonius Hospital, Nieuwegein, with Ethics Committee approval. All patients gave Informed Consent. Inclusion criteria were 1) internal carotid artery (ICA) stenosis of ≥ 70% on preoperative duplex ultrasound; 2) no preceding ipsilateral carotid intervention; 3) accessible transcranial window for TCD registration. Patients already on warfarin, dipyridamole, or Clopidogrel were excluded. Patients were defined asymptomatic in absence of cerebrovascular symptoms within 120 days prior to surgery.

Carotid endarterectomy

Patients underwent standard CEA under general anaesthesia. Surgery was executed by an experienced vascular surgeon or a vascular trainee under supervision. A shunt or patch was selectively used.

TCD monitoring

Continuous TCD monitoring of the ipsilateral MCA for the occurrence of MES was performed during operation and during the second hour postoperatively. Four successive stages of operation were: 1) dissection (skin preparation to carotid clamping; 2) shunt manipulation (shunt introduction to shunt removal); 3) clamp release; and 4) wound closure [21]. All TCD data were stored on CD Rom for offline analysis. Technical details of intraoperative [22] and postoperative [23] monitoring have been described previously. Postoperative embolization was quantified using standardized consensus criteria [23,24]. All TCD measurements were performed by a single highly experienced technician (MvdM). High grade postoperative embolization was defined as > 20 MES per hour.

Trial Medication

Three different antiplatelet regimens (APT) were compared in patients undergoing CEA.

Group I: Asasantin 25/200 mg (dipyridamol 200mg /aspirin 25mg) 2dd orally. Started at least 3 days preoperative and continued for 3 months postoperative.

Group II: As group I but with addition of Clopidogrel 1dd 75mg; started at least 3 days preoperative and also continued for 3 months postoperative.

Group III: As group I with addition of Rheomacrodex (Dextran 40) solution 100 g/L iv; 500 ml during the first 6 postoperative hours starting during skin closure.

In all patients, heparin (5.000 IU) was administered before cross-clamping; protamine

reversal was not used. Platelet aggregation tests were not performed. Trial medication was blinded for both the surgeon and TCD technician. Analysis of CD-rom stored TCD data was performed on distance by T.H. and R.A. who were also blinded for trial medication. Heparin dose-response relationship was calculated with the activated clotting time (ACT).

Study outcome

Primary outcomes were the number of postoperative MES and the occurrence of adverse clinical neurological symptoms. Secondary outcome was the occurrence of any bleeding complication. Before and after surgery, patients were evaluated by an independent neurologist. Any new neurological deficit lasting for > 24 hours in the first 30 days was classified as a stroke. The severity of stroke was graded according to the modified Rankin scale [23]. Intraoperative stroke was defined as a persistent neurological deficit that became obvious at the conclusion of the operation, or at awakening from general anaesthesia. Postoperative stroke was defined as a persistent neurological deficit that developed within 48 hours after a symptom free interval.

Group size

Power calculations could not be performed. The present study was therefore a pilot with 30 patients planned in each subgroup.

Protocol intervention

Patients were operated on with intention to treat. Protocol intervention was defined as any reoperation or change in trial medication. Change of antiplatelet medication after the initial monitoring hour (second postoperative hour) was not considered to interfere with protocol. Any patient suffering high grade postoperative embolization was started on Rheomacrodex according to hospital protocol [20]. In these cases, TCD registration was prolonged for 1 extra hour to monitor the effect of drug intervention.

Statistical analysis

Data were analyzed using SPSS version 11.5 (SPSS Inc. Chicago, Illinois). Groups were compared with Students-T and chi-square test, or Mann-Whitney/ Kruskal-Wallis (K-W) tests for non-normally distributed variables. Correlations were tested using Pearson correlation coefficient, or Spearman/Kendall (S/K) for non-normally distributed data. Probability values $p > 0.05$ were considered non-significant. To obtain a normal distribution, and for display purposes, a square root (sqrt) transformation of the number of emboli was employed.

RESULTS

Demographics

We included 102 patients (76 male mean age 67.5 ; sd = 7.9, and 26 women mean age 64.7 ; sd = 10.1 (p = 0.21)). In 53 patients (52%) the operation was performed on the right side. Seventy-nine patients (77.5%) were symptomatic (amaurosis fugax (AF) 9 (8.8%), transient ischaemic attack (TIA) 34 (33.3%), minor stroke 32 (31.4%), and vertebro basilar insufficiency (VBI) 4 (3.9%). A shunt was used in 27 (36.3%) and a patch in 80 procedures (venous 47 (46%), Dacron 33 (32%)). All groups were well matched, with no significant difference in age, sex, weight, atherosclerotic risk factors, or presenting symptom.

Trial medication

Allocation of trial medication: Group I (Asasantin): 39 (38.2%), Group II (Asa/Plavix) 33 (32.4%), Group III (Asa/Rheo) 30 (29.4%). The allocation of men and women in medication groups was statistically not different (Chi ^{2}) [Table 1].

		Inclusion group		
		Asasantin	Asa/Plavix	Asa/Rheo
Sex	Male	27	24	25
	Female	12	9	5

Table 1. Allocation of men and women in 3 medication groups.

There was also no statistical significant difference in medication group allocation between the various clinical groups (Chi ^{2}) [Table 2].

		Inclusion group			
		Asasantin	Asa/Plavix	Asa/Rheo	Total
Symptomatology	Asympt	11	7	5	23
	TIA	9	14	11	34
	Minor Stroke	14	6	12	32
	AF	5	3	1	9
	Other	0	3	1	4
Total		39	33	30	102

Table 2. Allocation of preoperative symptoms to treatment groups.

TCD registered micro-embolization

There was no correlation between the number of intraoperative MES during the 4 different operative phases (S/K correlation). The number of intraoperative emboli showed no difference between men and women (Mann-Whitney). There was no correlation between the intra- and postoperative MES (S/K coefficient: NS) [Figure 1].

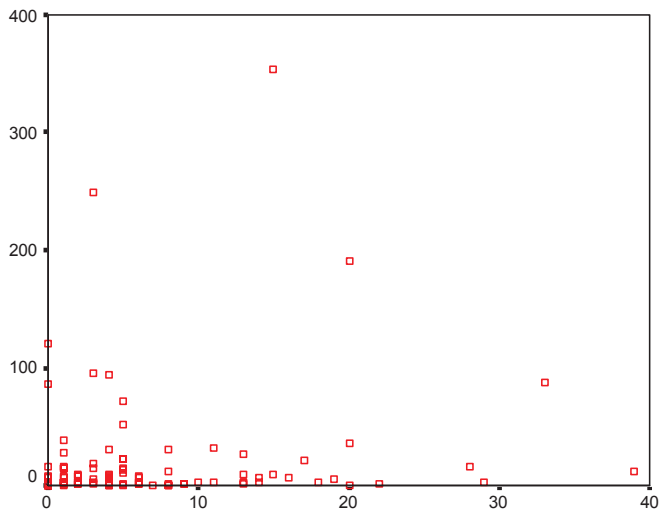

Figure 1. Correlation of intra- and postoperative embolization. Non-parametric correlation: Spearman / Kendall correlation coefficients: non significant. (Total number of emboli during second postoperative hour versus Total number of emboli during carotid endarterectomy).

Interestingly, only the number of emboli during woundclosure showed a correlation with postoperative MES (S/K r=0.26/0.20, p = 0.008/0.011) [Figure 2].

The total number of postoperative emboli in the second postoperative hour showed a wide range of variation [Table 3]; and therefore a skewed distribution pattern [Figure 3]. Even after Sqrt (x) transformation the population mean was influenced by high individual outliers [Figure 4]. However, different approaches of analysis all showed a gradual decrease of MES in the second postoperative hour [Figure 5]. This effect was seen throughout the spectrum from low- to high-grade embolization. Women showed significantly more postoperative emboli than men. There was no significant correlation between the side of surgery (p=0.75), the use of patch nor type of patch (p=0.89) and/or shunt and the occurrence of postoperative embolization.

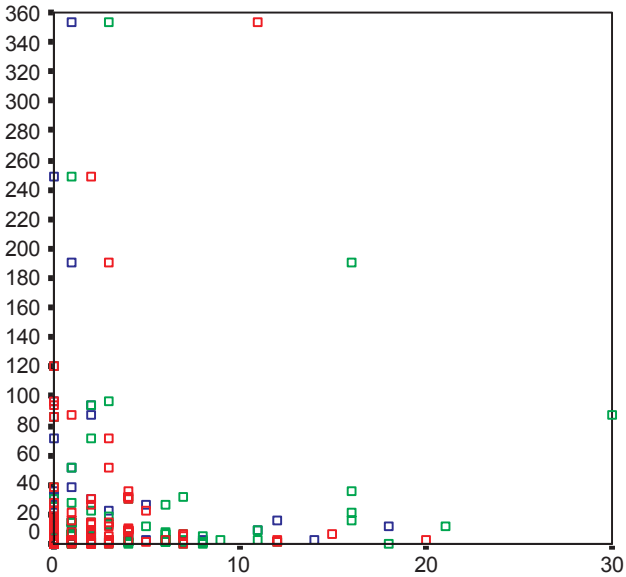

Figure 2. Correlation of intraoperative parameters with postoperative embolization. (Blue = closure of the arteriotomy, green = restoration of circulation, red = dissection). (Postoperative number of emboli vs perioperative emboli). Only the number of emboli during woundclosure showed some correlation with the postoperative number of emboli (S/K r 0.26/ 0.20, p = 0.008/ 0.011).

N	Valid	102
	Missing	0
Mean		20.29
Median		5.00
Std. Deviation		49.693
Range		354
Minimum		0
Maximum		354
Percentiles	25	1.00
	50	5.00
	75	15.00
	80	19.20
	90	47.40

Table 3. Total number of TCD detected emboli in complete study group during the second postoperative hour (N=102).

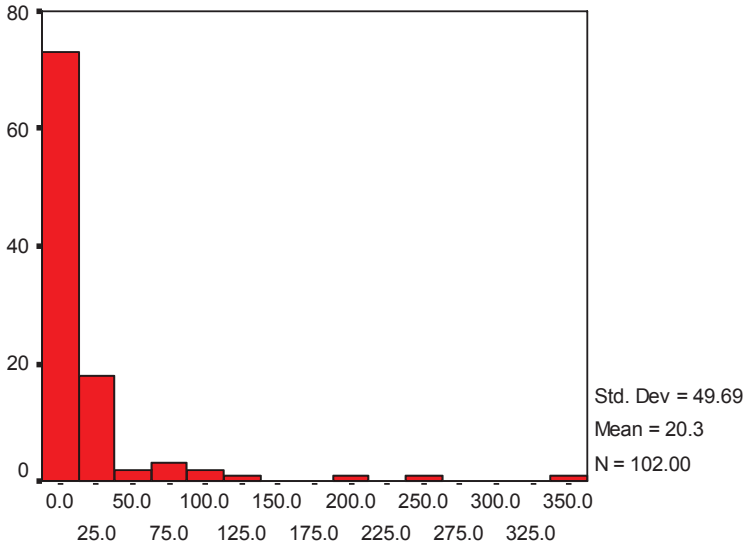

Figure 3. Total number of TCD detected emboli during the second postoperative hour. (Frequency vs total number of emboli).

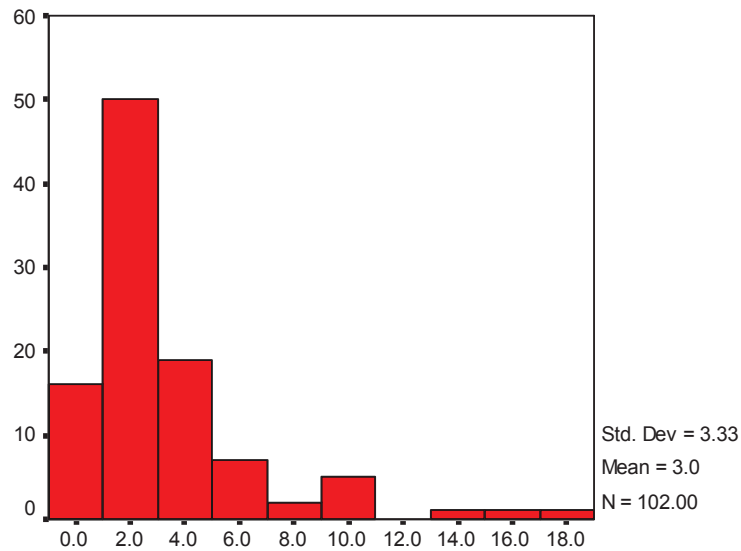

Figure 4. Total number of TCD detected emboli during the second postoperative hour after transformation. (Frequency vs Sqrt total number of emboli). Outliers are marked with an arrow.

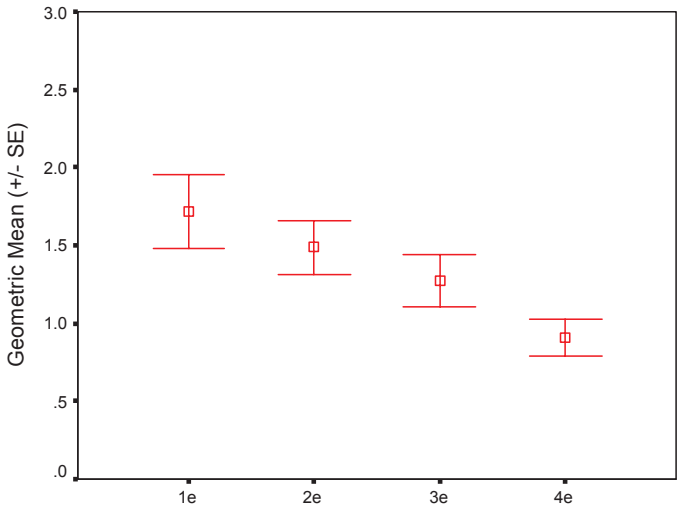

Figure 5. Total number of TCD detected emboli during the second postoperative hour. Data for complete study group after transformation, after splitting up for the separate quarters.

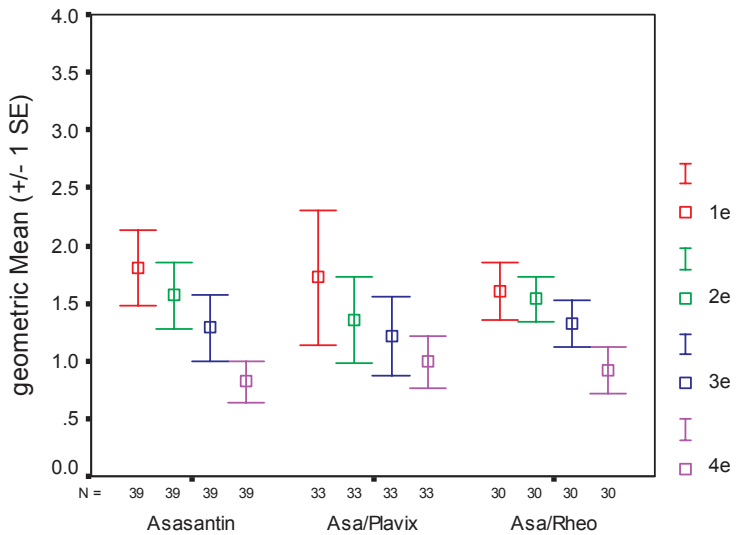

Figure 6. Postoperative number of TCD detected emboli for complete study group after splitting up for different medication sub-groups. (Red = first quarter, green = second quarter, blue = third quarter, pink = fourth quarter).

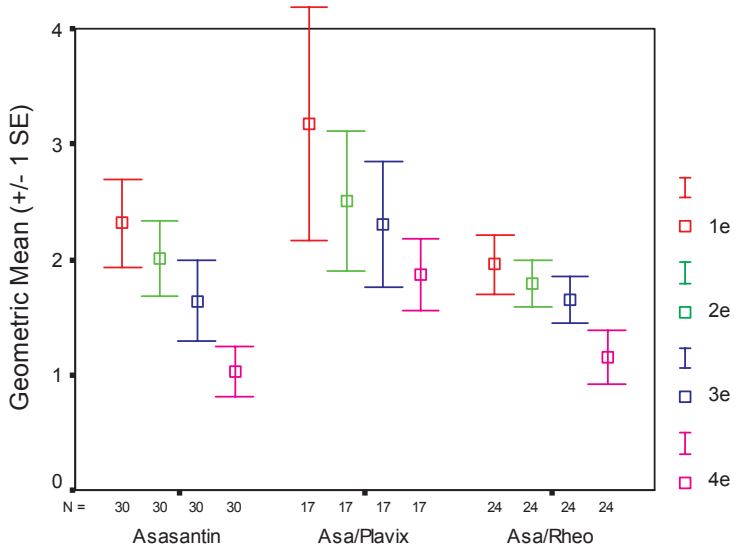

Figure 7. Postoperative number of TCD detected emboli for patients with ≥ 1 emboli, after splitting up for different medication sub-groups. (Red = first quarter, green = second quarter, blue = third quarter, pink = fourth quarter).

There was no significant difference between the number of postoperative emboli and different antiplatelet regimens (K-W) [Figure 6 + 7]. Sub-analyses on sex, patients with ≥ 1 emboli, or only patients > 20 emboli /hour also did not reach statistical significance.
Besides group III patients, another 8 patients (5M, 3F) required Rheomacrodex to control continued embolization (Group I (4) and Group II (4)). In all 8 patients Rheomacrodex successfully decreased the embolic rate, and no other adverse cerebral events occurred in these 8 patients. None of these patients was indicated for re-exploration.

	Group I	Group II	Group III	
Variable	Asasantin (n=39)	Clopidogrel (n=33)	Rheomacrodex (n=30)	p
Transfusion	1	1	0	NS
Reexploration	1	2	2	NS

Table 4. Bleeding complications in the three medication groups.

Clinical outcome

No major strokes or deaths occurred. Adverse cerebral events occurred in 3 patients (3%). Two patients showed an intraoperative ipsilateral TIA (1 group II, 1 group III). In 1 patient

an ipsilateral postoperative minor stroke was observed (group I). With this complication rate our study was underpowered to analyse a relationship between adverse cerebral events and APT. The patient with minor stroke had no preceding high-rate embolization. Five patients received re-exploration, all because of bleeding complication (NS) [Table 4].

DISCUSSION

In the present pilot study, we could not show a significant influence of different antiplatelet regimens on TCD detected postoperative embolization following CEA. In all 3 treatment sub-groups a gradual decrease of emboli in the second postoperative hour was shown. Women showed significantly more postoperative emboli than men, but there was no significant difference between sex and emboli in relation to APT. Two intraoperative TIA's and 1 postoperative minor stroke were noted. Eight patients required TCD directed Rheomacrodex to control continued embolization, which showed to be successful in lowering the embolic rate in all 8.

Postoperative stroke was previously assumed to follow technical error. However, in patients re-explored for postoperative cerebral deficit, a platelet-rich thrombus was invariably found adherent to an otherwise normal endarterectomy zone [7,23,25]. This suggested that it might be the patients' inherent platelet activity that determined those at risk of postoperative thrombotic stroke, and not technical error [25]. CEA involves the removal of atherosclerotic plaque with resulting exposure of a relatively large area of underlying medial collagen and adventitia. This injury to the arterial wall leads to platelet adherence on the denuded vessel immediately after CEA in humans [26]. The thrombogenic endarterectomy zone can subsequently become the source of emboli following flow restoration.

Stroke due to post-operative carotid thrombosis (POCT) still complicates 2-3% of CEA's and has long been thought to be unpreventable. With the evidence of increasing postoperative embolisation preceding any neurological deficit [4,8-13] this view has changed. These TCD detected MES can serve as a marker of stroke risk and as a surrogate marker to evaluate and monitor antiplatelet agents [8,10,11]. Administration of Dextran has been shown to both reduce high-grade postoperative embolization and prevent thromboembolic stroke, providing further evidence of the important association between these two events [4,13,20]. Following the introduction of TCD-directed Dextran therapy, the rate of thrombotic stroke after CEA was shown to fall from 2.7 per cent to zero [4,27]. Although several authors have proposed a threshold of MES for increased risk of adverse cerebral events [4,10,12,13,28], their outcome was highly variable and thus at present no consensus exists on which threshold to use.

Several hours of postoperative TCD monitoring is impractical outside a research programme; however, the technique appears to work in smaller periods without loss of clinical yield [23]. In our previous work one hour monitoring appeared to be effective to select patients in whom the number of microemboli did not spontaneously decrease [23]. In the present study, patients thus underwent 1-hour of monitoring which had a sufficiently alarming function, since in 8 patients with sustained embolization (range 49 -354/ hour; mean 149/ hour) Rheomacrodex was successful in lowering the embolic rate, and none of these 8 developed adverse cerebral events after leaving the recovery room. These 8 patients should be considered as failures within their own APT group (4 group I, 4 group II). Unfortunately, retrospectively, we found no relation between embolization during woundclosure (0 emboli (5), 1 emboli (2), 2 emboli (1)) and development of high-grade postoperative embolization. Identification of embolization during woundclosure therefore does not seem to be helpful in selecting patients who need pharmacological intervention. Targeted modification of pre-operative APT will probably be a promising alternative way in the prevention of perioperative MES and subsequent devastating cerebral events. Ideally, a "one-size-fits-all" APT could be designed. It is important to note that commonly used pretreatment regimens with antiplatelet agents, in most cases aspirin, do not abolish thrombo-embolization in the early postoperative period [17]. Aspirin inhibits only 1 of the several pathways of platelet activation, and platelet activation through an aspirin insensitive pathway may be more important in the occurrence of thrombo-embolization. Furthermore, a significant proportion of patients taking aspirin do not show laboratory evidence of platelet inhibition [18] although resistance to other antiplatelet regimens also must be considered.

Dual therapy with aspirin may prove more effective in reducing thrombo-embolic complications [15,19,29]. Ex-vivo experiments have confirmed the synergistic antithrombotic effects of a combined therapy and showed the early benefit obtained with a loading dose of Clopidogrel [15]. Hayes et al have also shown that in CEA patients, the preoperative response of platelets to adenosine diphosphate (ADP) was predictive of postoperative embolization, concluding that platelet ADP-receptor antagonism could prevent perioperative cerebral embolization [16]. More recent evidence showed a significant reduction in postoperative embolization by the administration of a single 75 mg dose of Clopidogrel the night prior to surgery (in addition to regular aspirin) [19]. Clopidogrel also showed significant reduction in expression of markers of platelet activation in response to ADP compared to aspirin or aspirin with dipyridamole [30]. Clopidogrel therefore seems more efficacious than other APTs at a molecular level but its clinical role remains controversial [4]. In our study, the number of postoperative MES was lower in the Clopidogrel group compared to group I and III but this difference was not statistically significant [Figure 6]. When comparing patients with ≥ 1 emboli , the number of emboli was even higher in the group of patients receiving

Clopidogrel, but also this effect was not statistically significant [Figure 7].
In vivo, combined therapy with Clopidogrel and aspirin significantly increased the bleeding time [31]. In our study, re-explorations were performed in 5 patients for bleeding complications which is in excess of expectations following CEA. APT groups were too small to find a relationship between bleeding complication and APT [Table 4]. Therefore, future studies have to search for APT that balance between minimal embolization rate and minimum of bleeding complications. In particular we need to know: 1) are certain patients at increased risk of postoperative embolization and thrombosis, and if so how can we identify them ?; 2) what is the best treatment for patients with sustained embolization ?; 3) what is the optimal preoperative APT in lowering both postoperative MES and adverse cerebral deficit ?
The correlation of microemboli during wound closure with ongoing postoperative embolization is pathophysiologically interesting and theoretically of help in identifying patients at risk for sustained embolization [14]. However, as described above, our 8 patients that were provided additional Rheomacrodex hardly showed embolization during woundclosure. Stork et al identified 3 factors associated with postoperative MES: female sex, left-sided CEA, and absence of preoperative APT [14]. Two of these are non-modifiable risk factors, leaving only preoperative APT as a modifiable factor influencing outcome.
Our study has several potential limitations. First, > 60 minutes monitoring might be needed to identify differences in embolic rate. Second, it is important to note that the analysis reported here was a pilot with small group size. The study may therefore have been underpowered. Third, plaque characteristics were not studied in the present population. Fourth, aggregation tests were not performed, but heparin effect was checked by ACT. Based on ACT measurements, no additional heparin was provided in this study population. Fifth, a surrogate (MES) served as a marker for clinical outcome (stroke). We believe that this surrogate marker reliably predicts clinical outcome following CEA [4,27]. However, it is harder to show that the desired outcome (reduced thromboembolic stroke incidence) is based on the drug effect on the surrogate. Although the dramatic reduction in embolic events in patients treated with Dextran or Rheomacrodex is encouraging, the fact that one of our patients without warning signals on TCD still experienced postoperative minor stroke is discouraging.
Despite, inhibiting postoperative embolization seems to represent a therapeutic strategy in reducing stroke after CEA. Nevertheless, the role and clinical efficacy of TCD detected microemboli as a surrogate measure for stroke after CEA remains to be better validated. First, further well-powered studies need to be undertaken to determine the optimum perioperative APT in reducing postoperative embolization. Future research has to focus on potentially more effective combinations of ASA with other antiplatelet drugs. Although TCD

may still be used to identify patients at high risk in the early postoperative period, it seems likely that the optimal role for TCD will be to develop novel targeted modification of pre-operative APT, so that, ultimately, no postoperative monitoring is necessary at all.

Conclusion

In the present study no significant difference between the number of postoperative emboli and different antiplatelet regimens was found. In all study subgroups, linear regression of emboli in the second postoperative hour was observed. TCD directed Rheomacrodex infusion showed successful in lowering MES rate.

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CHAPTER 4

DURABILITY OF SURGERY FOR RESTENOSIS AFTER CAROTID ENDARTERECTOMY.

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ABSTRACT

Background: The role of carotid surgery for the management of post-endarterectomy restenosis is challenged by Carotid Angioplasty and Stenting (CAS). We reviewed a consecutive series of redo Carotid Endarterectomy (CEA) to determine the safety, durability and long-term benefit associated with repeat surgical treatment for restenosis.

Methods: A consecutive series of 73 redo procedures in 72 patients (57% man, mean age 66 years; range 49-81) was analyzed. The mean interval between prior CEA to re-CEA was 53 months (range 8 to 192 months). Operative indications included symptomatic restenosis in 28 (38%) patients. In 62 patients (85%) a patch angioplasty was performed. The main outcome measures included perioperative and late stroke and death, and development of secondary restenosis.

Results: There were no perioperative deaths or strokes. Over a mean follow-up of 52 months (range 12 to 144 months), the Kaplan-Meier cumulative survival was 85% at 5 years. The cumulative freedom from all stroke rate was 98% and from ipsilateral stroke 100% at 5 years respectively. After secondary procedures re-recurrent stenosis ≥ 50% occurred in 10 patients (13.7%). The cumulative freedom from re-restenosis (≥50%) was 85% at 5 years. Five patients (7%) received tertiary carotid reconstructions.

Conclusion: Repeat carotid endarterectomy for recurrent stenosis can be performed safely with excellent long term protection for stroke. These data provide a standard against which the results of CAS can be compared.

INTRODUCTION

The benefit of revascularization procedures for carotid artery stenosis is hampered by the occurrence of restenosis, which is associated with a modestly increased risk of stroke [1,2]. Restenosis after previous carotid endarterectomy (CEA) has been detected with increasing frequency because of the use of non-invasive testing [1,2]. 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 redo CEA is an accepted treatment for recurrent stenosis, morbidity rates relating to surgery for restenosis are reportedly higher than those of endarterectomy for primary lesions [5-7]. Consequently, virtually every carotid intervention trial includes reoperative CEA among the high-risk inclusion criteria [8]. This high-risk classification, though supported in the literature, has been a subject of continued debate [9]. Some authors advocate the use of carotid angioplasty and stenting (CAS) in the management of this reportedly "high-risk" condition [5,10]. The reports of CAS for post-CEA restenosis published so far are mostly single center series that have shown good feasibility and encouraging early results. However, data on long-term results of CAS are limited and will still need to be compared with those of redo CEA [11,12]. Although the literature is replete with papers on perioperative results of redo surgery [5-7,13-38], long-term outcome with objective documentation of the patency and the occurrence of late symptoms is relatively scarce [Table 1].

This study therefore describes our experience with redo CEA in the management of patients with a recurrent stenosis following endarterectomy. It was undertaken to delineate the operative risk, long-term durability, and stroke-free survival benefit of reoperative CEA in a contemporary surgical series in the context of minimally invasive approaches to recurrent cerebrovascular disease.

METHODS

Patient selection and data collection

From our computerized vascular registry all patients undergoing redo CEA between 1985 and January 2006 were analyzed. Inclusion criteria were: 1) complete data on primary and redo-surgery; 2) complete follow-up (both clinical and duplex ultrasound (US)) between primary and redo-surgery; 3) clinical and duplex US follow-up of at least 1 year after redo-

surgery. Patients with primary surgery in another center were included pending inclusion criteria 1 and 2. Excluded were patients with: 1) early postoperative redo-surgery (first 30 days); 2) interposition bypass repair; 3) CEA in conjunction with cardiac surgery. All patients with a greater than 70% symptomatic or a greater than 80% asymptomatic stenosis were considered for surgery. Condition for treatment of asymptomatic patients was three or four diseased (> 50% stenosis) extracranial cerebropetal vessels. Specific endpoints analyzed included perioperative death and stroke, late clinical outcome, and secondary restenosis (≥ 50%).

Preoperative patients characteristics

In 72 patients 73 procedures were performed. Age, gender, and preoperative cerebral symptoms were documented [Table 2]. In 14 patients primary CEA was performed elsewhere. Patients were defined asymptomatic in absence of cerebrovascular symptoms within 120 days prior to surgery. The mean interval from primary CEA to repeat intervention was 53 months (range 8-192) [Figure 1]. In 17 patients (23%) redo CEA was performed within 2 years of primary CEA. Revascularization procedures (17; CEA or CAS) of the contralateral side were performed in 16 patients. The contralateral ICA was occluded in 17 patients at time of primary and in 18 patients at redo CEA. Contralateral subtotal stenosis (90-99%) was noticed in 1 primary and 4 redo CEA's respectively.

Operative procedure

All patients were operated on under general anaesthesia by an experienced vascular surgeon or by a specialist vascular trainee under supervision. The decision for re-endarterectomy, re-endarterectomy with patch angioplasty, or patch angioplasty alone was based on operative findings. Technical details of intraoperative monitoring have been described previously [39]. Before cross-clamping an intravenous injection of heparin (5000 IU) was administered; protamine reversal was not used. Preoperatively, patients were started on 100 mg aspirin daily, or 225 mg Asasantin twice daily which was continued postoperatively.

Author	Timeframe	Patients	Procedures	Male (%)	Age (years)	Age range	Primary Clos. ± CEA	Interval (years)	Range	Early redo <2Y (%)	Asympt (%)	Redo patch (%)	Periop death (%)	Periop stroke (%)	Periop TIA (%)	Periop MI (%)	Cranial N Injury (%)	Permanent (%)	Haematoma (%)	FU (months)	Range	Late stroke (%)	Late stroke ipsi/contr	Occlusion in FU	Stroke-free rate 5y (%)	Stroke-free rate 10y (%)	Restenosis (%) DEF.	Restenosis > 50%	>70%	Sympt restenosis (%)	Restein free surv 5y (%)	Restein free surv 10y (%)	Tertiary procedures (%)	Interposition Bypass (%)
Stoner	1989 - 2002	145	153	56	69 ± 1.3	NS	68	73	3 - 240	41	64	93	0	1.9	0	0	1.3	0.6	3.2	52.8	1 - 152	3.9	NS	NS	96	NS	50%	9.2	1.3	0	NS	NS	0	0
Cho	1990-2000	64	66	52	68.2	38-84	17	77.5	1 - 292	NS	50	85	0	3.1	3.1	5	6	1.5	3	51.6	3 - 155	5	4 vs 1	1	92	74	80%	9	3	3	94	86	2	12
Abou-Zamzam	1990-2000	56	56	77	67	51-83	55	78	1 - 297	23	27	55	1.8	5.4	NS	1.8	1.7	0	NS	29	1 - 116	1.8	1 vs 0	1	90	NS	80%	5.4	5.4	NS	93	NS	3.6	45
O'Hara	1989-1999	199	206	66	68	47-86	NS	NS	NS	NS	57	94	1	3.4	NS	1	1	0	NS	51.6	1 - 122	3.9	NS	7	92	NS	60%	10	3	NS	83	NS	NS	4
AbuRahma	1991-1998	121	124	49	70.1	52-81	0	57.8	7 - 182	26	58	NS	0	4.8	4	0	17	1.6	0.8	49	NS	0	NS	NS	82	NS	50%	5.6	1.6	NS	95	NS	0	0
Archie Jr	1981-1999	66	69	44	68 ± 8.5	NS	20	75 ± 57	NS	NS	48	86	0	2.9	1.4	0	4.3	0	NS	50	1 - 180	4	2 vs 1 vs ?	NS	90	86	50%	13	4	1.4	88	68	4.3	13
Gorlitzer	1992-1998	41	42	71	66.6	48-85	NS	60	3 - 276	NS	40	86	0	2.4	4.8	0	14.3	NS	4.8	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	6
Hill	1993-1998	40	40	NS	72 ± 8	42-93	NS	72	5 - 252	42	50	64	0	0	NS	5	8	0	0	14	1 - 52	0	0	NS	NS	NS	50%	5	5	NS	NS	NS	0	50
Rockman	1980-1996	74	82	53	67.5	41-85	NS	53	2 - 163	NS	42	57	0	3.7	1.2	0	1.2	0	NS	35	1 - 150	0	0	5	NS	NS	50%	4.8	NS	3.6	83.5	NS	4.9	42.7
Dillavou	1980-1998	27	27	52	67	55-79	85	55	5 - 148	33	48	85	0	0	0	3.7	NS	0	3.7	54	6 - 152	3	3 vs 0	NS	85	65	50%	21	8.7	3.7	NS	NS	7.4	7.5
Hobson	1989-1996	14	16	50	64.5	NS	44	NS	NS	NS	44	75	0	0	0	0	6.2	6.2	NS	30	NS	1	1 vs 0	1	NS	NS	NS	6.2	0	0	NS	NS	0	25
Munn	1988-1997	40	43	45	65	51-85	81	47.3	NS	56	42	70	2.3	0	0	2.3	9.3	0	4.6	34	3 - 108	1	1 vs 0	1	87	NS	50%	4.6	NS	4.6	NS	NS	2.3	23
Ballinger	1984-1995	67	70	70	67.9	40-84	55	78.1	1 - 240	NS	35	74	1.4	1.4	NS	1.4	NS	2.8	1.4	48	1 - 162	6	2 vs 4	NS	93.6	NS	NS	NS	NS	NS	NS	NS	0	10
Mansour	1976-1996	69	82	48	66 ± 7.7	NS	NS	65	3 - 361	NS	34	74	0	4.8	1.2	2	7.3	1.2	2.4	NS	NS	NS	NS	NS	92.3	NS	NS	8	NS	NS	92.3	NS	0	24
O'Donnell	1983-1994	44	48	75	64.5	NS	NS	45.4	NS	27	44	NS	2.1	2.1	4.2	6.3	19	0	4.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	NS
Rosenthal	redo	31	31	26	59.9	NS	NS	73.1	11 - 168	16	16	97	0	0	3.2	0	6.4	6.4	NS	39.8	NS	irr	irr	irr	irr	irr	irr	irr	irr	irr	irr	NS	100	3
Coyle	1983-1992	69	69	62	66.1	51-81	NS	83	5 - 312	NS	46	87	2.9	1.4	NS	2.9	0	0	8.7	57	1 - 132	1	1 vs 0	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	0
AbuRahma	1988-1993	46	46	62	65.5	43-79	NS	67	NS	NS	28	94	0	7	0	0	7.5	5	NS	30.9	6 - 73	0	0	NS	85	NS	50%	2	0	2.2	NS	NS	2.2	0
Meyer	1972-1992	82	92	62	NS	NS	49	NS	NS	NS	7	NS	4.3	5.4	4.3	2.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	24
Gagne	1970-1991	42	47	64	65.9	44-85	7	NS	NS	25	27	86	0	0	6.8	0	4.5	2.2	2.2	54	9 - 202	1	1 vs 0	5	96	96	50%	10.3	6.9	2.1	NS	NS	7	13
Treiman	1974-1991	162	162	50	65	35-84	NS	NS	NS	20	7	65	1	1.9	0	0	2.4	0	1	64	2 - 149	5	5 vs 0	1	NS	NS	50%	22	15	20	NS	NS	20	35
Gagne	1970-1988	29	29	66	64.5	48-76	10	66	1 - 173	27	21	100	0	0	10.3	0	3.4	3.4	NS	50	11 - 182	1	1 vs 0	3	NS	NS	50%	21	5.3	6.9	NS	NS	11	0
Nitzberg	1961-1986	27	29	72	63.8	46-73	NS	50.2	2 - 226	56	35	67	0	3.4	6.8	3.4	17	0	3.4	47.2	1 - 127	2	1 vs 1	NS	83.3	83.3	50%	8.3	0	0	NS	NS	3.4	NS
Kazmers	1979-1986	14	14	100	62 ± 9.3	46-78	NS	66.3	8 - 165	14	0	93	0	0	0	0	14	7.1	NS	27.4	4 - 87	0	0	NS	NS	NS	50%	7.1	0	0	NS	NS	14	7
Bartlett	1957-1985	99	116	NS	NS	NS	NS	NS	NS	40	30	1	1.7	4.3	2	0	17	NS	3.4	NS	NS	NS	NS	NS	NS	NS	NS	5	NS	NS	94	NS	NS	5
Piepgras	1972-1984	51	57	70	NS	NS	55	table	NS	25	9	89	0	6	2	2	NS	NS	NS	NS	NS	NS	NS	1	NS	NS	NS	NS	NS	NS	NS	NS	NS	10
Das	1979-1983	61	65	64	NS	NS	NS	42	3 - 194	43	51	91	3.1	1.5	0	0	9.2	1.6	NS	23	1 - 137	1	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	5
Rapp	1957-1984	90	109	NS	NS	NS	NS	NS	1 - 180	NS	27	43	2	3	3	0	15	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	9
Cossman	8 year period	14	16	21	60	NS	NS	NS	NS	69	21	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0
Hertzer	1958-1978	15	16	73	58.6	47-69	NS	45	7 - 156	56	NS	94	0	0	6.3	0	NS	NS	0	18	1 to 70	0	0	0	NS	NS	NS	NS	NS	NS	NS	NS	NS	6

Table 1. Literature data on redo-carotid endarterectomy. References 5-7 and 13 – 38. NS = Not specified.

Demographics	N	%
Patients	72	
Age (years; mean at redo CEA)	66	
Male gender	41	56
Procedures	73	
Left	36	49
Asymptomatic at first CEA	22	30
Symptomatic at first CEA	51	70
Stroke (minor/major)	9(7/2)	
TIA	30	
AFX	9	
VB	3	
Asymptomatic at redo CEA	45	60
Symptomatic at redo CEA	28	40
Stroke	6(4/2)	
TIA	15	
AFX	6	
VBI	1	
Contralateral occlusion at first CEA	17	23
Contralateral occlusion at redo CEA	18	25

Table 2. Patient characteristics of present series (N=73).

Follow-up

After surgery patients had a clinical and duplex US follow-up at 1 day, 3 and 12 months and every year thereafter. Five categories of ultrasonographic stenosis were defined: 1) 0-49%, 2) 50-69%, 3) 70-89%, 4) 90-99%, and 5) occlusion. Recurrent stenosis was defined as an stenosis of ≥ 50%. Criteria for defining a stenosis of 50% include peak systolic velocity of more than 125 cm/sec. Following redo surgery patients re-entered the carotid surveillance programme.

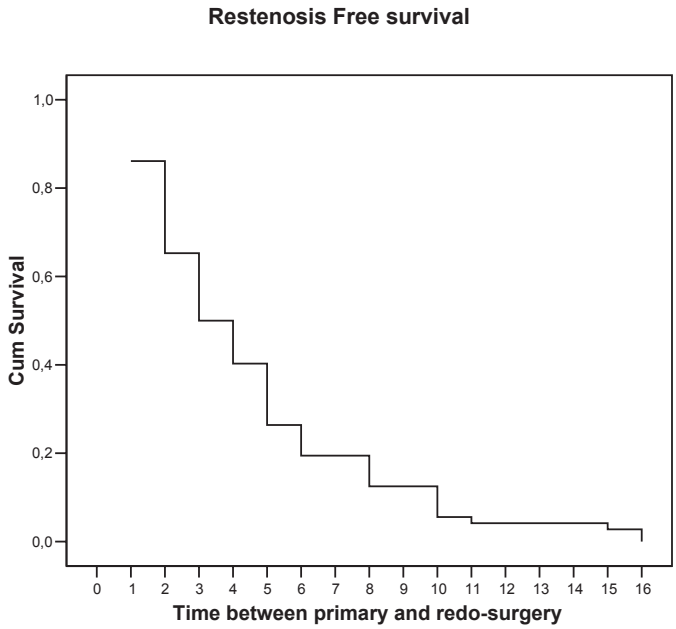

Figure 1. Time of development of restenosis after primary carotid endarterectomy (N=73).

Outcome

Perioperatively, patients were evaluated by an independent neurologist. Any new neurological deficit lasting for > 24 hours in the first 30 days was classified as a stroke. Major stroke was defined as a persistent and disabling neurologic deficit that was present at the time of discharge. Minor stroke was defined as a persistent but non-disabling neurologic deficit that was present at the time of discharge. Cranial nerve injury was considered when symptoms prompted further clinical (otolaryngologic) evaluation with which an injury was confirmed. Periprocedural haematoma was defined as any bleeding needing re-exploration or transfusion.

Statistical analysis

Data were analyzed using SPSS version 12.0 (SPSS Inc. Chicago, Illinois). Actuarial survival analysis was performed by using Kaplan-Meier life tables. A p-value of < 0.05 (log-rank) was considered significant for all statistical analyses.

RESULTS

There were no operative deaths and no operative strokes [Table 4]. Perioperative morbidity occurred in 7 patients consisting of myocardial infarction (1), perioperative TIA (2), cranial nerve injury (1). Three patients had a bleeding complication requiring re-exploration. Repeat endarterectomy with patch angioplasty was the most common procedure performed [Table 3]

	N	%
primary CEA	26	36
Shunt	17	23
Venous Patch	17	
Prosthetic Patch	9	
Redo CEA	32	44
Shunt	56	77
Procedure	11	15
CEA with Patch	56	77
CEA without Patch	11	15
Patch angioplasty alone	6	8
Patch		
Venous	43	
Prosthetic	19	
Total Venous patch	43	
Total Prosthetic patch	19	
Time between CEA and redoCEA (Months)	53	
Contralateral CEA / CAS	11	15

Table 3. Surgical characteristics of present series (N=73).

	N	%
Perioperative		
Mortality	0	0
Stroke	0	0
TIA	2	2.8
Myocardial infarction	1	1.4
Haematoma	3	4.1
Nerve injury	1	1.4
Long-term clinical outcome		
Mortality	8	11
All stroke	1	1.4
Ipsilateral stroke	0	0
TIA	1	1.4
VBI	1	1.4
Durability		
Restenosis	10	13.7
Tertiary CEA	5	6.8
Time to tertiary CEA	5.4 (3 – 8)	

Table 4. Perioperative and long-term clinical outcome after redo CEA (N=73).

Symptom free survival

Post redo surgery, during follow-up of a mean 52 months (range 12-144) 8 late deaths occurred [Figure 2]. Causes of death were cardiac in 5, pulmonary 1, and malignancy in 1 patient. In 1 patient the cause was undetermined. Kaplan-Meier estimate for the probability of overall survival was 85% at 5 years. Two patients were lost to follow-up. During follow-up 3 patients became symptomatic. Late stroke occurred in 1 patient (1.4%) [Table 4]. This patient had a symptomatic contralateral occlusion 3 years after redo CEA. One patient suffered from repeating TIA's at 23 months, and one from VBI at 46 months of follow-up. The all cerebral symptom free survival was 93% at 5 years [Figure 3]. At 5 years, the probability of freedom from any stroke was 98%, and the probability of freedom from ipsilateral stroke was 100%. No patients had a clinically evident late TIA or stroke after redo CEA without the evidence of secondary recurrent stenosis. The patients' symptom status at the time of recurrent stenosis did not influence the outcome after redo surgery.

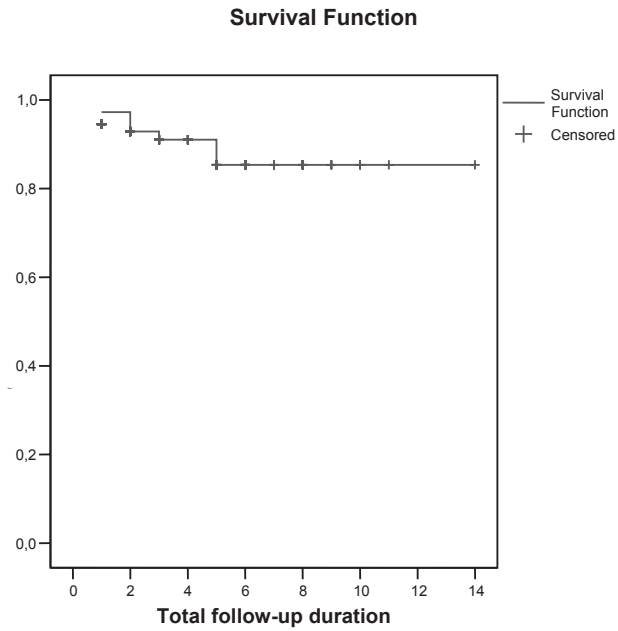

Figure 2. Survival after redo-carotid endarterectomy. Kaplan-Meier estimates for probability of overall survival was 85% at 5 years (SE 0.051). Number of patients remaining were 73, 57, 36, 22, 9, 3, and 0 at 2, 4, 6, 8, 10, and 12 years of follow-up respectively.

Secondary restenosis

All duplex scans obtained within 3 months after CEA demonstrated patent ICA and velocity spectra of less than 50% stenosis. Secondary restenosis was detected in 10 patients (13.7%). Three of these were symptomatic (1 stroke, 1 repeating TIA, 1 VBI). There were no ipsilateral occlusions during follow-up. Kaplan-Meier estimates for freedom from secondary restenosis were 85 % at 5 years, and 73% at 10 years [Figure 4]. Five patients who had a secondary restenosis underwent a tertiary carotid reconstruction (venous bypass (1), PTFE bypass (1), CEA with patch (3)). Kaplan-Meier estimates for reintervention free survival were 94% at 5 years and 74% at 10 years [Figure 5]. Indications for a third operation included repeating TIA's (1), VBI (1), and asymptomatic high-grade stenosis with 4 vessel disease in 3 patients. Because the actual time of restenosis was likely to have occurred before its detection, the actual freedom from restenosis estimates is likely to be lower than calculated based on the date of duplex US detection.

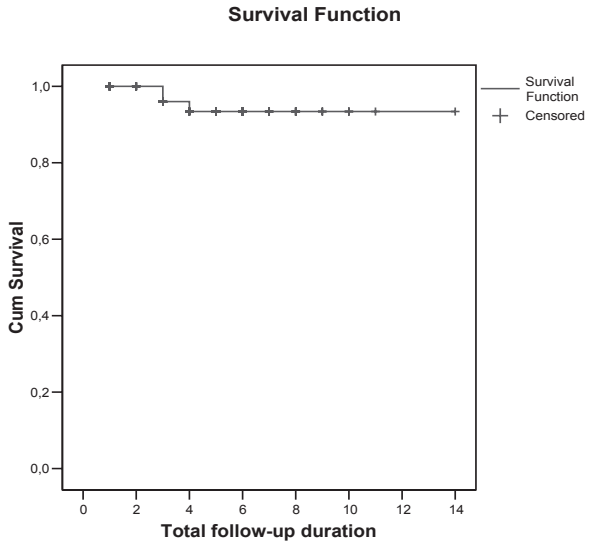

Figure 3. All symptom free survival after redo-carotid endarterectomy. Kaplan-Meier estimates 93% at 5 years (SE 0.0372). Number of patients remaining were 73, 57, 36, 22, 9, 3, and 0 at 2, 4, 6, 8, 10, and 12 years of follow-up respectively.

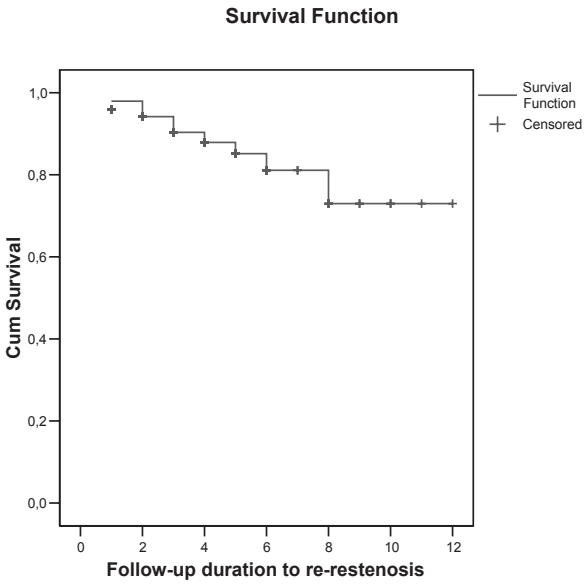

Figure 4. Restenosis (≥ 50%) free survival after redo-carotid endarterectomy. Kaplan-Meier estimates 85% at 5 years (SE 0.0507) and 73% at 10 years (SE 0.0952). Number of patients remaining were 73, 57, 36, 22, 9, 3, and 0 at 2, 4, 6, 8, 10, and 12 years of follow-up respectively.

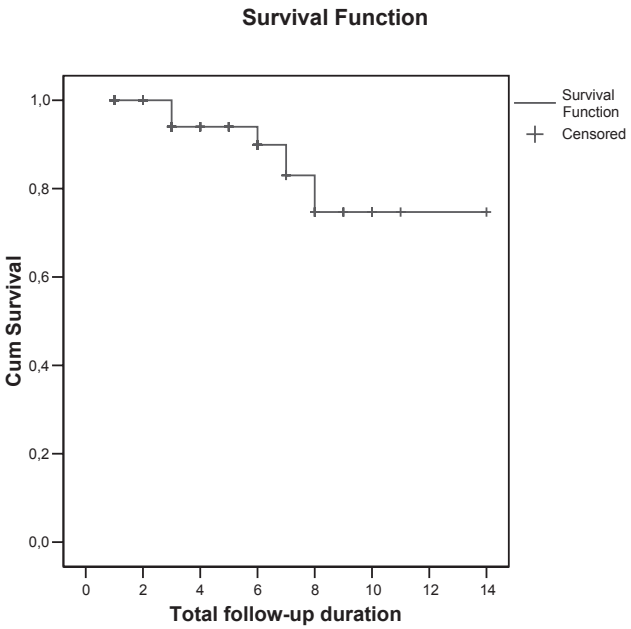

Figure 5. Re-intervention free survival after redo-carotid endarterectomy. Kaplan-Meier estimates 94% at 5 years (SE 0.0336) and 74% at 10 years (SE 0.1077). Number of patients remaining were 73, 57, 36, 22, 9, 3, and 0 at 2, 4, 6, 8, 10, and 12 years of follow-up respectively.

Localisation

Restenosis occurred in the previous endarterectomy site in 83%, proximal to the endarterectomy site in 3%, distally in the internal carotid artery (ICA) in 11%, and both proximal and distal but not within the site of endarterectomy in 3%. Of the 10 patients with secondary restenosis, four of five ICA re-recurrent stenoses had original recurrent stenosis in the ICA, whereas 2 of the 3 common carotid artery (CCA) re-recurrences had original recurrent stenosis in the CCA and 1 in the ICA.

DISCUSSION

Our results demonstrate that redo-endarterectomy for recurrent carotid stenosis (1) can be performed with acceptably low perioperative stroke and death rate; (2) has a high long-term stroke-free rate; and (3) has a high long-term secondary restenosis free rate. The occurrence of another ipsilateral recurrent stenosis that requires a third carotid operation (7%) is rare.

Guidelines for primary CEA define an acceptable stroke/death rate of < 6% for symptomatic, and <3% for asymptomatic patients [40]. The upper limit of acceptable stroke/death rate for reoperative CEA has been defined to be 10% [41]. The low rate of perioperative major adverse outcome in this study is echoed by other reoperative series, with stroke/death rates noted between 0% and 7% [Table 1]. Our freedom from late stroke rate is also high and consistent with literature, with operative indications not different from others [Table 1]. The claimed higher complication rate after redo-CEA is particularly related to postoperative cranial nerve palsies, but could not be confirmed in our series. In literature, cranial nerve injuries are recorded in the 1% to 17% range [Table 1] where it shows that most nerve injuries are transient and without clinical significance. Reoperation for neck haematoma is only occasionally required.

Redo carotid surgery has been extensively reported, but only a few reports describe clear long-term evaluation [13,14,17,19]. Our results are consistent with the experience of other investigators that report on durability, despite differences in length of follow-up and criteria for determining and defining restenosis [Table 1].

The morphogenesis of recurrent lesions is a process of ongoing thrombogenesis beginning immediately after blood flow is restored across the endarterectomized surface [42]. The early lesion is subsequently formed as the thrombus organizes and smooth muscle cell ingrowth occurs, creating a supposed morphologic distinction between early (within 2 years of CEA) and late (over 2 years) recurrent carotid disease [43]. Later studies supported the contention that early and late recurrent lesions are truly one and the same, that is, myointimal hyperplasia (MIH), which undergoes progressive atherosclerotic change, just observed at different time points along a continuum [42].

Early (MIH) lesions tend to be smooth with little embolic potential [44] although others found half of those with MIH to have a symptomatic presentation [14,29]. In 17 of our patients reoperation was within 24 months of primary CEA and likely represented MIH lesion treatment. The majority of patients who become symptomatic due to a recurrent carotid stenosis, do so on the basis of a hemodynamic flow-related mechanism [44]. A systematic review in 1998 concluded that the risk of restenosis after CEA was 10% in the first, 3% in the second year and only 1% per year thereafter. The risk of stroke arising from a restenosis, although low, was highly variable, ranging from 0.1 to 10% [1]. We and others found that no patient had a clinically evident late TIA or stroke after redo CEA without the evidence of secondary recurrent stenosis [19]. On the other hand, the incidence of restenosis is surely not always associated with a parallel increase in late stroke [45].

In those instances in which a recurrent lesion becomes symptomatic, the management algorithm is straightforward: most surgeons consider this an indication for intervention. Unfortunately, the appropriate management of asymptomatic patients remains unclear [2,4,9].

Some authors assume that an asymptomatic recurrent stenosis confers an equivalent stroke risk to primary atherosclerotic lesions. Operative practice is usually justified by the results of the ACAS and ACST trials [46,47]. In a large non-randomised series of 401 redo CEA's the perioperative death/stroke risk was 5.7%. This might probably be a better reflection of true practice. Authors with compliction rates > 4% therefore cannot simply extrapolate the landmark trial data to justify intervention in asymptomatic patients with recurrent stenosis. Existing guidelines [41] should no longer be applied but critically revised instead.
Currently we have no accurate way to differentiate which highly stenotic lesions will cause a stroke and which will not. Therefore, it is still our policy to reoperate on symptomatic restenosis (> 70%), and on asymptomatic restenosis >80% in patients with three or four diseased (> 50% stenosis) extracranial cerebropetal vessels, or a contralateral occlusion. With a low perioperative complication rate, the risk-benefit ratio with this approach will remain appropriate.
There is increasing awareness of the contribution of carotid plaque instability to neurologic complications. Noninvasive plaque characterization is potentially extremely useful in several aspects of carotid management, for example in prediction of (silent) brain infarcts with CEA or symptomatic embolization with CAS [48,49]. In the future, plaque characterization could help in stratifying asymptomatic patients for conservative treatment versus revascularization[50].

The site of recurrent stenosis is primarily at the ends of or within the confines of the original endarterectomy site and suture lines. The recurrence is either in the ICA or the distal CCA or both [17,19,21,23,26] with a majority (70%) of restenotic lesions localised to the origin of the ICA [3,32,51]. In agreement with these findings, our results and pooled data from 4 reports that provided location data [17,21,23,43] counted a 30% incidence of the major restenosis being located in the distal CCA. Some regions of the artery wall are exposed simultaneously to low wall shear stress and high mechanical stress and these regions correspond to areas where atherosclerotic plaque develops [52]. It makes the carotid bulb a focus for disease because of its geometry coupled with pulsatile flow that produces low shear rates which in turn promote atherosclerosis in the sinus region [53].
Single center non-randomised reports on treatment of recurrent stenosis have claimed comparable perioperative outcomes for CAS and redo-CEA [44,54]. CAS however, although relatively safe in the short term, has shown limitations in terms of durability of results [12,13]. Currently, there are no completed studies with sufficient power to determine significant differences between CEA and CAS treatment for this condition. The only way to compare one treatment with the other would be with a randomized, controlled, multicenter trial.
In 25 years since Stoney, 29 studies on redo CEA have been published with varying sample size [Table 1]. There are only 6 reports of more than 100 procedures [6,13,16,30,33,36], 10

reports of 50 to 99 procedures [7,14,15,17,19,23,24,27,34,35] and 14 reports of < 49 procedures [5,18.20-22,25,26,28,29,31,32,37,38]. Several of these are initial and follow-up studies from the same single institution.

The reported 30-day stroke and death rates range from 0 to 5.4% [Table I]. Most important flaw of the majority of these reports is the lack of follow-up. A true meta-analysis of available databases with respect to restenosis is probably invalid, because the studies were not prospectively randomised nor were they homogenous with respect to definition of restenosis and type of reconstruction.

Several techniques have been advocated for the operative treatment of recurrent carotid artery stenosis depending on the pathology and the number of previous procedures. The traditional surgical approach has been repeat CEA with patch closure, with the incision and principles of exposure being the same as for a primary endarterectomy. Carotid resection with the placement of an interposition graft is another surgical option [19,30]. In our opinion, interposition grafting is a distinct procedure. Therefore it was an exclusion criterium. In the present series however two patients with secondary recurrent stenosis received an interposition graft as tertiary revascularization. A frequently raised question regarding patients requiring recurrent carotid artery operations is the role of primary reconstruction on the incidence of reoperation. The preponderance of data at least indicate that restenosis rates are generally lower with patch closure of the arteriotomy than with primary closure [3]. Most of the operations that were reviewed in this series consisted of redo endarterectomy with vein patch angioplasty (77%), or patch angioplasty alone (8%).

Analysis of these data is retrospective and suffers from well-known limitations. The registry was not designed to tell us about the perioperative stroke and death risk of the patients who were screened but did not have redo CEA. Two patients were lost to follow-up and may have had a recurrence of the stenosis or an occlusion that was symptomatic, unrecognized or treated elsewhere. It is a single center analysis with operative results from several surgeons over 20 years. However, it is a consecutive series with excellent results from a large vascular training center, providing insight in an important topic in an endovascular era.

Conclusion

This study clearly demonstrates that redo CEA can be performed with acceptable stroke and death rates. Redo carotid operation is a durable and effective means of stroke prevention with good long-term patency. Our results do not support the contention that patients who require reoperative CEA constitute a "high-risk" subgroup in whom reoperative therapy should be avoided. Therefore, in our opinion it still is the standard against which alternative treatments should be judged.

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CHAPTER 5

CAROTID ANGIOPLASTY AND STENTING FOR POST-ENDARTERECTOMY STENOSIS: LONG TERM FOLLOW-UP.

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ABSTRACT

Background: 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.

First Author	Yadav	Al-Mubarak	Hobson	New	Leger	Vitek	AbuRahma	AbuRahma	Alric	Bowser	Rockman	Koebbe
Year of publication	1996	1998	1999	2000	2001	2001	2001	2002	2002	2003	2004	2005
No procedures	25	10	17	358	8	110	25	22	17	52	16	23
No Patients	22	5	16	338	8	99	23	20	17	50	16	22
Mean age	69	72	66	71	62	70	71	70	69	NS	63	71
Sex (male)	15	4	7	201	4	66	11	7	16	35	7	NS
Indication CAS												
Asymptomatic	5 (23%)	2 (40%)	8 (50%)	218 (61%)	5 (63%)	40 (40%)	7 (28%)	5 (23%)	11 (65%)	21 (38%)	7 (43%)	1 (4%)
Symptomatic	17(77%)	3 (60%)	8 (50%)	140 (39%)	3 (37%)	59 (60%)	18 (72%)	17 (77%)	6 (35%)	31 (62%)	9 (56%)	22 (96%)
Type of stent	Wall 16	Wall	Wall	Wall 197	Wall	NS	Wall 13	Wall	Wall 13	Wall 27	SMART	SMART 22
	J&J 20			Palmaz 137			Smart 10		Palmaz 4	Precise 12		Acculink 1
	Cook 2			Other 24			Palmaz 2			SMART 6		
Interval CEA-CAS	73	61	14	66	29	25	43	15	19	50	26	28
Periprocedural events												
Major stroke/death	0	0	0	13 (3.7%)	0	2 (1.8%)	4(16%)	0	0	3 (5.7%)	1 (6.3%)	0
Minor stroke	1 (4%)	0	0	0	0	2 (1.8%)	0	1 (4.5%)	0	1 (1.9%)	0	0
TIA	0	0	0	8 (2.2%)	1(12.5%)	2 (1.8%)	1 (4%)	0	0	2 (3.8%)	0	0
Follow-up (Months)	8	14	11	14	20	20	20	24	16	26	14	36
Symptoms during FU												
Fatal stroke	0	0	0	1 (0.3%)	0	0	0	0	0	0	0	0
Non-fatal stroke	0	0	0	1 (0.3%)	0	0	0	0	0	0	0	0
TIA	0	0	0	3 (0.8%)	1 (12%)	0	0	1 (4.5%)	0	1(2%)	0	0
Restenosis	0	0	0	23 (6%)	6 (75%)	0	6 (24%)	7 (32%)	0	8 (15%)	2 (13%)	1 (5%)
Time to restenosis	0	0	0	NS	9	0	12(2),24(3),36(1)	20 (6-36)	0	4 < 12 M	NS	14
Measure for restenosis	> 50%	> 50%	> 50%	> 50%	> 60%	0	> 50	>50%	NS	> 50%	> 50%	NS
Redo after CAS	0	0	0	10 (2.6%)	Bypass 2	0	CAS 2	0	0	CAS 1, PTA 3	CAS 1	PTA 1

Table 1. Data on carotid angioplasty and stenting for restenosis after previous carotid endarterectomy. (References 5,8,14-24). All studies in this table specifically studied outcome of CAS for post-CEA restenosis. Studies with mixed study populations (both primary lesions and post-surgical stenoses) were not included. NS = not specified.

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. 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 aneurysm spurium of the femoral artery was discovered during follow-up which resolved spontaneously. The length of stay of an uncomplicated CAS procedure was 24 hours. Only five patients had a longer stay (range 48 – 96 h).

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.

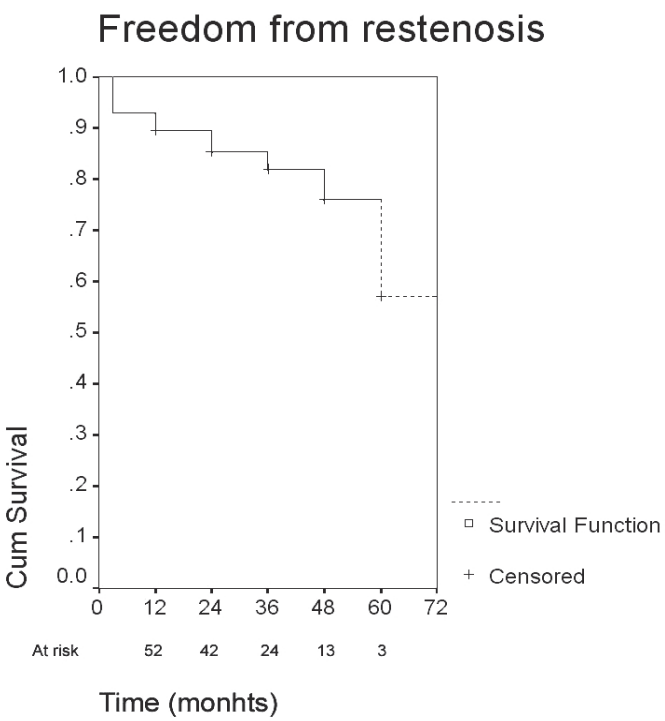

Figure 1. Stenosis-free (<50% diameter reduction) primary patency after CAS for restenosis post- carotid endarterectomy. Stenosis free patency (0 - 1) vs Months. Number of patients included in the analysis at each censored time point: 3 months (56), 12 months (52), 24 months (42), 36 months (24), 48 months (13), and 60 months (3). Standard error of cumulative in-stent free survival rate at 3 months (0.0338), 12 months (0.0406), 24 months (0.0482), 36 months (0.0571), 48 months (0.0774), and 60 months (0.1746).

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].

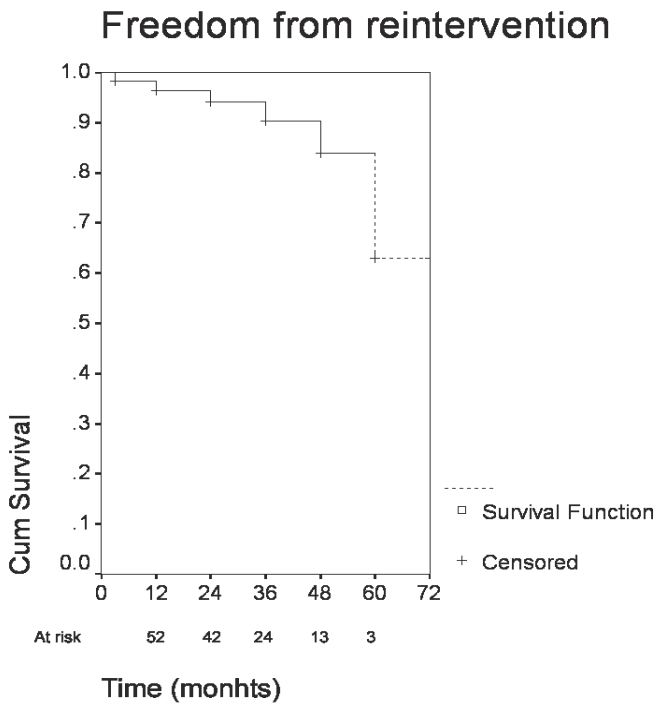

Figure 2. Re-intervention-free patency after CAS for restenosis post-carotid endarterectomy. Re-intervention- free patency (0 - 1) vs Months.

Number of patients included in the analysis at each censored time point: 3 months (56), 12 months (52), 24 months (42), 36 months (24), 48 months (13), and 60 months (3). Standard error of cumulative re-intervention free survival rate at 3 months (0.0174), 12 months (0.0251), 24 months (0.0330), 36 months (0.0486), 48 months (0.0769), and 60 months (0.1906).

DISCUSSION

In the present series of CAS performed upon 57 arteries in 55 patients with recurrent stenoses following ipsilateral CEA, there were no major strokes and only two patients experienced

perioprocedural TIA. During a mean follow-up of 36 months, a minor stroke occured in one patient and a TIA in one patient.There was only 1 groin complication (1.7%) which compares favorably with the 4 to 10% risk of wound haematoma 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 ischaemic symptoms is significantly increased with ipsilateral ≥ 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 conform with 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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CHAPTER 6

THE FATE OF THE EXTERNAL CAROTID ARTERY AFTER CAROTID ARTERY STENTING. A FOLLOW-UP STUDY WITH DUPLEX ULTRASONOGRAPHY.

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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).

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 occlusions 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 anaesthesia, 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.

Types and numbers of stents used		
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

Table 1. Type of stents as used in the present study (N = 312).

Duplex Ultrasound Scanning

All patients were evaluated initially preprocedurally and during follow-up with duplex ultrasonography (US) 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 US, 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.

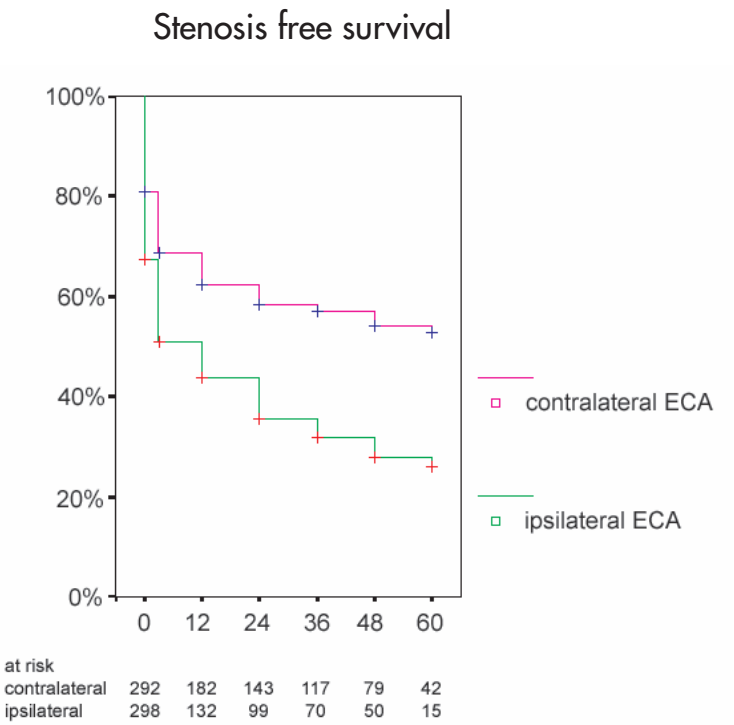

Figure 1. Kaplan Meier estimates of ECA stenosis free survival: ipsilateral ECA vs contralateral ECA (N=312) (p<0.001). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

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.

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).

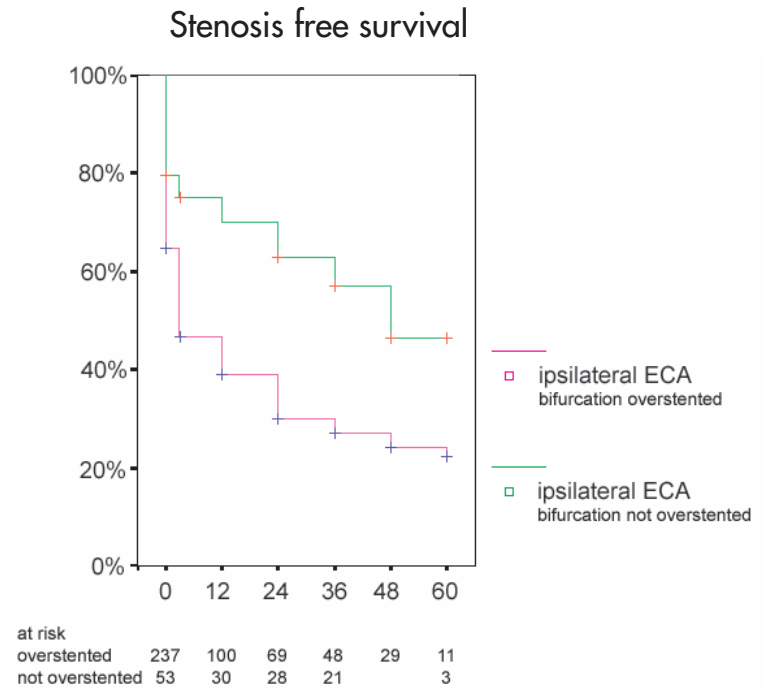

Figure 2. Kaplan Meier estimates of ECA stenosis free survival: ipsilateral non-overstented ECA (N=54) vs ipsilateral overstented ECA (N=238) (p=0.0004). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

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.

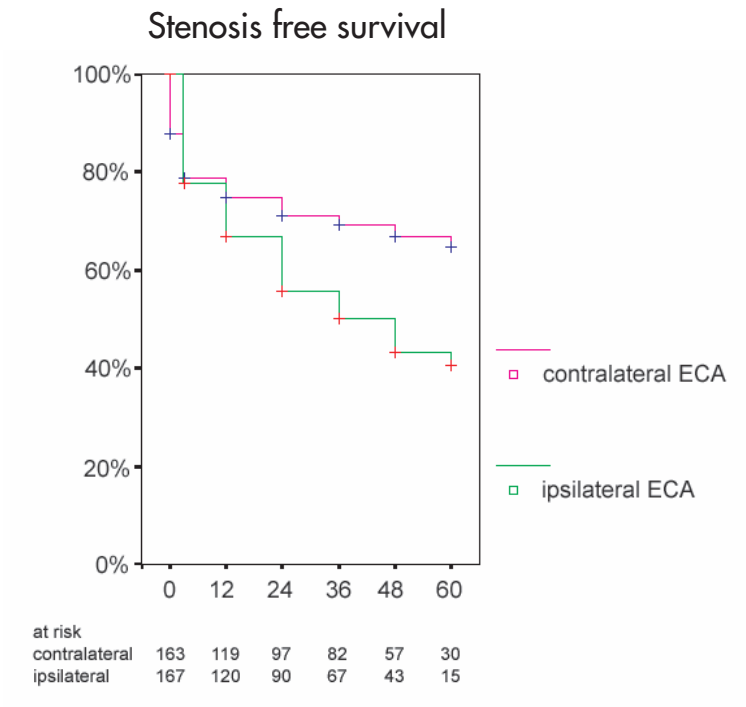

Figure 3. Kaplan Meier estimates of ECA stenosis free survival in selected patients with no stenosis at baseline ipsilateral ECA vs contralateral ECA (N=167) (p=0.0043). Time schedule: BASELINE- 3m-12m-24m-36m-48m 60m.

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.

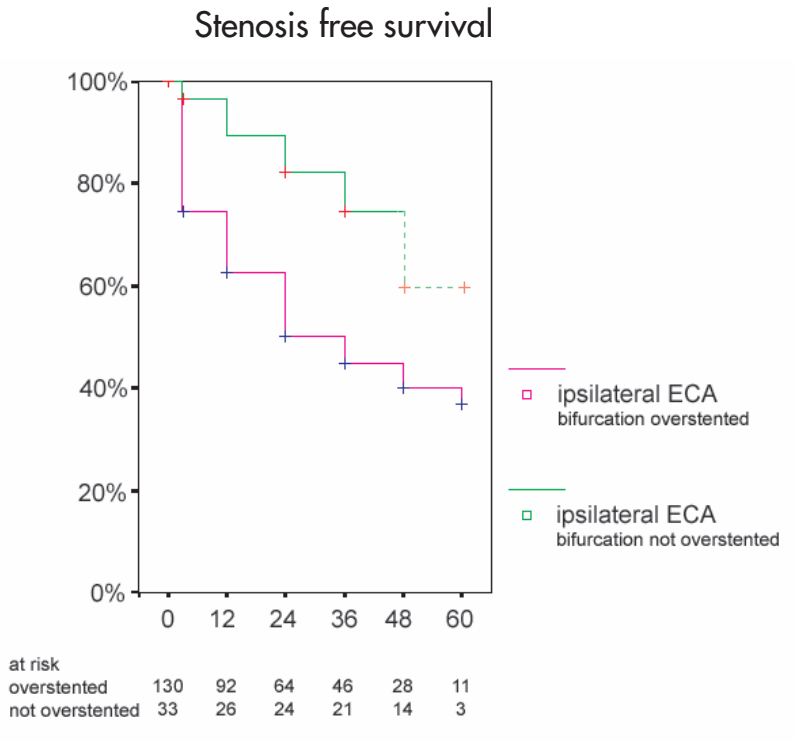

Figure 4. Kaplan Meier estimates of ECA stenosis free survival in patients with no ECA stenosis at baseline: ipsilateral non-overstented ECA (N=37) vs ipsilateral overstented ECA (N=139) (p=0.004). Time schedule: BASELINE- 3m-12m-24m-36m-48m-60m.

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.

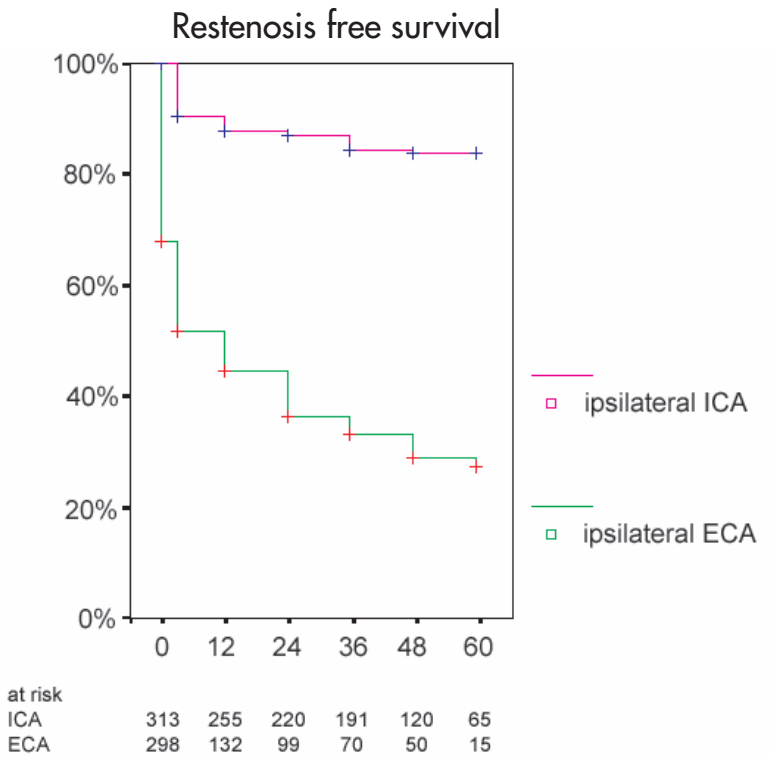

Figure 5. During follow-up in 48 patients stenosis ≥ 50% of the ipsilateral Internal Carotid Artery occurred. The incidence of in-stent recurrent stenosis (≥50%) therefore was 15,5% in the present study after a mean follow-up of 44 months.

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 ($\rho = 0.09$).

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 postoperative 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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CHAPTER 7

INTRA-PATIENT COMPARISON OF RESTENOSIS BETWEEN CAS AND CEA

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ABSTRACT

Purpose: Comparison of restenosis in patients who underwent both carotid artery angioplasty with stenting (CAS) and contralateral carotid endarterectomy (CEA).

Methods: From our CAS data registry (1998 - present) all patients with a history of contralateral CEA at any other time were selected (n = 63). Mean age was 70.6, sd=6.8 for CAS and 68.2, sd=6.1 for CEA and symptomatic carotid artery stenosis was present in 24% of patients pre-CAS and 40% pre-CEA. All CEA's were primary interventions, 19% of CAS were secondary to restenosis after previous ipsilateral CEA. All patients were followed up prospectively with duplex at 1 year (CAS: n=58, CEA: n=59), 2 years (CAS: n=44, CEA: n=53), 3 years (CAS: n=27, CEA: n=41), and every year thereafter. Within each patient we compared restenosis (>50%) between CAS and CEA procedures.

Results: After a follow-up of 28.7 months for CAS (sd=16.9) and 54.4 months for CEA (sd=39.5) the rate of ≥ 50% restenosis for CAS vs. CEA at 1,2, and 3 years was 23% vs. 10%; 31% vs. 19%; and 34 vs. 24%, respectively (log rank p=NS).

Conclusion: Our intra-patient comparison of patients who underwent both CAS and contralateral CEA did not reveal significant difference in restenosis between both procedures.

INTRODUCTION

Carotid endarterectomy (CEA) has shown to be effective in preventing stroke in both symptomatic and asymptomatic patients with high-grade carotid artery stenosis [1-3]. Carotid artery angioplasty and stenting (CAS) is a recently developed and emerging endovascular technique for treatment of occlusive carotid artery disease. Compared to carotid endarterectomy there is no need for general anesthesia and cranial nerve injuries is not an issue. Lesions with a difficult surgical exposure to CEA are better accessible to CAS, such as highly localized stenoses and lesions in irradiated necks.
Although in most single center series published so far CAS may have combined stroke/mortality rates comparable to CEA [4-9] its role as an effective and durable procedure in stroke prevention has to be established by ongoing randomized controlled trials (RCT) [10-13]. Especially, concern remains about the incidence of restenosis after stenting.
Previous case series have given an estimate of restenosis after CAS [9,14-16], but none of these studies had a control group of comparable patients undergoing CEA. Comparison of restenosis between CAS en CEA is therefore not feasible.
In the present study we performed an intra-patient comparison in patients who underwent both CAS and contralateral CEA in order to directly compare restenosis after both procedures.

PATIENTS AND METHODS

Patients
Data were retrieved from our CAS-data registry (St.Antonius Hospital, Nieuwegein; January 1998 – present). The criterion for inclusion was CAS and a contralateral CEA at any other time. Criteria for exclusion were: different operative procedure (e.g. carotid bypass), failed or incomplete CAS, and percutaneous transluminal angioplasty (PTA) without stent placement. If more interventions were performed at one side, the first intervention was studied. Secondary CAS because of restenosis was no reason for exclusion.

The following baseline characteristics were recorded: cardiovascular risk factors (blood pressure, diabetes mellitus, history of smoking, total cholesterol, body mass index), comorbidities (coronary artery disease, history of peripheral vascular disease, history of atrial fibrillation), drug use (anti-hypertensive drugs, anti-coagulants, cholesterol lowering drugs), and carotid artery specific factors (symptomatic or asymptomatic stenosis, degree of stenosis, degree of stenosis contralateral to the artery to be stented / operated on).

Blood pressure, body mass index and total cholesterol were retrieved from patient charts. They had to be measured within 1 year of the procedure to be valid. Blood pressure was defined as the mean of at least 2 non-intraoperative measurements. Coronary artery disease was defined as angina pectoris and/or stenosis of the coronary arteries on angiography. Symptomatic carotid artery disease was defined as: carotid artery stenosis and symptoms (amaurosis fugax, TIA, or stroke) of the hemisphere ipsilateral to the side stented / operated on.

Pre-procedural workup

Preoperative determination of the percentage (or degree of) stenosis was based on duplex ultrasonography (HP/Agilent, Sonos 2500 or 4500, Andover, USA) and DSA. Stenosis was divided into different categories: < 50%, 50 – 99% and occlusion. The criterion for ≥50% stenosis was a peak systolic flow velocity of ≥125 cm/sec.

PROCEDURES

CAS

CAS was performed under local anaesthesia from a common femoral artery access. It was performed in a standardized way by an interventional radiologist or an interventional cardiologist. The stenotic lesion was assessed, using Digital Subtraction Angiography (DSA) or 3D-rotational angiography, and predilated. Cerebral filter protection devices (used at the discretion of the interventionalist) were placed before stent deployment and if possible before predilation. After the stent had been deployed, high-pressure balloon angioplasty (8 to 14 atmospheres) was executed at the point of residual stenosis using a 5 or 6-mm-diameter balloon catheter. Following post-CAS angiographic visualization the access site was closed by manual compression or a transcatheter closure device.

Patients were monitored using continuous blood pressure measures, electrocardiography (ECG) and Transcranial Doppler (TCD) if a temporal window was available (n=60). Speech, alertness and motor function of the contralateral hand were assessed during the procedure.

An intravenous bolus of heparin (5000-10000 IU) was administered after sheath insertion; atropine (0.5 – 1.0 mg) was administered before predilation and/or poststent dilation. All patients received aspirin prior to the procedure and continued using aspirin lifelong. Clopidogrel (75 mg / day) was started 72 hours before the procedure and continued for 4 weeks.

CEA

CEA was performed under general anaesthesia. The operation was performed in a standardized way by a vascular surgeon or a trainee under specialist supervision. An indwelling shunt was selectively used on basis of intraoperative EEG and TCD parameters [17]. Venous or prosthetic patches were used selectively. The intracranial circulation was intra-operatively monitored using TCD if available (n=44) and electroencephalography (EEG). Patients received 5000 IU heparin before cross-clamping. All patients were started on aspirin 100 mg and dipyridamol (300 mg/day) before the operation. Dipyridamol use was continued for 3 months and aspirin use was continued lifelong.

Follow-up

Duplex measurements were obtained at 3 months, 1 year and each year after the intervention. In case of re-intervention the patient was lost to follow-up for the side of the re-intervention but not for the contralateral side. Duplex criteria for restenosis after CEA and restenosis after CAS were identical to the criteria for pre-operative stenosis. Clinical follow-up was retrieved from patient charts. Each patient was examined by a neurologist pre- and postprocedural. After hospital dismission, clinical follow-up was obtained at the same intervals as duplex follow-up.

Statistical analysis

Equality of baseline variables was tested using Student's T-test for normally distributed variables, Mann Whitney U test for non-normally distributed variables and Chi-square test for discrete variables. Restenosis was compared between CAS and CEA using Kaplan Meier life table estimates with the log rank test for significance.

RESULTS

Baseline characteristics

All baseline characteristics are outlined in Table 1. Patients were older at the time of CAS: mean age was 70.6 years in comparison to 68.2 years at the time of CEA ($p = 0.04$). With respect to cardiovascular risk factors and comorbidities there was no difference between the patients at the time of CEA and the study group at the time of CAS. At the time of CEA a higher proportion of the patients (40%) was symptomatic compared to the patients at the time of CAS (24%). Stenosis grade of the contralateral carotid was higher at the time of CAS but there was no statistical significant difference. Screening for carotid artery stenosis because of planned cardiac surgery led to 42 procedures in 29

patients who were all asymptomatic. Of these patients, 13 underwent CAS followed by contralateral CEA with CABG a few weeks later.

	CAS	CEA	p**
Age	70.6 (sd=6.8)	68.2 (sd=6.1)	0.04
range	55 - 83	53 - 79	
First intervention	25 (40%)	38 (60%)	
Months to contralateral intervention	6.77 (sd=8.7)	52.0 (sd=39)	
CABG related*	25 (40%)	17 (27%)	
Symptomatic	15 (24%)	23 (40%) *	NS
amaurosis fugax or TIA	3 (5%)	18 (16%) *	
Non-disabling stroke	0 (0%)	3 (5%) *	
symptomatic > 4months before intervention	12 (19%)	12 (19%) *	
% stenosis	91.0 (sd=6.5)	88.8 (sd=9.6)	NS
% stenosis cotralateral	47.6 (sd = 41.7)	38.6 (sd=40.5)	
Male	41 (65%)		
Systolic blood pressure (mmHg)	155 (sd=20)		
Diastolic blood pressure (mmHg)	79.9 (sd=9.7)		
Diabetes Mellitus	14 (22%)		
(Ex)-smoker	43 (69%)		
Coronary artery disease	50 (79%)		
History of peripheral vasc. disease	18 (29%)		
History of atrial fibrillation	6 (9.5%)		
Total cholesterol	5.23 (sd=1.3)		
BMI	26.0 (sd=3.7)		
Anti-coagulants	22 (35%)		
Anti-hypertensive drugs	56 (89%)		
Lipid lowering drugs	32 (51%)		

* 5 missing values

** Age: Students T-test, symptomatic: Chi-square , % Stenosis: Mann-Whitney U test

Table 1. Baseline variables

In 25 patients, CAS was performed at an earlier stage than the contralateral CEA. The other 38 patients received CEA first followed by a contralateral CAS at a later stage. If CAS was the first intervention, the mean time between CAS and CEA was 6.7 months; if CEA was the first intervention the mean time between the interventions was 52 months.

Procedures

Primary CAS was performed in 51 patients, in the other 12 patients secondary CAS for restenosis after CEA was performed. Stents used where Easy Wall (n = 11), Carotid Wall (n = 48), Precise Cordis (n = 3) and Palmaz stents (n = 1). Distal protection devices were used in 15 patients. In all patients primary CEA was performed. The arteriotomy was closed primarily (n = 17) or using a venous (n = 35) or prosthetic (n = 8) patch.

Duplex follow-up

Mean follow-up time was 28.7 months for CAS (sd=16.9) and 54.4 months for CEA (sd=39.5). Total follow-up was 151 person years on the CAS-side and 286 person years on the CEA side. During 106 of these follow-up years the patients were both in CAS follow-up and in CEA follow-up.

The Kaplan Meier estimate of ≥ 50% restenosis for CAS vs. CEA at 1,2, and 3 years was 23% vs. 10%; 31% vs. 19%; and 34 vs. 24%, respectively. There was no statistically significant difference in restenosis-free survival [Figure 1, log rank p = NS]. The 12 patients with secundary CAS did not have a higher rate of (re)restenosis [Figure 2]. In two patients having high-grade restenosis after CAS, CEA with removal of the stent was performed (7 months and 2.5 years). In 6 patients with high grade restenosis after CEA, re-CEA was performed after a mean time of 6.7 years.

Clinical follow-up

Peri- and postprocedural (30 days) no strokes were observed [Table 2]. CAS caused more TIA's: 7 (of which 6 occurred during the procedure) in comparison to 0 for the CEA's. The symptoms of those TIA's were amaurosis fugax (n = 2) and motor symptoms (n = 5). One TIA (paresis of the arm) occurred 14 days after CAS. There were 2 cases of myocardial infarction (MI) after CAS and 1 after CEA, none of these was life-threatening. All carotid interventions followed by MI were in patients who underwent a CABG workup. CAS was more frequently associated with asystole (p=0.02) and hypotension (p=0.02) during (n = 11) and after (n = 10) the intervention than CEA. There was no association between either asystole or hypotension and short-term neurological complications. In both groups bleeding complications requiring reintervention occurred: 3 after CAS and 2 after CEA. CEA caused 4 cranial nerve injuries (p=0.03).

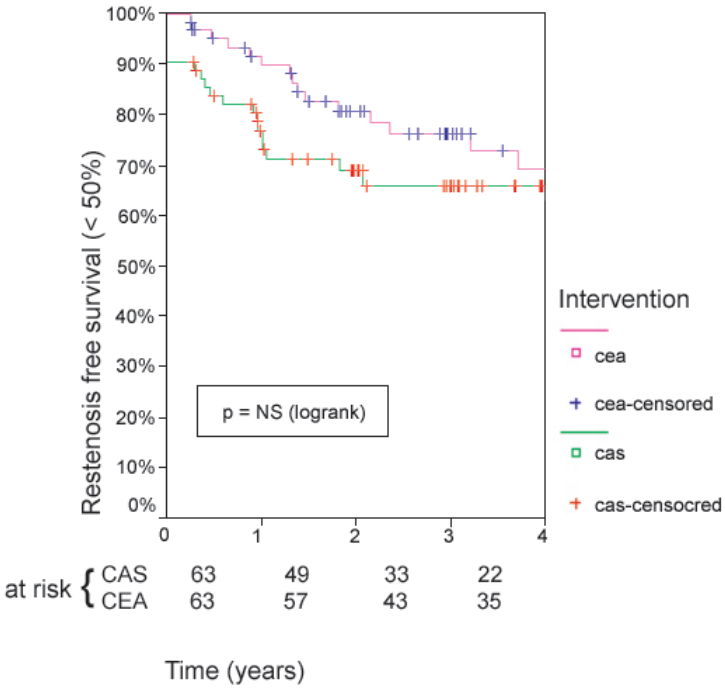

Figure 1. Restenosis free survival - CAS vs CEA

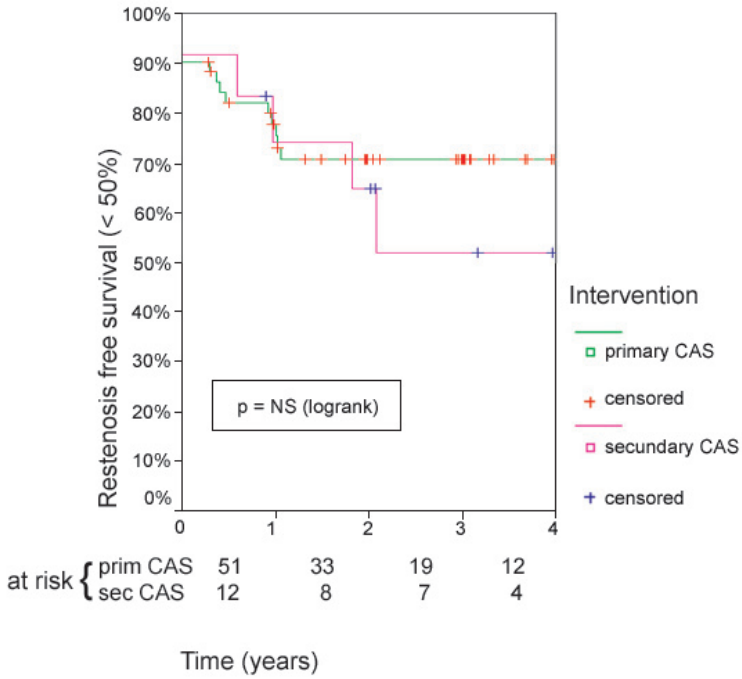

Figure 2. Restenosis free survival - primary

Long term follow-up showed 3 strokes at the CAS side and 3 strokes at the CEA side. All strokes were non-disabling, except for one disabling stroke which occured at the CAS-side after a myocardial infarction accompanied by atrial fibrillation 16 months after the CAS.

	CAS N	CEA N *	p**
Death	0 (0%)	0 (0%)	NS
Stroke	0 (0%)	0 (0%)	NS
TIA	7 (11%)	0 (0%)	0.01
Myocardial infarction	2 (3%)	1 (2%)	NS
Congestive heart failure	0 (0%)	0 (0%)	NS
Hypotension	15 (24%)	4 (7%)	0.02
Asystolism	6 (10%)	0 (0%)	0.02
Arrhythmia	2 (3%)	6 (11%)	NS
Dissection	1 (2%)	1 (2%)	NS
Vasospasm	1 (2%)	0 (0%)	NS
Occlusion	0 (0%)	0 (0%)	NS
Bleeding requiring re-intervention	3 (5%)	2 (4%)	NS
Wound infection	1 (2%)	0 (0%)	NS
Cranial nerve lesion	0 (0%)	4 (7%)	0.03

* 9 patients with missing values
** Chi-square

Table 2. Complications during hospital stay

DISCUSSION

The Kaplan Meier estimate of ≥ 50% restenosis for CAS vs. CEA at 1,2, and 3 years was 23% vs. 10%; 31% vs. 19%; and 34 vs. 24%, respectively. The one year's risk of in-stent restenosis we found (23%) is at the higher end of the spectrum, varying from 3% [9,18] to 40% [19] of patients having ≥ 50% restenosis at one year following CAS. Our patients, with

bilateral carotid artery stenosis and a high prevalence of coronary artery disease, clearly have a high atherosclerotic potential, so the restenosis rate in this particular group might be expected to be higher than the restenosis rate in a patient selection with unilateral carotid artery stenosis.

Recently there has been much concern about duplex criteria for stented carotids. Stented carotid arteries may need other duplex criteria for stenosis than operated carotid arteries, because of increased stiffness of the vessel after stenting. Since new criteria suggest a cut off PSV of 150 cm/sec for 20% stenosis [20], the cut off value for 50% stenosis would be much higher than the 125cm/sec we applied as a cut off for 50% stenosis. If applied to our duplex measures, this would lead to a tremendous reduction in restenosis in the stented arteries, because most in-stent restenoses in our study had relatively low flow velocities. Further studies are warranted to better determine the need for specified duplex criteria for restenosis following stenting of the carotid arteries.

Case series and reviews have shown that CAS can be performed with good results, showing 30-days stroke and death rates of 2 - 7% [4-9] and 3 years stroke rates of 8-12% [7,14]. These results are comparable to large randomized CEA trials [1-3,21,22]. Experience with CAS is growing and the use of protection devices may further decrease peri-interventional stroke [4,6,23]. The role of CAS will ultimately be defined by the ongoing RCT's: CREST, EVA-3s, ICSS and SPACE, of which CREST and EVA-3s only perform CAS with cerebral protection devices [10-13].

The main limitations of our study are sample size and inclusion bias: patients who died or suffered a disabling stroke after the first treatment are not included in this study. The bias has a positive effect on overall clinical outcome, but its effect (if any) on restenosis is uncertain. Clinical outcome was not a primary goal of this study because of the small number of patients. The relatively infrequent hard endpoints of stroke and major cardiovascular events and death require large study populations. Interestingly, we did find a statistically significant relation between CAS and peri-interventional TIA's. The patients were not totally comparable at the time of the CAS and the contralateral CEA: the patients were older at the time of CAS, but because of the intra-patient study design all other cardiovascular risk factors were constant. Further, the reason for intervention may have been different between CAS and CEA. CAS was performed because of restenosis in 12 patients. Thirteen patients were in a CABG protocol in which patients with bilateral carotid stenosis had one carotid artery stented 4 weeks before CABG and the contralateral carotid artery operated along with CABG in one session. The decision for the other patients for choosing treatment were

anatomy, cardiovascular risk and patient preference. Since CAS is the newer technique it was performed more recently and was the second intervention in most patients (after contralateral CEA).

Conclusion

Restenosis rates after CAS and CEA were comparable in this direct intra-patient comparison, and in combination with promising results and potential advantages for CAS in certain patient groups, this result should encourage the inclusion of patients in randomized clinical trials of CAS vs. CEA.

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CHAPTER 8

OPERATIVE MANAGEMENT OF CAROTID ARTERY IN-STENT RESTENOSIS: FIRST EXPERIENCES AND DUPLEX FOLLOW-UP.

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ABSTRACT

Objectives: Carotid Artery Stenting (CAS) may be comparable to Carotid Endarterectomy (CEA) as a durable and effective procedure in stroke prevention. Concern remains about the incidence of restenosis after stenting and its management. We evaluated the surgical managment of restenosis after CAS.

Design: Prospective study

Methods: Between December 1997 and april 2001, 217 CAS procedures were performed in 217 patients (155 men and 62 women; age 70 years ± 8.2). After a mean of 8 months post-stenting four patients (2 symptomatic, 2 asymptomatic with contralateral occlusion) with severe haemodynamic in-stent restenosis (90-99%) had surgical reintervention

Results: Standard CEA with removal of the stent was performed in all 4 patients. No major complications occurred. Intima hyperplasia showed to be the predominant mechanism leading to in-stent restenosis. All 4 surgically treated patients remained asymptomatic and without recurrent restenosis over a mean follow-up time of 13 months (range 3 – 20 months).

Conclusion: The optimal treatment of in-stent restenosis has yet to be defined, but standard CEA with removement of the stent appears to be feasible.

INTRODUCTION

Carotid artery stenting (CAS) may be comparable to CEA as a durable and effective procedure in stroke prevention [1,2]. The use of percutaneous carotid angioplasty, first reported in 1981 [3] was initially limited as a result of issues surrounding possible embolic complications, suboptimal angiographic results, acute vessel closure, elastic recoil, and restenosis. In the last decade, however, the introduction of adjunctive stenting has mitigated many of these concerns. Although still an emerging technique using evolving equipment, both single-center reports [2,4-6] and worldwide surveys [7] of carotid stenting have demonstrated procedural results appoaching those of endarterectomy, typically in the high-risk patient with significant comorbidities excluded from the previous surgical trials [8,9]. Complications of anaesthesia, infection, haemorrhage, myocardial infarction, and cranial nerve palsy are avoided with stenting, which has also shown the potential to shorten hospital stays and lower costs compared with endarterectomy [10]. However, concern remains about the incidence of restenosis after stenting and its management [11]. In-stent restenosis after CAS has been reported in 2 to 8% of cases [2,7,12]. The clinical follow-up in most of these reports is relatively short, generally less than 12 months. Clearly long term follow studies are needed [13].

Repeat angioplasty, carotid endarterectomy, and carotid artery reconstruction have all been used to treat restenosis after CAS. No definitive evidence exists concerning the optimal management of in-stent restenosis. While little experience exists with endovascular techniques for the management of in-stent restenosis we present our experience with the surgical treatment of restenosis after CAS. We report on 4 consecutive patients who developed severe in-stent restenosis, and subsequently underwent standard carotid endarterectomy with removement of the stent and follow-up with duplex scanning.

METHODS

Carotid Stent Protocol

Arteriography and stenting were performed with retrograde femoral access, using local anaesthesia. A cerebral protection device was not standardized in our protocol. Continuous electrocardiography with heart rate and blood pressure monitoring was performed throughout the intervention. All patients received aspirin (38-100 mg/day) prior to CAS. All patients were started on Clopidogrel (75 mg/day) 72 hours before the procedure and continued this for 2 to 4 weeks. Aspirin was continued life-long. During the procedure heparin (5000-10.000 IU) was injected intravenously and atropine sulphate

0.5-1.0 mg was given in all patients before balloon inflation. Either Easy Wall or Carotid Wall stents (Schneider/ Boston Scientific, Europe) were used. After stent deployment, high pressure balloon angioplasty (8-14 atmosphere) was executed at the point of residual stenosis by using a 5- or 6-mm diameter balloon catheter. Angiographic success after CAS was defined as < 30% residual stenosis.

Follow-up Protocol and patient selection

Patients had a clinical and duplex follow-up at 1 day, 3 and 12 months and every year thereafter. Residual or recurrent stenosis was defined as an ultrasonographic stenosis of ≥ 50%. All neurological investigations before, during, and after CAS were performed by an independent neurologist.

The detailed results of clinical and duplex follow-up of all CAS patients are described in the article by Christiaans et al. [14]. Four patients with severe haemodynamic (90-99%) in-stent restenosis (2 Carotid Wall and 2 easy Wall) had an indication for surgical reintervention. Two patients had a symptomatic (TIA, Amaurosis Fugax) restenosis and two patients had an asymptomatic restenosis with contralateral occlusion. Three of our treated in-stent restenoses developed in patients after an initial CAS procedure for de novo stenosis, whereas the fourth restenosis developed after a CAS procedure for post-CEA restenosis. In all 4 surgically treated patients explanted stents were examined histologically. All devices were dehydrated in a graded series of ethanol and embedded in methyl methacrylate. Sections were made with an innerlock diamond saw and routinely stained with methylene blue and basic fuchsine for light microscope evaluation.

RESULTS

In all four patients standard CEA with removal of the stent was performed. The traditional endarterectomy cleavage plane in the intima/media layer was remarkably accessible with a dissector. The stent surrounded by the intima core could be removed in toto in all 4 procedures. Special precautions, such as jaw luxation for high access were not necessary in these patients. All arteriotomies were closed with a venous patch. No additional reconstructions were required. Postoperatively, the patient with symptomatic presentation suffered from transient worsening of pre-existing paresis. No other complications occurred. Histologically, intima hyperplasia with smooth muscle cell proliferation showed the predominant mechanism leading to in-stent restenosis [Figure 1]. No specific inflammatory process was noted in the vessel wall.

During a mean follow-up of 13 months (range 3 – 20 months) all four surgically treated

patients remained asymptomatic and without recurrent restenosis. No further operative interventions have been performed in these patients.

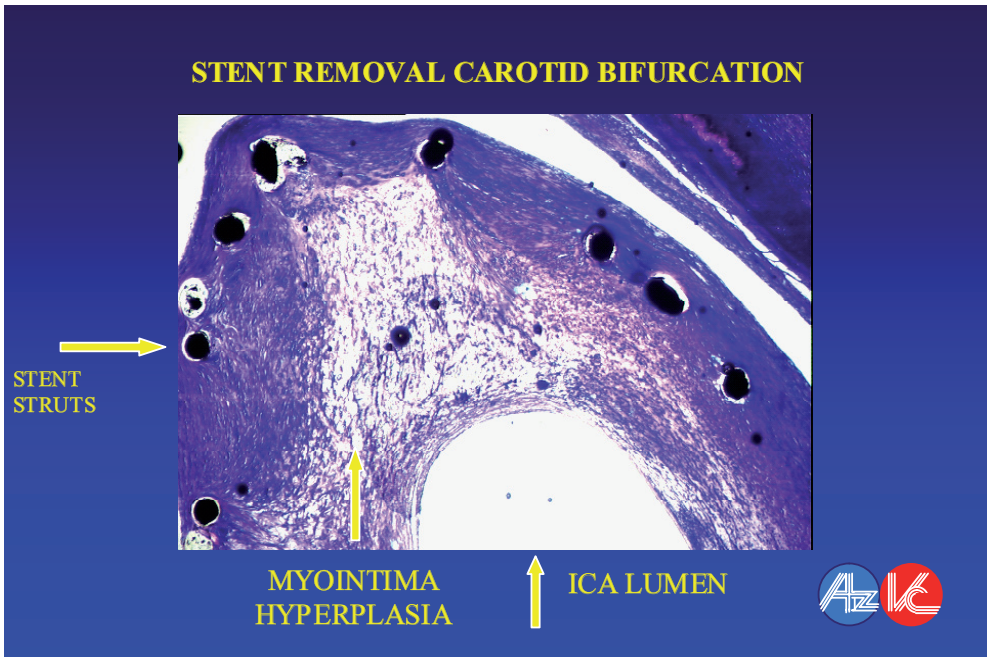

Figure 1. Transverse histologic section through the removed stent and surrounding intima. Intima hyperplasia shows to be the predominant mechanism of in-stent restenosis. No signs of inflammation are noted.

DISCUSSION

Initially stents were used only as a secondary procedure after full balloon inflation for inadequate vessel dilation or complications of treatment. Primary stenting is now accepted as best practice and has become the technique of choice for carotid stenosis, replacing balloon angioplasty alone in most cases. It is believed to be safer than simple balloon angioplasty because plaque rupture, arterial dissection, and acute occlusion of the carotid artery are less likely to arise [2,15]. Furthermore, stenting of coronary vessels has been associated with significantly lower rates of angiographic and clinical restenosis than angioplasty alone [16]. Myointimal hyperplasia with smooth muscle cell proliferation is the predominant mechanism leading to in-stent restenosis [17,18] as well as the underlying mechanism for restenosis occurring within 2 to 3 years of CEA [19,20]. Unlike carotid

endarterectomy, stenting does not remove the atheromatous plaque, and the insertion of a stent causes vascular injury. Although angiographic studies have indicated that in coronary arteries restenosis in stents with a central articulation occurs more frequently at the articulation [21], in a serial intravascular study neointimal tissue proliferation tended to be uniformly distributed over the length of the stent [22]. However, the determinants and biological basis of the response to stent imposed injury are not yet understood. The focal deep trauma of expanding struts, extensive early thrombus within days of stenting, permanent strain to the vessel wall, and foreign material remaining in the injured artery all seem to play a role [23,24]. From experimental models the construction of stents causing less vascular injury seems promising [25].

Repeat angioplasty, carotid endarterectomy, and carotid artery reconstruction have all been used to treat restenosis after CAS [26-29]. Recently one case has been described with deployment of a stent within a stent [30].No definitive evidence exists concerning the optimal management of in-stent restenosis. The first case of CEA after CAS was reported by Vale et al. [31]. Their patient experienced a 50% restenosis of the treated segment 6 months after stent deployment. Reedy et al. described successful stent removal in 2 patients without complications until hospital discharge but without histology or follow-up [32]. In his 5 year follow-up study Roubin et al. [9] only mentioned 1 patient to require CEA for restenosis and no details were given. In their series 16 patients (3%) required repeated angioplasty for restenosis. Uncomplicated stent removal for a less common complication such as detachment and distortion of the stent (both Palmaz stents) also has been reported [33,34]. So far no cases of stent removal resulting in major complications have been reported, although several authors do point at the technical difficulty of the procedure. Exposure of the carotid artery can be particularly difficult because of scarring and the need to access the artery proximal and distal to the stent containing segment [27,31]. Furthermore, inflammation of the carotid bifurcation can make the procedure more complicated. The inflammatory reaction within the stented artery causes the stent to become adherent to the arterial wall making identification of the endarterectomy plane hardly possible [28]. In the four procedures we performed no inflammation was noted and the traditional cleavage plane in the intima/media layer was well recognizable and accessible.

Carotid stenting brings significantly lower cost and resource utilization compared with CEA [10]. In an analogous comparison, studies of percutaneous angioplasty versus bypass surgery in patients with multivessel coronary disease have found significantly greater hospital costs associated with the surgical pathway but nearly equivalent costst at 5 years, largely because of the repeated intervention required in the angioplasty arm secondary to a significant rate of coronary restenosis [35]. Also if experience from superficial femoral and iliac artery stenting is considered, the early results of CAS must be tempered by

development of late complications requiring secondary intervention and thus more overall costs. There is an important need to establish the efficacy, safety, and durability of carotid stenting by comparison with surgery, before the technique is widely introduced.

Conclusion

The optimal treatment of in-stent restenosis has yet to be defined, but standard CEA with removement of the stent appears to be feasible and should be considered as an alternative when recurrent stenosis occurs after CAS. At short term follow-up, no restenosis occurs in the stent removed area, and so far the removal of a carotid stent in combination with a classic endarterectomy seems to be a durable procedure. All four patients with CEA after CAS remained asymptomatic and without recurrent restenosis with a mean follow-up of more than 1 year. Of course long term follow-up has to be awaited.

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CHAPTER 9

EFFECT OF CAROTID ANGIOPLASTY AND STENTING ON DUPLEX VELOCITY MEASUREMENTS. AN ANIMAL EXPERIMENTAL STUDY.

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ABSTRACT

Background: Velocity measurements are an integral part of duplex ultrasound (US) evaluation following treatment of extracranial carotid stenosis. Differences between velocities in native versus stented carotid arteries have been reported. An animal experiment was conducted to evaluate carotid diameter and velocity changes due to stent placement.

Methods: The common carotid artery of 5 pigs was exposed bilaterally (10 arteries). Diameters and velocities were measured by US in the proximal, mid and distal native artery segments. Diameter and velocity measurements were repeated after bilateral stent placement (Wall stent and contralateral Precise Cordis). Outcomes of native vs stented arteries and Wall vs Precise Cordis were statistically compared.

Results: Mean proximal stent diameter, 3.6 mm±0.1 (SE), was significantly smaller than the native proximal artery diameter, 4.2±0.1 by paired t-test (p=0.008), mostly due to narrowing of the Wall stent diameter to 3.4 ± 0.2mm (p=0.003). Proximal, mid, and distal segements of the Wall stents were narrower than those of the Precise stent, and associated peak systolic velocities (PSV) were higher: 266±17 vs 215±19 cm/sec, 306±32 vs 206±12 cm/sec, and 317±44 vs 228±21 cm/sec respectively. Wall stent PSVs were significantly higher than pre-stenting native artery PSVs , 187±14, 241±18, and 242±28 cm/sec at he proximal, mid and distal segments respectively.

Conclusions: Stent placement caused anatomical and haemodynamic alterations. Narrowings and associated increased velocities were noted. Such alterations, however, were stent dependent, and do not justify a general approach to new velocity criteria indiscriminately applied to all stents.

INTRODUCTION

Carotid angioplasty and stenting (CAS) has worldwide emerged as an alternative to carotid endarterectomy (CEA) in the treatment of haemodynamic significant carotid artery stenosis. The ultimate value of CAS compared with CEA will be based on ongoing prospective randomised trials [1,2]. In the interim, however, the number of patients undergoing CAS is increasing rapidly, and these patients require regular follow-up to monitor for in-stent recurrent stenosis (ISR) [3].

The utility of duplex ultrasound (US) in the detection of native carotid artery disease is well documented [4,5]. However, duplex US velocity criteria have not been well-established for follow-up of patients who underwent carotid artery stenting [6]. Several studies have questioned whether the standard velocity criteria used for grading stenosis after CEA can also be applied to grade carotid ISR [7-9], and some have concluded that assessment of standard duplex US criteria after CAS is inapplicable [10,11]. Although several types of stents have been used in these studies, surprisingly, a comparison for differences in outcome between stent types has not been studied.

A potential error in the interpretation of US velocities after CAS is failure to recognize that placement of a stent alters the biomechanical properties (increased elastic modulus (Ep), decreased compliance (Cp)) of the stented artery [9,12]. This may cause an increase in duplex-acquired velocity measurements in the absence of technical error, residual stenotic disease, or imaged myointimal thickening in the stent [7-11,13]. Therefore, the potential risk of using the generally accepted duplex US criteria for follow-up after CEA is an overestimation of the degree of restenosis after CAS. If so, this overestimation of restenosis both affects the individual patient and the long term outcome of ongoing prospective clinical trials [1]. The mechanism, magnitude, and significance of these alterations are ill-defined, and emphasizes the need to develop customized velocity criteria for use in patients with implanted stents.

An animal experimental study using a pig model was conducted to evaluate carotid diameter and velocity changes due to stent placement. Three questions were addressed:
1) Is stent placement associated with an elevation in duplex US velocity measurements ?;
2) Is stent type of influence on stent related anatomical and haemodynamic alterations ?;
3) Is there a need to revise duplex US velocity criteria for the stented carotid artery ?

METHODS

1.1 Study Design

We obtained to compare duplex US results pre- and post-CAS with emphasis on arterial diameter and velocity changes. The study protocol was approved by the Ethics Committee on Animal Studies Utrecht. Two commonly used stents in clinical practice today; the Carotid Wall stent (Boston Scientific; Natick, MA, USA) and a self-expanding Precise stent (Cordis Corporation; Miami, Fl, USA) were employed in this study. All experiments were performed under guidance of qualified BioSurgical personnel following standard operating procedures available at the test facility.

2. Test Species

2.1 Model

Study animals were 90 kg female Landrace pigs with an expected carotid artery diameter of 5 mm.

2.2 Number of Animals

A total of 5 animals (10 arteries) was used for this study. Since the outcome of our measurements was unknown, no statistical power analysis could be performed.

3. Test Materials

All test articles (stents, sheaths, etc.) were supplied by the department of Radiology, UMC Utrecht. A Philips iU22 Ultrasound System was provided by Philips Medical Systems, The Netherlands BV.

4. Duplex US

Peak systolic velocity (PSV) and end-diastolic velocity (EDV) and PSV/EDV ratio were obtained at the proximal, middle, and distal common carotid artery (CCA). The stent location was visualized in the B-mode. Stent apposition to the artery wall was imaged in both sagittal and transverse planes.

High resolution linear broadband transducers in the 5-MHz to 10-MHz range were used directly on the carotid artery using water as acoustic window. The Doppler angle of insonation was 60 degrees with angle cursor parallel to the vessel wall. The smallest sample volume was used and positioned center stream in the artery/stent [Figure 1]. In the stented CCA velocities were measured at the stent edges, proximal, mid, and distal. In addition the velocities at 1 cm proximal and distal to the stent edges were measured [Figure 2]. Multiple representative samples of the velocity spectra (PSV and EDV) were recorded.

The waveform with the highest PSV was used to classify degree of diameter reduction). Duplex measurements were performed in 2 steps. ***Step 1:*** measurement of the proximal, mid, and distal native carotid artery in the predetermined area of stent placement. ***Step 2:*** measurement after bilateral carotid stenting. Specific endpoints to be examined were arterial diameter change and velocity changes due to stent implantation. To optimize the accuracy of measurements, all subjects throughout the study were investigated by the same team of physicians.

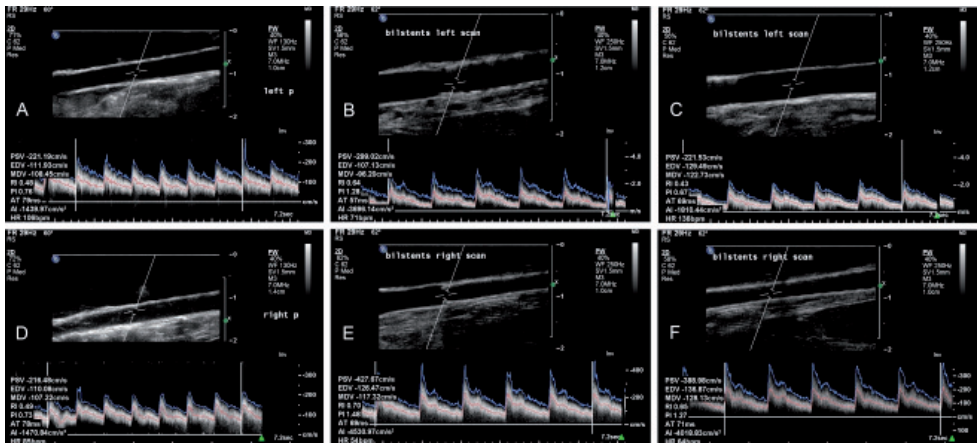

Figure 1. Measurement of the native carotid artery in the predetermined area of stent placement. The smallest sample volume was used and positioned center stream in the artery. The waveform with the highest PSV was used to classify degree of diameter reduction. (A-C Cordis stent, D-F Wall stent)

5. Surgical method

5.1 Animal preparation and anaesthesia.

Animals were premedicated with azaperon (2.0 mg/kg) and ketamine (1.5 mg/kg), administered by intramuscular injection. An intravenous line was established and each animal received intravenous thiopental (2.0 mg/kg) and atropine (1.0 mg). The pigs were endotracheally intubated and mechanically ventilated. Anaesthesia was maintained by supplying a mixture of oxygen and air (1:1 vol/vol), and intravenous infusion of midazolam (0,6 microgram/kg per hour) and sufentanil citrate (0,6 microgram/kg per hour) and Pancuromium (Pavulon). All ventilation parameters were adjusted to keep the arterial blood gasses and pH within the physiological range. A rectal temperature probe was placed to record core body temperature.

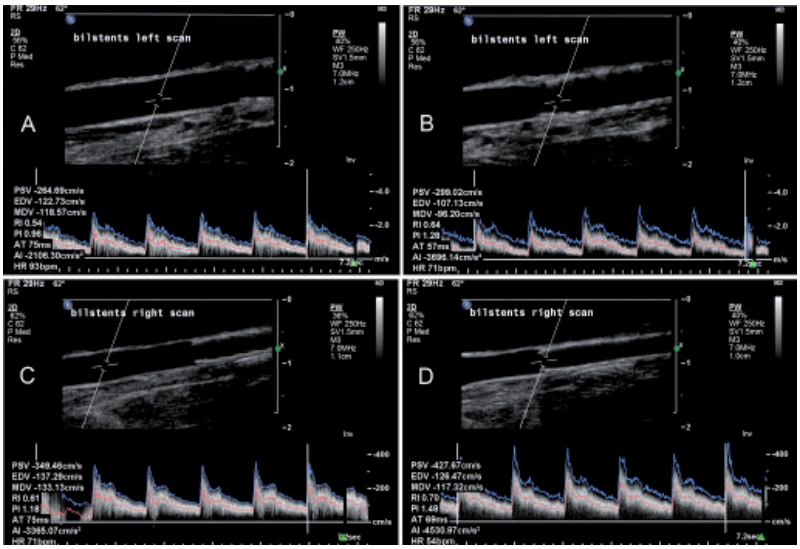

Figure 2. In the stented CCA velocities were measured at the stent edges, proximal, mid, and distal. In addition the velocities at 1 cm proximal and distal to the stent edges were measured. Multiple representative samples of the velocity spectra (PSV and EDV) were recorded. (A and B Cordis stent, C and D Wall stent)

5.2 Surgical technique.

The animal was placed on the operating table in a supine position and attached to the ventilator. The pig was surgically draped to expose the cervical and groin region. In each animal the left and right CCA were carefully exposed. Animals were anticoagulated with intravenous heparin (100 units/kg). In all animals the CCA was exposed on both the left and right side. Vessel loops were placed circumferentially around the artery. Using femoral access, stents were positioned in the CCA under fluoroscopic guidance. Stents were oversized with approximately 20%. Stent related spasms were counteracted with lidocaine 2% solution, in a constant water temperature of 39 degrees Celsius and with intra-arterial Papaverine HCL 50 mg/ml in 300 ml saline solution.

5.3 Termination

All results described in the present study were from experiments performed in an acute setting. No follow-up data were collected. At the end of the experiment the animal was euthanized with an overdose of barbiturate/saturated KCL solution intravenously.

6. Statistical analysis

All statistical analyses were performed with SPSS software version 11.5 (SPSS Inc. Chicago, Illinois). Groups were compared with paired t-test. Probability values $p > 0.05$ were considered non-significant.

RESULTS

1. A comparison of duplex baseline measurements with measurements taken after bilateral stenting, (n=10 arteries, 5 pigs) was as follows (Summarized in Table 1 + 2):

Diameter

1.1. Proximal stent diameter, 3.5±0.5 (SD) mm, was significantly smaller than proximal artery diameter, 4.2±0.4 (SD) (P=.004).

1.2. Mid stent diameter, 3.8±0.9 (SD) mm, was similar to mid artery diameter, 3.8±0.6 (SD) (P=.83).

1.3. Distal stent diameter, 3.4±0.7 (SD) mm, was smaller but not statistically significant at the P<.05 level than distal artery diameter, 4.0±0.8 (SD) (P=.083).

PSV

1.4. Proximal stent PSV, 232±45 (SD) cm/sec, was greater but not statistically significant at the P<.05 level, than proximal artery PSV, 196±40 (SD) cm/sec (P=.11).

1.5. Mid stent PSV, 238±76 (SD) cm/sec, was similar to mid artery PSV, 242±37 (SD) cm/sec (P=.85).

1.6. Distal stent PSV, 254±85 (SD) cm/sec, was similar to distal artery PSV, 248±49 (SD) cm/sec, (P=.83).

EDV

1.7. Proximal stent EDV, 105±35 (SD) cm/sec, was not significantly different than proximal artery EDV, 79±31(SD) cm/sec (P=.13).

1.8. Mid stent EDV, 103±37 (SD) cm/sec, was similar to mid artery EDV, 90±30 (SD) cm/sec (P=.47).

1.9. Distal stent EDV, 108±36 (SD) cm/sec, was similar to distal artery EDV, 95±36 (SD) cm/sec, (P=.47).

PSV ratios

1.10. The mid-to-proximal PSV ratio, 1.01±0.20 (SD), was significantly smaller after stenting than for the native artery, 1.28±0.31(SD) (P=.004).

1.11. The mid-to-distal PSV ratio, 0.94±0.08 (SD), was similar after stenting and for the native artery, 1.00±0.19(SD) (P=.38).

1.12. The distal-to-proximal PSV ratio, 1.08±0.22 (SD), was significantly smaller after stenting than for the native artery, 1.33±0.40(SD) (P=.019). This velocity ratio was more sensitive than PSV measurement to detect the increased velocity at the proximal end of the stent.

EDV ratios

1.13. The mid-to-proximal EDV ratio, 0.99±0.17 (SD), was significantly smaller after stenting than for the native artery, 1.18±0.19 (SD) (P=.003).

1.14. The mid-to-distal EDV ratio, 0.95±0.11 (SD), was similar after stenting and for the native artery, 0.98±0.21(SD) (P=.74).

1.15. The distal-to-proximal EDV ratio, 1.06±0.19 (SD), was significantly smaller after stenting than for the native artery, 1.26±0.32(SD) (P=.037).

2. A comparison of duplex measurements before and after bilateral stent placement : differences between stents (Wallstent versus Precise stent respectively).

2.1. The differences mentioned in the previous paragraphs were due primary to the Wall stent and not to the Precise stent. There were no statistically significant differences for PSV, EDV, or ratio measurements with the Precise stent.

2.2. The following differences were significant at the P<.05 level for the Wall stent.

2.2.1. ***Diameter.*** Proximal stent diameter, 3.2±0.5 (SD) mm, was significantly smaller than proximal artery diameter, 4.2±0.4 (SD) mm (P=.009). Mid stent diameter, 2.9±0.3 (SD) mm, was significantly smaller than mid artery diameter, 3.8±0.9 (SD) mm (P=.018). Distal stent diameter, 2.9±0.6 (SD) mm, was significantly smaller than mid artery diameter, 4.1±0.9 (SD) mm (P=.020).

2.2.2. ***PSV ratio.*** The mid-to-proximal PSV ratio, 1.05±0.28 (SD), was significantly smaller after stenting than for the native artery, 1.33±0.36(SD) (P=.010). The distal-to-proximal PSV ratio, 1.10±0.31 (SD), was significantly smaller after stenting than for the native artery, 1.34±0.42(SD) (P=.015).

2.2.3. ***EDV ratio.*** The mid-to-proximal EDV ratio, 1.05±0.22 (SD), was significantly smaller after stenting than for the native artery, 1.25±0.22 (SD) (P=.030). The distal-to-proximal EDV ratio, 1.05±0.24 (SD), was significantly smaller after stenting than for the native artery, 1.30±0.34(SD) (P=.016).

	Native artery	Stents (N=10)	Wallstent (N=5)
Diameter			
Prox	4.2 ± 0.4	3.5 ± 0.5	3.2 ± 0.5
Mid	3.8 ± 0.6	3.8 ± 0.9	2.9 ± 0.3
Dist	4.0 ± 0.8	3.4 ± 0.7	2.9 ± 0.6

Table 1. Diameter measurements at the proximal, mid, and distal CCA. Differences between native artery versus all stents (N=10) and Wallstents (N=5).

	Native artery	Stents (N=10)	Wall stent (N=5)	Cordisstent (N=5)
PSV				
Native prox to stent		184 ± 8	170 ± 5	194 ± 14
Prox	196 ± 40	232 ± 45	266 ± 17	215 ± 19
Mid	242 ± 37	238 ± 76	306 ± 32	206 ± 12
Dist	248 ± 49	254 ± 85	317 ± 44	228 ± 21
Native distal to stent		255 ± 17	286 ± 28	230 ± 17
PSV ratio				
Prox stent to prox native		1.31	1.56	1.1
Mid-Prox	1.28 ± 0.31	1.01 ± 0.20		
Mid-Dist	1.00 ± 0.19	0.94 ± 0.08		
Dist-Prox	1.33 ± 0.40	1.08 ± 0.22		
EDV				
Native prox to stent		83 ± 10	73 ± 15	92 ± 16
Prox	79 ± 31	105 ± 35	112 ± 18	97 ± 18
Mid	90 ± 30	103 ± 37	127 ± 19	88 ± 14
Dist	95 ± 36	108 ± 36	123 ± 21	100 ± 15
Native distal to stent		114 ± 11	119 ± 20	110 ± 16
EDV ratio				
Prox stent to prox native		1.3	1.61	1.05
Mid-Prox	1.18 ± 0.19	0.99 ± 0.17		
Mid-Dist	0.98 ± 0.21	0.95 ± 0.11		
Dist-Prox	1.26 ± 0.32	1.06 ± 0.19		

Table 2. Differences in PSV, PSV ratio, EDV, and EDV ratio between native artery and stented arteries (N=10). PSV and EDV in cm/sec ± SD.

DISCUSSION

In the present study, duplex US estimated carotid artery diameters and velocities at baseline were compared with measurements taken after bilateral stenting. The mean proximal stent diameter was significantly smaller than the mean proximal artery diameter. We found that the proximal end of stent had higher velocities than the proximal native artery. When we compared the effects of the two different stent types used, it showed that the Wall stents were responsible for all above mentioned differences in diameter and proximal increased velocities, whereas the Precise stent showed almost no differences in pre- and post-stenting diameters and velocities.

The number of patients undergoing CAS is still increasing, and larger numbers of patients will require surveillance to monitor the technical result of the procedure and to identify the development of ISR. The incidence of "early" ISR after CAS has been reported 4 – 21% of cases [3,6] depending on restenosis definition and duplex US criteria used. Guidelines for follow-up and surveillance after CAS therefore have yet to be established.

To our knowledge, six published studies have so far addressed the application of duplex US velocity criteria to assess the status of stented carotid arteries [7,9-11,13,14]. Both Robbin and Ringer et al. reviewed their experience with US immediately after carotid stent placement, and concluded that strict velocity criteria for recurrent stenosis were unreliable [7,10]. Both groups applied limited and randomly selected criteria to their data, but did not perform a systematic analysis to confirm their findings. Lal et al. found that currently accepted US velocity criteria for nonstented ICA's falsely classified several stented ICA's with normal diameter on carotid angiograms as having residual in-stent stenosis [9]. However, Lal et al examined the optimal threshold to predict > 20% stenosis which is not likely to become haemodynamically significant.

Willfort applied the same haemodynamic parameters to grade ISR, as those proposed by Nicolaides et al [15] for the native carotid artery, that is PSV and EDV within the narrowest site of the stent [16]. The basis for grading ISR, however, was the flow-ratio, calculated with the formula "In-stent ICA PSV/ CCA PSV". A flow ratio greater than 4 was reported to refer to greater than 70%, and a flow ratio greater than 2.6 to refer to greater than 50% recurrent stenosis respectively. Stanziale and Chi published the only 2 studies to date that examined the thresholds of US criteria to predict haemodynamically significant stenosis at the 50 and 70% levels [11,14]. Stanziale et al. concluded that PSV and ICA/CCA ratio increased with stenosis development to a greater extent in stented carotid arteries [14]. However, their newly proposed criteria were based on a retrospective review with only 6 patients with > 70% stenosis. The same observation was reported by Chi et al. [11] who noted that PSV and ICA/CCA ratio increased to a greater extent in 13 patients (8 Wallstents, 5 SMART stents)

with in-stent stenosis. Unfortunately, a comparison for differences in outcome between the 2 types of stents was not reported. Stanziale studied a mix of balloon expandable and self-expandable stents and also this report did not provide a specification for stent type in the results. Furthermore, Chi did not find the EDV nor the combination of PSV and ICA-CCA ratio to be useful in assessing either ≥ 50% or ≥ 70% ISR, opposed to Stanziale and Lal who found EDV to be significant. So although most studies suggest that stent placement in the carotid artery alters its biomechanical properties, leading to an increase in velocity measurements in the absence of residual stenosis, many uncertainties remain about the generalizability of these single centre results with small sample sizes.

Stents provide a scaffold to maintain the arterial lumen open. It causes radial strength to prevent elastic recoil of te vessel wall. The combination of stent and vessel wall thus becomes a rigid structure and can be viewed as a rigid segment within an otherwise elastic tube [17]. It is now established that stent placement is responsible for an acute compliance (Cp) mismatch between the stented part of the artery and its native upstream and downstream segments [9,12,18]. More important, Vernhet showed that the marked decrease in Cp observed immediately after stent deployment is a chronic, long lasting phenomenon [19].

A stent-impaired reduction in Cp due to increase in arterial stiffness may explain the elevated flow velocities observed [9]. However, basic hydrodynamic laws state that the higher the Cp, the higher the peak velocity. Some authors therefore probably not interpreted the Cp but the distensibility coefficient instead. The question then remains how the observed velocity increase by placement of a stent can be explained? We believe that a stent might theoretically cause a lower Cp and a significant decrease in the distensibility coefficient of the stented region when compared to the pre-stent vessel. This results in wave reflection and therefore a higher systolic pressure, which is subsequently responsible for a higher peak velocity. Furthermore, the stented artery segment must not be considered a static but preferentially a dynamic condition. The interwoven mesh design of stents affords unique mechanical properties. The elastic modulus (Ep) of stents is maximal when completely constrained and fully expanded, with lower values between these states. The stent Cp and Ep therefore vary with the diameter to which the stent has been expanded. In addition, in diseased arteries the arterial wall also contributes to the overall stiffness of the stented site, and this varies according to the amount of atherosclerosis and calcium load within the wall [20]. Therefore the final Cp and Ep of the stented ICA would be altered to various degrees. This might explain why US velocity measurements are significantly elevated in a percentage of patients but not all patients [11,20]. The mechanism, magnitude, and significance of these alterations however are ill-defined, and emphasizes the need to develop customized velocity criteria for use in patients with implanted stents.

ISR can be viewed as a biologic over-response to vessel injury caused by the endovascular

intervention. Currently used carotid stents are self-expanding in construction, and its diameters steadily increase over 2 years (positive arterial remodelling) [16,21]. Serial measurements of stent diameter have confirmed stent expansion after Wallstent deployment in the carotid artery – with most marked expansion most pronounced during the first 3 months after deployment, in the mid-stent region. This process is balanced by neointimal proliferation in the stent producing so-called negative remodelling [16,22]. Wallstents and other self-expanding prostheses continue to expand after implantation, and better expansion of the lumen might be achieved with time [23].

Our study was limited to treatment with 2 types of stents. The Wallstent is a stainless-steel stent with continuous filaments. The geometry changes of this type of stent could conceivably be quite different from findings with nitinol stents. In an in vitro study by Tanaka et al, testing 5 different types of self-expandable carotid stents, better wall apposition and less straitening and kinking of the carotid bifurcation model was found when segmented nitinol stents were used as compared with stents with continuous filaments [24]. Mathematical calculations also show that over-dilated stents produce less haemodynamic perturbations [12]. Piamsomboon found that with stent-oversizing, a high stent/artery diameter ratio was associated with a low late loss index [25]. Furthermore, anatomically correct positioning of appropriately sized stents does not lead to relevant flow disturbances [26]. Especially in the situation where stents are misplaced and too small, the central slipstreams are accelerated, while the velocities in the separation zones are decreased. A favoured feature of present stent design therefore is a radial force at all contact points. In our study, stents were slightly oversized for well-adaptation with the arterial wall.

Some limitations of the present study have to be acknowledged. This animal experimental study exclusively addressed self-expanding stents. However, we believe that the results provide basic data on the development of haemodynamic duplex parameters after stenting. In our animal model, there was no residual stenosis after stent expansion because the arteries were free of atherosclerotic disease before intervention [27]. This offered us the opportunity to observe the bare influence of a stent on velocity measurements in an undiseased artery.

Clinicians need to be aware of the limitations of duplex US when making management decisions. Vascular laboratories should realize that carotid stent placement itself lead to elevated duplex velocities, but that these alterations might well be highly stent type specific. Each center may therefore have to develop its own velocity criteria for the evaluation of patients with stented as opposed to native carotid arteries. Patients with mild elevation in PSV (125-150 cm/s) in carotid stented segments should therefore be interpreted with caution. The identified cohort could be followed more closely, or, if symptomatic, brought to further therapy.

Conclusion

Stent placement causes anatomical and haemodynamic alterations in the carotid artery. Narrowings were noted mostly at the proximal and distal ends of the stents, showing more prominent in the Wall stent. In the Wall stent, progressive velocity increases within stents were noted from the proximal to the distal positions. However, observed alterations seem to be stent type dependent. Vascular laboratories have to develop specific velocity criteria for the evaluation of patients after CAS.

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CHAPTER 10

GENERAL DISCUSSION

GENERAL DISCUSSION

In august 2007 it will be 54 years since DeBakey performed the first carotid endarterectomy (CEA). Is there a reason to celebrate and sit back ? Is carotid artery revascularization straightforward ? Unfortunately, the answer has to be NO ! Although being one of the most scrutinised areas of medicine, the management of carotid artery disease maintains an unparalleled and enduringly reputation for controversy.

Despite level I evidence supporting the role of CEA in symptomatic and asymptomatic patients [1-4], the paradox remains that the very operation undertaken to prevent stroke (in the long-term) is associated with a small, but important risk of stroke in the peri-operative period. This paradox has, of course, been recognised for more than 50 years. However, the debate as to how stroke and other cardiovascular complications might be prevented following CEA remains largely unresolved and has for a long time been inappropriately dominated by "single-issue" subjects.

The main controversies are related to: 1) improvements in the concept of "best medical therapy"; 2) the emergence of CAS as an alternative to surgery; 3) treatment of asymptomatic patients; 4) plaque morphology; 5) perioperative monitoring; and 6) timing of intervention.

1) Best Medical Therapy (BMT)

At time of recruiting patients for the landmark trials (ECST, NASCET) the concept of BMT was relatively simple meaning cessation of smoking, starting aspirin and treating hypertension. The "modern" BMT constitutes 1) dual or alternative antiplatelet therapy; 2) tighter thresholds on blood pressure control using multiple drugs; 3) low dose ACE inhibitor therapy; and 4) statin therapy. Each of these has been evaluated in trials and most have shown a 20-25% relative risk reduction in vascular death or non-fatal myocardial infarction and stroke [5,6]. However, 5 years of statin therapy did not confer any absolute risk reduction in late stroke in patients with pre-existing symptomatic cerebro-vascular disease [7]. Similarly, Clopidogrel was associated with a limited 0.9% absolute risk reduction in ischaemic stroke at 2 years in patients presenting initially with a stroke [5]. In other words, treating 1000 patients for 2 years would prevent only nine strokes. Furthermore, there is no evidence that combination antiplatelet therapy (Aspirin + Clopidogrel) reduces the long-term risk of stroke [8].

BMT therefore will not render CEA obsolete; CEA after all confers immediate benefit while BMT inevitably requires a lag-phase. The concept of advanced BMT will continue to complement rather than replace CEA; provided that surgery is performed within weeks of the presenting event with a low morbidity and mortality.

2) Carotid Angioplasty and Stenting (CAS).

Since its inception CAS has been a constant source of debate regarding initial succes and durability [9]. In CAVATAS the overall stroke and mortality rates for CAS at 3 years were comparable with CEA despite the use of stents in only 26% of patients [10]. CAS was shown safer than CEA in patients at high surgical risk owing to severe coronary artery disease, because of a lower risk of myocardial infarction within 30 days after CAS as compared with surgery [11]. It must be realised that there was no significant difference in the rates of stroke or death between CAS and CEA at either 30 days (3.6% vs 3.1%) or at 1 year, and although more asymptomatic than symptomatic patients were included in Sapphire, CAS was only approved for symptomatic patients at high surgical risk.

More recent trials however failed to prove the non-inferiority of CAS. The EVA-3S trial stopped early because of an excess 30-day incidence of stroke or death among CAS patients (9.6%) compared with surgery (3.9%) [12]. The trial received heavy criticism, as deficient methods and lack of experience on the part of the endovascular specialists had influenced its outcome, although operator experience was not a major determinant of the 30 day death/stroke risk [13].

EVA-3S results underscore the need to improve the safety of endovascular treatment before it can become an alternative to CEA. Patient selection and timing will be a key issue for the success of carotid stenting. Some carotid lesions cases remain difficult to treat surgically and angioplasty could be entertained in such situations. In the end, CAS will turn out to be an useful addition to the surgeon's array of procedures.

Although the issue of initial success of CAS is still going on, major concerns remain about durability. In-stent restenosis is detected in most centers by duplex ultrasonography. In Chapter 9 we show that in animals with undiseased vessels duplex velocity criteria for stented arteries might be different from accepted criteria as applied to non-stented arteries, but that these criteria might differ with the type of stent being used. Upcoming techniques, such as 3 dimensional CT , will bring support to duplex interpretation studies in the establishment of specified duplex acquired velocity criteria following stenting. In Chapter 8 we described our initial experiences with the surgical treatment of in-stent restenosis. These patients had early (symptomatic) restenosis, and the issue if and when treatment of late (> 3 years after first treatment) is indicated is still open for discussion.

Given the evidence to date, and assuming a complication rate of less than 6%, the only widely accepted indication for CAS remains its use in symptomatic patients who have stenosis of the ICA exceeding 70% and who should be placed ina clinical trial. All other patients should be treated medically, undergoing CEA if indicated.

3) How to deal with asymptomatic patients ?

Should any asymptomatic patient be considered high-risk for stroke ? Obviously a minority will be, but our problem remains to identify the 10-15% destined to suffer a stroke amongst 85-90% who won't. Accordingly, targeting CAS on asymptomatic patients because of some clinical factor that makes the patient high-risk for CEA will do little to reduce the overall risk of stroke in the general population.

Furthermore, it can no longer be justified to simply consider all asymptomatic men and women as if they would derive equivalent benefit. Should all asymptomatic women then be denied surgery ? It is inevitable, that certain women will gain considerable benefit from surgery, but can they be identified ? Future imaging and monitoring techniques such as the detection of microembolisation (using transcranial Doppler) may predict high-risk asymptomatic patients who should be considered for surgery [14]. In general, until we can identify predictors of increased stroke risk in asymptomatic patients, the term "high-risk" should only be applied to patients who are symptomatic.

4) Plaque morphology

4a. The plaque as crystal ball ?

Stable fibrous atherosclerotic plaques are less prone to cause ischemic events [15,16]. Carotid plaques obtained from women have a more stable, less inflammatory phenotype compared with men, independent of clinical presentation and cardiovascular risk profile, and this (especially in asymptomatic women) might explain the lower benefit from CEA for women [17]. Plaque instability is influenced by the presence of matrix metalloproteinase (MMP) activity [18,19]. Therapeutically, MMP production can be directly inhibited by statins [20]. Also, symptomatic plaques (but not asymptomatic plaques) contain immature microvessels similar to those found in tumors and healing wounds. Such vessels contribute to plaque instability by acting as sites of vascular leakage and may become future therapeutic targets for plaque stabilization [21].

Plasma markers have also been evaluated in symptomatic patients, but again few have been undertaken in asymptomatics. From the "symptomatic literature" elevated levels of C-reactive protein, fibrinogen and plasma MMP-9 have been predictive of increased risk for stroke and in identification of unstable plaques [22]. These markers should now be evaluated prospectively in asymptomatic patients but are also of interest in patients with recurrent stenosis.

In Chapter 4 and Chapter 5 the results of treatment of restenosis following CEA are described for redo endarterectomy and CAS respectively. The real debate however is not about the choice of technique but far more which restenosis should be treated and which not. In this respect future plaque monitoring studies (both imaging and TCD) will have to lead us the way.

4b. (Noninvasive) plaque imaging.
Echomorphology assessment of carotid plaques has demonstrated the association between plaque heterogeneity, intraplaque hemorrhage, and cerebral symptoms [23]. However, the subjectivity of this technique, associated with changes in both symptomatology and degree of stenosis has led to conflicting results in literature [24]. New imaging techniques such as high-resolution magnetic resonance imaging (MRI) that enables identification of luminal thrombus, single photon emission computed tomography may rejuvenate morphology studies and bring the potential of observed differences in plaque level into clinical practice [25]. MRI evidence of overlying luminal thrombus in an asymptomatic patient would certainly be a compelling reason for intervening prophylactically.
The fundamental problem remains that no one has successfully translated POSTOPERATIVE histological/ biochemical features into PREOPERATIVE plasma markers or ultrasound/ MRI parameters that can then reliably identify the high-risk setting in the outpatient clinic.
For the future, patients randomized in trials could undergo preoperative assessment of plasma markers and US/MRI. Surgical patients would provide samples for histological and biochemical analysis, whilst medically treated patients provide natural history data.

5) Perioperative monitoring
Transcranial Doppler (TCD) monitoring provides online surveillance of both haemodynamic changes and cerebral microembolism in the middle cerebral artery (MCA) on the side of surgery , and the intra-operative stroke rate from CEA has declined since its introduction[26].
In Chapter 2 we showed that perioperative stroke due to postoperative carotid thrombosis (POCT) still complicates 2-3% of CEA's. It is recognised that postoperative stroke is preceded by TCD detected increased embolisation during a 1-2 h window [27] and accordingly, modification of peri-operative antiplatelet therapy could be an innovative way of preventing postoperative embolisation and its subsequent devastating complications. In Chapter 3 the effect of different antiplatelet regimens on the rate of postoperative emboli following CEA was studied but no significant influence was found. More recent evidence suggests that post-operative thrombosis might be prevented by the administration of a single 75 mg dose of clopidogrel (in addition to regular aspirin) the night before surgery [28]. Future studies that evaluate the role of dual perioperative antiplatelet therapy in preventing POCT, and define the role of targeted monitoring should include the concept of "aspirin resistance" and the sensibility of the individual patient for the different antiplatelet therapies available.

6) Timing of intervention; when to act ?

Regarding the magnitude of stroke prevention, any debate about revascularization technique (CEA vs CAS) or if asymptomatic patients should be treated or not, turns into insignificance when compared with the effect of delay in treating patients with symptomatic carotid artery disease.

Previously, the risk of stroke after TIA was believed to be 2% at 7 days and 2-4% at one month [29]. These data came from patients who were recruited weeks or months after the index event. The true risk of stroke after TIA or minor stroke may be as high as 8-12% at seven days, 12-15% at 30 days, and 17-19% at three months [30]. Thus, the highest risk of stroke from a recently symptomatic carotid plaque is maximal immediately after the initial symptom, when the plaque is unstable and overlying thrombus is more likely to be encountered. As the plaque thereafter stabilises, the thrombus disappears and the risk of embolic stroke diminishes. In parallel, the clinical and cost-effectiveness of CEA also decreases. Unfortunately, as yet, there are almost no centres in the world in which the median delay to surgery is within the recommended "bench-mark" of 14 days [31,32].

The message must be that " The quicker one operates, the greater the number of strokes prevented in the long-term" and especially so in symptomatic women. This has to be balanced against understandable concerns that early surgery will incur increased procedural risk. Although advised in the past to defer CEA for 6 weeks in stroke patients, reassuring data have been published showing that early surgery (within 6 weeks) was not associated with a worse 30-day operative risk [33].

In conclusion, in 2007 we are still far from reaching consensus on the revascularization of the carotid artery. It is my view that in the mean we have asked all the right questions but have not been able to answer them, in part because outcomes of RCT's have been interpreted and subsequently applied in many different ways. Key issues for upcoming years will be the individual patients' preoperative risk assessment based on plaque imaging (especially in asymptomatic patients) and optimisation of perioperative antiplatelet therapy.

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SUMMARY

SUMMARY

In *Chapter 2* we analysed four years of carotid endarterectomy (CEA) (599 procedures) with respect to the underlying mechanism of perioperative stroke and the role of intraoperative monitoring. All patients were operated on under general anaesthesia with continuous cerebral monitoring using TCD and EEG. The causes of stroke were assessed by means of findings at immediate reoperation, postoperative head CT or MRI, duplex, postoperative TCD or arteriography.
The combined perioperative rate of stroke and stroke-related death rate was 3.3% (20 patients). In 4 patients stroke was apparent immediately after surgery. Mechanisms of these 4 intraoperative strokes were ipsilateral occlusion (1) and embolization (3). However, the majority of perioperative stroke (16 out of 20) developed after a symptom free interval (2-72 hrs, mean 18 hrs). Analysis of the mechanisms of these postoperative strokes showed in 9 out of 16 cases an occlusion on the side of surgery. Other mechanisms were: contralateral occlusion (1), hyperperfusion syndrome (1), contralateral ischaemia due to prolonged clamping (1), intracerebral haemorrhage (1), or an unknown cause (3). We concluded that in our vascular training centre, with only intraoperative monitoring of the cerebral function, strokes from CEA mainly developed in the postoperative phase after a symptom free interval. Since thromboembolism with occlusion of the operated artery showed most important in the pathogenesis of these strokes, we therefore suggested the introduction of additional TCD monitoring during the immediate postoperative phase in order to further reduce perioperative stroke rates.

Our subsequent experience with postoperative TCD measurements is described in *Chapter 3*. Patients destined to suffer an early postoperative stroke have a 1- to 2- hour period of increasing embolization before cerebral deficit becomes apparent. Emboli therefore can serve as a marker for stroke. We aimed to study the effect of different antiplatelet regimens (APT) on the rate of postoperative TCD registered micro-embolic signals (MES) following CEA.
The study group of 102 CEA patients was randomised to routine Asasantin (Dipyridamole 200mg / Aspirin 25mg) twice daily (group I), Asasantin plus 75mg Clopidogrel once daily (group II), or Asasantin plus Rheomacrodex (Dextran 40) (group III). TCD monitoring of the ipsilateral middle cerebral artery for the occurrence of MES was performed intra-operatively and during the second postoperative hour following CEA.
There were no deaths or major strokes. We observed 2 intraoperative TIA's (group II and III) and 1 postoperative minor stroke (group I). In comparison with placebo, Clopidogrel or Rheomacrodex in addition to Asasantin produced no significant reduction in the

number of postoperative MES. There was no significant difference between the number of postoperative MES and different antiplatelet regimens. The incidence of bleeding complications was not significantly different between the 3 APT groups. In conclusion, we could not show a significant influence of different antiplatelet regimens on TCD detected postoperative embolization following CEA.

Chapter 4 and *5* describe our experience with the management of patients with a recurrent stenosis following endarterectomy. In Chapter IV we reviewed a consecutive series of 73 redo CEA's in 72 patients to determine the safety, durability and long-term benefit associated with repeat surgical treatment. The mean interval between prior CEA to re-CEA was 53 months (range 8 to 192 months). Operative indications included symptomatic restenosis in 28 (38%) patients. There were no perioperative deaths or strokes. Over a mean follow-up of 52 months (range 12 to 144 months), the Kaplan-Meier cumulative survival was 85% at 5 years. The cumulative freedom from all stroke rate was 98% and from ipsilateral stroke 100% at 5 years respectively. After secondary procedures re-recurrent stenosis ≥ 50% occurred in 10 patients (13.7%). The cumulative freedom from re-restenosis (≥50%) was 85% at 5 years. Five patients (7%) received tertiary carotid reconstructions. Repeat carotid endarterectomy for recurrent stenosis can be performed safely with excellent long term protection for stroke. These data provide a standard against which the results of CAS must be compared.

Chapter 5 describes the long-term surveillance results of the endovascular alternative for treatment of post-CEA restenosis. Between 1998 and 2004, 57 carotid angioplasty and stenting (CAS) procedures were performed in 55 patients. Mean interval between CEA and CAS was 83 months (range 6 to 245). Nine patients (16%) were symptomatic. CAS was performed successfully in all patients, and no deaths or strokes occurred. Two patients suffered a periprocedural TIA. During a mean follow-up of 36 months 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. We concluded that CAS 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.

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 internal carotid artery (ICA), especially in patients with an incomplete circle of Willis. A possible disadvantage of CAS might be the covering of the external carotid artery (ECA) orifice.

In ***Chapter 6*** we evaluated the long-term effect of CAS of the ICA on the ipsilateral ECA. The pre- and post-interventional duplex scans were obtained from 312 patients who underwent CAS, to study progression of obstructive disease in the ipsilateral compared to the contralateral ECA. The duplex ultrasound criteria used to identify ECA stenosis ≥ 50% were Peak Systolic Velocities of ≥125 cm/s.
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 ($p = 0.004$).
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.

In ***Chapter 7*** we compared restenosis in patients who underwent both CAS and contralateral CEA. From our CAS data registry (1998 - present) all patients with a history of contralateral CEA at any other time were selected (n = 63). Mean age was 70.6, sd=6.8 for CAS and 68.2, sd=6.1 for CEA. Symptomatic stenosis was present in 24% of patients pre-CAS and 40% pre-CEA. All CEA's were primary interventions, 19% of CAS were secondary to restenosis after previous CEA. All patients were followed up prospectively with duplex at 1 year (CAS: n=58, CEA: n=59), 2 years (CAS: n=44, CEA: n=53), 3 years (CAS: n=27, CEA: n=41), and every year thereafter. Within each patient we compared restenosis (>50%) between CAS and CEA procedures. After a follow-up of 28.7 months for CAS (sd=16.9) and 54.4 months for CEA (sd=39.5) the rate of ≥ 50% restenosis for CAS vs. CEA at 1,2, and 3 years was 23% vs. 10%; 31% vs. 19%; and 34 vs. 24%, respectively (log rank p=NS). Our intra-patient comparison of patients

who underwent both CAS and contralateral CEA did not reveal significant difference in restenosis between both procedures.
Repeat angioplasty, redo CEA, and carotid artery reconstruction have all been used to treat restenosis after CAS. No definitive evidence exists concerning the optimal management of in-stent restenosis. While little experience exists with endovascular techniques for management of this condition, in ***Chapter 8*** we report on 4 consecutive patients with severe in-stent restenosis, who underwent standard CEA with removement of the stent. Between 1997 and 2001, 217 CAS procedures were performed in 217 patients (155 men and 62 women; age 70 years ± 8.2). After a mean of 8 months post-stenting four patients (2 symptomatic, 2 asymptomatic with contralateral occlusion) with severe haemodynamic in-stent restenosis (90-99%) had surgical reintervention.
Standard CEA with removal of the stent was performed in all 4 patients. No major complications occurred. Intima hyperplasia showed to be the predominant mechanism leading to in-stent restenosis. All 4 surgically treated patients remained asymptomatic and without recurrent restenosis over a mean follow-up time of 13 months (range 3 – 20 months). The optimal treatment of in-stent restenosis has yet to be defined, but standard CEA with removement of the stent appears to be feasible.

Velocity measurements are an integral part of duplex ultrasound (US) evaluation following treatment of carotid stenosis. The utility of duplex US in the detection of native carotid artery disease is well documented but velocity criteria have not been well-established for follow-up after CAS. An error in the interpretation of US velocities after CAS is failure to recognize that placement of a stent alters the biomechanical properties (increased elastic modulus, decreased compliance) of the stented artery. This may cause an increase in duplex-acquired velocity measurements in the absence of technical error or residual stenotic disease. Therefore, the potential risk of using the generally accepted duplex US criteria for follow-up after CEA is an overestimation of the degree of restenosis after CAS. The mechanism, magnitude, and significance of these alterations are ill-defined, and emphasizes the need to develop customized velocity criteria for use in patients with implanted stents.

Chapter 9 reports on an animal experimental study using a pig model that was conducted to evaluate carotid diameter and velocity changes due to stent placement. Three questions were addressed: 1) Is stent placement associated with an elevation in duplex US velocity measurements ?; 2) Is stent type of influence on stent related anatomical and haemodynamic alterations ?; 3) Is there a need to revise duplex US velocity criteria for the stented carotid artery ?
The common carotid artery of 5 pigs was exposed bilaterally (10 arteries). Diameters and

velocities were measured by US in the proximal, mid and distal native artery segments. Diameter and velocity measurements were repeated after bilateral stent placement (Wall stent and contralateral Precise Cordis). Outcomes of native vs stented arteries and Wall vs Precise Cordis were statistically compared.

The mean proximal stent diameter, 3.6 mm±0.1 (SE), was significantly smaller than the native proximal artery diameter, 4.2±0.1 by paired t-test (p=0.008), mostly due to narrowing of the Wall stent diameter to 3.4 ± 0.2mm (p=0.003). Proximal, mid, and distal segements of the Wall stents were narrower than those of the Precise stent, and associated peak systolic velocities (PSV) were higher: 266±17 vs 215±19 cm/sec, 306±32 vs 206±12 cm/sec, and 317±44 vs 228±21 cm/sec respectively. Wall stent PSVs were significantly higher than pre-stenting native artery PSVs , 187±14, 241±18, and 242±28 cm/sec at the proximal, mid and distal segments respectively.

Stent placement caused anatomical and haemodynamic alterations. Narrowings and associated increased velocities were noted. Such alterations, however, were stent type dependent, and do not justify a general approach to new velocity criteria indiscriminately applied to all stents.

SAMENVATTING IN HET NEDERLANDS

SAMENVATTING IN HET NEDERLANDS (VOOR NIET-INGEWIJDEN).

Beroerte (in het Engels "CVA (cerebro-vasculair accident) of Stroke") omvat een verzameling van ziektebeelden waarbij er sprake is van een stoornis in de bloedvoorziening van de hersenen. De meest voorkomende aandoeningen zijn het herseninfarct en de hersenbloeding. Herseninfarcten komen viermaal vaker voor dan hersenbloedingen.

Cerebro-vasculaire stoornissen zijn verantwoordelijk voor ongeveer 10% van het totale aantal sterfgevallen in Nederland en vormen hiermee na kanker en het hartinfarct de derde doodsoorzaak in de Westerse wereld. Jaarlijks worden ongeveer 20 op 100.000 mensen voor het eerst getroffen door een beroerte [1]. De aandoening treft vooral oudere mensen; bij negen van de tien fatale beroerten is de patient 65 jaar of ouder. Uit onderzoek is gebleken dat 3.5% van de mannen en 1.9% van de vrouwen boven de 55 jaar ooit door een beroerte is getroffen [2]. Ongeveer tweederde van de patiënten met een beroerte wordt naar een ziekenhuis of verpleegafdeling van een verzorgingshuis verwezen. Ongeveer de helft van deze patiënten kan na een half jaar een min of meer zelfstandig leven leiden. De kans om te overlijden aan de gevolgen van een beroerte blijft echter aanzienlijk. Na 5 jaar is 57% van de patiënten groep overleden. In Nederland leven circa 190.000 patienten met de gevolgen van een beroerte.

De bloedvoorziening van de hersenen wordt verzorgd door vier in de hals gelegen slagaders: twee grote aan de voorzijde ter weerszijde van het strottenhoofd en twee kleinere (die verder buiten de beschouwing van dit proefschrift worden gelaten) meer achter in de hals, langs de wervelkolom. Deze 4 halslagaders garanderen gezamenlijk voldoende bloedtoevoer naar de hersenen. De medische naam van de voorste halsslagader is arteria carotis. De medische naam voor een vernauwing is stenose. Een vernauwing in de halsslagader heet dus carotis stenose.

In ongeveer een kwart van de gevallen is een carotis stenose als gevolg van aderverkalking (atherosclerotische plaque) de oorzaak van een beroerte. Vooral stenoses in de twee voorste halsslagaders hebben tot gevolg dat de bloedvoorziening van de hersenen tijdelijk of langduriger tekort schiet. Een stenose aan de arteria carotis leidt op zichzelf meestal niet tot een beroerte. De plaque in de stenotische halsslagader laat echter stolsels los, die doorschieten naar de bloedsomloop van de hersenen en daar in het bloedvat blijven steken (embolie). Het bloedvat raakt verstopt en het achterliggende hersenweefsel krijgt geen zuurstofrijk bloed meer aangevoerd. Dit geeft, afhankelijk van welk bloedvat verstopt is geraakt uitval van neurologische functies, die zich kunnen uiten als bijv spraakproblemen,

halfzijdige verlamming, scheef trekken van het gezicht of voorbijgaande blindheid aan 1 oog. Soms lost het stolsel snel op, kan het bloed weer doorstromen naar de hersenen en zijn de uitvalsverschijnselen weer voorbij. Dit noemen we een TIA (transient ischaemic attack). Gaan de verschijnselen echter niet over, dan is er sprake van blijvende schade als gevolg van langdurig zuurstoftekort en spreken we van een herseninfarct (ischaemisch CVA). Een TIA is een waarschuwingssignaal voor een toekomstige beroerte. Om een –invaliderend- herseninfarct in de toekomst te voorkomen, is behandeling na een doorgemaakte TIA dan ook noodzakelijk.

Ongeveer 20% van de patiënten die een herseninfarct krijgt, heeft in de periode die hieraan voorafgaat een waarschuwing gehad in de vorm van TIA. Omgekeerd krijgt dertig procent van de patiënten die een TIA of een klein herseninfarct met weinig restverschijnselen hebben doorgemaakt, binnen vijf jaar een CVA. Profylactisch gebruik van aspirine reduceert dit risico met een kwart [3]. Wanneer de TIA of het kleine herseninfarct door een carotis stenose ontstaat, hangt bovenvermeld risico sterk af van de mate van bloedvatvernauwing: het risico om binnen drie jaar na een TIA een beroerte te krijgen bedraagt 20% als de stenosegraad van de arteria carotis 75% is, en oplopend tot een kans van 40% als deze meer dan 90% is [4].

Wanneer op grond van anamnese (uitvragen van de aard en ernst van de klachten) en het neurologische onderzoek de diagnose TIA of een klein ischaemisch CVA wordt gesteld, worden de halsvaten in eerste instantie onderzocht met behulp van Duplex (een soort echo) onderzoek. Wanneer hiermee een ernstige stenose is aangetoond, verricht men verder beeldvormend onderzoek alvorens men in aanmerking komt voor een operatieve behandeling.

Behandeling

De chirurgische behandeling van de vernauwde halsslagader is in 1953 voor het eerst uitgevoerd. Daarvoor konden patiënten alleen met medicijnen worden behandeld bijvoorbeeld stollingsremmende medicijnen en medicijnen ter regulatie van te hoge bloeddruk. De operatie bestaat uit het via een snee in de hals opzoeken van de halsslagader, en na opensnijden van de slagaderwand wordt deze als het ware van binnen schoongemaakt. De medische term voor deze operatie is carotis endarteriectomie (CEA). Een niet ongevaarlijke behandeling, omdat er altijd het risico is dat juist datgene gebeurt wat je met de operatie had willen voorkomen: het losraken van een stolsel naar de bloedvaten in de hersenen en daardoor het optreden van een herseninfarct.

Er zijn veel onderzoeken gedaan om vast te kunnen stellen wanneer de voordelen van de operatie – namelijk de preventie van het optreden van een beroerte op kortere of langere termijn – opwegen tegen de complicatie risico's van de operatie (het rondom de operatie optreden van een infarct). Uiteindelijk is men tot de conclusie gekomen dat het schoonmaken van de halsslagader zinvol is als er sprake is van klachten (symptomatisch, zoals bijv een TIA) en er met duplex-onderzoek een stenose wordt gevonden van meer dan 70% van de uitgangsdiameter. In vrijwel alle andere gevallen is meestal het advies om alleen met medicijnen te behandelen.

Door het schoonmaken van de halsslagader kan in veel gevallen een beroerte voorkomen worden. Echter, ondanks deze gunstige resultaten zijn er ook complicaties en beperkingen aan deze operatie techniek verbonden. Mede gezien de complicaties van deze halsslagaderoperatie werd gezocht naar alternatieve behandelingsmogelijkheden zoals Carotis Angioplastiek met Stenting (CAS). CAS staat voor een combinatie van dotteren; het opblazen van een ballonnetje in een bloedvat ter plaatse van de stenose, en het vervolgens achterlaten van een stent ("kippengaasrolletje") dat voorkomt dat de vernauwing direct weer terugveert.

Het plaatsen van een stent in de halsslagader kan onder locale verdoving. Via een liesslagader wordt een catheter (holle voerdraad) ingebracht tot in de halsslagader. Daarmee kan contrastvloeistof in de slagader worden gespoten. Hierdoor kan de vernauwing worden afgebeeld. De stent wordt in een opgevouwen toestand via een catheter ingebracht en ter hoogte van de vernauwing ontplooit hij zich. Hoewel door velen gezien als een waardevolle nieuwe techniek, is tot op heden nog niet aangetoond dat stent plaatsing minstens even veilig is als de klassieke carotis endarteriectomie.

Om een effectieve behandeling te kunnen zijn in het voorkomen van stroke dient vanzelfsprekend het optreden van stroke tijdens of aansluitend aan CEA voorkomen te worden. Ondanks verbetering van de operatietechnieken treedt nog altijd bij 2 tot 5% van de geopereerde patienten major stroke of dood op. In ***Hoofdstuk 2*** beschrijven we het tijdstip en de mechanismen van stroke rondom de operatie. Onze analyse toont dat met de huidige operatie- en bewakings-technieken tijdens de operatie vrijwel geen strokes meer optreden, maar dat die voornamelijk in de eerste 72 uur na de ingreep onstaan. In meer dan de helft van de gevallen is het geopereerde bloedvat acuut weer dichtgeslipt met stolsels (thrombose) wat vervolgens leidt tot de stroke.

Uit de literatuur is bekend dat het optreden van stroke ten gevolge van dichtslippen van het bloedvat voorafgegaan wordt door het voorbijschieten van een toenemend aantal bloedpropjes in de vaten die aftakken van de carotis. Met behulp van Doppler (soort echo apparaat) zijn deze propjes, en dan met name de hoeveelheid propjes die per tijdseenheid voorbijschieten, door de schedel heen te detecteren. Theoretisch kan deze Doppler meting bij iedere patient na de operatie uitgevoerd worden, en kan in geval van toenemende aantallen propjes een sterker bloedverdunnend medicijn worden toegediend.
In de praktijk is deze techniek echter zeer tijdrovend en kostbaar. Het zou dus beter zijn om te zoeken naar een optimaal ingesteld ontstollend medicijn beleid dat rondom de operatie toegepast kan worden, en dat zorgt dat de kans dat deze propjes kunnen optreden aanzienlijk verkleint. In ***Hoofdstuk 3*** beschrijven we vergelijking van 3 verschillende soorten medicijnen die invloed hebben op de stolling. Helaas werd in de analyse geen relatie gevonden tussen het soort medicijn en het aantal gemeten propjes. Vooralsnog is dus nog geen optimaal ontstollings beleid gevonden en zal de ontstollende medicatie rondom CEA in de toekomst op individuele basis bepaald moeten worden.
Bij 8 tot 20 % van de patienten na CEA slipt het geopereerde bloedvat in de maanden of jaren na de ingreep weer geleidelijk dicht (re-stenose). Indien opnieuw neurologische klachten ontstaan of ook andere halsvaten in belangrijke mate zijn aangedaan is er een indicatie om opnieuw te behandelen.
Ook op dit vlak is de carotis endarteriectomie de gouden standaard, maar zijn er veel specialisten die denken dat stents (CAS) in deze situatie tenminste gelijkwaardige resultaten kunnen bieden. Zowel de chirurgische resultaten van de behandeling van restenose ***(Hoofdstuk 4)*** als de behandeling middels CAS ***(Hoofdstuk 5)*** zijn goed te noemen ten aanzien van het initiële technische succes en de langdurige bescherming tegen het optreden van stroke tijdens follow-up (het in de tijd controleren van de patient via de polikliniek). In de geopereerde groep waren 7 patienten die uiteindelijk nog een 3^{e} keer geopereerd werden, terwijl in de stent groep het percentage restenose zelfs 19% bedroeg na gemiddeld 36 maanden follow-up. Nog belangrijker wellicht was dat we zagen dat deze restenose bij de stent in tegenstelling tot wat eerder werd gedacht, niet alleen kort na het plaatsen van de stent optrad maar ook na langere follow-up van de patient nog kon optreden.

Het ontstaan van restenose in de stent kan dus een bedreiging vormen voor het lange termijn beschermende effect tegen het optreden van stroke. Een ander potentieel nadeel van de stent is dat deze in ongeveer driekwart van de gevallen een belangrijke zijtak van de carotis, genaamd carotis externa, overlapt. In een serie van 312 patienten die eerder een stent hadden gekregen hebben we het optreden van stenose of volledige

afsluiting (occlusie) aan de behandelde zijde vergeleken met de onbehandelde zijde *(Hoofdstuk 6)*.
Voorafgaande aan CAS werd aan beide kanten in ongeveer 30% van de patienten een meer dan 50% vernauwing van de carotis externa gemeten. Na stentplaatsing nam dit percentage aan de behandelde kant geleidelijk toe tot bijna 75% na 5 jaar vervolgen en aan de onbehandelde kant tot 47%. Dit verschil kwam nog duidelijker naar voren wanneer alleen de groep werd geanalyseerd waarbij de stent daadwerkelijk de carotis externa overlapte. Overigens werd tijdens follow-up vrijwel geen occlusie van de externa gezien. Een stent kan dus voor voor stroombelemmering zorgen, maar geeft geen volledige afsluiting.

In ***Hoofdstuk 7*** hebben we gekeken naar de ontwikkeling van re-stenose in patiënten die zowel een carotis operatie als een carotis stentprocedure hadden ondergaan. Door deze benadering schakel je maximaal alle patient gebonden invloeden op de ontwikkeling van re-stenose uit. In deze betrekkelijk kleine groep kon geen verschil in frequentie of ernst van de re-stenose ontwikkeling worden gemeten tussen de geopereerde carotis en de gestente carotis.

Re-stenose van een stent kan theoretisch op een aantal manieren worden behandeld. Opnieuw dotteren, eventueel met bijplaatsen van een tweede stent, danwel operatief door middel van een standaard endarteriectomie met verwijderen van de stent.
In ***Hoofdstuk 8*** worden de eerste ervaringen met het operatief verwijderen van een vrijwel volledig gestenoseerde stent beschreven. Technisch gezien traden er geen problemen op en ook tijdens het vervolgen van deze patiënten werden geen neurologische symptomen of re-stenose gezien. De indicatie en optimale behandelingstechnieken voor restenose in de stent moet echter nog worden uitgezocht.

De mate waarin een bloedvat is dichtgeslipt kan worden beoordeeld met duplex. Duplex meet stroomsnelheden van het passerende bloed, en deze snelheden representeren een bepaalde mate van vernauwing. Hoe hoger de stroomsnelheid hoe ernstiger de vernauwing. Deze stroomsnelheden zijn nauwkeurig bepaald voor controle van patiënten die een carotis endarterectomie hebben ondergaan, maar nog niet goed bepaald voor de situatie na stentplaatsing.
Na stentplaatsing kunnen namelijk door de stugheid van de stent zelf hogere bloedstroomsnelheden optreden waardoor foutief de indruk van een vernauwing ontstaat. In een diermodel met varkens (met gezonde bloedvaten) bleek inderdaad alleen al de aanwezigheid van de stent stroomsnelheids-veranderingen te veroorzaken ***(Hoofdstuk 9).***

Bovendien bleek de mate van stroomsnelheids-verandering afhankelijk te zijn van het type stent. Dit kan gevolgen hebben voor de resultaten van langere termijn controle van patiënten waarbij een stent geplaatst is.

Hoofdstuk 10 geeft tot slot een visie op de toekomst van de behandeling van carotis stenose en geeft aan waar de kernpunten van wetenschappelijk onderzoek dienen te liggen.

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APPENDIX

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LIST OF ABBREVIATIONS

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
ACT	Activated Clotting Time
ADP	Adenosine diphosphate
AF	Amaurosis Fugax
APT	Anti Platelet Therapy
ARR	Absolute Risk Reduction
BMT	Best Medical Treatment
CABG	Coronary Artery Bypass Grafting
CAS	Carotid Angioplasty and Stenting
CAVATAS	Carotid And Vertebral Artery Transluminal Angioplasty Study
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
Cp	Compliance
CPD	Cerebral Protection Device
CREST	Carotid Revascularization Endarterectomy versus Stent Trial
CT	Computerized Tomography
Duplex US	Duplex Ultrasonography
ECA	External Carotid Artery
ECG	Electro Cardio Graphy
ECST	European Carotid Surgery Trial
EDV	End Diastolic Velocity
EEG	Electro Encephalo Graphy
EVA-3S	Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis
iaDSA	intra-arterial Digital Subtraction Angiography
ICA	Internal Carotid Artery
ICSS	International Carotid Stenting Study
ISR	In Stent Restenosis
MCA	Middle Cerebral Artery
MES	Micro Embolic Signals
MIH	Myo-Intimal Hyperplasia
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NS	Non Significant

POCT	Post-operative Carotid Thrombosis
PSV	Peak Systolic Velocity
PTA	Percutaneous Transluminal Angioplasty
RCT	Randomized Controlled Trial
RRR	Relative Risk Reduction
SAPPHIRE	Stenting and Angioplasty with protection in Patients at High Risk for endarterectomy
SD	Standard Deviation
SPACE	Stent Protected Angioplasty versus Carotid Endarterectomy
TCD	Trans Cranial Doppler
TIA	Transient Ischaemic Attack
VBI	Vertebro Basilar Insufficiency

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Pap en Mam
Joanneke en Bart

Liefste Mylon, Met jou samen zijn is een feest. Je lach en onvoorwaardelijke liefde zijn onweerstaanbaar. Hou van je !

"Be careful with my brain, its my second favourite organ".

(Woody Allen)

CURRICULUM VITAE (AUCTORIS)

Gerrit Jan de Borst was born in Utrecht on december 14th, 1970. After graduating in 1989 he started medical school at the University of Utrecht in 1990. He obtained his doctorate degree in 1996 and graduated from medical school in September 1999. He performed a foreign clinical elective at the Gynaecology Department in Tel Aviv, Israel, and his research elective at the trauma department U.M.C. Utrecht (Prof. dr Chr van der Werken)

Subsequently he became a research fellow at the U.M.C. Utrecht (Prof. dr B.C. Eikelboom) where he participated in a substudy of the Dutch Bypass Oral anticoagulant or Aspirin Study (B.O.A. trial). In the same period he performed animal experiments on endovascular venous valve transplantation (Prof. dr F.L. Moll). This work was awarded with the Fellow Award at the GET 2001 Congress Monaco.

In 2001 he started his residency in general surgery in Diakonessenhuis Utrecht (Dr G.J. Clevers). In January 2003, the residency program was continued in the University Medical Centre Utrecht (Prof. dr I.H.M. Borel Rinkes). After returning to the Diakonessenhuis in 2005 to complete his final 2 years of residency, he registered as general surgeon in april 2007.

In the same time frame the research studies as described in this thesis were performed.

Part of the work as described in this thesis was awarded with the Frank Veith Abstract Award 2006 in New York, USA.

Starting the first of May 2007, he is currently working as a CHIVO (CHirurg In Vervolg Opleiding) Vascular Surgery at the U.M.C. Utrecht under the direction of Professor dr F.L. Moll. He lives in Bilthoven with his wife, Mylon, and their son, Gijs.