Carotid Artery Stenting and Endarterectomy

A Clinical Evaluation

Joke Hendriks

ISBN: 978-90-8559-282-2
Copyright photo cover: ANP Photo BV, Rijswijk, the Netherlands.
Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

Carotid Artery Stenting and Endarterectomy
A Clinical Evaluation

Klinische evaluatie van carotis stenting en endarteriëctomie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 26 januari 2011 om 11.30 uur

door

Johanna Maria Hendriks

geboren te Zevenbergen

PROMOTIECOMMISSIE

Promotoren:
Prof.dr. P.M.T. Pattynama
Prof.dr. H. van Urk

Overige leden:
Prof.dr. P.J. Koudstaal
Prof.dr. W.P.Th.M. Mali
Prof.dr. D. Poldermans

Copromotor:
Dr. M.R.H.M. van Sambeek

Aan mijn ouders

De daad die men naliet heeft meer kwaad dan de daad gedaan
Martinus Nijhoff, Het uur U

Contents

MANUSCRIPTS BASED ON STUDIES DESCRIBED IN THIS THESIS

Chapter 1

Johanna M Hendriks, Marc RHM van Sambeek. Carotid Stenting. J Cardiovasc Surg 2005; 46(4): 327-332.

van Sambeek MRHM, Hendriks JM, van Dijk LC. Management of complications during carotid artery stenting. In: Endovascular Interventions for Vascular Disease: Principles and Practice. Thomson M, Matsumura J, Morgan R, Loftus I (Eds). ISBN 10-0849339790 Taylor and Francis Books Inc, New York 2007 Chapter 18, 185-192.

Jorinde van Laanen, Johanna M Hendriks, Marc RHM van Sambeek. Carotid artery stenting 2008. Panminerva med 2008; 50(2): 153-159.

Chapter 2

Johanna M. Hendriks , Gerhard H.Visser, Lukas C. van Dijk, Peter MT Pattynama, Peter Koudstaal, Hero van Urk, Marc RHM van Sambeek. The use of Transcranial Doppler before and during carotid artery stenting. In: Carotid artery angioplasty and stenting. Minerva Medica Torino 2002; 174-177 ISBN 88-7711-422-3.

Chapter 3

Hendriks JM, Zindler JD, Van Dijk LC, Van Sambeek MRHM. Cerebral protection during percutaneous carotid interventions: which device should be used? Acta Chir Belg 2004 Jun; 104(3): 300-303.

Chapter 4

Johanna M. Hendriks, Jaap D. Zindler, Aad van der Lugt, Peter M.T. Pattynama, Marc R.H.M. van Sambeek, Johanna L. Bosch and Lukas C. van Dijk. Embolic Protection Filters for Carotid Stenting: Differences in flow obstruction depending on filter construction. J Endovasc Ther 2006; 13: 47-50.

Chapter 5

H. Zwenneke Flach, Mohamed Ouhlous, Johanna M. Hendriks, Marc RHM van Sambeek, Jifke F. Veenland, Peter J. Koudstaal, Lukas C. van Dijk and Aad van der Lugt. Cerebral ischemia after carotid intervention. J Endovasc Ther 2004; 11: 251-257.

Chapter 6

Mary Claire Barry, Johanna M. Hendriks, Gooitzen Alberts, Frans Boomsma, Lukas C. van Dijk, Peter M.T. Pattynama, Don Poldermans, David J. Bouchier-Hayes, Hero van Urk, and Marc R.H.M.

van Sambeek. Comparison of Catecholamine Hormone Release in Patients Undergoing Carotid Artery Stenting or Carotid Endarterectomy. J Endovasc Ther 2004; 11: 240-250.

Chapter 7

Johanna M. Hendriks, Mary Claire Barry, Lukas C. van Dijk, Theo HN. Groenland, Peter J. Koudstaal, Hero van Urk, Marc RHM. Van Sambeek.
Prophylactic administration of isoprenaline for the prevention of hemodynamic instability associated with carotid angioplasty and stenting. Submitted.

Chapter 8

Harm H.H. Feringa, Johanna M. Hendriks, Stefanos Karagiannis, Olaf Schouten, Radosav Vidakovic, Marc R.H.M. van Sambeek, Jan Klein, Peter Noordzij, Jeroen J. Bax, Don Poldermans.
Carotid artery stenting versus endarterectomy in relation to perioperative myocardial ischemia, troponin T release and major cardiac events. Coron Artery Dis 2007; 18(6): 483-487.

Chapter 9

J.D. Zindler, J.M. Hendriks, P.J. Koudstaal, P.M.T. Pattynama, M.R.H.M. Van Sambeek, L.C. Van Dijk. Complicaties in de eerste 30 dagen na plaatsing van een carotisstent met cerebrale bescherming bij patiënten met een aanzienlijke, symptomatische carotisstenose; Erasmus MC, Roterdam, 1999-2004. Ned Tijdschr Geneeskd 2006; 150: 730-734.

Chapter 10

Hendriks JM, Dijk van der LC, Schouten O, Koudstaal PJ, Lugt van der A, Pattynama PMT, Sambeek van MRHM. Mid-term results of carotid stenting in symptomatic patients. Submitted.

Van Laanen J, Hendriks JM, Sambeek van MRHM. Factors influencing restenosis after carotid artery stenting. J Cardiovasc Surg 2008; 49(6): 743-747.

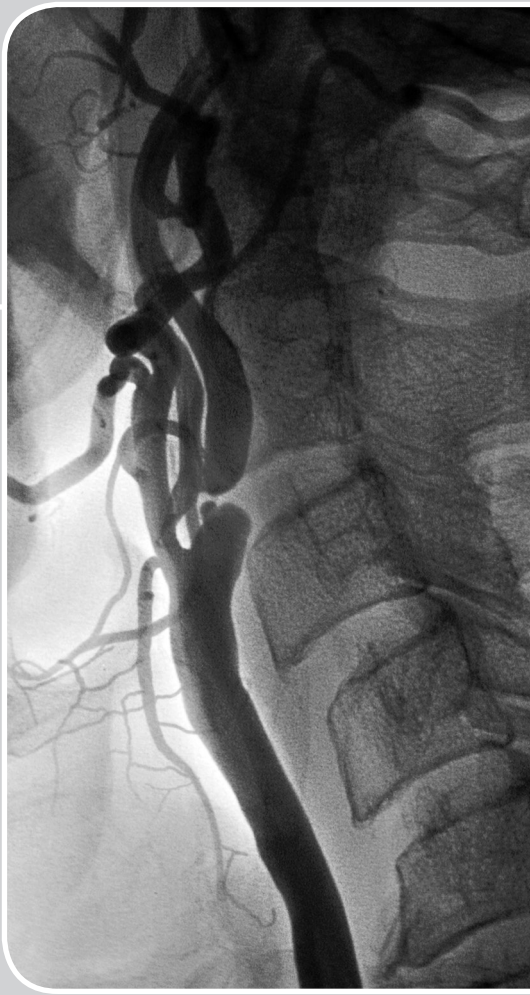
Chapter 11

International Carotid Stenting Study investigators, Elderle J, Dobson J. Featherstone RL, Bonati LH, van der Worp HB, de Bordt GJ, LO TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010; 375: 985-997.

Chapter 1

Introduction and outline of the thesis

J Cardiovasc Surg 2005; 46(4): 327-332
Panminerva med 2008; 50(2): 153-159



INTRODUCTION

Stroke is a major cause of mortality and morbidity in the western world. Atherosclerotic disease of the carotid arteries is in approximately 25% of the cases responsible for the cerebral infarction.[1] Since NASCET and ECST, carotid endarterectomy (CEA) is considered the standard treatment for severe atherosclerotic carotid obstructive disease in symptomatic patients.[2, 3]

Similar landmark studies were performed for asymptomatic carotid artery disease.[4, 5] On the basis of these trials the American Heart Association has recommended CEA for symptomatic patients with stenosis of 50% to 99% if the perioperative risk of stroke or death is <6%.[6] In asymptomatic patients CEA is recommended for a stenosis of 60% to 99% if the perioperative of stroke or death is < 3%.

In an effort to minimise interventions, in the last decade carotid artery stenting (CAS) has been suggested as an alternative to surgical endarterectomy for patients with symptomatic and asymptomatic extra cranial obstructive disease. Initially, percutaneous transluminal balloon angioplasty (PTA) was used. Later stent placement was introduced and has been used with or without initial PTA. Current data on CAS and CEA suggest that CAS is quickly gaining ground on CEA as a first-line treatment

The advantages of CAS include avoidance of general anaesthesia, an incision in the neck and the risk of cranial and cutaneous nerve damage from the dissection. Surgically inaccessible lesion can be treated with CAS and both procedure- and admission times are usually shorter than for surgery, therefore reducing some cost. On the other hand, devices used for CAS are more expensive.

At this moment many interventionists embrace carotid stenting, in particular for patients with obvious contraindications for surgical endarterectomy like high cardiopulmonary risk, high cervical lesion or "hostile neck".

CAS is relatively new compared to CEA and it should be acknowledged that CAS is an evolving technique and dedicated materials became only available recently.

CLINICAL RESULTS OF CAROTID STENTING

Single- and multicenter randomised clinical trials have directly compared CEA to CAS, and generated a widespread debate with conflicting results. (Table 1)

The first large RCT, comparing carotid angioplasty and carotid endarterectomy for patients with symptomatic high-grade stenosis, was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)[7] including 504 symptomatic patients. In the endovascular group only 26% of the patients were treated with PTA and stent placement and 74% of the patients with PTA alone. Embolic protection devices (EPD) were not available for this study. There was no statistical difference in the numbers of disabling stroke and death at 30-day for the CEA and

Table 1. 30-day stroke or death rate in individual randomised trials

Study	Year	Number of patients	30-day stroke/ death CAS (%)	30-day stroke/ death CEA (%)	Odds ratio (95%-CI)
CAVATAS	2001	504	25/251 (10%)	25/253 (9.9%)	1.01 (0.56-1.81)
Leicester	1998	23	5/11 (45.5%)	0/12 (0%)	12.88 (1.85-89.61)
Kentucky	2001	189	0/96 (0%)	1/93 (1.1%)	0.13 (0-6.61)
Wallstent	2001	219	13/107 (12.1%)	5/112 (4.5%)	2.76 (1.05-7.22)
SAPPHIRE	2004	334	8/167 (4.8%)	9/167 (5.4%)	0.88 (0.33-2.34)
EVA-3S	2006	527	25/261 (9.6%)	10/259(3.9%)	2.48 (1.25-4.93)
SPACE	2006	1183	46/599 (7.6%)	38/584 (6.5%)	1.19 (0.77-1.86)
TOTAL		2979	122/1492 (8.2%)	88/1480 (5.9%)	1.41 (1.07-1.87)

CI = Confidence Interval

angioplasty group (9.9% vs. 10%). This trial showed similar outcome, but room for improvement in both arms. Nowadays technique and materials have been significantly improved.

Two randomised trials of CAS versus CEA were stopped early because of poor outcomes in stent group. The Leicester Trial (including only symptomatic patients) was stopped after treating only 17 of the 23 randomised patients because 5 out of 11 patients randomised for stent had a procedural stroke.[8] The multicenter Wallstent Study was stopped after 219 symptomatic patients had been randomised. The 30-day stroke or death rate was significantly higher in the stented group than those who underwent CEA (12.1% versus 4.5%)[10]

The Kentucky Study was a single centre randomised trial.[9] The trial comprised a symptomatic arm (104 patients) and as asymptomatic arm (85 patients). One patient died from myocardial infarction after CEA. There were no complications in the endovascular arm.

The Stenting and Angioplasty with Protection in Patients at High Risk For Endarterectomy (SAPPHIRE) trial randomised 334 patients that were considered high risk for CEA.[11] Only 29% of the patients were symptomatic. The primary objective of SAPPHIRE was to compare the safety and effectiveness of carotid stenting with an embolic protection device to endarterectomy in the treatment of carotid artery disease. The primary endpoint of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke between 31 days and 1 year. This primary endpoint occurred in 20 of 167 patients assigned to stenting (cumulative incidence 12.2%) and in 32 of the 167 patients assigned to surgery (cumulative incidence 20.1%). The 30-day stroke or death rate in this trial was 4.8% with CAS and 5.4% with CEA. The authors conclude that carotid stenting with the use of an embolic protection device (EPD) and in the hands of very experienced operators is not inferior to carotid endarterectomy.

EVA-3S randomised 527 symptomatic patients to CAS or CEA.[12] CEA operators performed at least 25 procedures in the previous year, whereas CAS operators had performed 12 CAS procedures ever, or 35 stent-procedures in the supra-aortic trunks, including 5 CAS procedures,

or being supervised by an experienced tutor. The 30-day stroke or death rate was 3.9% for CEA versus 9.6% for CAS. This trial noted a significant difference between CAS with or without EPD: 30 day stroke or death rate was 7.7% with EPD and 25% without EPD. Many experts in the field outlined concerns about this trial including lack of routine use of EPD and the relative inexperience of the CAS operators compared to the CEA operators.

SPACE randomised 1200, but analysed 1183 symptomatic patients to CAS or CEA.[13] Only 27% of the CAS procedures were performed using EPD. The 30-day stroke or death rate was 7.6% with CAS and 6.5% with CEA. After an interim analysis the steering committee stopped the trial. Point estimates were similar between arms; but with 1183 patients SPACE failed to prove non-inferiority at the prespecified delta of 2.5%.

Several meta-analyses have been performed, all with somewhat similar conclusions.[14-16] CAS is continually developing into a safer and more efficacious therapy for extracranial obstructive disease. In patients at high risk for CEA, CAS is an equivalent, maybe better alternative. In symptomatic patients at standard risk for CEA CAS has not proven non-inferior, and is worse when performed by relatively inexperienced operators without EPD compared to highly experienced CEA surgeons.[17]

Currently there are 2 more ongoing randomised trials comparing CAS with CEA: the International Carotid Stenting Study (ICSS) and Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) adding another 4000 patients for further analysis.[18, 19] (The results of the ICSS will be discussed in chapter 11).

CEREBRAL PROTECTION

Despite the improvements in technical skills and materials, embolic complications remain the major unpredictable clinical event. Atherosclerotic material or thrombus can be dislodged either by the guide wire or PTA balloon and may embolise to the cerebral circulation and result in cerebral ischemia and infarction. Using Transcranial Doppler (TCD) monitoring Jordan et al.[20] detected eight times more emboli during CAS compared to CEA. Jaeger et al.[21] performed diffusion- weighted MRI in 67 patients with 70 high-grade stenosis, before and 24 hours after CAS. The neurological status was unchanged after 69 of the 70 procedures. Nevertheless, new ipsilateral lesions were found in 20 patients (29%) and new contralateral lesions in 6 patients (9%). In all patients except one, the new lesions were clinically asymptomatic. Protection devices such as occlusion balloons, filters and reversed flow devices are currently undergoing clinical evaluation. Distal balloon occlusion was the first of all protection devices. The balloon is inflated in the internal carotid artery (ICA), distal to the stenosis, and temporarily occludes the flow during the critical phases of the endovascular procedure. The principal of a distal filter is that it collects the debris during the procedure while preserving the flow in the ICA. With a proximal balloon occlusion the flow is stopped or even reversed in the ICA before treatment of

the lesion. Cremonesi et al.[22] published the results of protected CAS in 442 patients. In-hospital stroke/death and 30-day ipsilateral stroke/death rate was 1.1%. The overall complication rate was 3.4%. The cerebral protection device-related complications were 0.9%. Reimers et al.[23] evaluated in a multicenter study the short-term outcome of 753 patients who underwent carotid stenting with the routine use of EPDs. The 30-day incidence of stroke and death was 3.3%. Protection device-related vascular complications, none of witch led to neurological complications, occurred in 1.1% of the cases.

From a database of 4 high-volume centres a total of 3160 CAS procedures using nine EPDs were analyzed.[24] The risk of a procedural adverse event was 0.9% in protected and 2.3% in unprotected procedures (P = 0.12). There was no significant difference in the risk of procedural adverse events for any of the EPDs used.

Vos et al.[25] compared protected and unprotected CAS by measuring emboli with TCD. Patients were divided in 3 groups: 161 patients treated before EPDs had become available, 151 patients treated with filtering EPDs, and 197 patients without EPD after EPDs had become available. They measured a higher number of micro emboli during filter-protected CAS than during unprotected CAS. Macro emboli occurred only in the unprotected groups but only during the first 186 procedures. Of the 8 patients with a macro embolus 5 patients were symptomatic.

Although there was already consensus among opinion leaders that a protection device should be used in 2001,[26] evidence either for or against the use of cerebral protection is still lacking. Only a large randomised multicenter trial can solve this dilemma, although it is doubtful that this study will ever be carried out.

HEMODYNAMIC ASPECTS

Cerebral autoregulation is the major mechanism to ensure a stable cerebral blood flow (CBF) despite fluctuations in cerebral perfusion pressure (CPP). If CPP changes, CBF can be kept constant by changes in cerebral vascular resistance (CVR). In certain circumstances (obstructive carotid disease or critical perfusion) the cerebral autoregulation mechanism is used upon it's extend. In these situations changes in blood pressure can lead to a significant decrease in the cerebral blood flow and consequently ischemic events. Hemodynamic changes during the intervention may therefore complicate the stent procedure. Stents or balloons distend the carotid sinus, thereby activating stretch-sensitive mechanoreceptors that send impulses to the brain stem. This will trigger a reduction of sympatic tone in peripheral blood vessels and decreasing blood pressure. Impulses from the carotid sinus also enhanced parasympatic stimulation of the heart, which lowers the heart rate. Several authors report both bradycardia and hypotension[27, 28] and these may be associated with neurological complications. A retrospective analysis[29] of 471 patients showed that 7% of the patients had severe hypotension or bradycardia despite routine premedication with atropine and adequate fluid balance. Neurological

complications were 7% in the hemodynamic stable group compared with 12% in the instable group. This difference was not statistically significant. Howell et al.[30] concluded that patients with a severely elevated systolic blood (>180 mmHg) may be at higher risk for hemodynamic instability. The greater the change in systolic blood pressure the more severe the neurological event seems to be. There were no neurological events in patients with a < 50 mmHg change in systolic blood pressure.

From a retrospective analysis including the data on 500 consecutive CAS procedures performed over a 5-year period could be concluded that patients who develop hemodynamic instability are at an increased risk of periprocedural major adverse clinical events and stroke.[31] Hemodynamic instability was defined as periprocedural hypotension (systolic blood pressure <90 mm Hg) or bradycardia (heart rate <60 beats/min). Hemodynamic instability occurred during 210 procedures (42%), whereas prolonged hemodynamic instability occurred in 84 procedures (17%). Patients who developed prolonged hemodynamic instability were at a significantly increased risk of a periprocedural major adverse clinical event (OR 3.05: range 1.35 to 5.23) or stroke (OR 3.34: range 1.13 to 9.90)

Different techniques have been used to prevent hemodynamic instability. Most interventionists will use prophylactic Atropine to prevent hemodynamic instability. Atropine is a muscarine antagonist that abolishes the effect of acetylcholine. However it does not have effect on the sympatic system and will cause only a modest tachycardia. Some interventionists prefer prophylactic β-adrenergic agonists that stimulate both heart rate and contractility by stimulating β_1 receptors in the heart. Others[32] use a temporary pacemaker, although this is another invasive procedure.

ANTITHROMBOTIC THERAPY

At the inception of endovascular carotid intervention, patients with a significant carotid artery stenosis were treated with balloon angioplasty alone.[33] In patients with coronary artery disease the clinical and angiographic outcomes were better in patients who received a stent.[34] As a consequence of this observation, angioplasty and stenting became standard for carotid endovascular intervention and is likely to be safer, because dissection and occlusion of the carotid artery are less likely to occur. Clopidogrel was approved for clinical use by the FDA in 1998 and subsequently has rapidly replaced ticlopidine as part of combination antiplatelet therapy following coronary stenting.[35, 36] In coronary stenting clopidogrel with aspirin is the regimen of choice to prevent stent thrombosis although the optimal dosing regimen is still a subject of research.

The role of antithrombotic therapy in carotid stenting has not been fully characterised. Bhatt et al.[37] showed in a small group of patients that dual antiplatelet therapy with Clopidogrel plus Aspirin in patients receiving carotid artery stents is associated with a low rate of ischemic events.

A randomised controlled trial was performed comparing Aspirin and 24-hours Heparin with Aspirin and Clopidogrel for patients undergoing CAS.[38] Bleeding complications occurred in 17% of the heparin and 9% of the Clopidogrel group (p=0.35). The neurological complication rate in the 24-hours Heparin group was 25% compared to 0% in the Clopidogrel group (p=0.02). The 30-day 50-100% stenosis rates were 26% in the Heparin group and 5% in the Clopidogrel group (p=0.10). The conclusion from this relatively small study was that dual anti-platelet regime has a significant impact on reducing adverse neurological outcomes without an additional increase in bleeding complications. This study was terminated prematurely due to an unacceptable level of complications in the Heparin arm of the trial.

Most centres now give a combination of Aspirin and Clopidogrel at the time of stenting to reduce the risk of in-stent thrombosis and treatment related stroke.

HYPERPERFUSION SYNDROME

Originally hyperperfusion syndrome was described in patients undergoing carotid endarterectomy for severe carotid stenosis but, more recently it is also described following carotid stenting. It is not yet known if the risk for a hyperperfusion syndrome is comparable between carotid endarterectomy and carotid stenting (1-3%). Hyperperfusion syndrome is a neurological syndrome, which consists of a triad of ipsilateral throbbing headache with or without nausea, seizures and focal neurological symptoms. In its extreme form it can present as an intracerebral haemorrhage and death.

Hypertension, the severity of the treated stenosis, and the presence of a contralateral stenosis or occlusion are identified as potential risk factors for hyperperfusion syndrome.

Hyperperfusion is a well-recognised complication, caused by an increased cerebral blood flow in combination with an impaired cerebral autoregulation. The chronic low-flow state induced by severe carotid disease results in a compensatory dilatation of cerebral vessels. As a result of the chronic dilatation the vessels lose their ability to autoregulate vascular resistance in response to changes in blood pressure. This results in increased cerebral blood flow after recanalisation; hyperperfusion.

Symptoms of hyperfusion usually occur between the second and fifth postoperative day.

Transcranial Doppler (TCD) may be able to predict which patients are at increased risk of hyperperfusion syndrome by measuring increased mean flow velocities in the ipsilateral middle cerebral artery.[39]

Prevention of hyperperfusion is critical. The most important component of perioperative management is vigilant monitoring and control of systemic blood pressure. Additional efforts to reduce the risk of hyperperfusion may include limiting the duration of balloon inflation and employing EPD.[40]

If patients develop clinical symptoms suggestive of hyperperfusion or if patients have a documented elevation of the middle cerebral artery blood flow velocities it is suggested to withhold antiplatelet agents and administer antihypertensive medication until symptoms have resolved and the blood pressure is optimally controlled.

INTERMEDIATE AND LONG-TERM FOLLOW-UP

Recurrent stenosis is a concern with both CEA and CAS.

In a systemic review about recurrent stenosis after CEA it was found that the data were very heterogeneous.[41] The risk of recurrent stenosis was 10% in the first year, 3% in the second and 2% in the third year. Extreme heterogeneity was found in the relative risk of stroke in patients with recurrent stenosis compared with patients without recurrent stenosis (range from 10 to 0.10).

In the ACAS study[42] similar early restenosis rates were found in 7.6% to 11.4% of the cases. Late restenosis occurred in 1.9% to 4.9% of the cases. There was no correlation between late stroke and recurrent stenosis.

In contrast, the long-term patency rates of carotid stents have not been established in larger trials. A systematic review of multiple single centre series[43] reporting restenosis rates from 3%-22%. Bergeron et al.[44] published their 11-year experience with CAS, with an average follow up of 2.7 years (1 month to 9.3 years). The restenosis rates at 6 months, 1, 2 and 4.5 years were, respectively, 1.4%, 2.3%. 3.7% and 5.9%. The annual risk of a new neurological event, new ipsilateral neurological event, any stroke, and ipsilateral stroke were 1%, 0.8%, 0.4%, and 0.2%, respectively. In this study asymptomatic lesions and the use of balloon-expandable stents were found to be predictors of in-stent restenosis.

Long-term outcome of carotid stenting appears to be competitive with surgery, however randomised trials with long term follow-up are necessary to evaluate this.

AIM AND OUTLINE OF THIS THESIS

Carotid artery stenting is a promising technique which is continually developing. Until today, major improvements have been made in technique and materials, which make carotid artery stenting safer.

The aim of this thesis is to evaluate different aspects of the stenting procedure. We discuss our own experience (short-term and mid-term) and present the results of the ICSS-study.

In **chapter 2** we describe the use of Transcranial Doppler before and during carotid stenting. **Chapter 3** provides an overview of the three different types of embolic protection devices. In **chapter 4** we assessed new cerebral lesions using DW-MRI in symptomatic patients with carotid artery disease undergoing protected carotid artery stenting or carotid endarterectomy.

In **chapter 5** we investigated in an in vitro experiment the pressure gradient and degree of flow reduction associated with embolus protection filters.

In **chapter 6** we compared the pattern of catecholamine response in patients undergoing carotid endarterectomy or carotid artery stenting. In **chapter 7** we evaluated the use of prophylactic administration of isoprenaline to prevent hemodynamic instability during carotid angioplasty and stenting. In **chapter 8** we examined differences in preoperative myocardial ischemia, troponine T release and clinical cardiac events in patients undergoing carotid angioplasty and stenting compared to endarterectomy.

In **chapter 9** we discuss our results of the first 98 patients with a significant, symptomatic carotid artery stenosis, who were treated with angioplasty and stenting.

In **chapter 10** we retrospectively evaluated the incidence of mid-term stroke after carotid stenting in symptomatic patients. In **chapter 11** we present the short-term results of the International Carotid Stenting Study (ICSS). These data are summarized in **chapter 12**.

REFERENCES

1. Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. Stroke 1992; 23: 486-491.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445-453
3. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379-1387.
4. Young B, Moore WS, Robertson JT, Toole JF, Ernst CB, Cohen SN et al, ACAS investigators. An analysis of perioperative surgical mortality and morbidity in the asymptomatic carotid atherosclerosis study. Stroke 1996; 27: 2216-2224.
5. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J et al. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363: 1491-1502.
6. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for the prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on stroke: co-sponsored by the Council on Cardiovascular radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation 2006; 113: e409-449.
7. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357: 1729-1737.
8. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N et al. Randomised study of carotid angioplasty and stenting versus carotid endarterectomy: A stopped trial. J Vasc Surg 1998; 28: 326-334.
9. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. J Am Coll Cardiol 2001; 38: 1589-1595.
10. Alberts JM. Results of a multicentre prospective randomised trial of carotid artery stenting vs. endarterectomy. Stroke 2001; 31: 325.
11. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ et al, SAPPHIRE investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 1493-1501.
12. Mas JL, Catelier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al for the EVA-3S investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Eng J Med 2006; 355: 1660-1671.
13. The SPACE Collaborative Group. 30-day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368: 1239-1246.
14. Luebke T, Aleksic M, Brunkwall J. Meta-analysis of randomized trials comparing carotid endarterectomy and endovascular treatment. Eur J Vasc Endovasc Surg 2007; 34: 470-479.
15. Brahmanandam S, Ding EL, Conte MS, Belkin M, Nguyen LL. Clinical results of carotid artery stenting compared with carotid endarterectomy. J Vasc Surg 2008; 47: 343-349.
16. Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database of Systematic Reviews 2007 Issue 4 art. No: CD000515.
17. Matsumura JS, van Sambeek MRHM. Current controversies in carotid artery stenting. EuroIntervention 2007; 2: 413-415.

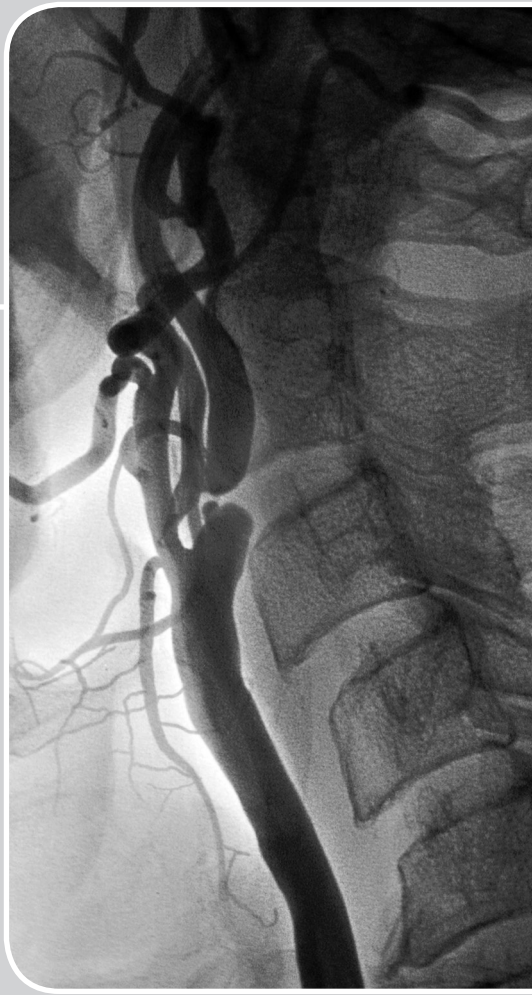
18. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004; 18: 69-74.
19. Hobson 2nd RW. CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. Semin Vasc Surg 2000; 13: 139-143.
20. Jordan WD, Voellinger DC, Doblar DD, Plyushsheva NP, Fisher WS, Mc Dowell HA. Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. Cardiovasc Surgery 1999; 7:33-38.
21. Jaeger HJ, Mathias KD, Hauth E, Drescher R, Gissler HM, Hennigs S, Christmann A. Cerebral ischemia detected with diffusion-weighted MR imaging after stent implantation in the carotid artery. Am J Neuroradiol 2002; 23: 200-207.
22. Cremonesi A, Manetti R, Setacci F, Setacci C Castriota F. Protected carotid stenting: clinical advantages and complications in 442 consecutive patients. Stroke 2003; 34: 1936-1941.
23. Reimers B, Schluter M, Castriota F, Tubler T, Corvaja N, Cernetti C et al. Routine use of cerebral protection during carotid artery stenting: results of a multicenter registry of 753 patients. Am J Med 2004; 116: 217-222.
24. Iyer V, de Donato G, Deloose K, Peeters P, Castriota F, Cremonesi A, et al. The type of embolic protection does not influence the outcome in carotid artery stenting. J Vasc Surg 2007; 46: 251-256
25. Vos JA, van den Berg JC, Ernst SM, Suttorp MJ, Overtoom TT, Mauser HW et al. Carotid angioplasty and stent placement: comparison of transcranial Doppler US data and clinical outcome with and without filtering cerebral protection devices in 509 patients. Radiology 2005; 234: 493-499.
26. Veith FJ, Amor M, Ohki T Beebe HG, Bell PR, Bolia A et al. Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. J Vasc Surg 2001; 33: S111-116.
27. Qureshi AI, Luft AR, Sharma M, Janardhan V, Lopes DK, Khan J et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke 1999; 30: 2086-2093.
28. Mendelsohn FO. Wiessman NJ, Lederman RJ, Crowley JJ, Gray JL Phillips HR et al. Acute hemodynamic changes during carotid artery stenting. Am J Cardiol 1998; 82: 1077-1081.
29. Mlekusch W. Schillinger M, Sabeti S, Nachtmann T, Lang W, Ahmadi R et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. J Endovasc Ther 2003; 10: 851-859.
30. Howell M, Krajcer Z, Dougherty K, Strickman N, Skolkin M, Toombs B et al. Correlation of periprocedural systolic blood pressure changes with neurological events in high-risk patients. J Endovasc Ther 2002; 9: 810-816.
31. Gupta R, Abou-Chebl A, Bajzer CT, Schumacher HC, Yadav JS. Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. J Am Coll Cardiol 2006; 47: 1538-1543.
32. Harrop JS, Sharan AD, Benitez RP. Armanda R, Thomas J, Rosenwasser RH. Prevention of carotid angioplasty-induced bradycardia and hypotension with temporary venous pacemaker. Neurosurgery 2001; 49: 814-822.
33. Bockenheimer S, Mathias K. Percutaneous transluminal angioplasty in atherosclerotic internal carotid artery disease. Am J Neuroradiol 1983 ;4: 791-792.
34. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent study group. N Engl J Med 1994; 331: 489-495.
35. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000; 102: 624-629.
36. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001; 104: 539-543.

37. Bhatt BL, Kapadia SR, Bajzer CT, Chew DP, Ziada KM, Mukherjee D, et al. Dual antiplatelet therapy with clopidogrel and aspirin after carotid artery stenting. J Invasive Cardiol 2001; 13: 767-771.
38. McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. Eur J Vasc Endovasc Surg 2005; 29: 522-527.
39. Jansen C, Sprengers AM, Moll FL, Vermeulen FE, Hamerlijnck RP, van Gijn J, et al.. Prediction of intracerebral haemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring: results of 233 operations. Eur J Vasc Surg 1994; 8: 220-225.
40. Abou-Chebl A, Yadav JS, Reginelly JP, Bajzer C, Bhatt D, Krieger DW. Intracranial haemorrhage and hyperperfusion syndrome following carotid artery stenting. J Am Coll Cardiol 2004; 43: 1596-1601.
41. Frericks H, Kievit J, van Baalen JM, van Bockel JH. Carotid recurrent stenosis and risk of ipsilateral stroke: a systemic review of literature. Stroke 1998; 29: 244-250.
42. Moore WS, Kempczinski RF, Nelson JJ, Toole JF. Recurrent carotid stenosis: results of the asymptomatic carotid atherosclerosis study. Stroke 1998; 29: 2018-2025.
43. Gröschel K, Riecker A, Schulz JB, Ernemann U, Kastrup A. Systematic review of early recurrent stenosis after carotid angioplasty and stenting. Stroke 2005 ;36: 367-373.
44. Bergeron P, Roux M, Khanoyan P, Douillez V, Bras J, Gay J. Long-term results of carotid stenting are competitive with surgery. J Vasc Surg 2005; 41: 213-221.
45. Levy EI, Mocco J, Samuelson RM, Ecker RD, Jahromi BS, Hopkins NL. Optimal treatment of carotid artery disease. J Am Coll Cardiol 2008; 51: 979-985.

Chapter 2

Monitoring

Minerva Medica Torino 2002; 174-177, ISBN 88-7711-422-3



INTRODUCTION

Transcranial Doppler sonography (TCD) has been a diagnostic and monitoring modality for more than 20 years. By using a pulsed Doppler system with a relatively low frequency of insonation, it has been possible to penetrate the skull to measure shift of Doppler at different levels. The implication for clinical practice has been that it is possible to determine blood flow velocity (BFV) in the large intracranial vessels. It is used to diagnose intracranial stenosis, to evaluate the intracranial collateral circulation (an additional carotid compression test can be performed) and to investigate the intracranial autoregulation. Furthermore, long-term registration can be performed to record High- Intensity Transient Signals or HITS.

Finally, it is used as a monitoring device during operative procedures to record hemodynamic changes and/or HITS.

THE USE OF TCD BEFORE CAROTID STENTING

Circle of Willis and collateral circulation

The hemodynamic effect of an internal carotid artery (ICA) stenosis is determined by the severity of the stenosis, the quality of the collateral circulation and the presence of compensatory vasodilatation.

The blood flow toward the brain originates from the two ICA's and the basilar artery (BA).

Each internal carotid bifurcates into the middle cerebral (MCA) and the anterior cerebral artery (ACA). The BA bifurcates into the left and right posterior cerebral artery (PCA). The circular vessel structure is completed by an anterior communicating artery (ACoA) and two posterior communicating arteries (PCoA) and is called the Circle of Willis. If one or more of the feeding arteries is obstructed, the circle of Willis provides an effective collateral blood flow. Blood flow can be recruited within seconds through the ACoA or PCoA. However, the anatomy of the circle of Willis can vary, and these anatomical variations can often interfere with adequate compensation through the collateral circulation.

TCD has been used as a monitoring tool during carotid endarterectomy (CEA) to determine hemodynamic changes in the MCA. The blood flow velocity can be considered in the decision for shunt placement during carotid occlusion portion of the carotid endarterectomy surgical procedure. If preoperative investigations could reliably identify which patients will need a shunt during CEA, intraoperative monitoring could be omitted. Various methods have been investigated, such as the common carotid artery (CCA) compression test with monitoring of clinical symptoms or EEG changes, ocular pletysmography, and TCD with cerebrovascular reactivity tests or with CCA compression test. None of these preoperative tests could predict shunt requirement with a probability higher then about 50%[1]. Visser et al.[2] were able, by using TCD and the CCA compression test, to predict a subgroup of patients who did not need a shunt during operation.

During angioplasty and stenting the carotid artery is not clamped, but it can be expected that not every patient tolerate some of the protection devices (balloon-occlusion or reversed flow). Perhaps in the future these patients can be selected by the use of TCD with the CCA compression test.

Cerebral autoregulation

Besides the quality of the circle of Willis, the presence of compensatory vasodilatation is also an important factor in determining the hemodynamic effect of an ICA stenosis. Cerebral autoregulation is the major mechanism to ensure a stable cerebral blood flow despite fluctuations in cerebral perfusion pressure.

CBF = CPP / CVR	CPP = ABP – ICP
CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CVR = cerebrovascular resistance; ABP = arterial blood pressure; ICP = intracranial pressure	

If CPP changes, CBF can be kept constant by decreasing the CVR, which is the result of cerebral vasodilatation.

This mechanism can be investigated with TCD using the CO_2 reactivity test. Under normal physiological conditions hypercapnia induces vasodilatation. However, an already existing vasodilatation will interfere with the ability of the cerebral vessels to dilate further in response to hypercapnia. The CO_2 reactivity provides information about the extent of pre-existing vasodilatation, which in turn reflects the reserve capacity of the cerebral autoregulation. A diminished or even absent CO_2 reactivity is indicative of a decreased reserve capacity in patients with ICA stenosis or occlusion and is considered a risk for ischemic complications. The significance of impaired vasodilatory reserve in patients with internal carotid artery stenosis has not been evaluated in large prospective studies. However, in a prospective follow up study in patients with carotid artery occlusions a severely reduced reactivity has been shown to be associated with markedly increased stroke rate[3]. So it seems important to improve cerebral reserve capacity. Cerebral hemodynamics improves after carotid endartectomy[4]. Markus et al.[5] showed by using the CO_2 reactivity test that cerebral hemodynamics also improve after angioplasty and the degree of improvement is similar to that seen after carotid endarterectomy.

TCD DURING CAROTID ANGIOPLASTY AND STENTING

Blood flow velocity

One criticism of carotid angioplasty is that balloon inflation results in occlusion of the carotid artery with the risk of cerebral ischemia and infarction. Eckert et al.[6] have shown that with a

decrease of more than 50% in blood flow velocity in the middle cerebral artery, 50% of the patients developed neurological complications.

Crawley et al.[7] performed also monitoring during angioplasty and endarterectomy. They compared the duration of ischemia time during both procedures and found that this ischemic period was much shorter during angioplasty. Although there were a couple of patients in both groups with a blood flow reduction in the MCA to less than a third of baseline, they couldn't find any relation with neurological complications. More research has to be done to find out what these flow reductions mean, and how important this is for this group of patients. The combined monitoring of TCD with EEG has the advantage to monitor the effect of blood flow reduction (TCD) on brain function (EEG).

HITS

Another concern in carotid angioplasty is that atherosclerotic material during the procedure and may embolize to the cerebral circulation and result in cerebral ischemia and infarction.

Several TCD studies found significantly more HITS (microemboli) during angioplasty and stenting than during endarterectomy. Jordan et al.[8] detected eight times more emboli during angioplasty. But Crawley et al.[9] showed that despite the higher embolic load during angioplasty, this was not associated with more cerebral complications. Although the evidence that HITS represent micremboli is well established, their use as a marker of embolic during angioplasty and stenting may have a limitation[10]. On the other hand, we know from diffusion- weighted MRI that after angioplasty and stenting infarcts can be seen in the brain without clinical symptoms[11]. We still don't know the actual functional consequences of these "silent infarcts". Recent studies have shown that a protection device significantly reduces the amount of micremboli detected by TCD[12, 13].

CONCLUSION

Transcranial Doppler is safe, non invasive and in expensive. It gives a good impression of the collateral circulation before the intervention and can delineate a group of patients who are at risk for ischemic complications. During the angioplasty blood flow velocity and the occurrence of microemboli (HITS) can be monitored continuously. This provides the ability to compare different protection devices and to have some quality control during the procedure.

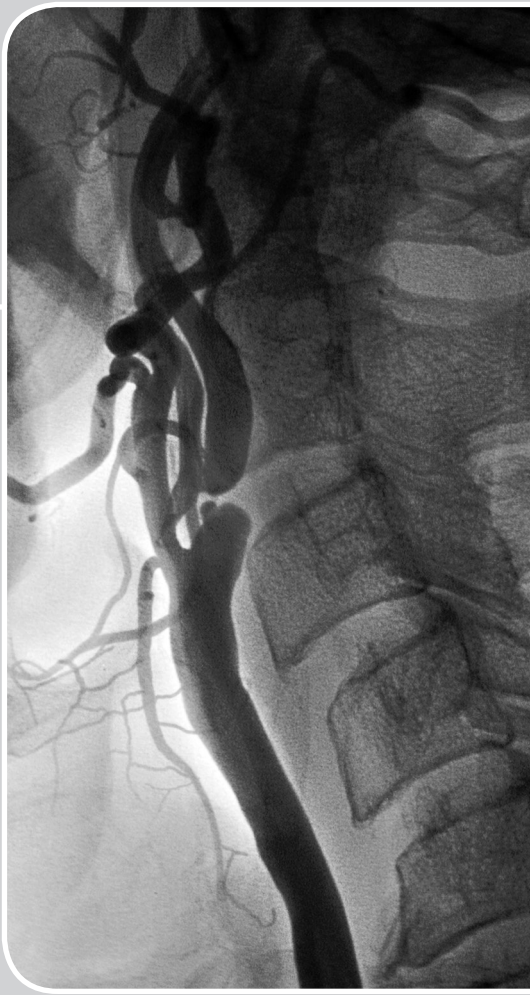
REFERENCES

1. Eikelboom BC, Ackerstaf RGA. Preoperative prediction of cerebral ischemia due to carotid occlusion. Eur J Vasc Surg 1993; 7(Suppl.A): 21-24.
2. Visser GH, Wieneke GH, Huffelen van AC, et al. The use of preoperative transcranial Doppler variables to predict which patients do not need a shunt during carotid endarterectomy. Eur J Vasc Endovasc Surg 2000; 19: 226-232.
3. Keiser B, Widder B. Carotid artery occlusions with impaired cerebrovascular reactivity. Stroke 1992; 23: 172-174.
4. Visser GH, Huffelen van AC, Wieneke GH, Eikelboomb BC. Bilateral increase in CO2 reactivity after unilateral carotid endarterectomy. Stroke 1997; 28(5): 899-905.
5. Markus HS, Clifton A, Buckenham T, Taylor R, et al. Improvement in cerebral hemodynamics after carotid angioplasty. Stroke 1996; 27: 612-616.
6. Eckert B, Thie A, Valdueza J, Zanella F, et al. Transcranial Doppler Sonographic monitoring during percutaneous transluminal angioplasty of the internal carotid artery. Neuroradiology 1997; 39: 229-234.
7. Crawley F, Clifton A, Buckenham T, et al. Comparison of hemodynamic cerebral ischemia and microembolic signals detected during carotid endarterectomy and carotid angioplasty. Stroke 1997; 28: 2460-2464.
8. Jordan WD, Voellinger DC, Doblar DD, et al. Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. Cardiovasc Surg 1999; 7(1): 33-38.
9. Crawley F, Stygall J, Lunn S, Harrison M, et al. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of surgery and percutaneous transluminal angioplasty. Stroke 2000; 31: 1329-1334.
10. Markus HS. Monitoring embolism in real time. Circulation 2000; 102: 826-828.
11. Lövblad KO, Plüschke W, Remonda L, Gruber-Wiest D, Do DD, Barth A, Kniemeyer HW, Bassetti C, Mattle HP, Schroth G. Diffusion-weighted MRI for monitoring neurovascular interventions. Neuroradiology 2000; 42: 134-138.
12. Al-Mubarak N, Roubin GS, Vitek JJ, et al. Effect of the distal-balloon protection system on microembolization during carotid stenting, Circulation 2001; 104 (17): 1999-2002.
13. Parodi JC, La Mura R, Ferreira LM, et al. Initial evaluation of carotid angioplasty and stenting with three different cerebral protection devices. J Vasc Surg 2000; 32: 1127-1136.

Chapter 3

Cerebral protection

Acta Chir Belg 2004 Jun; 104(3): 300-303



ABSTRACT

Embolic complications remain the major and unpredictable clinical event during carotid angioplasty and stenting. Cerebral protection devices could play an important role in the prevention of such emboli. Protection devices such as occlusion balloons, filters and reversed flow devices are currently undergoing clinical evaluation and appear to be promising in reducing the incidence of embolic events. This article provides an overview of the three different types of embolic protection devices.

INTRODUCTION

Stroke is a major cause of mortality and morbidity in the western world. Atherosclerotic disease of the carotid arteries is responsible for approximately 25% of all cerebral infarction cases.[1] The traditional standard of care in treating cervical artery stenosis has been carotid endarterectomy (CEA). This procedure was initially performed in the 1950s[2] and has proved its efficacy and superiority over medical management for treatment of high-grade symptomatic lesions.[3, 4]

In the last decade carotid angioplasty and stenting (CAS) has been recommended as an alternative to surgical endarterectomy to minimise invasive interventions. Experiences of physicians around the world have demonstrated that carotid artery stent placement is an effective and relatively safe method of treating cervical carotid artery disease.[5-7] However, dedicated catheter and stent technology for carotid procedures have only recently been developed.

The major complication of CAS is intracerebral embolism by fragments of plaque or clot with consecutive stroke or death. From literature is known that during CAS eight times more High Intensity Transient Signals (HITS) can be observed than during CEA. This is measured by Trans Cranial Doppler (TCD).[8] In order to prevent this complication, embolic protection devices (EPD) have been introduced during clinical practice. The common goal of these devices is to capture any material that may be liberated during angioplasty and stenting.

This is either achieved by temporary distal or proximal occlusion or by the placement of a filter device distal to the lesion. Currently, a consensus exists among specialists that some form of EPD should be routinely used during CAS.[7, 9]

EMBOLIC PROTECTION DEVICES

Distal balloon occlusion

Distal balloon occlusion (figure 1)as a form of EPD during CAS was the first of all protection devices. Pioneer in this field was Theron. Already in 1990 Theron et al.[10] published a series of articles with good results using this protection device. In the mid-nineties, commercially available distal occlusion protection devices such as the PercuSurge Guardwire™ (Medtronic AVE) were produced.

The balloon catheter is the first device that crosses the lesion in the internal carotid artery (ICA). The balloon is inflated distal to the stenosis, which temporarily occludes the outflow during the procedure or during critical phases of the procedure. It is important to inflate the balloon sufficiently to prevent leaking. An angiogram demonstrates when the balloon completely occludes the ICA. The debris that enters the blood during manipulation of the stenosis stays in the standing column of blood and is aspirated and discarded after the stent is placed.[11, 12]

The Guardwire™ has a low crossing profile (2.7 F), is flexible, and gives you complete protection of the distal ICA during occlusion.

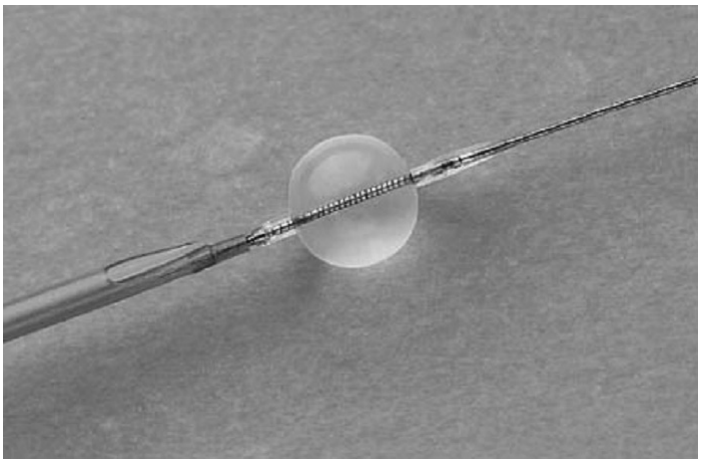


Figure 1. Distal balloon occlusion, PercuSurge Guardwire™ (Medtronic AVE)

On the other hand, the stenotic lesion needs to be crossed to place the balloon in the distal ICA and it may be difficult to pass tight and tortuous lesions. The blood flow is redirected towards the external carotid artery (ECA) and this is a potential route for embolisation to the brain. Further, there is a risk of spasm and intimal damage of the ICA due to balloon inflation. In addition, some patients do not tolerate the interruption of the flow and careful neurological monitoring of the patient is needed.

Several studies evaluated carotid artery stenting under protection of a distal balloon protection system. The study of Albuquerque and colleagues[13] describes that in one patient the non-detachable silicone balloon catheter (Target Therapeutics, Fremont, CA) could not be advanced across the stenosis. The patient experienced a transient ischemic attack (TIA) after unprotected angioplasty. Fifteen patients that were treated under protection of a distal balloon experienced no complications.

Al-Moubarak et al.[14] demonstrated that the use of a distal balloon catheter significantly reduces the frequency of TCD detected HITS during CAS. The 37 patients that underwent unprotected CAS had a mean number of 168±108 HITS whereas the protected patients had a mean number of 63±83 HITS.

Whitlow et al.[15] described that 5 (12%) of the 75 patients treated with CAS under balloon protection developed a TIA. However, none of these patients developed a minor or major stroke within 30 days.

Theron et al.[16] showed that the use of a distal balloon protection system reduces the frequency of embolic complications during CAS. Three (8%) of the 38 patients in the unprotected group experienced embolic complications in comparison to the two (1%) of the 136 protected patients.

Proximal balloon occlusion

The principle of this device is to reverse the flow (figure 2) in the ICA before treatment of the lesion. There are two different proximal balloon occlusion devices commercially available.

The Parodi anti-embolisation system (PAES) (ArteriA Medical Science, Inc) is a guiding catheter with three lumens and a balloon at the distal end of the catheter. The main lumen provides access for catheters needed for angioplasty and stent placement. The balloon at the distal end of the catheter is inflated in the common carotid artery (CCA), which creates a negative pressure gradient distal to the balloon occlusion. In addition, the ECA is occluded with a balloon catheter through one of the side-lumens and the flow reversal is established by connecting the arterial sheath with a venous sheath placed in the femoral vein. A filter located in the arteriovenous shunt prevents embolic particles to enter the venous system.

Another proximal occlusion device is the MO.MA (Invatec). In this device two balloons are attached to a single guiding catheter. Close to the proximal balloon, the exit port of the guiding catheter enables advancement of angioplasty materials and the aspiration of debris containing blood after the procedure.

With a proximal occlusion device the lesion is not crossed before the reversal of the flow in the ICA. This makes the system suitable for lesions with thrombus that are at risk to embolise.

These devices require a larger puncture site in the groin than the occluding devices and the PAES needs a femoral venous access. Under- or over inflation should be prevented, just as with the distal balloon occlusion. In addition, with the proximal balloon catheter there is a risk for cerebral hypoperfusion, which is the main concern when this device is used.

In a nonrandomised, prospective multi-centre trial the safety and efficacy of the PAES was investigated in 30 patients.[17] Technical error and access-related difficulties prevented establishment of flow reversal in two patients. Among the 28 treated patients, four developed

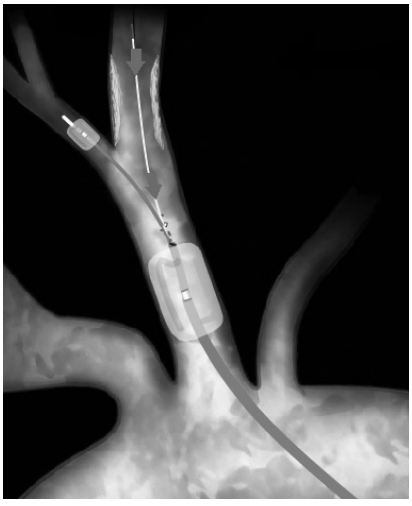


Figure 2. Proximal balloon occlusion, MO.MA (Invatec)

temporarily neurological deficits caused by procedural related cerebral hypoperfusion, yet after 30 days none of the patients had remaining neurological deficits.

Distal filter

The principle of a distal filter (figure 3) is that it collects the debris during the procedure while preserving the flow in the ICA. The filter has to cross the lesion to reach the anatomical target site where the delivery sheath is removed and the filter is deployed. Until now several types of filters are developed and they can be categorised in: filters with or without a nitinol endoskeleton and fixed-wire and bare wire systems.

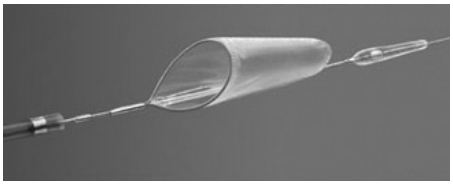


Figure 3. Filter, E.P.I. FilterWire EZ™ (Boston Scientific)

Filter devices are especially suitable for patients, who have a lesion in the contra lateral ICA or a cerebral vascular anatomy that does not allow an occlusive device. A disadvantage is that a filter has to cross the lesion and its relatively large crossing profile (2.9-3.9 F) may give complications when passing difficult and tortuous lesions. The developed filters have different pore sizes (50 µm – 140 µm). The pores may not be too small because of resistance of the blood flow and potential thrombosis. Particles that are smaller than the pore size may pass the filter. To functionally collect the debris, the filter has to fit to the vessel wall to prevent debris passing between the vessel wall and the filter. Irritation of the vessel wall may cause vasospasm or intimal damage.

In several studies the feasibility and safety of filters during CAS have been investigated. In a multicentre trial[18] with 162 patients filter (MedNova Neuroshield™ Cerebral Protection System, Abbott) placement was successful in 154 (94%) of the patients.

Under protection of a filter one patient developed a minor stroke and two patients died within 30 days of the procedure. One of the deaths was cardiac arrhythmic related, and the other due to a hyperperfusion-related intracerebral hemorrhage. The results of the prospective cohort analysis from Macdonald et al.[19] were comparable. In 98% of the procedures filter placement was successful and one (2%) of the 50 patients developed a minor stroke. Two deaths occurred that were not atheroembolic related. Angelini et al.[20] reported that filter placement was possible in 37 (97%) of the 38 procedures and that no neurological sequelae occurred. The study from Reimers and colleagues[21] showed comparable results.

DISCUSSION

Despite the improvement in technical skills, embolic complications remain *the* major and unpredictable clinical event during CAS. Several TCD studies found significantly more HITS during angioplasty and stenting than during endarterectomy. Although it is well established that HITS represent microemboli, their use as a marker of emboli may have limitations.[22] Jordan et al.[8] detected eight times more emboli during angioplasty without an EPD than during CEA. However, Crawley et al.[23] showed that the higher embolic load measured with TCD (compared with CEA) was not associated with increased cerebral complications.

With a diffusion-weighted MRI silent infarcts can be detected after an intervention and several groups evaluated the efficiency of the protection devices. After using a protection device, Matthias[24] found less new lesions on the diffusion- weighted MRI and observed less complications than during unprotected CAS. The actual functional consequences of these silent infarcts remain unclear. Jaeger and colleagues[25] saw after 8 (22%) of the 37 procedures, in arteries supplying the brain, new lesions with diffusion-weighted MRI without neurological symptoms or deficits.

There is consensus among the current leaders in the field that a protection device should be used.[9] At the moment it is not clear which type is the safest and most effective. The group of Ohki[26] and the group of Parodi[27] tested the three different devices. Both groups concluded that all devices can be used safely and that every device has its own strengths and weaknesses. Nowadays, the choice of the protection device is dependent on the opinion of the interventionist and on the patient's characteristics.

It seems logical that a stenosis with thrombus is best treated with protection of a proximal occlusion device. In patients with critical perfusion of the brain a filter device might be better tolerated. A 90-99% stenosis may be difficult to pass with a filter device and in these cases a distal occlusion device could be preferable. Another option is to perform an unprotected predilation so that afterwards a filter can be placed.

However, which EPD is best in which situation remains to be determined.

REFERENCES

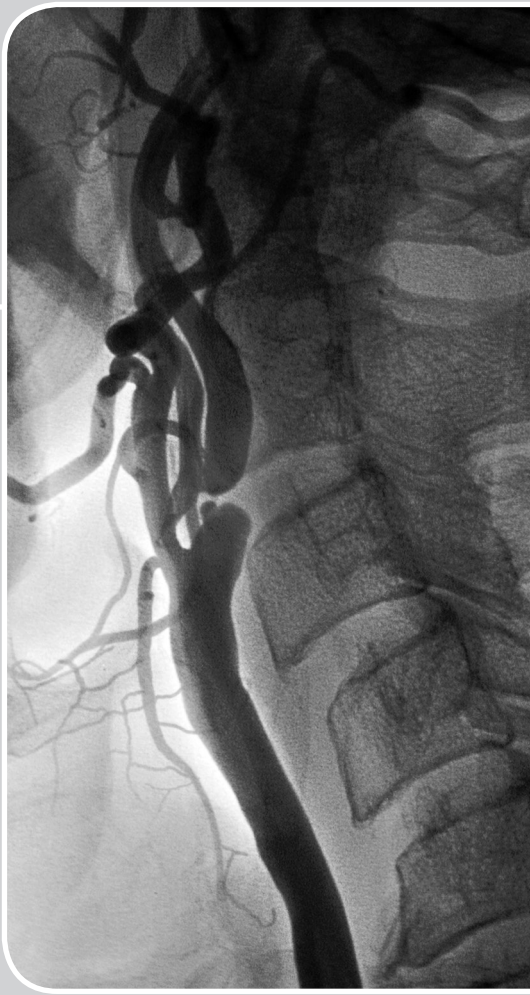
1. Timsit SG, Sacco RL, Mohr JP, et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. Stroke 1992; 23: 486-491.
2. Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. Lancet 1954; 267: 994-996.
3. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325: 445-453.
4. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379-1387.
5. Kachel R. Results of balloon angioplasty in the carotid arteries. J Endovasc Surg 1996; 3: 22-30.
6. Roubin GS, New G, Iyer EE, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. Circulation 2001; 103: 532-537.
7. Wholey MH, Al-Mubarak N. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv 2003; 60: 259-266.
8. Jordan Jr WD, Voellinger DC, Bobalar DD, et al. Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. Cardiovascular Surgery 1999; 7: 33-38.
9. Veith FJ, Amor M, Ohki T, et al. Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. J Vasc Surg 2001; 33: S111-116.
10. Theron J, Courtheoux P, Alachkar F, et al. New triple coaxial catheter system for carotid angioplasty with cerebral protection. AJNR Am J Neuroradiol 1990; 11: 869-874; discussion 75-77.
11. MacDonald s, Gaines PA, Current concepts of mechanical cerebral protection during percutaneous carotid intervention. Vasc Med 2003; 8: 25-32.
12. Ohki T, Veith FJ. Carotid artery stenting; utility of cerebral protection devices. J Invasive Cardiol 2001; 13: 47-55.
13. Albuquerque FC, Teitelbaum GP, Lavine SD, et al. Balloon-protected carotid angioplasty. Neurosurgery 2000; 46: 918-21; discussion 22-23.
14. Al-Mubarak N, Roubin GS, Vitek JJ, et al. Effect of the distal-balloon protection system on microembolization during carotid stenting. Circulation 2001; 104: 1999-2002.
15. Whitlow PL, Lylyk P, Londero H, et al. Carotid Artery Stenting Protected With an Emboli Containment System. Stroke 2002; 33: 1308-1314.
16. Theron JG, Payelle GG, Coskun O, et al. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. Radiology 1996; 201: 627-636.
17. Adami CA, Scuro A, Spinamano L, et al Use of the Parodi anti-embolism system in carotid stenting: Italian trial results. J Endovasc Ther 2002; 9: 147-154.
18. Al-Mubarak N, Colombo A, Gaines PA, et al. Multicentre evaluation of carotid artery stenting with a filter protection system. Journal of the American College of Cardiology 2002; 39: 841-846.
19. MacDonald S, Venables G, Cleveland T, et al. Protected carotid stenting: Safety and efficacy of the MedNova NeuroShield filter. Journal of Vascular Surgery 2002; 35: 966-972.
20. Angelini A, Reimers B, Della Barbera M, et al. Cerebral protection during carotid artery stenting; collection and histopathologic analysis of embolized debris. Stroke 2002; 33: 456-461.
21. Reimers B, Corvaja N, Moshiri S, et al. Cerebral protection with filter devices during carotid artery stenting. Circulation 2001; 104: 12-15.
22. Markus H, Monitoring embolism in real time. Circulation 2000; 102: 826-828.
23. Crawley F, Stygall J, Lunn S, et al. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. Stroke 2000; 31: 1329-1334.

24. Mathias K. Presentation: protected vs unprotected CAS: a DW-MRI analysis, in ISET, 2002: Miami.
25. Jaeger HJ, Mathias KD, Drescher R, et al. Diffusion-weighted MR imaging after angioplasty or angioplasty plus stenting of arteries supplying the brain. ANJR Am J Neuroradiol 2001; 22: 1251-1259.
26. Ohki T, Veith FJ, Grenell S, et al. Initial experience with cerebral protection devices to prevent embolization during carotid artery stenting. J.Vasc Surg 2002; 36: 1175-1185.
27. Parodi J, La Mura R, Ferreira L, et al. Initial evaluation of carotid angioplasty and stenting with three different cerebral protection devices. Journal of Vascular Surgery 2000; 32: 1127-1136.

Chapter 4

Flow obstruction

J Endovasc Ther 2006;13:47-50



ABSTRACT

Purpose: To investigate the pressure gradient and degree of flow reduction associated with embolus protection filters for carotid stenting in an in vitro experiment.

Methods: Three filter devices with a perforated membrane design and one wire mesh type filter were tested. At a pressure of 70 mmHg, the flow reduction and pressure gradient were measured in a 5-mm tube using blood-mimicking fluid.

Results: The pressure gradient in the wire mesh filter was 1.65±0.49 mmHg (95% CI 1.32 to 1.86). The mean pressure gradient in the perforated membrane filters was 6.88±2.62 mmHg (95% CI 6.22 to 7.55, $p<0.0001$). There was also a significant correlation between pressure gradient and flow reduction ($r=-0.77$, $p<0.01$).

Conclusions: Embolic protection filters cause a pressure gradient and obstruct blood flow. This effect is marked in perforated membrane filters and almost absent in the wire mesh filter.

INTRODUCTION

Carotid artery stenting (CAS) is gaining acceptance as a minimally invasive alternative to surgical carotid endarterectomy. Neurological complications due to embolization are a serious drawback to this method. These events were the impetus for the development of embolus protection devices (EPD), which were designed to capture material liberated during angioplasty and stenting by temporary distal or proximal occlusion or by placing a filter distal to the lesion. In a review of the literature by Kastrup et al.,[1] the authors concluded that these EPDs appear to reduce thromboembolic complications during CAS.

Hemodynamic changes during carotid stenting have also been associated with a greater likelihood of neurological events.[2-5] Bradycardia and hypotension are reported to occur in up to 30% of CAS patients,[6] mostly due to the reaction of the carotid sinus during postdilation. Filters potentially obstruct cerebral blood flow, and if this occurs during a phase of bradycardia and hypotension, the resistance to flow could be decisive for the outcome of a procedure.

In terms of device construction, the embolic capture potential relies either on a perforated membrane or a wire mesh. In this study, we measured the effect of various filter constructions on blood flow in an in-vitro setup. We hypothesized that there is no difference in pressure gradient between the two filter types.

METHODS

Four different devices (Fig. 1) were studied: 3 perforated membrane filters (Angioguard RX [Cordis, a Johnson & Johnson company, Miami Lakes, FL, USA]; RX AccuNet [Guidant Corporation, Santa Clara, CA, USA]; and FilterWire EZ [Boston Scientific, Natick, MA, USA]) and a wire mesh filter (Spider; EV3, Plymouth, MN, USA).

A 5-mm-diameter tube was used as a model for the internal carotid artery (ICA). The tube was connected to a reservoir filled with blood-mimicking fluid (Shelley Medical Imaging Technologies, Arca Tech, Quebec, Canada). A pilot study at 3 different input pressures (90, 70, and 40 mmHg) was performed first, taking 10 measurements per filter at each pressure. Simultaneous pressure recordings were made with pressure transducers positioned proximally and distally to the filter (Fig. 2). Volume flow was assessed using a calibrated container and a stopwatch; the collected fluid volume was measured after 60 seconds.

Because the input pressure did not have any influence on the results, the definitive measurements were performed with an input pressure of 70 mmHg; the outflow resistance was fixed. This combination of pressure and outflow resulted in a flow of ~200 mL/min. For comparison, the normal blood flow to the brain is ~750 mL/min (range 500–900), of which 40%, or >200 mL/min, passes through each ICA. The measurements were repeated 20 times for each filter.

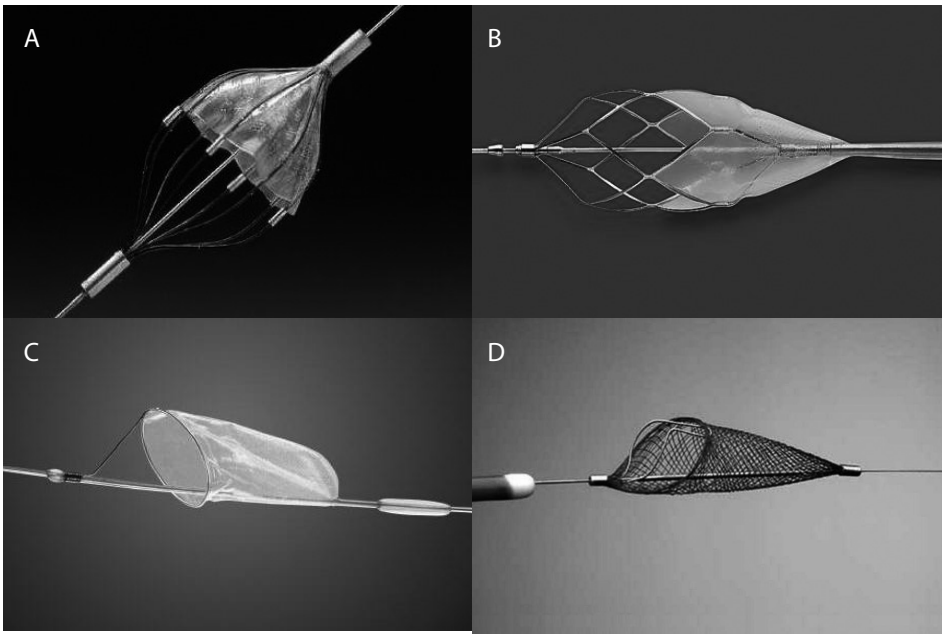


Figure 1. (**A**) Angioguard RX, (**B**) RX Accunet, (**C**) Filterwire EZ, (**D**) Spider.

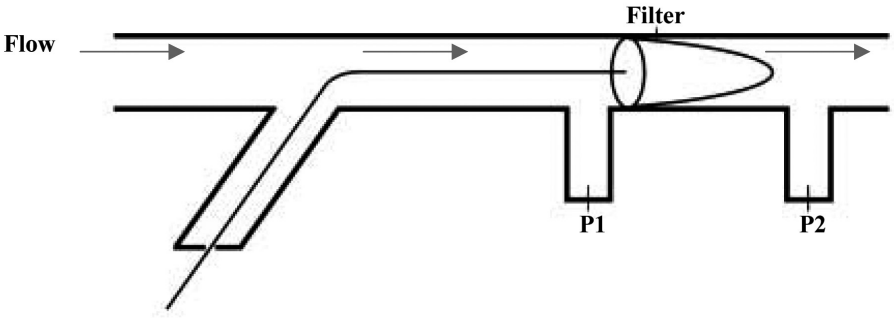


Figure 2. Picture of in vitro setup.

Statistical Analysis

The pressure gradient was calculated by subtracting the pressure distal to the filter from the pressure proximal to the filter. Continuous variables are presented as the mean ± standard deviation and 95% confidence intervals (CI). Comparisons of the variables were assessed with a paired 2-tailed Student *t* test. The Pearson's product moment correlation, *r*, was used to assess correlation between pressure gradient and flow reduction. Statistical significance was assumed at $p<0.05$.

RESULTS

The mean pressure gradient of the wire mesh filter was 1.65±0.49 mmHg (95% CI 1.32 to 1.86), which differed significantly from the mean pressure gradient of all the perforated membrane filters (6.88±2.62 mmHg, 95% CI 6.22 to 7.55; p<0.0001). Among the perforated membrane filters (Table), the AccuNet had significantly less pressure gradient than the other 2 perforated membrane filters (p<0.0001). There was also a significant correlation between the pressure gradient and flow reduction (*r*=–0.77, p<0.01, Fig. 3).

Table. Pressure gradient according to filter type

	Number	Pressure gradient
Spider	20	1.65±0.49
All perforated membrane filters	60	6.88±2.62
Accunet	20	3.90±0.30
Filterwire EZ	20	7.95±1.76
Angioguard	20	8.80±1.91

Data presented as mean ± standard deviation.

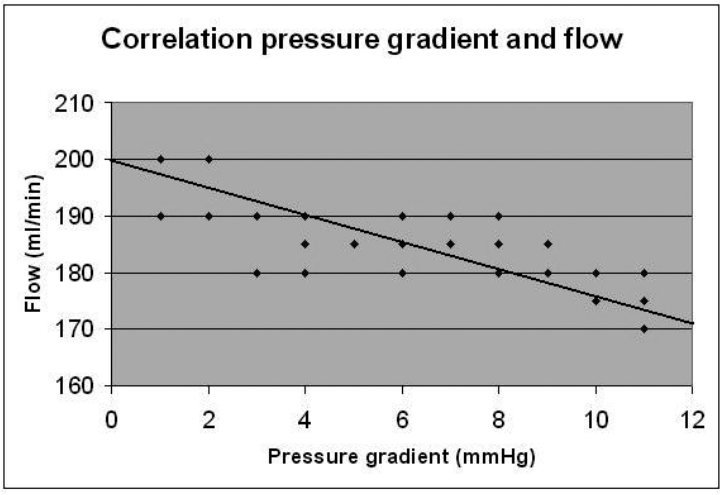


Figure 3. There was a significant correlation between pressure gradient and flow reduction (*r*=–0.77, p<0.01)

DISCUSSION

The major complication of CAS is intracerebral embolism of plaque fragments or clot, with consequent stroke or death. It has been demonstrated that CAS generates 8 times more high intensity transient signals (HITS) observed by transcranial Doppler (TCD) than carotid endarterectomy (CEA).[7] To prevent this embolization, EPDs were introduced to collect debris during the CAS procedure while preserving ICA flow. Several studies have investigated the feasibility and safety of filters during CAS: macroscopically visible particles were retrieved in 35% to 83.7% of the filters.[8-10] Muller-Hulsbeck et al.[11] tested 5 filter devices in an in vitro setting and found differences in the rate of emboli capture ranging from 95.6% to 99.2%. The resistance to flow was not reported in this study.

The clinical relevance of pressure drop and cerebral flow reduction is unclear, although a correlation between periprocedural hypotension and neurological events has been suggested.[2-5] Mlekusch and colleagues[3] found more neurological events in patients with hemodynamic instability (12% versus 7%). Although this difference was not statistically significant, the higher frequencies of neurological complications in these patients admonish us to be careful. Howell et al.[2] showed a significant linear correlation between increasing systolic blood pressure (SBP) changes and greater severity of neurological events ($r=0.74$, $p<0.001$). The greater the change in SBP, the more severe the neurological event seems to be.

In our study, we varied the pressure and not the flow rate because this most closely resembles natural brain circulation. Cerebral autoregulation ensures stable cerebral blood flow (CBF) despite fluctuations in cerebral perfusion pressure (CPP). If the CPP changes, the CBF can be kept constant by changing the cerebral vascular resistance (CVR): CBF=CPP/CVR. In general, this mechanism is intact in patients with a carotid artery stenosis; only in situations of critical perfusion is this mechanism exhausted.

Our data show that, depending on the design, distal filters may cause a pressure gradient and may seriously reduce antegrade flow. This effect is marked in perforated membrane filters and almost absent in the wire mesh filter. Whenever a filter is in place during a phase of bradycardia and hypotension, it is reasonable to suppose that the cerebral blood flow may fall below a critical level. Although the significance of periprocedural hypotension and reduced cerebral blood flow on neurological complications is at present unproven, it seems reasonable to include potential flow obstruction of the filter as a criterion when selecting a particular EPD, among other recognized characteristics, such as emboli capture rate, ease of placement, and utility of the filter in various grades of ICA tortuosity.

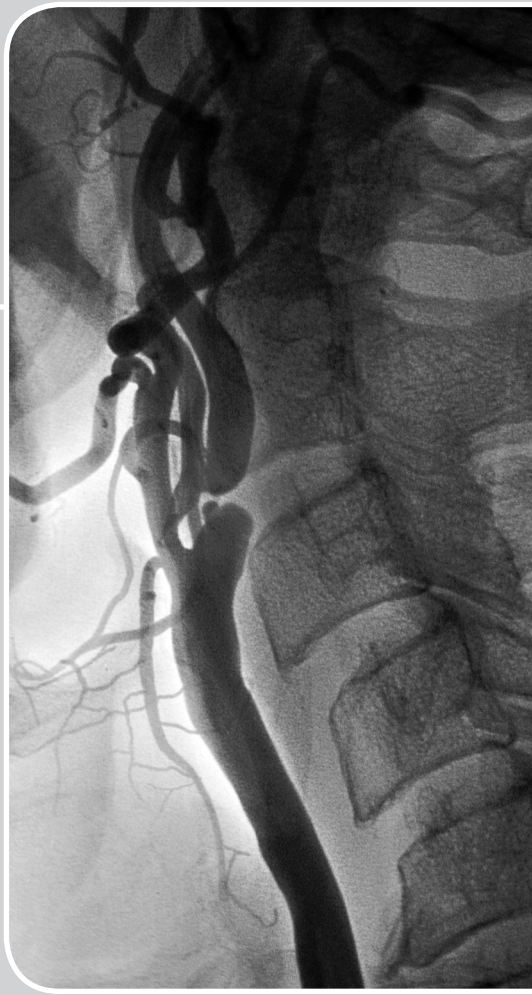
REFERENCES

1. Kastrup A, Groschel K, Krapf H, et al. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. Stroke 2003; 34: 813-819.
2. Howell M, Krajcer Z, Dougherty K, et al. Correlation of periprocedural systolic blood pressure changes with neurological events in high-risk carotid stent patients. J Endovasc Ther 2002; 9: 810-816.
3. Mlekusch W, Schillinger M, Sabeti S, et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. J Endovasc Ther 2003; 10: 851-859.
4. Mendelsohn FO, Weissman NJ, Lederman RJ, et al. Acute hemodynamic changes during carotid artery stenting. Am J Cardiol 1998; 82: 1077-1081.
5. Qureshi AI, Suri MF, Ali Z, et al. Carotid angioplasty and stent placement: a prospective analysis of perioperative complications and impact of intravenously administered abciximab. Neurosurgery 2002; 50: 466-475.
6. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke 1999; 30: 2086-2093.
7. Jordan WD, Voellinger DC, Doblar DD, et al. Microemboli detected by transcranial Doppler monitoring in patients during carotid angioplasty versus carotid endarterectomy. Cardiovasc Surg 1999; 7: 33-38.
8. Angelini A, Reimers B, Della Barbera M, et al. Cerebral protection during carotid artery stenting. Collection and histopathologic analysis of embolized debris. Stroke 2002; 33: 456-461.
9. Reimers B, Corvaja N, Moshiri S, et al. Cerebral protection with filter devices during carotid artery stenting. Circulation 2001; 104: 12-15.
10. Al-Mubarak N, Colombo A, Gaines P, et al. Multicenter evaluation of carotid artery stenting with a filter protection system. J Am Coll Cardiol 2002; 39: 841-846.
11. Müller-Hülsbeck S, Husler EJ, Schaffner SR, et al. An in vitro analysis of a carotid artery stent with a protective membrane. J Vasc Interv Radiol 2004; 15: 1295-1305.

Chapter 5

Cerebral ischemia

J Endovasc Ther 2004; 11: 251-257



ABSTRACT

Purpose: To determine the incidence of symptomatic and asymptomatic cerebral ischemic lesions found on diffusion-weighted magnetic resonance imaging (DW-MRI) after carotid interventions.

Methods: A prospective study was conducted to assess new cerebral ischemic lesions using DW-MRI in symptomatic patients with carotid artery disease undergoing protected carotid artery stenting (CAS) or carotid endarterectomy (CEA). DW-MRI was performed before and after the intervention in 44 patients (21 CAS and 23 CEA). Two experienced radiologists not involved in the carotid procedures or neurological assessment compared the postprocedural DW-MR images with those acquired before the intervention.

Results: Three (6.8%) of the 44 patients suffered strokes: 1 major and 1 minor stroke after CEA and 1 minor stroke after CAS. DW-MRI showed 15 new hyperintense lesions in 2 (9%) of 23 CEA patients; 31 new hyperintense lesions were found in 9 (43%) of the 21 CAS patients. The majority of new lesions were located in the ipsilateral vascular territory; 2 CAS patients also showed 6 new hyperintense lesions in the cerebellum. The mean lesion load per patient was 2.52 cm^3 (range 0.31–4.74) in the CEA group and 1.74 cm^3 (0.03–9.72) in the CAS group (p=0.35). The volume of the individual lesions in CEA patients was 0.39 cm^3 (range 0.01–2.16) compared to 0.52 cm^3 (range 0.01–5.47) in the CAS group (p=0.23). Patients who were asymptomatic after the intervention had fewer lesions (p=0.03) and a smaller lesion load than symptomatic patients.

Conclusions: Ischemic lesions were more frequently seen on DW-MRI after carotid stenting than after endarterectomy. The majority of the detected lesions did not cause neurological deficits.

INTRODUCTION

About 20% of all ischemic strokes are caused by atherosclerotic disease of the carotid artery.[1] Carotid endarterectomy (CEA) combined with medical treatment is an established therapy in patients with symptomatic carotid artery stenosis.[2-4] Carotid artery stenting (CAS) has been recently advocated as a less invasive alternative to CEA. Case series of endovascular treatment with angioplasty or stenting have shown morbidity and mortality (4.9% to 10% 30-day stroke and death rates) comparable with CEA.[5-10] The randomized Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) showed similar major risks and efficacy with respect to prevention of stroke within the first 3 years for carotid balloon angioplasty or stenting compared with CEA.[10] Randomized multicenter studies are currently comparing CAS and CEA; these trials have stroke-free survival as primary outcome. Because the differences in stroke rate in the 2 treatment arms are expected to be small, large numbers of patients have to be included in these studies.

Asymptomatic or "silent" ischemic lesions detected with diffusion-weighted magnetic resonance imaging (DW-MRI) have been reported more frequently than clinical events after carotid interventions.[11-15] Vermeer et al.[16] recently found that silent brain infarcts are associated with cognitive dysfunction in the general population, so these silent lesions may become a valuable outcome measure in clinical trials of CAS versus CEA. The aim of this study was to determine the incidence of symptomatic and asymptomatic cerebral ischemic lesions on DW-MRI after surgical and endovascular carotid intervention in a single-center setting.

METHODS

Study design and patient sample

in June 1999, CAS was introduced in our center for the treatment of high-grade symptomatic carotid stenosis (>70%) in high-risk patients. In a 1.5-year pilot phase, 12 high-risk patients were treated with CAS while 57 low-risk patients underwent CEA. Since February 2001, all patients with a symptomatic carotid stenosis appropriate for endovascular repair have been offered their preference of stenting or CEA after having been extensively informed about the procedures. At the same time, a prospective study was started to monitor cerebral ischemic lesions in both endovascularly and surgically treated patients using pre and postprocedural DW-MRI. Informed consent was obtained from each patient.

From February 2001 until November 2002, 101 patients were treated (42 CAS, 59 CEA), of which DW-MRI was performed before and after carotid intervention in 44 (21 CAS and 23 CEA) patients (35 men; mean age 69 years, range 45 to 84). DW-MRI could not performed in 57 patients for various reasons: (1) the MRI scanner was not available within 48 hours of the

procedure; (2) patient refusal to participate in the study; and (3) standard contraindications for MRI, including claustrophobia.

All patients underwent neurological examination before and 24 hours after the carotid intervention. Stroke was defined as major if the Rankin grade was ≥3 and as minor if the grade was <3.[17]

CEA procedure

Carotid endarterectomy was performed by experienced vascular surgeons on patients under general anesthesia and monitored with intraoperative electroencephalography (EEG). All patients received 5000 units of heparin intravenously before clamping. A shunt was used when EEG monitoring revealed asymmetrical activity. The endarterectomy was performed in classical fashion (not everted); the arteriotomy was closed with a patch when indicated. Antithrombotic treatment (aspirin 80 mg/d) was started in all patients before surgery and continued for life.

CAS procedure

Clopidogrel (300 mg) was given 1 day before CAS procedures, which were performed under local anesthesia via percutaneous transfemoral access by an experienced team consisting of an interventional radiologist and a vascular surgeon. After placement of an 8 to 10-F guiding catheter in the common carotid artery (CCA) and intravenous administration of 5000 units of heparin, angiography was performed. Two methods of cerebral embolic protection were used: a filter device (Angioguard, [Cordis, a Johnson & Johnson company, Miami Lakes, FL, USA]) or Filterwire [Boston Scientific, Natick, MA, USA] or a protection system based on the reversed flow principle (Parodi Anti-Emboli System, [ArteriA Medical Science, Inc., San Francisco, CA, USA]). In the majority of patients, the lesion was predilated with a 3-mm-diameter coronary balloon after placement of the protection device. The stents (Carotid Wallstent, [Boston Scientific]; Dynalink, Acculink, and Herculink [Guidant Corporation, Indianapolis, IN, USA]; SMART, [Cordis]): were placed and subsequently postdilated with a 5 to 6-mm balloon depending on the diameter of the internal carotid artery as determined by the preprocedural duplex scan. The operators attempted to achieve <30% residual stenosis. Finally, an angiogram of the treated carotid artery and the intracranial circulation was obtained. Antithrombotic medication consisted of clopidogrel (75 mg/d) for 1 month and aspirin (80 mg/d) for life. Doppler ultrasound surveillance was performed in the CAS patients.

MRI technique and analysis

mR imaging of the brain was performed before and after treatment using a 1.5-T Sigma scanner (General Electric, Milwaukee, WI, USA) with a head coil. The MRI protocol before and after the intervention consisted of a DW-MRI sequence with a slice thickness of 5 mm and b value of 1000 s/mm^2 (SE/EPI [spin echo/echo planar imaging], repetition time [TR]=12999, minimum echo time [ET], 24×19-cm field of view [FOV], 128×160 matrix, and number of excitations [NEX]=3).

The images were acquired with diffusion sensitization gradients successively activated in 3 orthogonal directions, and isotropic (trace of the tensor) images were generated and analyzed.

Two experienced radiologists who were not involved in the carotid procedures or assessment of neurological outcome compared the postprocedural DW-MR images with those acquired before the intervention. The number, location (ipsilateral versus contralateral), and volume (cm^3) of new hyperintense lesions were recorded. Disagreements were settled by consensus. Ipsilateral lesions were those on the side of the treated carotid artery; contralateral lesions included those on the opposite side to the treated carotid artery and also in the cerebellum.

To calculate the volume of the hyperintense lesions on DW-MRI, a semi-automated segmentation software was developed using MATLAB (The Math Works Inc., Natick, MA, USA). Two interactive methods were used to start the automated segmentation of the lesion. For large, clearly visible lesions, a box could be drawn around the lesion. For small lesions with low contrast, a seed was placed in the lesion. A threshold was automatically determined based on the local gradients in the volume surrounding the lesion. Using a 3D region-growing technique based on pixel intensities and local gradients, the lesion was segmented and the volume calculated.

Statistical analysis

differences between categorical data were analyzed with a chi-square test; continuous data were analyzed with a Wilcoxon rank sum test. $P<0.05$ was considered indicative of a significant difference.

RESULTS

Clinical outcomes

among all 101 patients undergoing carotid interventions in the study period (Table 1), 2 major and 5 minor strokes were registered (6.9% stroke rate). In the 59 CEA patients, the patient with major stroke developed a contralateral arm paresis caused by a total occlusion of the ipsilateral carotid artery the day after the procedure. The 2 minor neurological complications in this subgroup were a cerebral hematoma 5 days after surgery in 1 patient and, in the other case, a postprocedural cerebral ischemic event with hemianesthesia and an infarct on a control computed tomographic (CT) scan 4 months later.

In the 42-patient CAS cohort, predilation was performed in 28 procedures and poststent dilation in 38. In 1 patient, the stenotic origin of the CCA was dilated before a guiding catheter could be advanced and a reversed flow neuroprotection device deployed; the patient experienced a minor stroke after the procedure. Two other patients experienced minor strokes, and 1 patient died of a major stroke. Postprocedural ultrasound scans showed that all stents were patent.

Table 1. Complications in 101 carotid interventions and diffusion weighted magnetic resonance imaging (DW-MRI) studies in a 44-patient subgroup

	Complications		DW-MRI	
	Major	Minor	Performed	Not performed
CEA (n=59)	1	2	23 (1 major, 1 minor)*	31 (1 minor)
CAS (n=42)	1	3	21 (1 minor)	16 (1 major, 2 minor)
Totals	2	5	44	57

CEA: carotid endarterectomy, CAS: carotid stenting.
*One minor complication (cerebral hematoma after 5 days) occurred after a normal postprocedural DW-MRI study.

Ischemic lesions

postprocedural DW-MRI was performed in the 44 patients within 2 days in all but 2 cases (2 at <3 days). In 3 (6.8%) of the 44 pretreatment scans, 6 hyperintense lesions were found. In the post-treatment scans (Table 2), 15 new hyperintense lesions were recorded in 2 (9%) of the 23 surgical procedures (Fig. 1), while 31 new hyperintense lesions (Fig. 2) were seen in 9 (43%) of the 21 patients after endovascular procedures (p=0.02). In the 9 CAS patients with new hyperintense lesions, predilation was performed in 5, whereas the other 4 patients were primarily stented. In 8 of these 9 patients, postdilation was performed: a 6-mm balloon in 3 patients, a 5.5-mm balloon in 1, and a 5-mm balloon in 3 patients. The majority of new lesions were located in the vascular territory of the treated carotid artery, but 2 CAS patients also showed 6 new hyperintense lesions in the vascular territory of the posterior inferior cerebellar artery. There were no significant differences in the number of lesions per patient after the intervention (p=0.34), the lesion load per patient (p=0.35), or the volume of the individual lesions (p=0.23).

Table 2. Number and volume of new lesions in patients who underwent carotid endarterectomy (CEA) or stent placement (CAS)

	CEA (n=23)	CAS (n=21)	p
Patients with DW-MRI lesions	2 (9%)	9 (43%)	0.02
Number of new lesions	15	31	
Ipsilateral/contralateral	15/0	25/6	
Number of lesions/patient	7.5 (2–13)	3.4 (1–10)	0.34
Per-patient lesion load, cm^3	2.52 (0.31–4.74)	1.74 (0.03–9.72)	0.35
Per-lesion volume, cm^3	0.39 (0.01–2.16)	0.52 (0.01–5.47)	0.23

Per-patient and per-lesion data are presented as mean (range).
DW-MRI: diffusion weighted magnetic resonance imaging.

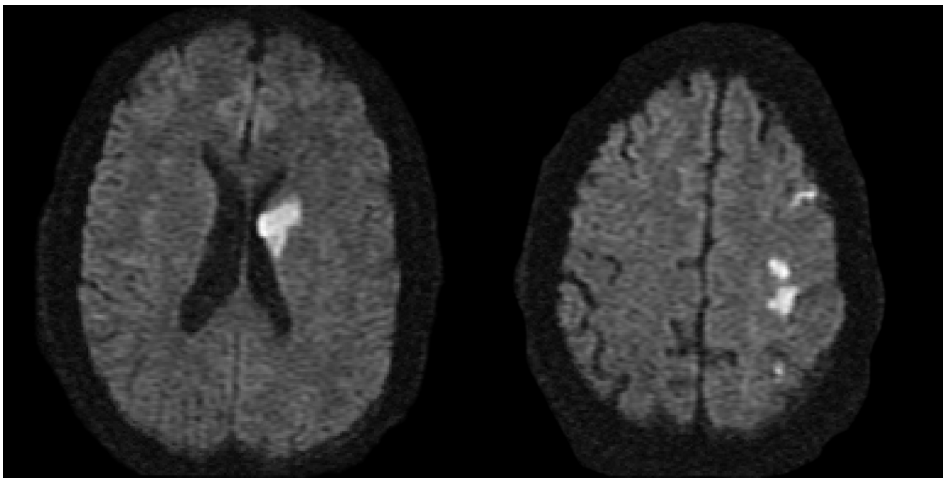


Figure 1. Axial diffusion-weighted MR images with hyperintense lesions in the vascular territory of the treated carotid artery in a patient with a major stroke after carotid endarterectomy.

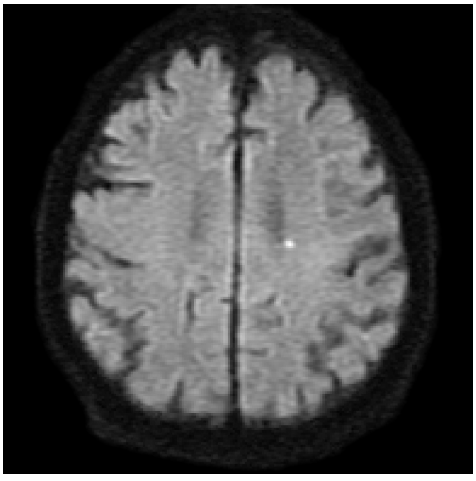


Figure 2. Axial diffusion-weighted MR image with one hyperintense lesion in the vascular territory of the treated carotid artery in a patient without neurological symptoms after carotid artery stenting.

The patient with a cerebral hematoma 5 days after surgery did not have any lesion on the DW-MRI performed 1 day after the procedure, so he was included in the postprocedural asymptomatic group for analysis. Patients who were asymptomatic after the carotid intervention had fewer lesions (p=0.03) and a smaller lesion load (p=0.06) than symptomatic patients (Table 3).

Table 3. Number and volume of lesions in postprocedural symptomatic and asymptomatic patients

	Symptomatic (n=2)	Asymptomatic (n=9)*	P
Number of new lesions	23	23	
Number of lesions/patient	11.5 (10–13)	2.6 (1–6)	0.03
Per-patient lesion load, cm^3	7.23 (4.74–9.72)	0.69(0.03–4.78)	0.06
Per-lesion volume, cm^3	0.66 (0.01–5.47)	0.30 (0.01–3.25)	0.30

Per-patient and per-lesions data are presented as mean (range).
*The patient with a cerebral hematoma 5 days after surgery did not have any lesion on the postprocedural DW-MRI, so he was included in the postprocedural asymptomatic group for analysis.

DISCUSSION

This study investigated the frequency of new hyperintense DW-MRI lesions in patients who underwent a percutaneous or surgical carotid intervention. In this single-center setting, DW-MRI lesions were more commonly seen after CAS than after CEA, and the frequency of new hyperintense lesions was much higher than the rate of symptomatic neurological events. Comparison between postprocedural symptomatic and asymptomatic patients revealed fewer lesions and a smaller lesion load in asymptomatic patients.

Our 9% frequency of new lesions in surgically treated patients falls within the range in previous studies: Müller et al.[18] reported the highest frequency (34% in 77 patients), while others saw these lesions in less than 12% of their patients.[10,11,14,18] On the other hand, our 43% rate of new hyperintense lesions in the CAS group falls beyond the 21% to 37% range previously reported.[14,19,20] All these studies except one[11] included patients with and without postprocedural symptoms. For this reason, the frequency of silent postprocedural lesions is slightly lower than their reported rates. However, the overall impression that more silent cerebral lesions can be found after endovascular treatment remains valid.

The most likely cause of all new hyperintense lesions is embolization of thrombotic or atherosclerotic plaque material to the cerebral circulation. The majority of the lesions were located in the ipsilateral hemisphere, which suggests manipulation prior to, during, or after stent placement as the most probable cause of these lesions in CAS patients. In this study, new lesions were also seen in other vascular territories (cerebellum) in 2 of the 21 patients with new lesions after endovascular treatment. This observation was also reported by Jaeger et al.,[14] who found contralateral lesions in 6 (9%) of their 52 patients, and by Koch et al.[21] in 22 (20%) of their 108 patients. The contralateral location of new lesions in endovascularly treated patients may in part be explained by manipulation of the guidewires and guiding catheters in the aortic arch.

Notably, the antiplatelet regime varies among different centers. The aspirin dose we used is lower than that prescribed by some interventionists, but it has not been proven that a larger

dose of aspirin is beneficial for the outcome after intervention, while a higher dose increases the rate of bleeding complications.[22]

What is the clinical importance of new DW-MRI lesions in view of the observation that most patients were clinically asymptomatic? DW-MRI abnormalities after a frank infarct (with and without clinical symptoms) normally lead to infarcts that could also be disclosed on follow-up studies with other MRI sequences. It is not known whether subclinical DW-MRI lesions seen after carotid intervention will produce structural damage to the brain, nor is it known whether these lesions may cause neuropsychological deterioration. Previous studies have revealed an increase in neuropsychometric changes after carotid endarterectomy, which may have been mediated by silent infarcts.[23-25] In addition, population-based studies have demonstrated an increased frequency of dementia in patients with lacunar infarcts and white matter lesions.[16] In a subgroup of CAVATAS patients in whom transcranial Doppler was used, the investigators found that despite an increased number of microembolic signals in the endovascular arm compared to CEA, there was no difference in neuropsychological dysfunction between groups.[26] The presence or absence of neurological symptoms is mainly dependent on the location of the new hyperintense DW-MRI lesions. It may also depend on the total volume of the lesion(s).

Our study revealed fewer lesions and a smaller lesion load in the patients without neurological symptoms after carotid intervention compared to patients with neurological sequelae, which could imply that the onset of clinical symptoms is also dependent on the amount of brain tissue damaged. DW-MRI lesions can be considered as a surrogate endpoint in the evaluation of CAS compared with CEA and in the evaluation of treatment modification (filter device, periprocedural medication).

Because of the higher frequency of subclinical lesions than clinical symptoms, power calculations for randomized studies would indicate a lower number of patients needed to reach statistically significant results. The semi-automated measurement of lesion load may be a further improvement, as lesion load may better reflect ischemic damage than the number of lesions.

This study has several limitations that should be considered before drawing conclusions about the safety of the surgical and endovascular procedures. The first limitation is the rather low frequency of DW-MRI studies in both groups (39% and 50%), resulting in a nonconsecutive cohort of patients. However, medical conditions were not the reason why the DW-MRI studies could not be performed in the remaining patients. The second and most important limitation is the nonrandomized comparison of both treatments. A valid comparison between CAS and CEA with regard to clinical outcome and DW-MRI lesions requires a randomized trial.

In conclusion, we found that DW-MRI revealed ischemic lesions more often after protected CAS than after CEA and that most of these lesions did not cause focal neurological deficits. If future studies demonstrate that these lesions are associated with cognitive dysfunction, DW-MRI may become a valuable outcome measure in future randomized clinical trials.

REFERENCES

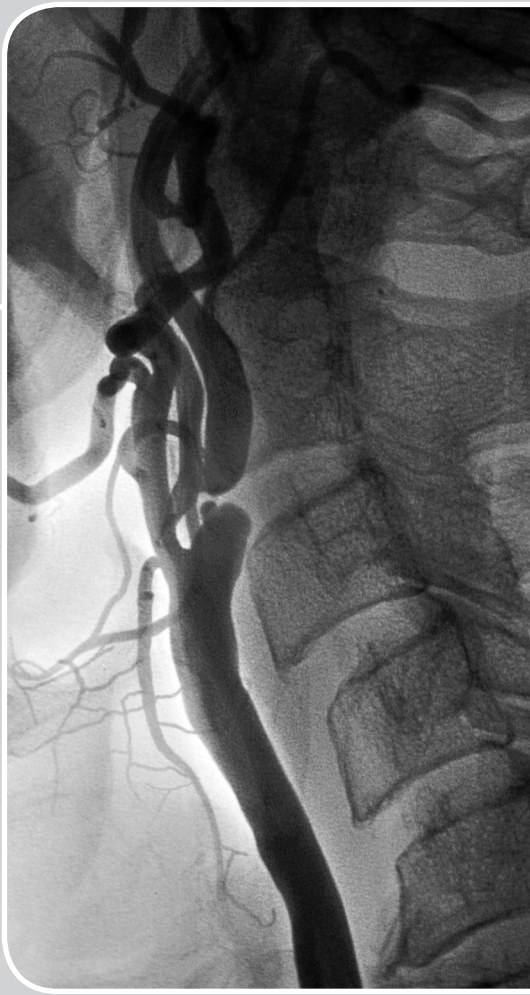
1. Lindgren A, Roijer A, Norrving B, et al. Carotid artery and heart disease in subtypes of cerebral infarction. Stroke 1994; 25: 2356-2362.
2. Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991; 337: 1235-1243.
3. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445-453.
4. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379-1387.
5. Mathur A, Roubin GS, Iyer SS, et al. Predictors of stroke complicating carotid artery stenting. Circulation 1998; 97: 1239-1245.
6. Théron JG, Payelle GG, Coskun O, et al. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. Radiology 1996; 201: 627-636.
7. Gil-Peralta A, Mayol A, Marcos JR, et al. Percutaneous transluminal angioplasty of the symptomatic atherosclerotic carotid arteries. Results, complications, and follow-up. Stroke 1996; 27: 2271-2273.
8. Roubin GS, New G, Iyer SS, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis. Circulation 2001; 103: 532-537.
9. Brown MM. Carotid angioplasty and stenting: are they therapeutic alternatives? Cerebrovasc Dis 2001; 11(Suppl 1): 112-118.
10. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357: 1729-1737.
11. Barth A, Remonda L, Lovblad KO, et al. Silent cerebral ischemia detected by diffusion-weighted MRI after carotid endarterectomy. Stroke 2000; 31: 1824-1828.
12. Feiwell RJ, Besmertis L, Sarkar R, et al. Detection of clinically silent infarcts after carotid endarterectomy by use of diffusion-weighted imaging. AJNR Am J Neuroradiol 2001; 22: 646-649.
13. Jaeger HJ, Mathias KD, Drescher R, et al. Diffusion-weighted MR imaging after angioplasty or angioplasty plus stenting of arteries supplying the brain. AJNR Am J Neuroradiol 2001; 22: 1251-1259.
14. Jaeger HJ, Mathias KD, Hauth E, et al. Cerebral ischemia detected with diffusion-weighted MR imaging after stent implantation in the carotid artery. AJNR Am J Neuroradiol 2002; 23: 200-207.
15. Tomczak R, Wunderlich A, Liewald F, et al. Diffusion-weighted MRI: detection of cerebral ischemia before and after carotid thromboendarterectomy. J Comput Assist Tomogr 2001; 25: 247-250.
16. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003; 348: 1215-1222.
17. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988; 19: 604-607.
18. Müller M, Reiche W, Langenscheidt P, et al. Ischemia after carotid endarterectomy: comparison between transcranial Doppler sonography and diffusion-weighted MR imaging. AJNR Am J Neuroradiol 2000; 21: 47-54.
19. Forbes KP, Shill HA, Britt PM, et al. Assessment of silent embolism from carotid endarterectomy by use of diffusion-weighted imaging: work in progress. AJNR Am J Neuroradiol 2001; 22: 650-653.
20. Lovblad JO, Pluschke W, Remonda L, et al. Diffusion-weighted MRI for monitoring neurovascular interventions. Neuroradiology 2000; 42: 134-138.
21. Koch C, Kucinski T, Eckert B, et al. Endovascular therapy of high-degree stenoses of the neck vessels-stent-supported percutaneous angioplasty of the carotid artery without cerebral protection [in German]. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2002; 174: 1506-1510.

22. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the clopidogrel in unstable angina to prevent recurrent events (CURE) study. Circulation 2003; 108: 1682-1687.
23. Heyer EJ, Adams DC, Solomon RA, et al. Neuropsychometric changes in patients after carotid endarterectomy. Stroke 1998; 29: 1110-1115.
24. Heyer EJ, Sharma R, Rampersad A, et al. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. Arch Neurol 2002; 59: 217-222.
25. Vanninen E, Vanninen R, Äikiä M, et al. Frequency of carotid endarterectomy-related subclinical cerebral complications. Cerebrovasc Dis 1996; 6: 272-280.
26. Crawley F, Stygall J, Lunn S, et al. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. Stroke 2000; 31: 1329-1334.

Chapter 6

Catecholamine release

J Endovasc Ther 2004; 11: 240-250



ABSTRACT

Purpose: To investigate the pattern of catecholamine response in patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS).

Methods: Adrenaline, noradrenaline, and renin levels were measured at 5 time points in 12 patients undergoing 13 CEAs (1 bilateral) and 13 patients undergoing unilateral CAS. Arterial blood samples were taken at the following time points: (1) after induction in CEA patients or 5 minutes following first contrast injection in CAS patients, (2) 5 minutes following ICA clamp release in surgical patients or deflation of the balloon in the CAS cohort, (3) 60 minutes following ICA clamp release in surgical patients or deflation of the balloon in the CAS cohort, and (4) 24 hours following the procedure. Intraoperative blood pressure and heart rate were recorded using radial arterial monitoring. Changes in adrenaline, noradrenaline, and renin levels are expressed as ratios versus baseline.

Results: Patterns of adrenaline and noradrenaline release were significantly different in patients undergoing CAS and CEA, with much higher and more variable surges of adrenaline and noradrenaline occurring in CEA patients. Adrenaline and noradrenaline levels increased significantly over baseline following carotid artery clamping in patients undergoing CEA (noradrenaline ratio before clamping: 1.54±1.25, 24 hours after unclamping: 8.38±16.35 [$p<0.001$]; adrenaline ratio before clamping: 1.12±0.49, 60 minutes after unclamping: 17.59±19.14 [$p<0.001$]). Conversely, in patients undergoing CAS, catecholamine levels remained unchanged (noradrenaline ratio before dilation: 0.96±0.23, 24 hours after the procedure: 0.92±0.32 [p=NS]; adrenaline ratio before dilation: 0.83±0.33, 60 minutes after balloon deflation: 0.56±0.32 [p=NS]).

Conclusions: CAS is associated with a significantly less marked catecholamine response than CEA, which may reflect down-regulation of the sympathetic nervous system in response to carotid sinus stimulation during carotid angioplasty.

INTRODUCTION

Patients undergoing carotid endarterectomy (CEA) are especially prone to peri and postoperative myocardial complications because of the high prevalence of ischemic heart disease in this group.[1-4] Carotid artery angioplasty and stenting (CAS) has been proposed as an alternative to CEA in patients with significant carotid stenosis; even those at high risk owing to severe coronary artery disease have been successfully treated with CAS.[1] This latter group may prove to be those who derive the most benefit from CAS. Previously, the only options available were CEA performed under local anesthesia or a combined CEA and coronary artery bypass procedure. Unfortunately, the use of local anesthesia has not been shown to reduce cardiac morbidity,[2, 5, 6] probably because catecholamine levels are significantly higher in patients operated upon under local anesthesia compared to general anesthesia.[7]

Some degree of hemodynamic instability (hypertension, hypotension, and bradycardia) commonly develops after CEA.[8-12] Although these postoperative cardiovascular fluctuations are usually transient, hemodynamic instability after CEA has been linked to surgical mortality and morbidity, especially the occurrence of stroke and cardiac complications.[13] The mechanism of post CEA hemodynamic instability remains unclear. Animal studies have shown that acute cerebral ischemia causes the sympathetic nervous system to stimulate renal renin release, leading to elevated angiotensin levels and hypertension. Further studies have implicated a sympathetic nervous system neuroamine, such as adrenaline or noradrenaline.[9]

Hemodynamic instability has been described after CAS and may also have clinical implications.[14-16] Pre-existing cardiac arrhythmias may be exacerbated, and the risk of hypoperfusion and stroke may increase in the postoperative period. The pathophysiology underlying the phenomenon of hemodynamic instability in patients undergoing CAS is likely due to direct mechanical dilation of the carotid bulb and sinus, resulting in increased parasympathetic discharge and decreased systemic arterial smooth muscle tone, thus causing hypotension.[15, 16] The aim of this study was to investigate the relationship between fluctuations in plasma adrenaline and noradrenaline levels in patients undergoing CEA or CAS.

METHODS

Study design and patient sample

This was a prospective nonrandomized study carried out under local ethics committee approval. Twenty-five patients (20 men; mean age 67.8±9.9 years) undergoing CEA (n=13) or CAS (n=13) were enrolled. All patients were symptomatic owing to a high-grade carotid artery stenosis. The decision to perform CAS was subjectively based on the angiographic appearance of the stenotic lesion and the suitability of the carotid vasculature for a cerebral protection device. Following informed consent, patients were allocated to CEA or protected CAS depending on

the angiographic appearance of the carotid stenosis. Patients did not routinely undergo a neurological evaluation before or after either type of carotid intervention.

The patients were similar with regard to demographics, ASA (American Society of Anesthesiologists) grade, baseline risk factors, and indications for treatment (Table 1). There was no difference in the preoperative use of antihypertensive medication. One CAS patient had previously undergone a CEA and redo CEA with patch angioplasty 2 years later. One CEA patient was diabetic, the only one in the entire sample. One patient had bilateral CEAs in staged procedures.

Table 1. Patient demographics and risk factors

	CEA (=12)	CAS (n=13)	p
Men	8	12	NS
Age, y	64.3±10.9	67.7±9.96	NS
ASA grade			
I	0	0	
II	10	12	
III	1	1	
IV	1	0	NS
Hypertension	4	5	
Cardiac history			NS
Previous myocardial infarction	1	2	
Dysrhythimia	2	2	
Preoperative medication			NS
Calcium channel blockers	3	4	
Beta-blockers	3	2	
Indication for intervention*			
Amaurosis fugax	5	1	
Transient ischemic attack	5	8	
Cerebrovascular accident	3	4	

Continuous data are presented as mean ± standard deviation. NS: not significant.
* Per hemisphere; 1 patient had bilateral CEAs in staged procedures.

Carotid endarterectomy

Carotid endarterectomy was carried out under general anesthesia induced with thiopental sodium and maintained with nitrous oxide, fentanyl, and isoflurane. Carotid endarterectomy was performed using a transverse cervical incision with full heparinization and electroencephalographic (EEG) monitoring; a shunt was used if the EEG became asymmetrical. Polytetrafluoroethylene (W.L. Gore & Associates, Flagstaff, AZ, USA) or venous patches were used where the artery caliber was too small to allow primary closure. All patients were extubated immediately following wound closure.

Carotid artery stenting

Patients received clopidogrel (300 mg; Sanofi Pharmaceuticals, New York, NY, USA) 12 hours before the procedure, which was carried out under local anesthesia with continuous intra-arterial blood pressure, cardiac, and neurological monitoring (EEG and transcranial Doppler) in the interventional radiology suite. Control angiograms were performed following administration of 5000 units of heparin. Using a roadmap technique, the stenosis was crossed with an AngioGuard filter device (Cordis, a Johnson & Johnson company, Miami Lakes, FL, USA) for cerebral protection. An isoprenaline infusion (0.01 μg/kg/min) was begun immediately before balloon inflation in all patients to reduce the incidence of bradycardia and hypotension. Predilation was selectively performed in heavily calcified lesions or tight stenoses that would not accommodate the stent. A noncompliant balloon was delivered over a long exchange wire and inflated to a maximum pressure of 4 atmospheres. Self-expanding stents (Wallstent, Boston Scientific, Natick, MA, USA; SMART, Cordis; and Dynalink, Guidant, Indianapolis, IN, USA) were sized to match the common carotid artery diameter measured on the preprocedural duplex scan and the control angiogram. After the stent was deployed and dilated (maximum of 8 to 10 atmospheres), a control angiogram was performed. Patients were continued on clopidogrel (75 mg/d) for 1 month following the procedure.

Blood samples and assays

All patients had radial arterial lines inserted before induction of anesthesia or before commencement of the stenting procedure. Blood samples were drawn from the arterial line, transferred to heparinized glass containers, and placed immediately on ice. In CEA patients, samples were drawn after induction of anesthesia (baseline), 5 minutes after internal carotid artery (ICA) clamping, and at 5 and 60 minutes after restoration of cerebral circulation. A further sample was taken at 24 hours postoperatively only if the radial arterial line was still in place, as catecholamine levels have been shown to vary between the arterial and venous sides of the circulation.[17] Patients undergoing CAS had blood taken 15 minutes after radial arterial line insertion (baseline), immediately after the first contrast injection, at 5 and 60 minutes after deflation of the angioplasty balloon, and 24 hours following the procedure. All patients were returned to the intensive care unit for postprocedural monitoring.

Plasma catecholamines (adrenaline and noradrenaline) were measured using high performance liquid chromatography with electrochemical detection. Samples were analyzed 3 months after commencement of the study. Renin concentrations were determined by radioimmunoassay.

Statistical analysis

Data were tested for normality. Continuous data are presented as the mean ± standard deviation. Changes in hemodynamic variables (heart rate, blood pressure) and hormone levels are expressed as a ratio of the baseline value. Due to wide individual variation in individual

catecholamine levels, data are presented as a plot of each patient's ratio of change. The Student t test was used to compare paired data and the chi-square test for proportional analyses. A 2-way analysis of variance (ANOVA) for repeated measurements with Bonferroni post-hoc correction was used for multiple comparisons. All analyses were performed with the Instat statistical software package (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Mean duration of carotid artery clamping in CEA patients was 34.0±12.7 minutes in a procedure that lasted a mean 121.5±27.1 minutes (Table 2). One CEA patient had a shunt placed. In CAS patients, 6 Wallstents, 3 SMART stents, and 4 Dynalink stents were implanted in protected procedures averaging 86.6±24.9 minutes. There were no major strokes or death, but 1 patient in each group suffered minor neurological complications. One CEA patient developed weakness of his right hand 6 hours following a left CEA; carotid duplex showed an occluded ICA. However, as the patient's neurological condition remained stable, no further intervention was carried out. One CAS patient developed a transient arm weakness that resolved within 24 hours. This patient had experienced hypotension and extreme bradycardia during balloon angioplasty, and the cerebral protection device had become occluded. He subsequently made an uneventful recovery.

Table 2. Intraprocedural data for patients undergoing carotid artery stenting (CAS) or carotid endarterectomy (CEA)

	CEA	CAS	p
Duration of procedure, min	121.5±27.1	86.6±24.9	<0.005
Intravenous fluids, mL	3150±1355	1400±374	<0.006
Fluid infusion, mL/min	26.7±3.9	17.1±2.4	<0.046

Continuous data are presented as mean ± standard deviation.

Hemodynamic data

There was no difference in mean heart rate between groups at the start of the procedure (CAS: 71±12 beats/minute, CEA 74±15 beats/ minute) (p=0.81), and no significant changes were evident between groups at various time points in the procedures (Table 3). However, systolic blood pressure was significantly higher at baseline in the CAS group (171±26 mmHg) compared to CEA (134±20 mmHg; p<0.05). A significant decrease in blood pressure was seen 5 minutes following balloon dilation in the CAS group (–32±28 mmHg) compared to a mild increase in blood pressure (8.3±28.1 mmHg; p=0.01) 5 minutes following cerebral reperfusion in the CEA group.

Table 3. Changes in heart rate and blood pressure from baseline in patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS)

CEA					
	Before clamping*	After clamping	5 minutes after unclamping	60 minutes after unclamping	End of surgery
Heart rate, beats	-4.08±13.17	-6.70±12.60	-9.30±13.90	-3.50±13.90	1.30±14.50
Blood pressure, mmHg	3.25±22.91	5.58±36.50	8.33±28.07	-2.25±24.78	4.41±23.94
CAS					
	Before cath†	After contrast injection	Before dilation	5 minutes after dilation	60 minutes after dilation
Heart rate, beats	0.91±10.72	11.17±11.15	18.50±13.67	-1.30±25.70	6.42±15.24
Blood pressure, mmHg	-5.00±13.69	-7.69±13.78	-2.69±19.43	-32.31±28.20	-23.85±21.00

Continuous data are presented as mean ± standard deviation.
* After induction of anesthesia.
† Fifteen minutes after radial line insertion.

Catecholamine and renin levels

Patterns of adrenaline (Fig. 1) and noradrenaline (Fig. 2) release were significantly different in patients undergoing CAS and CEA, with much higher and more variable surges of adrenaline and noradrenaline occurring in CEA patients. The ratios of adrenaline and noradrenaline change increased significantly following carotid artery clamping in patients undergoing CEA (noradrenaline ratio before clamping: 1.54±1.25 and 24 hours after unclamping: 8.38±16.38 [$p<0.001$]; adrenaline ratio before clamping: 1.12±0.49 and 60 minutes after unclamping: 17.59±19.14 [$p<0.001$]). Conversely, in CAS patients, catecholamine levels remained unchanged (noradrenaline ratio before dilation: 0.96±0.23 and 24 hours after dilation: 0.92±0.32 [p=NS]; adrenaline ratio before dilation: 0.83±0.33 and 60 minutes after balloon deflation: 0.56±0.32 [p=NS]).

When direct comparisons between catecholamine levels in CAS and CEA patients were made, the most marked differences were seen in adrenaline ratios at 60 minutes following either ICA clamping in CEA patients (17.59±19.14) or balloon deflation in CAS patients (0.56±0.32, $p<0.001$). Noradrenaline ratios were higher in CEA patients at 60 minutes following ICA clamping (8.38±16.35) compared to levels in CAS patients 60 minutes following balloon deflation (0.92±0.32), but this difference was not statistically significant.

Catecholamine levels at 24 hours postprocedure were available in 6 of 12 patients who underwent CEA and 7 of 13 patients who underwent CAS. When the patients who suffered minor neurological events (1 per group) were excluded, a reanalysis of the catecholamine data did not show a difference in the trends. Similarly, when the CEA patient who required a shunt was removed from the analysis, there was no significant difference observed.

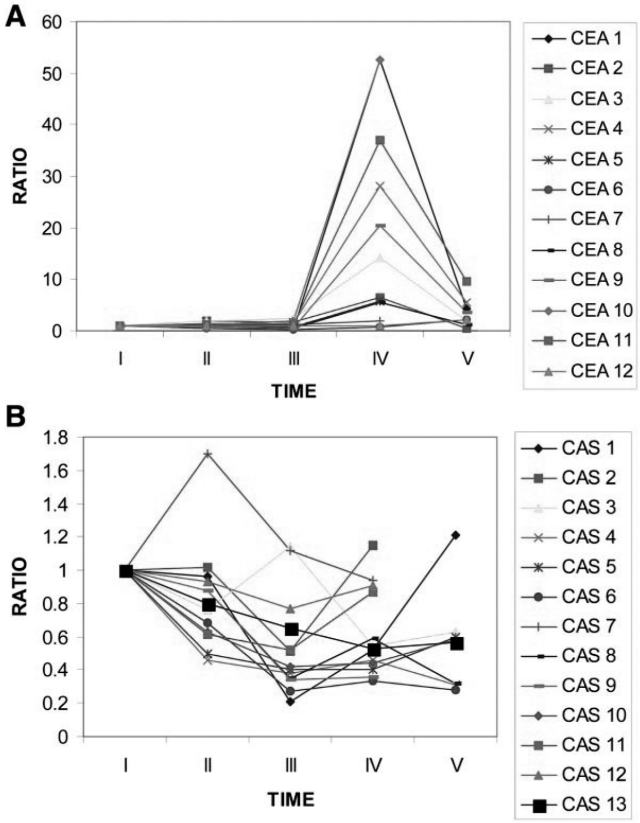


Figure 1. Adrenaline levels for individual (A) CEA and (B) CAS patients. Values are the ratio of change from baseline (I). II: after induction in CEA or 5 minutes following first contrast injection in CAS, III: 5 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort, IV: 60 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort, and V: 24 hours postoperatively

As with the catecholamines, there was significant individual variation in plasma renin levels (Table 4), but no significant differences in the ratios of renin values between the groups or within the groups at any time point.

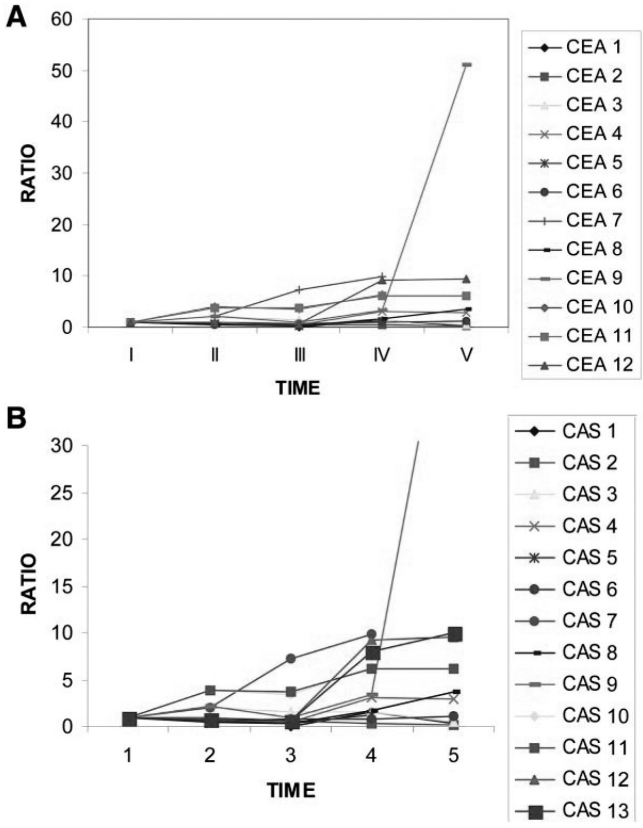


Figure 2. Individual noradrenaline data for patients undergoing (A) CEA or (B) CAS. Values are ratios of change from baseline (I). II: after induction in CEA or 5 minutes following first contrast injection in CAS, III: 5 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort, IV: 60 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort, and V: 24 hours postoperatively

Table 4. Changes in renin levels* in patients undergoing carotid artery stenting (CAS) or carotid endarterectomy (CEA)

Time	CAS	CEA
I	1.00	1.00
II	0.88±0.36	1.02±0.35
III	0.83±0.38	1.10±0.20
IV	0.50±0.50	0.92±0.34

Continuous data are presented as mean ± standard deviation.
* Values are changes from baseline (I) expressed as ratios. II: after induction in CEA or 5 minutes following first contrast injection in CAS, III: 5 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort, and IV: 60 minutes following ICA clamp release in surgical patients or deflation of angioplasty balloon in CAS cohort.

DISCUSSION

Carotid artery stenting is emerging as a potential alternative to carotid endarterectomy for symptomatic carotid artery stenosis, particularly in high-risk patients.[18-20] However, there have been sporadic reports of hemodynamic disturbances in the form of bradycardia and hypotension occurring at the time of stent deployment,[14-16] notably in elderly patients and those with coronary artery disease.[21] Carotid angioplasty involves extensive manipulation in the region of both adventitial receptors and the carotid sinus. According to experimental studies using electrical stimulation,[22] carotid sinus manipulation dampens the sympathetic nervous system influence on cardiovascular dynamics, resulting in bradycardia, reduced arterial resistance, increased venous capacitance, and decreased cardiac output.

There is conflicting evidence, however, as to whether periprocedural hemodynamic instability is associated with poor neurological outcome.[21, 23, 24] One study has demonstrated that patients who experience hypotension during CAS have significantly worse short and midterm prognoses than those who remain hemodynamically stable.[24] On the other hand, Mlekusch et al.[21] showed no increased risk of neurological deficit associated with hypotension and bradycardia in elective CAS.

The present study was undertaken to investigate the pattern of changes in catecholamine levels in patients undergoing CEA under general anesthesia compared to CAS patients treated under local anesthesia. It is difficult to measure sympathetic nervous system (SNS) activity directly, but fluctuations in sympathetic tone can be estimated indirectly by recording changes in plasma noradrenaline.[25] Differences between noradrenaline re-uptake, clearance, and conjugation can make it difficult to interpret individual patient data.[25] For that reason, we used ratios of change from baseline as a comparative measure.

Case reports have been published describing significant cardiac arrhythmias and hypotension immediately following balloon deflation and for up to 36 hours after the procedure in CAS patients.[15] In a retrospective review of 51 CAS patients, Qureshi et al.[14] presented respective rates for hypertension, hypotension, and bradycardia of 38%, 22%, and 27.5%. Other investigators have reported rates for bradycardia and hypotension together of 68% and 71%.[14, 16] The most likely explanation for this is a disturbance of adventitial receptors and modification in the elasticity of the arterial wall, which may alter the sensitivity of carotid receptors.[26] Animal studies have shown that the adaptation of carotid sinus receptors to changes in mechanical properties is slow and incomplete.[27] Angell-James et al.[28] showed that post-CEA hypotension was caused by increased sinus nerve activity resulting from increased diameter of the carotid sinus. Therefore, carotid angioplasty may lead to a steady-state increase in sinus baroreceptor stimulation and activity, in turn resulting in inhibition of sympathetic tone to peripheral blood vessels, thus causing systemic hypotension.[14] This mechanism is in keeping with our finding of decreased levels of noradrenaline and adrenaline and also works well with the finding of Sleight et al.,[29] who reported that the increased noradrenaline levels during exercise and the

associated change in blood pressure are inversely proportional to resting baroreceptor sensitivity and correlate with changes in sympathetic nervous system activity.

In the current study, patients were allocated to an endovascular or surgical procedure according to the radiological appearance of the carotid lesion rather than on the basis of medical risk. A study of CAS patients in our institution identified a significant incidence of bradycardia and hypotension that proved unresponsive to the pre-emptive administration of atropine in many cases (unpublished data). Others having this experience have speculated that hemodynamic instability may be a feature of the learning curve: inexperience in determining the optimal level of balloon dilation and sizing of stents, for example, has been cited as a possible explanation.[14, 16, 18] Excessive balloon dilation followed by exaggerated radial pressure caused by an oversized stent could be expected to increase both the incidence and duration of postprocedural hypotension. Studies have already shown that the incidence of hemodynamic instability is significantly higher in patients treated with balloon-expandable compared to self-expanding stents.[18,23] Our current practice is to administer isoprenaline before balloon inflation. We have found this to be effective, and it significantly reduced the incidence of bradycardia and hypotension associated with stent deployment (unpublished data). Because all patients undergoing CAS in the current study had an isoprenaline infusion before balloon inflation, the plasma catecholamine levels may have been skewed. However, in spite of administered catecholamines, overall levels still remained significantly lower than in CEA patients having no inotropic support.

Howell et al.[24] have recently recommended treating high-risk patients more aggressively with vasopressor agents to reduce the number of neurological events. A criticism of the use of pressors is their potential to aggravate pre-existing coronary artery disease by reducing myocardial perfusion during diastole. Injudicious use of atropine is likely to give rise to similar problems. Qureshi et al.[14] saw a higher incidence of postprocedural bradycardia in patients given atropine prophylactically.[14] Furthermore, the prolonged pressure transmission against the carotid sinus induced by stent placement differs from the transient force applied by balloon dilation; stents thus cause a more pronounced baroreceptor reflex, which may not respond to atropine.[16] Insertion of a temporary venous pacemaker has been proposed as a means of preventing intraprocedural hemodynamic instability. While this avoids the risks of myocardial ischemia induced by vasopressor agents, it is an invasive maneuver. Harrop et al.[12] reported venous pacemaker activation rates of 73% during CAS.

Postoperative hypertension following CEA may be caused by dysfunction of adventitial baroreceptors in the endarterectomized carotid artery segment.[14, 16] An association between baroreceptor failure caused by neck irradiation or bilateral carotid body tumors has been shown with elevated levels of adrenaline and noradrenaline.[30] Abnormal input from damaged baroreceptors is likely to lead to increased SNS activity. Lesser degrees of baroreceptor failure have been detected by hemodynamic monitoring during or soon after CEA or following carotid body surgery.[31,32] Several reports have demonstrated elevated concentrations of renin and

noradrenaline in jugular venous blood during and after CEA, which may reflect a generalized increase in sympathetic nervous system activation.[9, 33] It is possible that cranial hypoperfusion during carotid artery cross-clamping results in transient disruption of the blood-brain barrier, prompting increased catecholamine release into the jugular vein.[9] It is possible to speculate that the much shorter period of cerebral ischemia associated with CAS may explain the lower catecholamine levels we observed in this group compared to CEA, but we saw no alteration in renin levels, similar to findings in other studies. Ahn et al.,[9] for example, demonstrated increased levels of cranial renin but no change in peripheral levels in patients who had undergone CEA. Estimation of cranial renin levels in our patients undergoing CAS was beyond the scope of this study.

Modification of baroreceptor sensitivity after angioplasty does not persist indefinitely. Hypotension and magnitude of fluctuations are most prominent in patients without previous CEA. Hypotension immediately after CEA has been postulated to arise from changes in carotid sinus behavior caused by removal of the rigid atheromatous plaque.[34, 35] The incidence of post-operative hypotension in patients undergoing CEA was only 15% in this series. Previous studies have shown that infusion of adequate volumes of colloid markedly reduce the incidence of postoperative hypotension.[36] In the current study, significantly less fluid volume was required to maintain a stable blood pressure in the CAS group.

A criticism of this study is the absence of general anesthesia in the CAS group. Factors such as a surgical wound, retraction, more prolonged brain ischemia, and postoperative pain may explain the more exaggerated catecholamine response in the CEA group. Patients undergoing CEA under local anesthesia show a more marked cardiovascular stress reaction than patients having general anesthesia.[37] Takolander et al.[7] recorded higher levels of catecholamine release in CEA patients given local anesthesia versus patients treated under general anesthesia. This observation may be explained by the fact that inhalational anesthetics produce marked sympathetic inhibition by decreasing noradrenaline clearance from the circulation and inhibit noradrenaline release at the prejunctional level.[38, 39]

In conclusion, this study demonstrated marked differences in neuroendocrine responses to CEA and CAS. Although numbers are small in the current study, there also appear to be differences in hemodynamic responses to the procedures, likely due to differing SNS reactions to carotid artery clamping compared to carotid sinus stretching during CAS.

REFERENCES

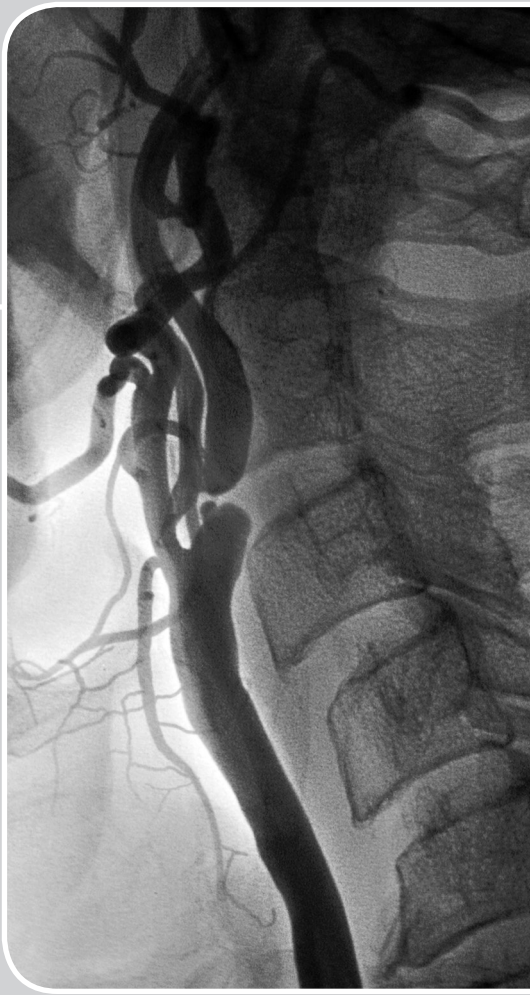
1. Waigand J, Gross CM, Uhlich F. et al. Elective stenting of carotid artery stenosis in patients with severe coronary artery disease. Eur Heart J 1998; 19: 1365–1370.
2. Sbarigia E, DarioVizza C, Antonini M. et al. Locoregional versus general anesthesia in carotid surgery: is there an impact on perioperative myocardial ischemia? Results of a prospective monocentric randomized trial. J Vasc Surg 1999; 30: 131–138.
3. Hans SS, Glover JL. The relationship of cardiac and neurological complications to blood pressure changes following carotid endarterectomy. Am Surg 1995; 61: 356–359.
4. Paciaroni M, Eliasziw M, Kappelle LJ. et al. Medical complications associated with carotid endarterectomy. North American Symptomatic Carotid Endarterectomy Trial (NASCET). Stroke 1999; 30: 1759–1763.
5. Ombrellaro MP, Freeman MB, Stevens SL. et al. Effect of anesthetic technique on cardiac morbidity following carotid artery surgery. Am J Surg 1996; 171: 387–390.
6. McCleary AJ, Maritati G, Gough MJ. Carotid endarterectomy; local or general anaesthesia? Eur J Vasc Endovasc Surg 2001; 22: 1–12.
7. Takolander R, Bergqvist D, Hulthen UL. et al. Carotid artery surgery. Local versus general anaesthesia as related to sympathetic activity and cardiovascular effects. Eur J Vasc Surg 1990; 4: 265–270.
8. Wong JH, Findlay JM, Suarez-Almazor ME. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. Neurosurgery 1997; 41: 35–43.
9. Ahn SS, Marcus DR, Moore WS. Post-carotid endarterectomy hypertension: association with elevated cranial norepinephrine. J Vasc Surg 1989; 9: 351–360.
10. Goldberg ME, Seltzer JL, Azad SS. et al. Intravenous labetalol for the treatment of hypertension after carotid endarterectomy. J Cardiothorac Anesth 1989; 3: 411–417.
11. Jordan WD, Voellinger DC, Fisher WS. et al. A comparison of carotid angioplasty with stenting versus endarterectomy with regional anesthesia. J Vasc Surg 1998; 28: 397–403.
12. Harrop JS, Sharan AD, Benitez RP. et al. Prevention of carotid angioplasty-induced bradycardia and hypotension with temporary venous pacemakers. Neurosurgery 2001; 49: 814–821.
13. Ille O, Woimant F, Pruna A. et al. Hypertensive encephalopathy after bilateral carotid endarterectomy. Stroke 1995; 26: 488–491.
14. Qureshi AI, Luft AR, Sharma M. et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke 1999; 30: 2086–2093.
15. Qureshi AI, Luft AR, Lopes DK. et al. Postoperative hypotension after carotid angioplasty and stenting: report of three cases. Neurosurgery 1999; 44: 1320–1324.
16. Mendelsohn FO, Weissman NJ, Lederman RJ. et al. Acute hemodynamic changes during carotid artery stenting. Am J Cardiol 1998; 82: 1077–1081.
17. Henriksen JH, Ring-Larsen H, Christensen NJ. Catecholamines in plasma from artery, cubital vein, and femoral vein in patients with cirrhosis. Significance of sampling site. Scand J Clin Lab Invest 1986; 46: 39–44.
18. Roubin GS, New G, Iyer SS. et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis. Circulation 2001; 103: 532–537.
19. Wholey MH, Wholey M, Mathias K. et al. Global experience in cervical carotid artery stent placement. Catheter Cardiovasc Interv 2000; 50: 160–167.
20. Shawl FA, Kadro W, Domanski MJ. et al. Safety and efficacy of elective carotid artery stenting in high-risk patients. J Am Coll Cardiol 2000; 35: 1721–1728.
21. Mlekusch W, Schillinger M, Sabeti S. et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. J Endovasc Ther 2003; 10: 851–859.
22. Rothfeld EL, Parsonnet V, Raman KV. et al. The effect of carotid sinus nerve stimulation on cardiovascular dynamics in man. Angiology 1969; 20: 213–218.

23. Dangas G, Laird JR, Satler LF. et al. Postprocedural hypotension after carotid artery stent placement: predictors and short- and long-term clinical outcomes. Radiology 2000 ;215: 677–683.
24. Howell M, Krajcer Z, Dougherty K. et al. Correlation of periprocedural systolic blood pressure changes with neurological events in high-risk carotid stent patients. J Endovasc Ther 2002; 9 :810–816.
25. Floras J, Vann Jones J, Hassan MO. et al. Failure of plasma norepinephrine to consistently reflect sympathetic activity in humans. Hypertension 1986; 8: 641–649.
26. Heath D, Smith P, Harris P. et al. The atherosclerotic carotid sinus. J Pathol 1973; 110: 49–58.
27. Bagshaw RJ, Barrer SJ. Effects of angioplasty upon carotid sinus mechanical properties and blood pressure control in the dog. Neurosurgery 1987; 21: 324–330.
28. Angell-James JE, Lumley JS. The effects of carotid endarterectomy on the mechanical properties of the carotid sinus and carotid sinus nerve activity in atherosclerotic patients. Br J Surg 1974; 61: 805–810.
29. Sleight P, Floras JS, Hassan MO. et al. Baroreceptor control of blood pressure and plasma noradrenaline during exercise in essential hypertension. Clin Sci (London) 1979; 57: (Suppl 5) 169s–171s.
30. Hirschl M, Kundi M, Blazek G. Five-year follow-up of patients after thromboendarterectomy of the internal carotid artery. Relevance of baroreceptor sensitivity. Stroke 1996; 27: 1167–1172.
31. Robertson D, Hollister AS, Biaggioni I. et al. The diagnosis and treatment of baroreflex failure. N Engl J Med 1993; 329: 1449–1455.
32. Manger WM. Baroreflex failure–a diagnostic challenge. N Engl J Med 1993; 329: 1494–1495.
33. Lilly MP, Brunner MJ, Wehberg KE. et al. Jugular venous vasopressin increases during carotid endarterectomy after cerebral reperfusion. J Vasc Surg 1992; 16: 1–9.
34. Tyden G, Samnegard H, Melcher A. et al. Effect of carotid endarterectomy on the antihypertensive properties of the carotid sinus reflex. Acta Chir Scand 1981; 147: 15–17.
35. Smith BL. Hypertension following carotid endarterectomy: the role of cerebral renin production. J Vasc Surg 1984; 1: 623–627.
36. Dehn TC, Angell-James JE. Long-term effect of carotid endarterectomy on carotid sinus baroreceptor function and blood pressure control. Br J Surg 1987; 74: 997–1000.
37. McCarthy RJ, Walker R, McAteer P. et al. Patient and hospital benefits of local anaesthesia for carotid endarterectomy. Eur J Vasc Endovasc Surg 2001; 22: 13–18.
38. Wood M. Effect of general anesthesia on modulation of sympathetic nervous system function. Adv Pharmacol 1994; 31: 449–459.
39. Muzi M, Ebert TJ. Randomized, prospective comparison of halothane, isoflurane and enflurane on baroreflex control of heart rate in humans. Adv Pharmacol 1994; 31: 379–387.

Chapter 7

Prevention of hemodynamic instability

Submitted



ABSTRACT

Purpose: To evaluate the use of prophylactic administration of isoprenaline to prevent hemodynamic instability during carotid angioplasty and stenting.

Methods: Nineteen consecutive patients with a symptomatic carotid artery stenosis were treated with angioplasty and stenting. Eleven patients received prophylactic isoprenaline (isoprenaline group) during the procedure and 8 patients did not receive medication (control group). The day before the procedure the mean systolic blood pressure (MAP) was calculated and regarded as our baseline value. The blood pressure (BP) and heart rate (HR) of all patients was monitored before and 10 minutes after balloon dilatation. The average decrease in BP and HR after dilatation in the isoprenaline group was compared with the decrease in BP and HR in the control group. Data were expressed as percentage of baseline value.

Results: In the isoprenaline group the pre-dilatation MAP was increased by 25% following administration of isoprenaline compared to the control group. The magnitude of the blood pressure decrease was similar in both groups of patients following balloon dilatation of the internal carotid artery stenosis. However, in the Isoprenaline group the systolic BP did not drop below the 90 mmHg at any stage during the procedure (p=0.018). By contrast, there was a 50% incidence of hypotension in the control group. Bradycardia tended to occur more often in the control group (88% vs. 45%). None of the patients given prophylactic isoprenaline suffered asystole compared to those in the control group (0% vs. 38%, p=0.058).

Conclusion: Hypotension during carotid angioplasty and stenting occurred less often in patients treated with isoprenaline compared with control patients. This was caused by an elevation of average BP before the start of the procedure.

INTRODUCTION

Carotid angioplasty with stenting (CAS) is becoming an established treatment modality for patients with a symptomatic carotid artery stenosis. Neurological complications remain the most challenging drawback of the method. Advanced age, long or multiple stenoses has been suggested as risk factors for these events.[1] Another recognized source of neurological sequelae during carotid stenting is hypoperfusion.[2-4, 16] Baroreceptor stimulation can cause bradycardia and hypotension. Stents or balloons distend the carotid sinus, thereby activating stretch-sensitive mechanoreceptors that send impulses to the brain stem, triggering a reduction of sympathetic tone in peripheral blood vessels resulting in systemic hypotension. Impulses from the carotid sinus also cause enhanced parasympathetic stimulation of the heart, which lowers the heart rate (HR). Patients who develop persistent hemodynamic instability are at an increased risk of periprocedural major adverse clinical events and stroke.[16]

Several techniques have been used to prevent bradycardia and hypotension. The muscarine antagonist atropine has been commonly used. Others have suggested the use of a temporary pacemaker, despite this being an invasive procedure.[5]

Isoprenaline is a β-adrenergic agonist. It stimulates both the HR and contractility by stimulating β_1-receptors in the heart.[6] The aim of this study was to investigate the hemodynamic effects of the prophylactic use of the vasoactive drug, Isoprenaline, during CAS.

METHODS

Patients

Nineteen consecutive patients (table 1) underwent carotid artery angioplasty and stenting. A policy of prophylactic isoprenaline administration was instituted after the first 8 patients described in this series had been treated (isoprenaline group). Patients with a symptomatic stenosis in the carotid artery of 70% or more were included. The nature and degree of the stenosis were established using conventional angiography. All patients were administered aspirin (100 mg/day) and clopidogrel (75 mg/day) before the procedure.

Procedure

The groin area was infiltrated with lidocain 2% for local anesthesia. An 8F short introducer catheter was placed in the femoral artery. A bolus of 5000 IE heparin was given. An 8F neuro-guiding catheter was placed in the common carotid artery and control angiograms performed. An Angioguard filter protection device (Cordis Corporation, Miami, FL, USA) was introduced into the internal carotid artery approximately 4 cm above the lesion. After deployment of the cerebral protection device a 3mm coronary balloon was used for predilatation. After deployment of the stent, the lesion was post-dilated depending on the residual stenosis. The protection device

was removed and a control angiogram performed. After completion of the procedure vascular sheaths were removed and the patients were transferred to the ICU.

Table 1. Baseline characteristics of patients

	Control group	Isoprenaline group
Number of patients, n	8	11
Age, y	73 ± 7	63 ± 16
Male sex, n	4 (50%)	9 (82%)
Diabetes Mellitus	2 (25%)	0 (0%)
Smoking	4 (50%)	4 (36%)
Hypertension controlled with medication	4 (50%)	5 (45%)
Hypercholesterolemia	1 (25%)	6 (55%)

Hemodynamic measurements

Procedures were carried out under local anesthesia in the interventional radiology suite with an anesthetist in attendance, using continuous intra-arterial blood pressure, cardiac and neurological monitoring (EEG and transcranial Doppler). Bradycardia was defined as a HR < 60 beats/min, hypotension as a systolic BP of less than 110 mmHg, severe hypotension as a decrease of the BP below 90 mmHg and asystole was defined as an absence of cardiac contraction lasting a minimum duration of 3 seconds.

The day before the procedure the BP was measured at three different time-points and the mean arterial pressure calculated and taken to be the baseline MAP for that individual patient. MAP measurements in all the patients were monitored before and until 10 minutes after balloon dilatation. Data were expressed as percentage of baseline value.

The mean percentage decrease in HR and BP after dilatation in the Isoprenaline group was compared with the mean percentage decrease in HR and BP in the control group. For the purposes of this study, periods of asystole were not included in the MAP calculation.

Statistics

Differences between dichotomous variables were assessed with a Fisher-exact test. Significance was set at $p<0.05$.

RESULTS

The clinical characteristics of the patients included are described in table 1.

The incidence of hypotension in the isoprenaline group differed significantly from the incidence in the control group (figure 1). The systolic BP never dropped under the 90 mmHg in

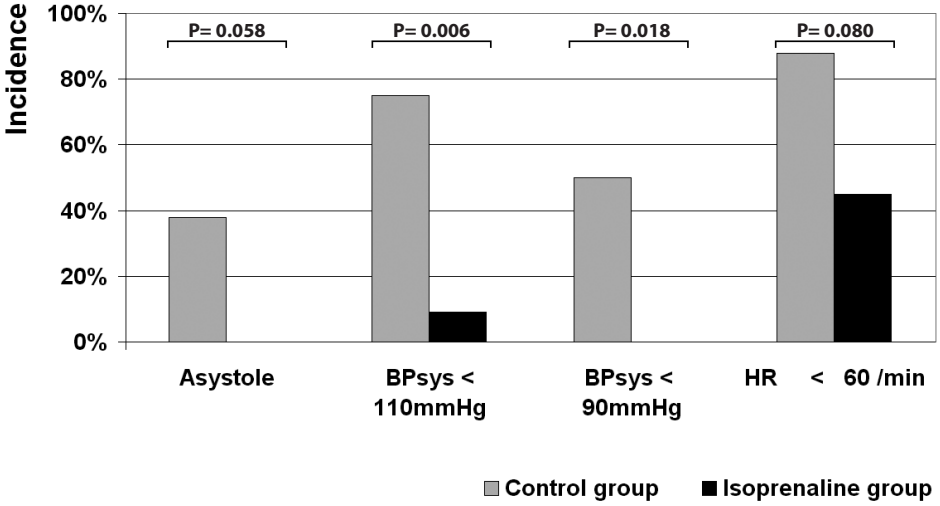


Figure 1. Isoprenaline prevents mild and severe hypotension

the isoprenaline group in contrast to the control group in which it occurred in 50% of patients (p=0.018). In the isoprenaline group the average BP before dilation was elevated by 25%. In both groups the magnitude of the decrease in BP after dilatation was similar. However because of the prophylactic elevation of BP in the Isoprenaline group these patients did not suffer significant hypotension (figure 2).

In both the groups there was a variation in HR during CAS. Bradycardia occurred more often in the control group compared to the isoprenaline group (88% vs. 45%) although this was not statistically significant (p=0.08) (figure 1). None of the patients given prophylactic Isoprenaline suffered asystole compared to those in the control group (0% vs38%, p=0.058). One patient in the control group developed hemodynamic instability during the procedure and suffered a postoperative stroke.

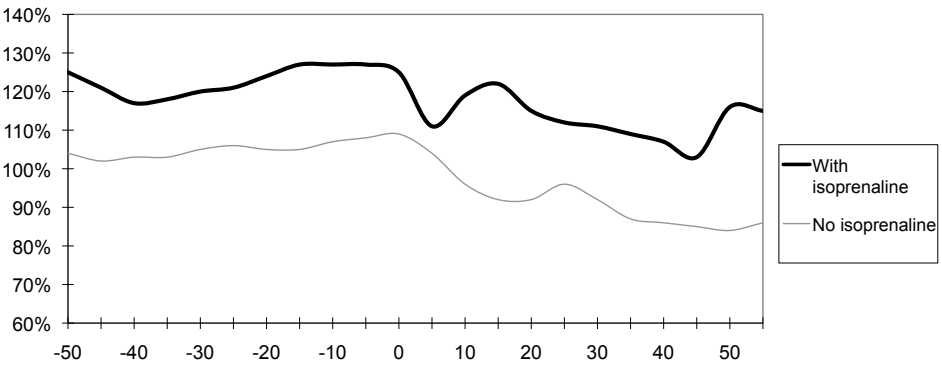


Figure 2. Effect of isoprenaline on systolic bloodpressure

DISCUSSION

In this study we evaluated the prophylactic use of isoprenaline during carotid artery stenting. We found that this treatment led to an increase in the BP at the start of the procedure and thereby prevented severe hypotension during the procedure despite the normal decline in BP after manipulation in the carotid sinus area. Bradycardia did occur less often after prophylactic Isoprenaline and none of the patients developed asystole. On the basis of these findings it can be postulated that administration of isoprenaline before carotid angioplasty will prevent cerebral blood flow from dropping below a critical level. Hemodynamic instability has been described during and after CAS, occurring in up to 30% of patients[7] and may complicate the procedure. Studies of hemodynamic alterations associated with carotid endarterectomy suggest that bradycardia is a frequent but benign perioperative finding.[8, 9] Compared with bradycardia, patients undergoing carotid interventions may have limited tolerance for hypotension. Hypotension in association with carotid endarterectomy has been shown to increase the rate of stroke[10,11] and myocardial infarction associated with the procedure.[12,13] From a retrospective analysis including the data on 500 consecutive CAS procedures performed over a 5-year period could be concluded that patients who develop hemodynamic instability are at an increased risk of periprocedural major adverse clinical events and stroke.[16] Hemodynamic instability was defined as periprocedural hypotension (systolic blood pressure <90 mmHg) or bradycardia (heart rate <60/min). Hemodynamic instability occurred during 210 procedures (42%), whereas prolonged hemodynamic instability occurred in 84 procedures (17%). Patients who developed prolonged hemodynamic instability were at a significantly increased risk of periprocedural major adverse clinical events (OR 3.05: range 1.35 to 5.23) or stroke (OR 3.34: range 1.13 to 9.90)

Atropine is used prophylactically to counteract hemodynamic instability during CAS. Atropine is a muscarine antagonist and it abolishes the effect of acetylcholine. Because it does not have an effect on the sympathetic system it only causes a modest tachycardia (80-90-beats/min).[6] Leisch et al.[14] showed that prophylactic Atropine administration prevented asystole during second balloon dilatation in 37 out of 39 patients (95%). Two patients failed to respond and developed an asystole for 4.5 and 11 seconds respectively. In their study atropine was ineffective in the treatment of hypotension. Mendelsohn et al.[15] observed that prophylactic Atropine effectively increased HR during the predilatation period. However changes in HR were not significantly different between patients who received atropine and patients without atropine. Prophylactic atropine also did not reduce the incidence of braycardia during any period.

Isoprenaline is a synthetic catecholamine. It is a β_1 and β_2 agonist and has no α effects. It increases cardiac output by three mechanisms. The HR is increased, the contractility is increased and there is a reduction of the afterload (systemic vascular resistance). BP is frequently decreased but may increase as well. There are several indications during cardiac surgery to use isoprenaline, especially for a situation in which inotropy is needed and tachycardia is not detrimental.

Hemodynamic instability, particular hypotension, during CAS is a likely contributing factor in the development of peri- and post-procedural cardiac and neurological complications. Therefore there is a need to eliminate hemodynamic instability during CAS. Our study has several weaknesses, the most important of which are the sample size and the retrospective, non-randomized design. Nonetheless, our study suggests that the prophylactic use of a vaso-active drug may help to prevent hemodynamic instability during carotid stenting, a recognized cause of severe cardiac and neurological complications. Future, larger studies are needed to definitively demonstrate the value of this treatment.

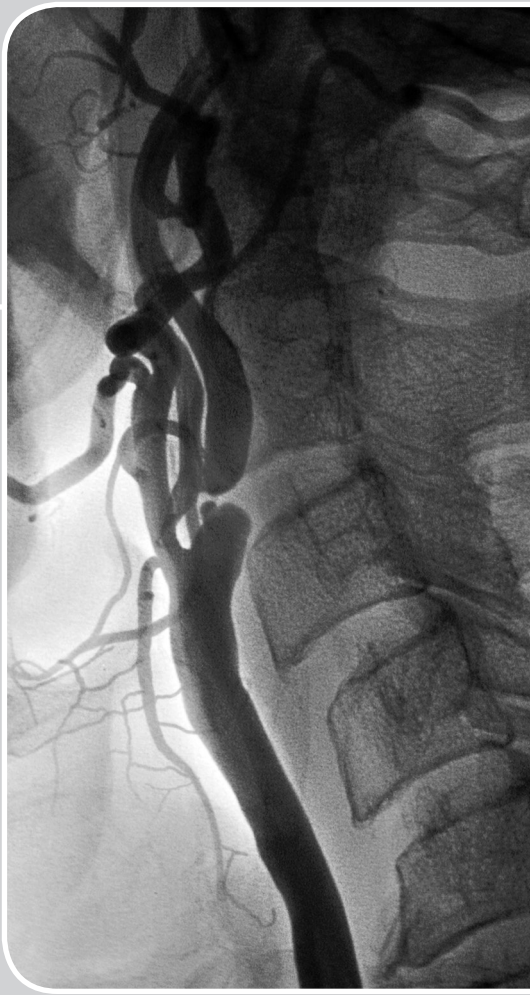
REFERENCES

1. Mathur A, Roubin GS, Iyer SS, et al. Predictors of stroke complicating carotid artery stenting. Circulation 1998; 97: 1239-1245.
2. Howell M, Krajcer Z, Dougherty K, et al. Correlation of periprocedural systolic blood pressure changes with neurological events in high-risk carotid stent patients. J Endovasc Ther 2002; 9: 810-816.
3. Mlekusch W, Schillinger M, Sabeti S, et al. Hypotension and bradycardia after elective carotid stenting: Frequency and risk factors. J Endovasc Ther 2003; 10: 851-859.
4. Qureshi AI, Suri MFK, Ali Z, et al. Carotid angioplasty and stent placement: A prospective analysis pf perioperative complications and impact of intravenously administered abciximab. Neurosurgery 2002; 50: 466-475.
5. Harrop JS, Sharan AD, Benitez RP, et al. Prevention of carotid angioplasty-induced bradycardia and hypotension with temporary venous pacemaker. Neurosurgery 2001; 49: 814-822.
6. Rang HP, Dale MM, Ritter JM. Noradrenergic transmission. Pharmacology ISBN 0443- 059748 fourth edition 1999; 130-142.
7. Qureshi AI, Luft AR, Sharma M, et al. Frequency and determinants of postprocedural hemodynamic instability after carotid angioplasty and stenting. Stroke 1999; 30: 2086-2093.
8. Margulies DR, Hestrin MA, Lemus JF, et al. Bradycardia following carotid endarterectomy. Am Surg 1993; 59: 778-581.
9. Wong JH, Findlay JM, Suarez-Almazor ME, et al. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. Neurosurgery 1997; 41: 35-43.
10. Bove EL, Fry WJ, Gross WS, et al. Hypotension and hypertension as consequences of baroreceptor dysfunction after carotid endarterectomy. Surgery 1979; 85: 633-637.
11. Owens ML, Wilson SE. Prevention of neurological complications of carotid endarterectomy. Arch Surg 1982; 117: 551-555.
12. Ranson JHC, Imparato AM, Clauss RH, et al. Factors in the mortality and morbidity associated with surgical treatment of cerebrovascular insufficiency. Circulation 1969; 39(suppl I): I-269 – I-274.
13. Riles TS, Kopelman I, Imparato AM. Myocardial infarction following carotid endarterectomy: a review of 683 operations. Surgery 1979; 85: 249-252.
14. Leisch F, Kerschner K, Hofmann R, et al. Carotid sinus reaction during carotid artery stenting: Predictors, incidence, and influence on clinical outcome. Cathet Cardiovasc Intervent 2003; 58: 516-523.
15. Mendelsohn FO, Wiessman, NJ, Lederman RJ. Acute hemodynamic changes during carotid artery stenting. Am J Cardiol 1998; 82: 1077-1081.
16. Gupta R, Abou-Chebl A, Bajzer CT et al. Rate , predictors and consequences of hemodynamic depression after carotid artery stenting. J Am Coll Cardiol 2006; 47: 1538-1543.

Chapter 8

Myocardial ischemia

Coron Artery Dis 2007; 18(6): 483-487



ABSTRACT

Purpose: Carotid artery stenting (CAS) is less invasive than endarterectomy. This study examined differences in perioperative myocardial ischemia, troponin T release and clinical cardiac events in patients undergoing CAS compared to endarterectomy.

Methods: In an observational study, CAS was performed in 24 and carotid endarterectomy in 44 patients. Prior to surgery, clinical risk factors were noted and dobutamine stress echocardiography was performed for cardiac risk assessment. Perioperative continuous 72-hour 12-lead electrocardiographic monitoring was used for myocardial ischemia detection. Troponin T (>0.03 ng/ml) was measured on postoperative day 1, 3, 7 or before discharge. Cardiac events (cardiac death or Q-wave myocardial infarction) were noted during hospital stay and during follow-up (mean: 1.2 years).

Results: No significant differences were observed between patients with CAS and endarterectomy in terms of baseline clinical characteristics, dobutamine stress echocardiography results and cardiovascular medication. Perioperative myocardial ischemia was detected in 9 patients (13%), perioperative troponin T release in 7 patients (10%), early cardiac events in 1 patient (1%) and late cardiac events in 3 patients (4%). Significantly less perioperative myocardial ischemia was observed in patients with CAS compared to endarterectomy (0% versus 21%, p=0.02). Troponin T release was also significantly lower in CAS, compared to endarterectomy (0% versus 16%, p=0.04). Early (0% versus 2%, p=0.5) and late (0% versus 7%, p=0.2) cardiac events were lower after CAS, compared to endarterectomy, although these differences were not significant.

Conclusions: CAS is associated with a lower incidence of perioperative myocardial ischemia and troponin T release, compared to endarterectomy

INTRODUCTION

Stroke is the third leading cause of death in the United States, behind heart disease and cancer[1]. In the year 2003, about 273 000 Americans died due to stroke as underlying or contributing cause [1]. Randomized clinical trials have established the efficacy of carotid endarterectomy in preventing stroke in patients with atherosclerotic carotid stenosis [2-8]. However, carotid endarterectomy has been contraindicated in patients at increased predicted perioperative risk of stroke or death[9]. In these patients, stenting of the carotid artery is a reasonable alternative.

The advantages of carotid artery stenting (CAS) compared to endarterectomy include the use of locoregional anesthesia, reduced tissue injury, reduced wound complications and shorter hospital stay[10]. In addition, the incidence of procedure-related stroke during CAS has reduced considerably with advances in embolic protection devices,[11-15]. Limited information is available about cardiovascular outcome in patients undergoing either CAS or endarterectomy. More invasive surgery and surgical stress may be associated with increased perioperative myocardial ischemia due to a mismatch in myocardial oxygen supply and demand. Prolonged myocardial ischemia may lead to myocardial injury that poses the patient at subsequent increased risk of cardiovascular events[16]. Therefore, CAS may be superior to carotid artery endarterectomy in the prevention of cardiovascular events.

This study reports the differences in perioperative myocardial ischemia, perioperative troponin T release and early and late cardiovascular events in patients with CAS as compared to carotid artery endarterectomy.

METHODS

A total of 68 intermediate to high risk cardiovascular patients underwent elective CAS or endarterectomy at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period 2005 to 2006. The study was performed with informed consent of all patients and approved by the hospital's ethics committee. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block and atrial fibrillation were excluded. Patients who participated in clinical intervention trials in or outside the Erasmus Medical Center were also excluded. At study enrolment, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥140/90 mmHg), diabetes (fasting glucose ≥7.0 mmol/L, or insulin therapy), renal failure (serum creatinine ≥ 2.0 mg/dL (177 μmol/L)), smoking and a history of cerebrovascular events. β-Blockers were considered to achieve resting heart rates of 60-65 beats per minute. Before surgery, patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease.

Surgery

Surgery was performed by experienced surgeons and interventional physicians. Patients with transient ischemic attack or non-disabling stroke within 3 months before enrolment and/or with carotid artery stenosis ≥70% as confirmed by catheter angiography or magnetic resonance angiography were considered for CAS or carotid endarterectomy. CAS was carried out through the femoral route with generally available stents and protection devices. Locoregional and a combination of locoregional and general anesthesia were used for CAS and carotid endarterectomy, respectively. Inotropic agents were used in patients presenting with perioperative bradycardia. All patients received standard perioperative pain management. β-Blockers were continued postoperatively.

Assessment of perioperative myocardial ischemia and troponin T release

Patients were continuously monitored with a 10-electrode, 12-lead digital ECG recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc. Massachusetts), starting 1 day before up to 2 days after surgery. Recording lengths were 10 seconds every minute. The frequency response was 0.05 – 150Hz. Electrocardiographic data were processed by a technician and analyzed by 2 experienced cardiologists blinded to the patient's clinical data. After excluding all abnormal QRS complexes, the recordings were analyzed for ST-segment deviations. A continuous ST segment trend was generated and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting >1 minute and shifting from baseline to >0.1 mV (1 mm). The baseline ST segment level was defined as the average ST segment during a stable period (duration of 20 minutes) preceding each ischemic episode. ST segment change was measured 60 ms after the J point. If the J point fell within the T-wave, the ST segment change was measured 40 ms after that point.

Troponin T levels were measured on postoperative day 1, 3, 7 or before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels since lower levels do not meet the imprecision criteria of <10%.

Heart rate and heart rate variability

Mean heart rate was calculated before, during and after surgery. Heart rate variability was computed using time-domain analysis of short-term 5-minute recordings. Consecutive 5-minute recordings of 2-hour periods were obtained in a standard fashion at the evening before surgery, during the first 2-hours of surgery and at the second evening after surgery. The standard deviation of the NN intervals (SDNN (ms)) was calculated.

Clinical outcome

During a mean follow-up of 1.2 years, outpatient visits were scheduled every 3 months after discharge. Study end points were all-cause mortality and major cardiac events (cardiac death and non-fatal Q-wave myocardial infarction) during hospital stay and follow-up. Non-fatal Q-wave myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or >30 ms), and typical symptoms of angina pectoris. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. No patients were lost to follow-up.

Statistical analysis

The study group was divided according to CAS and open repair. Baseline characteristics and outcome between the two types of procedure were compared using the Student t test or chi-square test. For all tests, a p value <0.05 (two-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Out of 68 patients, 44 patients (65%) received carotid artery endarterectomy and 24 patients (35%) underwent CAS. No significant differences were observed between CAS and carotid endarterectomy in terms of baseline clinical characteristics, dobutamine stress echocardiography results and cardiovascular medication therapy (Table 1). Mean preoperative heart rate and heart rate variability was similar between CAS and carotid endarterectomy (Table 2). Duration of surgery and total fluid infusion, however, were significantly lower in patients with CAS (Table 1).

Myocardial ischemia and troponin T release

Myocardial ischemia during continuous 12-lead electrocardiography was detected in 9 patients (13%). A total of 11 episodes of myocardial ischemia were detected. The median duration of ischemic events was 61 minutes (interquartile range: 52-145 minutes) and the median ST-segment deviation was 1.9 mm (interquartile range: 1.0-3.5 mm). Troponin T release was detected in 7 patients (10%). The median troponin T value was 0.09 ng/ml (interquartile range 0.04-1.2 ng/ml). Perioperative myocardial ischemia was significantly lower in patients with CAS, compared to carotid artery endarterectomy (Table 3). Troponin T release was also significantly lower in patients with CAS, compared to carotid artery endarterectomy (Table 3).

Clinical cardiac outcome

Perioperative mortality did not occur in the study population. A perioperative non-fatal myocardial infarction was observed in one patient who received endarterectomy. A major

Table 1. Baseline characteristics of the study population (n=68).

Characteristic	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
Age (years)	66 ± 11	64 ± 11	0.5
Male gender	14 (58.3%)	34 (77.3%)	0.1
Angina pectoris	2 (8.3%)	6 (13.6%)	0.5
History of myocardial infarction	6 (25.0%)	10 (22.7%)	0.9
Previous coronary revascularization	1 (4.2%)	2 (4.5%)	0.9
History of congestive heart failure	0 (0%)	0 (0%)	-
History of cerebrovascular accident	12 (50.0%)	23 (52.3%)	0.9
History of transient ischemic attack	12 (50.0%)	21 (47.7%)	0.9
Renal failure	0 (0%)	1 (2.3%)	0.5
Diabetes	3 (12.5%)	6 (13.6%)	0.9
Hypertension	9 (37.5%)	18 (40.9%)	0.8
Hypercholesterolemia	10 (41.7%)	21 (47.7%)	0.6
Current or past smoking	15 (62.5%)	29 (65.9%)	0.8
Aspirin	22 (91.6%)	41 (93.2%)	0.8
Angiotensin-converting enzyme inhibitors	6 (25.0%)	7 (15.9%)	0.4
Beta-blockers	12 (50.0%)	31 (70.5%)	0.1
Calcium channel blockers	5 (20.8%)	10 (22.7%)	0.9
Statins	13 (54.2%)	29 (65.9%)	0.3
Stress-induced myocardial ischemia	2 (8.3%)	2 (4.5%)	0.5
Duration of surgery (hours)	1.9 ± 0.6	3.0 ± 0.9	<0.001
Fluid infusion during surgery (liters)	0.06 ± 0.1	0.2 ± 0.4	<0.001
Heart rate (beats/minute)	70 ± 14	69 ± 13	0.9

Values are expressed as mean (± SD) or number (%).

perioperative stroke with right hemiplegia occurred in one patient who received CAS. During follow-up, mortality, cardiac death, non-fatal myocardial infarction and stroke occurred in 3 (4.4%), 1 (1.5%), 2 (2.9%) and 3 (4.4%) patients, respectively. Major cardiac events during follow-up were observed in 3 patients with carotid endarterectomy, while no major cardiac events during follow-up were observed in patients with CAS (Table 3). Two out of 3 patients with late cardiac events (67%) had perioperative myocardial ischemia as detected by continuous 12-lead electrocardiography.

Table 2. Perioperative heart rate and heart rate variability.

	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
Heart rate	70 ± 13	72 ± 13	0.7
Before surgery (bpm)	69 ± 14	70 ± 12	0.9
During surgery (bpm)	71 ± 15	75 ± 14	0.4
After surgery (bpm)	70 ± 15	72 ± 13	0.8
Heart rate variability (SDNN*)			
Before surgery (ms)	49 ± 32	51 ± 29	0.9
During surgery (ms)	56 ± 40	50 ± 27	0.7
After surgery (ms)	59 ± 29	49 ± 56	0.5

*SDNN = standard deviation of the normal-to-normal RR intervals. Values are expressed as mean (± SD)

Table 3. Myocardial ischemia, troponin T release and clinical outcome after carotid artery stenting or carotid artery endarterectomy.

	Carotid artery stenosis (n=68)		
	Stenting (n=24)	Open (n=44)	P value
ST-segment changes*	0 (0%)	9 (20.5%)	0.02
Before surgery	0 (0%)	1 (2.3%)	0.5
During surgery	0 (0%)	5 (11.4%)	0.09
After surgery	0 (0%)	5 (11.4%)	0.09
Troponin T release	0 (0%)	7 (15.9%)	0.04
Myocardial injury†	0 (0%)	9 (20.5%)	0.02
Perioperative mortality	0 (0%)	0 (0%)	-
Late mortality	1 (4.2%)	2 (4.5%)	0.9
Perioperative cardiac events	0 (0%)	1 (2.3%)	0.5
Late cardiac events	0 (0%)	3 (6.8%)	0.2
Perioperative stroke	1 (4.2%)	0 (0%)	0.2
Late stroke	2 (8.3%)	1 (2.3%)	0.2

*During continuous 72-hour 12-lead electrocardiography. †Composite of myocardial ischemia and troponin T release.

DISCUSSION

In this study, a lower incidence of perioperative myocardial ischemia and troponin T release was observed in patients with CAS compared to endarterectomy, despite comparable baseline characteristics. Perioperative and late cardiac events were not observed in patients with CAS, but did occur in patients with carotid endarterectomy.

The dominance held by carotid artery endarterectomy is currently challenged by CAS. Numerous studies have expressed concerns about the safety of CAS. Although perioperative stroke in CAS is a leading complication, substantial progress in safety has been made due to embolic protection devices. At our institution, patients scheduled for CAS more often presented with a history of myocardial infarction and stress induced ischemia, while patients scheduled for endarterectomy more commonly presented with angina pectoris. These differences, however, were not significant. Most of the intermediate to high-risk cardiovascular patients at our institution received endarterectomy, which is still considered as gold-standard.

An important finding of this study was that the incidence of subclinical myocardial ischemia and injury was lower in patients undergoing CAS, compared to endarterectomy. Favourable results have been reported of CAS among patients with severe cardiac disease. In a study of 170 patients, in whom 92% had angiographically proven coronary artery disease, no deaths or myocardial infarctions were observed at 30 days [17]. In a retrospective study of 167 patients with cardiac disease, CAS followed by open heart surgery was associated with a lower incidence of myocardial infarction, compared to combined endarterectomy and open heart surgery (3% versus 13%, p=0.06) [18] . Finally, a lower incidence of troponin I release has also been shown in patients undergoing CAS, as compared to endarterectomy [19].

These results are in contrast to a study that included 21 high cardiac risk patients, in whom the incidence of perioperative myocardial infarction and congestive heart failure was non-significantly higher in CAS, compared to endarterectomy [20]. The authors discussed that additional strain on the heart due to bradycardia and lower coronary perfusion pressure may have resulted in adverse cardiac events in the CAS treatment group. We observed similar perioperative heart rates between the two treatment groups. Inotropic agents were used in patients presenting with perioperative bradycardia. However, surgery duration and total fluid infusion were significantly increased in patients undergoing endarterectomy. Invasive surgical procedures have been associated with significant changes in mean arterial pressure, cardiac output, systemic vascular resistance and significant increases in blood lactate, catecholamine and arterial pH [21,22]. Increased sympathetic activity associated with invasive procedures may lead to a mismatch in oxygen supply and demand. Prolonged myocardial ischemia can lead to myocardial injury and subsequent cardiac events [16]. Indeed, 2 out of 3 patients with late cardiac events had perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring.

Several limitations should be noted. First, owing to the small number of patients in each treatment group, the results should be interpreted cautiously. Second, treatment was not randomly assigned to patients. However, the two treatment groups were comparable in baseline characteristics and may not explain the large differences in perioperative myocardial ischemia and troponin T release. Third, because no cardiovascular events occurred in patients with CAS, adjusted relative risk ratios could not be calculated. Fourth, follow-up was relatively short. Future studies should assess cardiovascular outcome beyond 1.2 years of follow-up.

In conclusion, the results of this contemporary study showed that patients with CAS have a lower incidence of perioperative myocardial ischemia and troponin T release, compared to carotid endarterectomy.

REFERENCES

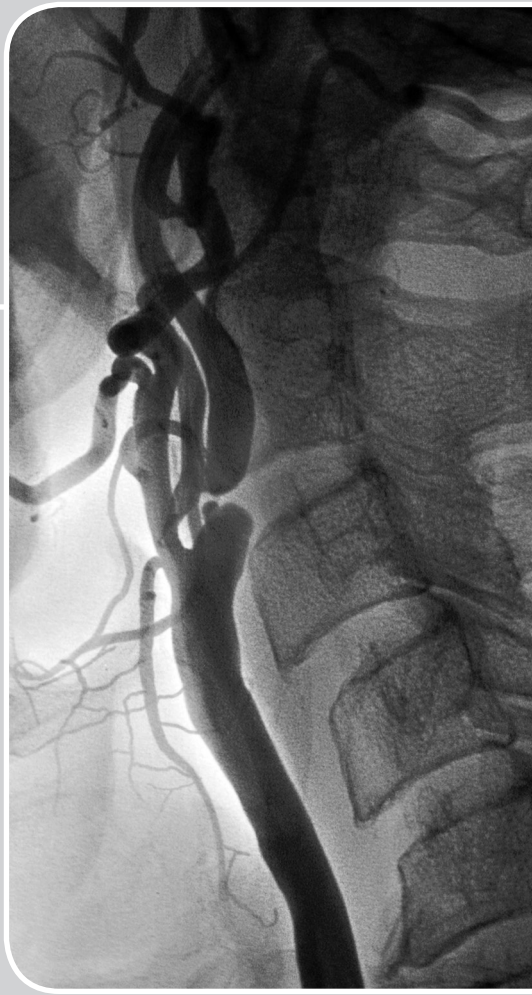
1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006 ;113: e85-151.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445-453.
3. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998; 339: 1415-1425.
4. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993; 328: 221-227.
5. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995; 273: 1421-1428.
6. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. JAMA 1991; 266: 3289-3294.
7. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363: 1491-1502.
8. European Carotid Surgery Trial. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC ECST. Lancet 1998; 351: 1379-1387.
9. Biller J, Feinberg WM, Castaldo JE, et al. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. Circulation 1998; 97: 501-509.
10. Coward LJ, Featherstone RL, Brown MM. Safety and efficacy of endovascular treatment of carotid artery stenosis compared with carotid endarterectomy: a Cochrane systematic review of the randomized evidence. Stroke 2005; 36: 905-911.
11. Yadav JS, Wholey MH, Kuntz RE, et al. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 1493-1501.
12. Mas JL, Chatellier G, Beyssen B. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. Stroke 2004; 35: e18-20.
13. CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. J Vasc Surg 2005; 42: 213-219.
14. Kastrup A, Groschel K, Krapf H, et al. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. Stroke 2003; 34: 813-819.
15. Zahn R, Mark B, Niedermaier N, et al. Embolic protection devices for carotid artery stenting: better results than stenting without protection? Eur Heart J 2004; 25: 1550-1558.
16. Landesberg G, Luria MH, Cotev S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 1993; 341: 715-719.
17. Shawl F, Kadro W, Domanski MJ, et al. Safety and efficacy of elective carotid artery stenting in high-risk patients. J Am Coll Cardiol 2000; 35: 1721-1728.
18. Ziada KM, Yadav JS, Mukherjee D, et al. Comparison of results of carotid stenting followed by open heart surgery versus combined carotid endarterectomy and open heart surgery (coronary bypass with or without another procedure). Am J Cardiol 2005; 96: 519-523.
19. Motamed C, Motamed-Kazerounian G, Merle JC, et al. Cardiac troponin I assessment and late cardiac complications after carotid stenting or endarterectomy. J Vasc Surg 2005; 41: 769-774.
20. Kasirajan K, Matteson B, Marek JM, et al. Comparison of nonneurological events in high-risk patients treated by carotid angioplasty versus endarterectomy. Am J Surg 2003; 185: 301-304.

21. Baxendale BR, Baker DM, Hutchinson A, et al. Haemodynamic and metabolic response to endovascular repair of infra-renal aortic aneurysms. Br J Anaesth 1996 ;77: 581-585.
22. Thompson JP, Boyle JR, Thompson MM, et al. Cardiovascular and catecholamine responses during endovascular and conventional abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 1999; 17: 326-333.

Chapter 9

Single center results

Ned Tijdschr Geneeskd 2006; 150: 730-734



ABSTRACT

Purpose: In the last decade carotid stenting has been recommended as an alternative to surgical endarterectomy for patients with a symptomatic and significant stenosis of the carotid artery. This study evaluates the safety of carotid stenting.

Methods: From 1999 until 2004, 98 patients with a symptomatic and significant (≥70%) carotid artery stenosis were selected for stenting with cerebral protection in the Erasmus MC in Rotterdam, The Netherlands. Outcome measures were complications within 30 days following intervention.

Results: Four (4.1%) patients were excluded in the period between diagnosis and stenting. Thirty days after treatment the severe morbidity and mortality was 3.1% (N=3). The incidence of transient neurological complications with complete recovery was 4.1% (N=4). A dissection of the renal artery occurred in 1.0% (N=1) of the patients. Vascular damage of the internal carotid artery was not observed in any patient.

Results: This study seems to show an obvious learning curve. The three major adverse events and three of the four minor adverse events occurred in the first 47 treated patients. None of the last 47 treated patients developed major adverse events.

INTRODUCTION

Cerebrovascular accidents are a major cause of death in Western society. Approximately a quarter of brain infarcts are caused by a significant stenosis of the carotid artery. The standard treatment for symptomatic and high grade carotid plaque is surgical removal by carotid endarterectomy. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have shown that endarterectomy lowers the 5-year mortality and serious morbidity rate when compared with drug treatment.[1-3]

Over the past decade, it has also been possible to treat patients with a symptomatic carotid artery stenosis endovascular using carotid stenting (figure 1). This procedure has a number of advantages compared to carotid endarterectomy:

- stenting is less invasive and can be carried out under local anaesthetic
- it avoids neck dissection with the risk of damage to the cranial nerves
- upper cervical disorders can also be treated

The first studies on endovascular treatment of carotid artery stenosis were carried out using percutaneous transluminal angioplasty (PTA) only.[4-7] The concept of placing a carotid stent was developed and subsequently used in practice following the results achieved for stenting in coronary arteries.[8] Angioplasty alone can lead to dissection of the treated blood vessel or even total occlusion. Stents are inserted in order to reduce the risk of dissection and to secure the plaque to the vessel wall.[9]

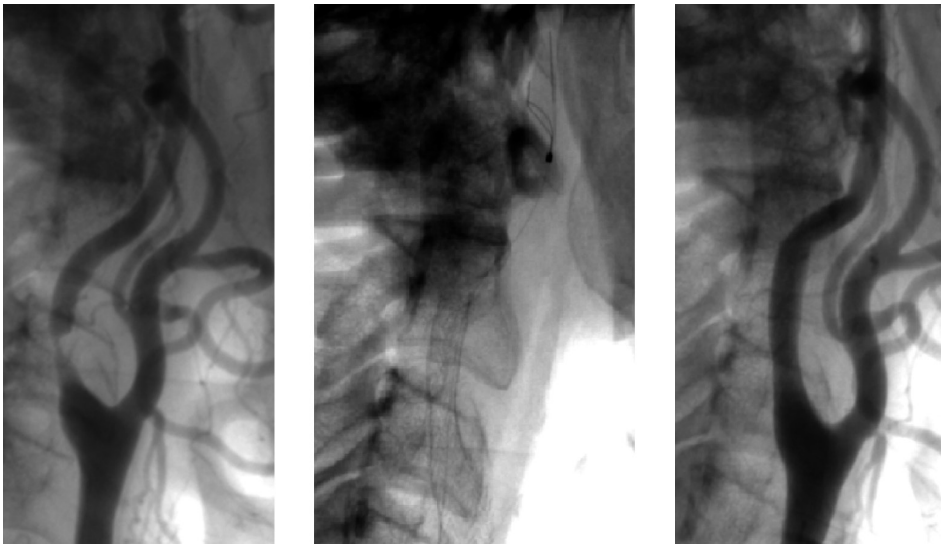


Figure 1. Carotid stenting
Left: angiogram of a 75-year old man with a symptomatic and significant internal carotid artery stenosis
Middle: the temporary filter is still visible cranially immediately after stenting
Right: the stenosis is resolved once the stent has been inserted

Debris dislodged in the carotid bifurcation during manipulation flows downstream and becomes lodged in cerebral arteries. This increases the risk of neurological complications.[10] Various techniques have been developed to catch pieces of plaque dislodged into the bloodstream during the procedure: a filter, an occlusion balloon and the "Parodi antiembolism system".[11-14] The use of these techniques is referred to as cerebral protection.

Endovascular treatment of patients with symptomatic carotid artery stenosis is becoming increasingly common in the Netherlands. It is therefore important to gain insight into this treatment. There are currently two large multi centre studies underway which compare carotid endarterectomy with carotid stenting:

- The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) in North America
- The International Carotid Stenting Study (ICSS) in Europe

The ICCS is examining the risks, benefits and cost effectiveness of both treatments in patients with high grade stenosis. The follow-up period is five years. It will be several years before the results of the ICCS and the CREST are known.[15]

This study describes the first experiences of carotid stenting with cerebral protection encountered by one of the ICSS centres with all the required expertise. The patients were treated according to a protocolled, multidisciplinary approach.

METHODS

The following end points were defined for 30 days after the procedure in this retrospective study: major complications, minor complications, peripheral complications, cranial nerve damage and myocardial infarction. Major complications are: death, cerebral infarction or cerebral haemorrhage. Minor complications were defined as transient neurological complications which resolved fully within 7 days. Peripheral complications were defined as damage to a blood vessel other than the carotid artery or a complication involving a haemorrhage. In addition to the results for stenting, the results for endarterectomy were also evaluated according to the method described above.

Patients with significant (≥ 70%) and symptomatic carotid stenosis were eligible for carotid stenting or endarterectomy. Patients with severe tortuosity of the carotid artery, or a suspected new thrombosis of the carotid artery were not eligible for treatment by carotid stenting for technical reasons. All patients were informed of the potential risks involved in carotid stenting before the procedure was carried out. Seventeen patients were selected for carotid stenting because they had an absolute or relative contraindication for endarterectomy (status following radiation treatment or neck surgery). Seventy-eight patients were eligible for stenting at their own request following an outpatient consultation. Patients were not treated by stenting unless they had given their consent. The last 3 patients to be stented were included as part of the ICCS.

Antithrombotics were prescribed around the time of the procedure. All patients were started on 100 mg carbasalate calcium daily (to be continued lifelong, theoretically) and 5000 units of heparin were also administered to the patients during the procedure. As of the 11th patient, clopidogrel was added to the protocol to prevent stent thrombosis: a single dose of 300 mg clopidogrel was prescribed the day before the procedure. A daily dose of 75 mg clopidogrel was prescribed on the day of the procedure and every day for one month following the procedure. The procedure was monitored using Transcranial Doppler (TCD) and electroencephalography (EEG). The femoral artery was punctured using ultrasound guidance and a guidewire was inserted as far as the common carotid artery. Cerebral protection was then applied in the form of a filter, a distal occlusion balloon or the "Parodi antiembolism system" (also called "reversed flow"). The lesion was then pre-dilated using a coronary angioplasty balloon with a diameter of 3 mm, after which the stent was inserted and then post-dilated. The diameter of the post-dilation balloon was determined according to the diameter of a non-stenosed section of the internal carotid artery. The cerebral protection was removed after stenting was completed.

RESULTS

In the period from 1999 to 2004, 98 patients were selected for carotid stenting. The average age was 68 years, and 21 (21.4%) patients were female. A total of 218 patients underwent carotid endarterectomy in the same period.

In the period between diagnosis and carotid stenting, it was decided that four patients would not undergo the planned procedure. The reasons for this were the development of a total carotid artery occlusion (N=2), preprocedural cardiac ischemia (N=1) or unsuitable vascular anatomy preventing insertion of the guidewire as far the common carotid artery (N=1). For one patient (1.0%), it was not possible to apply any form of cerebral protection.

Table 1 shows the results for the 98 patients who were selected for stenting and for the 218 patients who underwent carotid endarterectomy in the same period. Three (3.1%) of the patients developed a serious complication within 30 days following the procedure. These three patients underwent carotid stenting at their own request and had no contraindication for endarterectomy. One patient died of a cerebral haemorrhage, probably as a result of hyperperfusion. Another patient became haemodynamically unstable during and following the procedure and developed an ipsilateral watershed infarction. A third patient developed an acute stent thrombosis in the period immediately following the procedure, which was followed by an ipsilateral cerebral infarction.

Four (4.1%) patients developed new, transient neurological complications which resolved fully within a few days. These four patients also underwent carotid stenting at their own request and had no contraindication for endarterectomy. Three of these four patients were haemodynamically unstable during the procedure.

Table 1. Complications occurring within 30 days following carotid stenting and endarterectomy in the period between 1999 and 2004.

	Stented patients 1 to 47	Stented patients 48 to 94	Stenting	Endarterectomy
Number of patients selected	_	_	98	218
Excluded at 2nd stage*	_	_	4	0
Major complication**	3	0	3	6
Minor complication***	3	1	4	5
Peripheral complication****	0	1	1	5
Cranial nerve neuropraxy	0	0	0	10
Myocardial infarction	0	0	0	1

The patients have been numbered in chronological order of treatment.

* Excluded in the period between diagnosis and stenting being carried out or not completed

** Death and/or stroke

*** Transient neurological complications

**** Damage to a blood vessel other than the carotid artery or complication due to haemorrhage

Manipulation of the guidewire caused a renal artery dissection in one (1.0%) patient after which a stent had to be inserted. This patient was stented as part of the ICCS. No local vessel damage was seen in the internal carotid artery.

There appeared to be an obvious learning curve. The three major and three of the four minor complications occurred in the first 47 patients to be stented. None of the forty-seven patients who were stented developed major complications. Only one patient developed a minor complication and one patient a peripheral complication.

DISCUSSION

In this retrospective study, the results from the first 98 patients eligible for carotid stenting in the Erasmus University Hospital in Rotterdam were described. The total number of major complications was 3 (3.1%). There appears to be an obvious learning curve as none of the last 47 stented patients presented with major complications.

Treatment of the narrowing of the internal carotid artery resulted in a cerebral haemorrhage in one patient, probably caused by hyperperfusion following correction of the narrowing in the carotid artery. It is quite possible that this complication would also have occurred if an endarterectomy had been carried out. One patient had a stent thrombosis directly after the procedure. As a result of this complication, the protocol was changed and extra thrombocyte aggregation inhibitors were prescribed in the form of clopidogrel around the time of the procedure. Postprocedural stent thrombosis has not occurred since that time.

One patient with a major complication and three patients with transient neurological complications became haemodynamically unstable during the procedure. Balloon dilation at the level of the carotid sinus baroreceptors provoked a vasovagal response.[16] There is no consensus as yet regarding the relevance of haemodynamic instability during carotid angioplasty.[17-19]

The main cause of complications during carotid stenting is cerebral embolisation due to the dislodgement of debris from the stenosis. Cerebral protection is used almost everywhere in order to prevent this from happening. Although no convincing evidence is available, there are indications that cerebral protection really does increase the safety of carotid stenting.[20] New cerebral ischaemic lesions were seen in our patient group following stenting with cerebral protection.[21] Another unsolved issue is which type of cerebral protection is preferable.[22]

Other studies have been carried out in recent years to evaluate carotid stenting in symptomatic patients. In one study, the amount of major complications seen among 241 symptomatic patients 30 days after the procedure was 8%.[23] No cerebral protection was applied during the procedure. Remarkably, the same learning curve was evident in this study as with our own study. Other studies have recently been published in which cerebral protection *was* applied. Thee studies show results which are comparable to those in our study. The total percentage major morbidity and mortality seen in a study carried out in 2004 on 97 patients was 2.1%.[24] This was 3.3% in a recently published study carried out on 62 symptomatic patients.[25]

Despite these results, the question remains as to whether carotid stenting really is safer than endarterectomy in patients with symptomatic carotid artery stenosis. This question has also been discussed in the Dutch Journal of Medicine, the NTvG.[26] The conclusion was that compared to endarterectomy, stenting involves a comparable risk of major complications within 30 days following the procedure.[27-30] However, the randomised studies publicised provide insufficient proof that either one of the treatment methods is best in both the long and the short term. Neither the stenting method nor the inclusion criteria used in these studies were in accordance with those used in our study. We also evaluated the results of carotid endarterectomy in our study. A more in-depth comparison of the results of stenting and endarterectomy was not carried out as almost none of the patients were stented as part of the randomised study.

Asymptomatic patients also underwent stenting in other studies. A small number of symptomatic patients with high grade carotid stenosis underwent stenting in our study. One weak aspect of our study is that it is retrospective. The randomisation of patients a part of the ICCS at the Erasmus University Hospital is to be continued further to the results of our study.

For the time being, endarterectomy is to remain the standard method of treatment for patients with symptomatic and high grade carotid artery stenosis, although the results for stenting are very promising. Further research will provide more clarity with regard to the indications for carotid stenting and the optimum procedural techniques.

REFERENCES

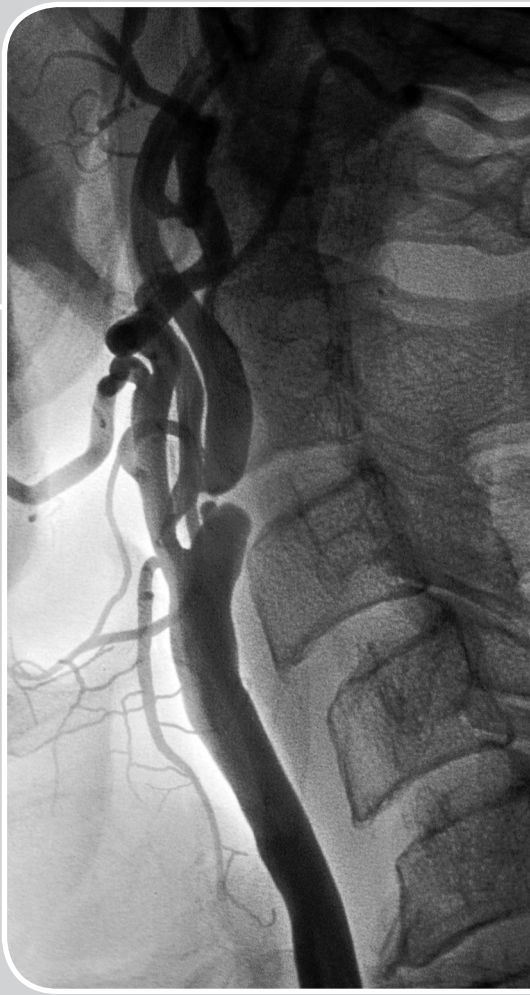
1. Dippel DWJ, Worp HB van der. Preventie van vasculaire complicaties na een TIA of beroerte: bloeddruk- en cholesterolverlagende therapie. Ned Tijdschr Geneeskunde 2004; 148: 820-824.
2. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325: 445-453.
3. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379-1387.
4. Bockenheimer SA, Mathias K. Percutaneous transluminal angioplasty in arteriosclerotic internal carotid artery stenosis. AJNR Am J Neuroradiol 1983; 4: 791-792.
5. Tsai Fy, Matovich V, Hieshima G, Shah DC, Mehringer CM, Tiu G, et al. Percutaneous transluminal angioplasty in arteriosclerotic internal carotid artery stenosis. AJNR Am J Neuroradiol 1986; 7: 349-358.
6. Becker GJ, Katzen BT, Dake MD. Noncoronary angioplasty. Radiology 1989; 170(3 Pt 2): 921-940.
7. Kachel R. Results of balloon angioplasty in the carotid arteries. J endovasc Surg 1996; 3: 22-30.
8. Serruys PW, Jaegere P de, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994; 331: 489-495.
9. Diethrich EB, Ndiaye M, Reid DB. Stenting in the carotid artery: initial experience in 110 patients. J Endovasc Surg 1996; 3: 42-62.
10. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. ICSS Investigators. Cerebrovasc Dis 2004; 18: 69-74.
11. Barry MC, Hendriks JM, Alberts G, Boomsma F, Dijk LC van, Pattynama PM, et al. Comparison of catecholamine hormone release in patients undergoing carotid artery stenting or carotid endarterectomy. J Endovasc Ther 2004; 11: 240-250.
12. Mendelsohn FO, Weismann NJ, Lederman RJ, Crowley JJ, Gray JL, Phillips HR, et al. Acute hemodynamic changes during carotid artery stenting. Am J Cardiol 1998; 82: 1077-1081.
13. Leisch F, Kerschner K, Hofmann R, Steinwender C, Grund M, Bibl D, et al. Carotid sinus reaction during carotid artery stenting: predictors, incidence, and influence on clinical outcome. Catheter Cardiovasc Interv 2003; 58: 616-523.
14. Mlekusch W, Schillinger M, Sabeti S, Nachtmann T, Lang W, Ahmadi r, et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. J Endovasc Ther 2003; 10: 851-861.
15. Transcranial Doppler monitoring in angioplasty and stenting of the carotid bifurcation. Antonius Carotid Endarterectomy, Angioplasty, and Stenting Group. J Endovasc Ther 2003; 10: 702-710.
16. Al-Mubarak N, Colombo A, Gaines PA, Iyer SS, Corvaja N, Cleveland TJ, et al. Multicenter evaluation of carotid artery stenting with a filter protection system. J Am Coll Cardiol 2002; 39: 841-846.
17. Theron JG, Payelle GG, Coskun O Huet HF, Guimaraens L. Carotid artery stenosis; treatment with protected balloon angioplasty and stent placement. Radiology 1996; 201: 627-636.
18. Al-Mubark N, Roubin GS, Vitek JJ, Iyer SS, New G, Leon MB. Effect of distal-balloon protection system on micrembolization during carotid stenting. Circulation 2001; 104: 1999-2002.
19. Adami CA, Scuro A, Spinamano L, Galvani E, Antoniucci D, Farello GA, et al. Use of the Parodi antiembolism system in carotid stenting: Italian trial results. J Endovasc Ther 2002; 9: 147-154.
20. Mas JL, Chatellier G, Beyssen B. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S). EVA-3S Investigators. Stroke 2004; 35: 18-20.
21. Flach HZ, Ouhlous M, Hendriks JM, Sambeek MR van, Veenland JF, Koudstaal PJ, et al. Cerebral ischemia after carotid interventions. J Endovasc Ther 2004; 11: 251-257.

22. Hendriks JM, Zindler JD, Dijk LC van, Sambeek MR van. Cerebral protection during percutaneous carotid intervention: which device should be used? Acta Chir Belg 2004; 104: 300-303.
23. Roubin GS, New G, IyerSS, Vitek JJ, Al-Mubarak N, Liu MW, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-yeat prospective analysis. Circulation 2001; 103: 532-537.
24. McKevitt FM, MacDonald S, Venables GS, Cleveland TJ, Gaines PA. Complications following carotid angioplasty and stenting in patients with carotid artery disease. Cerebrovasc Dis 2004; 17: 28-34.
25. Yen MH, Lee DS, Kapadia S, Sachar R, Bhatt DL, Bajzer CT et al. Symptomatic patients have similar outcomes compared with asymptomatic patients after carotid artery stenting with emboli protection. Am J Cardiol 2005; 95: 297-300.
26. Waaijer A, Lo TH, Kapelle LJ, Moll F, Mali WPThM. Behandelmogelijkheden voor patiënten met een symptomatische carotisstenose. Ned Tijdschr Geneeskd 2005; 149: 1261-1266.
27. Naylor AR, Bolia A, Abott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. J Vasc Surg 1998; 28: 326-334.
28. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVASTAS): a randomised trial. Lancet 2001; 357: 1729-1737.
29. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L, Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. J Am Coll Cardiol 2001; 39: 1589-1595.
30. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzan BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 1493-1501.

Chapter 10

Mid-term outcome

Submitted



ABSTRACT

Purpose: In his study we evaluated the incidence of mid-term stroke after carotid stenting in symptomatic patients in a Dutch university hospital. We also studied the long-term patency of the stent.

Methods: This is a retrospective analysis of the mid-term results of carotid stenting in consecutively treated patients in a period of 6 years in a Dutch university hospital, which was participating in the ICSS from 2004. Data were collected from the medical chart of the patient.

Results: 129 patients underwent carotid stenting and 133 carotid arteries were treated. From the stented patients, three (2.3%) were lost to follow-up. The mean follow-up was 2.8 years. During follow-up, the annual risk of late stroke was 0.9%. Four patients developed late stroke: two fatal strokes (one haemorrhagic, one unknown origin), one ischemic ipsilateral minor stroke on base of in-stent restenosis and one ischemic contralateral minor stroke.). Seven patients developed obstruction > 70%: two symptomatic restenosis (TIA and minor stroke), four asymptomatic restenosis and one symptomatic late stent thrombosis (TIA).

Conclusions: In this selected group of symptomatic patients the annual incidence of late stroke was in agreement with other carotid stent studies, but stent related neurological events did occur. Ongoing randomised trials will clarify if the incidence of late stroke after carotid stenting is competitive to the incidence of late stroke after carotid endarterectomy in symptomatic patients.

INTRODUCTION

Stroke is an important cause of death and permanent disability in western society.[1] In the USA, more than 150.000 persons die from stroke each year.[2] Approximately 20% of stroke is caused by carotid artery stenosis.[3] In the prevention of recurrent stroke, desobstruction of significant and symptomatic carotid stenosis has proven to be more effective than aspirin alone.[4,5] In the last decade carotid stenting is applied as a minimally invasive alternative to endarterectomy, especially in patients high-risk for carotid endarterectomy. Several studies are published with peri-operative results.[6-8] But whether it provides long term protection against stroke it is still unclear. Earlier studies with mid-term results describe a heterogeneous population from both symptomatic and asymptomatic patients.[9-12] Two randomized trials recently published there mid-term results and found little difference between carotid stenting and endarterectomy.[18,19] In this retrospective study we evaluated the incidence of mid-term stroke after carotid stenting in symptomatic patients in a Dutch university hospital. We also studied the long-term patency of the stent.

METHODS

This is a retrospective analysis of the mid term results of carotid stenting in consecutively treated patients in a period of 6 years in a Dutch university hospital, which was participating in the ICSS from 2004.[20] Data were collected from the medical chart of the patient. If follow-up was incomplete the general practitioner was contacted. The standard treatment in this period was endarterectomy, patients being selected for stenting, with a vascular surgeon, interventional radiologist, and a neurologist involved. Ten patients were stented after randomisation in the ICSS.

Patients

Patients were eligible for carotid stenting if they had had a hemispheric or retinal transient ischemic attack or a non-disabling stroke or retinal infarct, and had a stenosis of 70% to 99% in the symptomatic carotid artery, as determined by the method of North American Symptomatic Carotid Endarterectomy Trial (NASCET).[21] The presence of ipsilateral carotid stenosis of 70% or more had to be confirmed by means of catheter angiography of the carotid artery.

Patients were considered to ineligible for carotid stenting if one of the following was present: severe disability because of suffered stroke; non-atherosclerotic carotid disease; severe tandem lesions (stenosis of the proximal common carotid artery or intracranial artery that was more severe than the cervical lesion); history of bleeding disorder; uncontrolled hypertension or diabetes or a contraindication to heparin, aspirin, or clopidogrel.

All patients were screened for age, hypertension (i.e., medical therapy to control hypertension), neurological events, ischemic heart disease, renal failure (i.e., a serum creatinine of >2.0 mg/dL), diabetes mellitus, and smoking.

Carotid stenting

Vascular access was obtained through the femoral artery. Carotid stenting was carried out with the use of stents and protection devices approved by the accreditation committee.

Antiplatelet therapy

At least one week before carotid stenting 100 mg aspirin (Ascal®) a day was started and was continued lifelong. From the eleventh stented patient (November 2000), clopidogrel was added to the protocol. The day before stenting, the patient received one loading dose of 300 mg clopidogrel. Postprocedurally, the patient received 75 mg clopidogrel daily until 30 days after the procedure. During the procedure patients received 5000 U heparin.

Follow-up

The follow-up after carotid stenting was done according to protocol at 1 month, 6 months, 1 year and every year thereafter. Duplex ultrasound surveillance of the stented carotid artery was done, and the patient was systematically asked about his neurological symptoms. If the medical chart contained incomplete follow-up, the general practitioner was contacted and was asked if the patient was still alive, had developed acute neurological events, or other diseases (especially cardiovascular).

Outcome

The ECST stroke classification has been described previously.[5] Primary endpoint was major or fatal stroke and secondary endpoint was minor stroke. Primary endpoint for obstruction of the stent was a lesion of more than 70% measured by echo-duplex.

Statistics

SPSS software (version 10.1.0) was used for calculation of the mean, standard deviation and to plot Kaplan-Meier curves for primary and secondary endpoints.

RESULTS

Patient characteristics

129 patients underwent carotid stenting and 133 carotid arteries were treated. Patient characteristics are described in table 1. The mean age was 68 years and 74% of the patients were male. Three (2.3%) patients were lost to follow-up.

Table 1. Patient characteristics

Number of patients	129
Treated carotid arteries	133
Age +/- sd (years)	68 +/- 9.6
Male sex	96 (74%)
History of ipsilateral TIA or stroke	129 (100%)
Previous CEA	7 (5%)
Previous ipsilateral radiation	5 (4%)
Contralateral stenosis > 50%	50 (39%)
Hypertension	67 (52%)
Hypercholesterolemia	39 (30%)
Smoking	53 (41%)
Diabetes mellitus	20 (16%)
Renal disease	9 (7%)
Ischemic heart disease	35 (27%)

Stroke within 30 days after carotid stenting

The procedural results have already been published.[22] Self-expandable stents were placed during all 133 procedures. Cerebral protection was used during 131 procedures: filters (n=106), reverse flow (n=21), distal balloon (n=4). In two patients it was impossible to pass the stenosis with filter, and these patients were stented without cerebral protection. Eight (6.2%) patients developed neurological complications within 30 days after carotid stenting: Four (3.1%) major or fatal strokes and four (3.1%) minor strokes with complete recovery within seven days.

Mid-term stroke

From the stented patients, three (2.3%) were lost to follow-up. The mean follow-up was 2.8 years. Figure 1 and 2 show the mid-term results. During follow-up, the annual risk of stroke was 0.9%. Four patients developed late stroke: two fatal strokes (one haemorrhagic, one unknown origin), one ischemic ipsilateral minor stroke on base of in-stent restenosis and one ischemic contralateral minor stroke. Three patients reported TIA during follow-up: one patient on base

of in-stent restenosis, one patient on base of late stent thrombosis, and one patient without in-stent restenosis (table 2). In total eleven patients died from non-stroke causes.

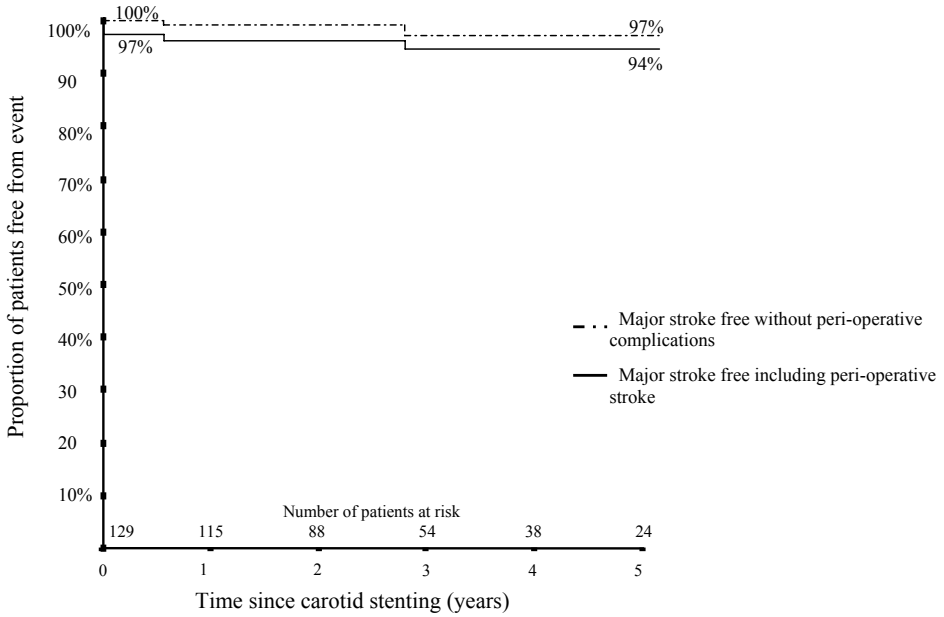


Figure 1. Incidence of major stroke on the mid-term

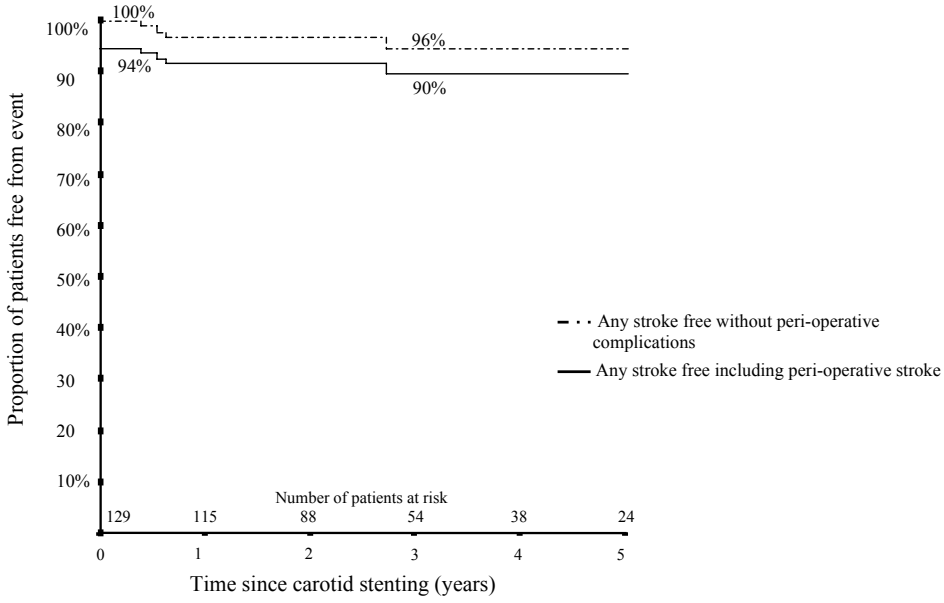


Figure 2. Incidence of any stroke on the mid-term

Table 2. Neurological events after carotid stenting during 5 years follow-up

Event	Patients (n=133)
Fatal strokes	2 (1 hemorrhagic, 1 unknown origin)
Minor ipsilateral ischemic stroke	1
Minor contralateral ischemic stroke	1
TIA	3

In-stent restenosis and surgical conversions

During five years follow-up, 90% of the patients remained free from stent obstruction of more than 70% (figure 3). Seven patients developed obstruction > 70%: two symptomatic restenosis (TIA and minor stroke), four asymptomatic restenosis and one symptomatic late stent thrombosis (TIA). The four asymptomatic restenosis and the late stent thrombosis were treated conservatively and patients remained stroke-free during further follow-up (median 15 months, range 6 – 46 months).

Two patients were treated for a symptomatic in-stent restenosis >70%. The first patient underwent again carotid stenting, but because of recurrent symptoms afterward surgical removal of the stent. The other patient the stent was surgical removed. Re-interventions were performed without complications.

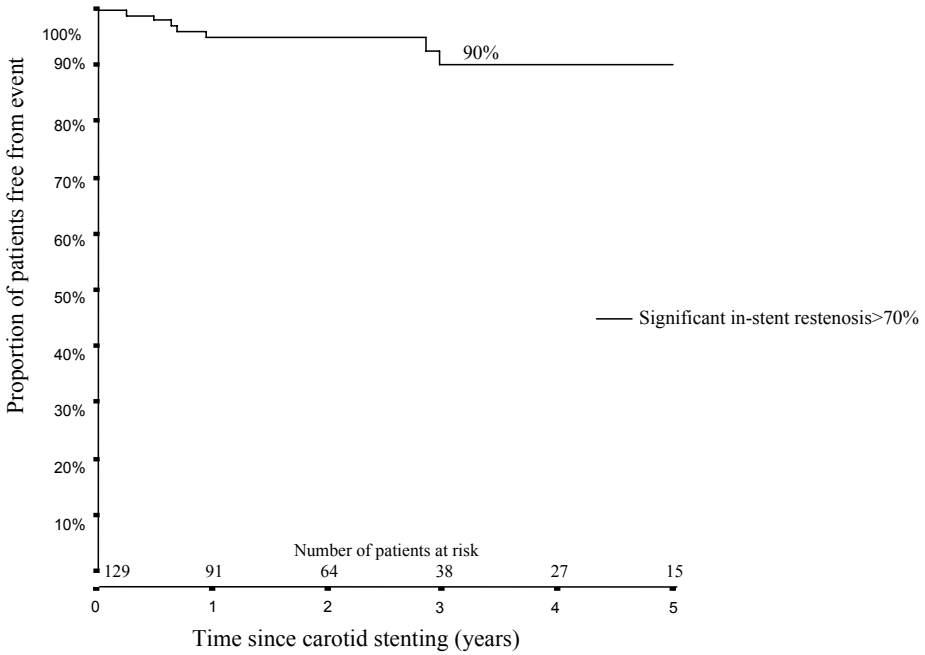


Figure 3. Incidence of significant (>70%) in-stent restenosis

DISCUSSION

The aim of the treatment of carotid stenosis is prevention of stroke and it remains to be established whether or not stenting is as effective as endarterectomy in the long- term prevention of stroke beyond the perioperative period. After carotid endarterectomy the cause of late stroke is mainly non-carotid.[23] The long-term patency rates of carotid stents have not been established in larger trials. A systematic review of multiple single center series[12] reporting restenosis rates from 3%-22%. Bergeron et al.[11] published their 11-year experience with CAS, with an average follow up of 2.7 years (1 month to 9.3 years). The restenosis rates at 6 months, 1, 2 and 4.5 years were, respectively, 1.4%, 2.3%. 3.7% and 5.9%. The annual risk of a new neurological event, new ipsilateral neurological event, any stroke, and ipsilateral stroke were 1%, 0.8%, 0.4%, and 0.2%, respectively. In this study asymptomatic lesions and the use of balloon-expandable stents were found to be predictors of in-stent restenosis. Skelly et al. evaluated 101 patients undergoing CAS.[13] > 80% in-stent restenosis occurred in 4.6%. All in-stent restenoses were asymptomatic in this series. Steinbauer et al reported on long-term follow-up of a randomized trial comparing CAS vs. CEA.[14] Although the number on enrolled patients is quite small in this series, the 1-year results revealed a trend towards a higher neurological complication rate and asymptomatic ipsilateral cerebral lesions on magnetic resonance after CAS. The final follow-up of this study was performed after 66±14.2 months in CAS patients and 64±12.1 months after CEA significantly higher rate of ipsilateral stroke after CAS (4/42) was observed compared with CEA (0/42).They observed a significantly higher restenosis of >70% and occlusion rate after CAS (6/32:19%) compared with CEA (0/29: 0%). Furthermore, a medium-grade (<70%) restenosis of the ipsilateral internal carotid artery was detected in 8/32 CAS patients (25%) and in 1/29 CEA patients (3.4%). De Donato et al. studied the influence of different stent properties (stent material and free cell area on the incidence of in-stent restenosis in their cohort of 3179 patients.[15] Although the authors published a substantial difference in early adverse event rates between different cell designs[17], uni- and multivariate analyses on long-term results showed that stent characteristics were not significantly associated with in-stent restenosis. The authors suggest that scaffolding properties of the stent play an important role in the early post-operative period, but it end when the endothelialisation of the stent is complete, and has therefore no influence on the long-term outcome.

In the series from de Donato, in-stent restenosis (≥50%) was detected in 88 patients, of which only 8 were symptomatic. Life-table analysis showed freedom from in-stent restenosis at 1, 3 and 5 years of 98.4%, 96.1%, and 94%.

AbuRahma et al. published their series on 100 consecutive patients who underwent CAS.[16] All 13 patients with ≥50% in-stent restenosis were asymptomatic. EVA-3S and SPACE found little difference in the rates of ipsilateral non-perioperative stroke occurring more than 30 days after carotid stenting compared to endarterectomy, but the length of follow-up was limited to a maximum of 4 and 2 years, respectively.[18, 19]

This retrospective study describes the mid-term results of carotid stenting in symptomatic patients. We found an annual incidence of any late stroke of 0.9% during five years follow-up.

One patient with ipsilateral minor stroke and two patients that mentioned TIA had significant restenosis. Two other strokes were not stent-related (one fatal hemorrhagic stroke, one contralateral ischemic minor stroke) and the origin of the fourth stroke (fatal stroke) was unknown. Seven patients (cumulative incidence is 10% after five years) developed obstruction of >70% of the stent during five years follow-up. One patient with a history of cervical radiation developed late stent thrombosis and a TIA three years after carotid stenting. The patient was treated conservatively and did not develop stroke during further follow-up. Patients with previous cervical radiation have worse anatomical outcome than other patients, but the incidence of late stroke seems not to be higher.[24] Close monitoring of these patients after carotid stenting is warranted.

The limitation of this study is that it is retrospective, but in this selected group of symptomatic patients the annual incidence of late stroke was in agreement with other carotid stent studies. Stent related neurological events did occur. Ongoing randomised trials[20, 25] will clarify if the incidence of late stroke after carotid stenting is competitive to the incidence of late stroke after carotid endarterectomy in symptomatic patients. Until publication of these results carotid endarterectomy remains the standard treatment for patients with symptomatic carotid stenosis.

REFERENCES

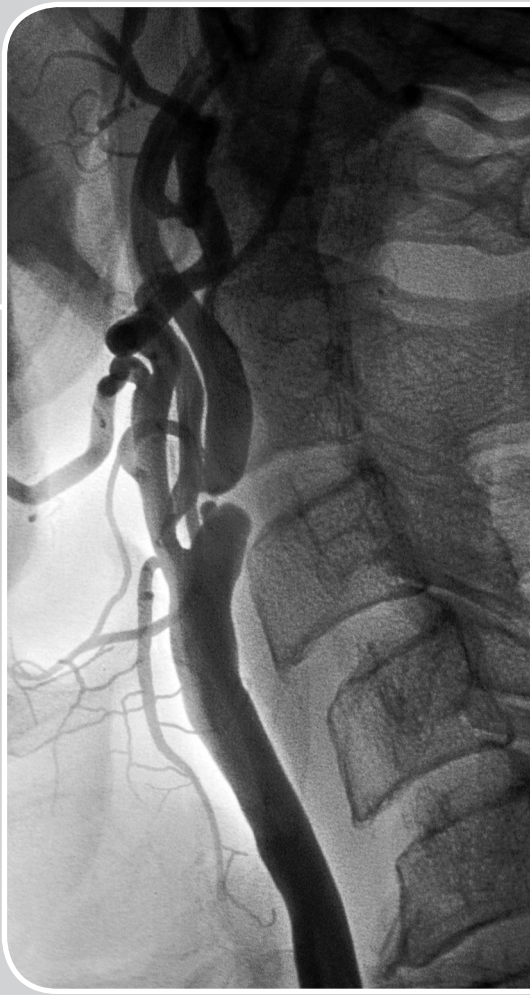
1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997 ; 349: 1269-76.
2. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke 1997; 28: 491-499.
3. Zhu CZ, Norris JW. Role of carotid stenosis in ischemic stroke. Stroke 1990; 21: 1131-1134.
4. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325: 445-53.
5. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379-1387.
6. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 1493-1501.
7. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355: 1660-71.
8. Ringleb PA, Kunze A, Allenberg JR, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368: 1239-1247.
9. Roubin GS, New G, Iyer SS, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. Circulation 2001; 103: 532-537.
10. Gröschel K, Rieker A, Schulz JB, Ernemann U, Kastrup A. Systemic review of early recurrent stenosis after carotid angioplasty and stenting. Stroke 2005; 36: 367-373.
11. Bergeron P, Roux M, Khanoyan P, Douillez V, Bras J, Gay J. Long-term results of carotid stenting are competitive with surgery. J Vasc Surg 2005; 41: 213-221; discussion 221-222.
12. Lal BK, Hobson RW, 2nd, Goldstein J, et al. In-stent recurrent stenosis after carotid artery stenting: life table analysis and clinical relevance. J Vasc Surg 2003; 38: 1162-8; discussion 1169.
13. Skelly CL, Gallagher K, Fairman RM, Carpenter JP, Velazquez OC, Parmer SS, et al. Risk factors for restenosis after carotid angioplasty and stenting. J Vasc Surg 2006; 44: 1010-1015.
14. Steinbauer MGM, Pfister K, Griendl M, Schlashetzki F, Borisch I, Schruirer G, et al. Alert for increased long-term follow-up after carotid artery stenting: Results of a prospective, randomized, single-center trail of carotid artery stenting vs. carotid endarterectomy. J Vasc Surg 2008; 48: 93-98.
15. De Donato G, Setacci C, Deloose K, Peeters P, Cremonesi A, Bosiers M. Long-term results of carotid artery stenting. J Vasc Surg 2008; 46(6): 1431-1440.
16. AbuRahma AF, Bates MC, Eads K, Armistead L, Flaherty SK. Safety and efficacy of carotid angioplasty/stenting in 100 consecutive high surgical risk patients: Immediate and long-term follow-up. Vasc Endovasc Surg 2008; 42(5): 433-439.
17. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg 2007; 33: 135-141.
18. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. Lancet Neurol 2008; 7(10): 885-892.
19. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenosis at 2 years: a multinational, prospective, randomised trial. Lancet Neurol 2008; 7(10): 893-902.
20. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004; 18: 69-74.

21. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991; 22: 711-720.
22. Zindler JD, Hendriks JM, Koudstaal PJ, Pattynama PM, van Sambeek MR, van Dijk LC. Complications within 30 days following placement of a carotid stent with cerebral protection in patients with considerable symptomatic carotid stenosis; Erasmus MC, Rotterdam, 1999-2004. Ned Tijdschr Geneeskd 2006; 150: 730-734.
23. Cunningham EJ, Bond R, Mehta Z, Mayberg MR, Warlow CP, Rothwell PM. Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. Stroke 2002; 33: 2658-2663.
24. Protack CD, Bakken AM, Saad WA, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? J Vasc Surg 2007; 45: 110-117.
25. Hobson RW, 2nd, Howard VJ, Brott TG, Howard G, Roubin GS, Ferguson RD. Organizing the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): National Institutes of Health, Health Care Financing Administration, and industry funding. Curr Control Trials Cardiovasc Med 2001; 2: 160-164.

Chapter 11

International Carotid Stenting Study

Lancet 2010; 395: 985-997



ABSTRACT

Purpose: Stents are an alternative treatment to carotid endarterectomy for symptomatic carotid stenosis, but previous trials have not established equivalent safety and efficacy. We compared the safety of carotid artery stenting with that of carotid endarterectomy.

Methods: The International Carotid Stenting Study (ICSS) is a multicentre, international, randomised controlled trial with blinded adjudication of outcomes. Patients with recently symptomatic carotid artery stenosis were randomly assigned in a 1:1 ratio to receive carotid artery stenting or carotid endarterectomy. Randomisation was by telephone call or fax to a central computerised service and was stratified by centre with minimisation for sex, age, contralateral occlusion, and side of the randomised artery. Patients and investigators were not masked to treatment assignment. Patients were followed up by independent clinicians not directly involved in delivering the randomised treatment. The primary outcome measure of the trial is the 3-year rate of fatal or disabling stroke in any territory, which has not been analysed yet. The main outcome measure for the interim safety analysis was the 120-day rate of stroke, death, or procedural myocardial infarction. Analysis was by intention to treat (ITT). This study is registered, number ISRCTN25337470.

Results: The trial enrolled 1713 patients (stenting group, n=855; endarterectomy group, n=858). Two patients in the stenting group and one in the endarterectomy group withdrew immediately after randomisation, and were not included in the ITT analysis. Between randomisation and 120 days, there were 34 (Kaplan-Meier estimate 4·0%) events of disabling stroke or death in the stenting group compared with 27 (3·2%) events in the endarterectomy group (hazard ratio [HR] 1·28, 95% CI 0·77–2·11). The incidence of stroke, death, or procedural myocardial infarction was 8·5% in the stenting group compared with 5·2% in the endarterectomy group (72 *vs* 44 events; HR 1·69, 1·16–2·45, p=0·006). Risks of any stroke (65 *vs* 35 events; HR 1·92, 1·27–2·89) and all-cause death (19 *vs* seven events; HR 2·76, 1·16–6·56) were higher in the stenting group than in the endarterectomy group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group. There was one event of cranial nerve palsy in the stenting group compared with 45 in the endarterectomy group. There were also fewer haematomas of any severity in the stenting group than in the endarterectomy group (31 *vs* 50 events; p=0·0197).

Conclusions: Completion of long-term follow-up is needed to establish the efficacy of carotid artery stenting compared with endarterectomy. In the meantime, carotid endarterectomy should remain the treatment of choice for patients suitable for surgery.

Funding: Medical Research Council, the Stroke Association, Sanofi-Synthélabo, European Union.

INTRODUCTION

Carotid endarterectomy became the treatment of choice for patients with recently symptomatic, severe carotid artery stenosis after the publication of results from large randomised trials that compared endarterectomy with best medical treatment alone.[1], [2] and [3] The potential benefit of endovascular treatment (angioplasty with or without stenting) as an alternative to carotid endarterectomy was first highlighted by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).[4] This trial showed that endovascular treatment largely avoided the main complications of the endarterectomy incision (namely cranial nerve injury and severe haematoma). However, the rate of stroke or death within 30 days after treatment was high in both groups. Since completion of CAVATAS, stenting has largely replaced angioplasty, and stents and protection devices specifically designed for the carotid artery have been introduced. Two large randomised trials comparing use of carotid stenting with endarterectomy for symptomatic stenosis have subsequently published short-term outcomes and longer term results. [5], [6], [7] and [8] The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial in symptomatic patients did not show non-inferiority of stenting compared with endarterectomy within 30 days after treatment and was stopped early for reasons of futility and cost.[6] The Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was stopped early because of a significantly lower rate of periprocedural stroke or death in the endarterectomy group than in the stenting group.[5] We report the short-term results of the International Carotid Stenting Study (ICSS), a randomised trial comparing stenting versus endarterectomy for recently symptomatic carotid artery stenosis.

METHODS

Study centres and participants

ICSS is an international, multicentre, open, randomised controlled trial designed to compare the safety and long-term efficacy of carotid stenting and endarterectomy. The protocol was published in 2004[9] and is publically available on the trial website. ICSS was approved by the Northwest Multicentre Research Ethics Committee in the UK and participating centres had to obtain site-specific approval from their local ethics committees. All patients provided written informed consent.

Participating centres had a team of investigators consisting of at least one neurologist or physician with an interest in stroke, a surgeon with experience in endarterectomy, and a physician or surgeon with expertise in carotid angiography, angioplasty, and stenting. All centres were required to hold regular multidisciplinary meetings between the investigators to discuss the management of patients with carotid stenosis. Investigators submitted their curriculum vitae and audit data that documented satisfactory training and results of carotid treatment

to the credential committee. Centres were then enrolled as either experienced or supervised centres on the recommendation of the committee. To qualify as experienced, a centre had to have a surgeon who had done at least 50 carotid operations (ten or more cases per year) and a physician or surgeon who had done a minimum of 50 stenting procedures, with at least ten cases in the carotid artery. Centres not fulfilling these criteria joined as supervised centres and their trial procedures had to be proctored by an outside surgeon or interventionist, appointed by the trial steering committee, until the proctor was satisfied that the centre was proficient in undertaking the procedure. Supervised centres were promoted to experienced centres after randomisation and treatment of 20 cases within the trial if their results were deemed acceptable by the proctor and the credential committee.

Patients were eligible for enrolment if they were older than 40 years of age and had symptomatic atheromatous carotid artery stenosis measured as more than 50% by the North American Symptomatic Carotid Endarterectomy Trial criteria[2] (or non-invasive equivalent) deemed to require treatment. Symptoms attributable to the randomised artery needed to have occurred within 12 months before randomisation.

Non-invasive imaging of the carotid artery, including duplex ultrasound, was acceptable for study entry. Catheter angiography before randomisation was not required. Exclusion criteria included major stroke without useful recovery of function, previous carotid endarterectomy or stenting in the randomised artery, contraindications for either treatment, and planned coronary artery bypass grafting or other major surgery.

At randomisation, patients had to be deemed suitable for both surgery and stenting by the investigators, who also had to be uncertain which of the two treatments was the best option for the patient. Patients unsuitable for stenting because of tortuous anatomy proximal or distal to the stenosis, visible thrombus, proximal common carotid artery stenosis, or internal carotid artery pseudo-occlusion were excluded, as were patients unsuitable for endarterectomy because of the distal site of the stenosis, a rigid neck, or risk factors for surgical complications. No record was kept of patients screened who were ineligible or treated outside the trial. It was recommended that patients randomised to stenting after non-invasive investigation, in which subsequent angiography before stenting showed one or more exclusion criteria, should have the procedure abandoned and be treated by surgery, if appropriate, or medical care alone. A similar approach was taken in patients randomised to surgery.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to receive carotid artery stenting or carotid endarterectomy by use of a computerised service provided by Oxford Clinical Trials Service Unit staff who were not involved in other parts of the trial. The allocated treatment was communicated to investigators or one of their research team by telephone or fax after they provided baseline data for the patient. Randomisation was stratified by centre with minimisation for sex, age, contralateral occlusion, and side of the randomised artery. Investigators were kept

masked about the randomisation program to prevent them anticipating the next assignment. Patients and individuals who delivered the interventions were not masked to treatment assignment. Patients were followed up by independent clinicians who were not masked to treatment assignment but who were not directly involved in delivering the randomised treatment. Adjudication of outcomes was blinded. Apart from the trial statistician and the data monitoring committee, all investigators, including the chief investigator, remained masked to the results of the trial until after recruitment was completed.

Procedures

Carotid stenting or endarterectomy was deemed initiated if the patient had been given general or local anaesthetic in preparation for the intervention, even if the procedure was subsequently abandoned before stent deployment or endarterectomy. Stents and other devices used for carotid stenting were chosen at the discretion of the interventionist but had to have a CE mark. The protocol recommended that a cerebral protection device should be used whenever the local investigator thought that one could be used safely, but this was not mandatory. A combination of aspirin and clopidogrel to cover stenting procedures was recommended. Use of heparin and atropine or similar agent during the procedure was mandatory. Surgeons were free to use standard or eversion endarterectomy. The use of local or general anaesthesia, shunts, and patches was left to the discretion of the surgeon.

Outcome events and trial safety

The protocol specified that patients should be seen before randomisation and then followed up 30 days after treatment, 6 months after randomisation, and then once a year after randomisation by a clinician who was not involved in the revascularisation procedure. At every visit, levels of impairment were assessed with the modified Rankin scale. Outcome events were reported in detail to the central office by the local neurologist or stroke physician. Major outcome events were submitted to an independent external adjudicator, who was masked to treatment allocation and who determined the cause, severity, and duration of the event. If this assessment differed from the initial assessment, a second external adjudicator reviewed the event and any differences were resolved by consensus.

The primary analysis specified in the protocol was the difference between groups in long-term rate of fatal or disabling stroke in any territory. Long-term was defined as 3 years and therefore data are not yet available for this analysis. Here, we report the first secondary analysis specified in the protocol: the differences in mortality and morbidity between groups within 30 days of carotid treatment. The main endpoint for this analysis was defined before analysis as any stroke, death, or procedural myocardial infarction. Secondary endpoints of particular interest were any stroke, any stroke or death, any stroke or procedural death, disabling stroke or death, and all-cause death. Events relating to the various components of the main endpoint,

cranial nerve palsies, and haematomas requiring surgery, transfusion, or extended hospital stay, were analysed.

Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin. Stroke was classified as fatal if death attributed to stroke occurred within 30 days of onset of stroke. Stroke or cranial nerve palsy were classified as disabling if there was an increase in the Rankin score to 3 or more, attributable to the event at 30 days after onset. The remaining non-fatal strokes were classified as non-disabling. Myocardial infarction was defined by the presence of two of the following three criteria: specific cardiac enzymes more than twice the upper limit of normal; history of chest discomfort for at least 30 min; or the development of specific abnormalities (eg, Q waves) on a standard 12-lead electrocardiograph. Death or myocardial infarction was defined as procedural if it occurred within 30 days of stenting or endarterectomy. Transient ischaemic attack was defined as an acute disturbance of focal neurological function with symptoms lasting less than 24 h attributed to cerebrovascular disease, but was not included as an outcome event in the analyses reported here.

The rate of reported events at individual centres was monitored at the central office. The independent data monitoring committee met on a regular basis to review the accumulating data and to monitor trial safety.

Statistical analysis

A large difference in outcomes between the stenting and endarterectomy groups was not expected and the sample size was calculated to provide a reasonable estimate of the treatment effect. A sample size of 1500 patients from experienced centres was chosen on the basis that this would allow a 95% CI to be measured with a width of ±3·3 percentage points for the difference in risk of disabling stroke or death between treatment groups, based on an average of 12·5% of patients having the outcome. We also calculated that this sample size would allow a 95% CI to be measured with a width ±3·0 percentage points for the secondary short-term outcome of 30-day stroke, death, or procedural myocardial infarction, on the basis of an average of 10% of patients having the outcome.

Because some patients did not receive their allocated treatment and the timing of treatment after randomisation varied, we undertook two main analyses: an intention-to-treat (ITT) analysis of all events occurring up to 120 days after randomisation and a per-protocol analysis of the procedural risk within 30 days of allocated treatment. All main analyses combined patients from experienced and supervised centres.

The ITT analysis included all randomised patients and compared those allocated to stenting with those allocated to endarterectomy, irrespective of whether they received their allocated treatment or not. All events between randomisation and 120 days were included in the ITT analysis, irrespective of whether they occurred within 30 days of treatment or not. This analysis therefore compared the initial policy of referral for stenting with referral for endarterectomy

in terms of outcome over 120 days. The period of 120 days was chosen because most patients should have had their treatment within 3 months of randomisation and their 30-day post-treatment follow-up appointment within 4 months after randomisation.

Patients with less than 120 days of follow-up and without an event were censored on the date of last follow-up. Censoring was assumed to be non-informative—ie, a censored patient was assumed to have the same risk of an outcome event as those who had complete 120-day follow-up. Kaplan-Meier methods were used to estimate 120-day probabilities of an event and subsequently the absolute risk difference between the two treatment groups and corresponding 95% CIs. Cox proportional hazard methods were used to calculate the relative difference between treatment groups (hazard ratio, HR) and 95% CIs with endarterectomy as the reference group. Log-rank tests were used to compare the two survival curves.

The 30-day per-protocol analysis of the procedural risk included only patients in whom the allocated treatment was initiated as their first ipsilateral revascularisation procedure. Patients who received the alternative revascularisation procedure as their first treatment (cross-overs), or who received no revascularisation treatment were excluded from this analysis. All outcome events occurring within 30 days after initiation of the first allocated treatment were included. We included every patient in whom the allocated treatment was initiated in the per-protocol analysis, even if the date of treatment was more than 120 days after randomisation, or if the treatment was aborted after initiation. This per-protocol analysis therefore compared the 30-day procedural risks of the two treatments in those patients in whom the allocated procedure was completed or initiated. Binomial regression methods were used to estimate the 30-day absolute risk differences and relative risk ratios together with 95% CIs. χ^2 tests were used to test for differences between the two treatment groups.

Several predefined exploratory subgroup analyses were undertaken to investigate whether the relative treatment effect for the 120-day ITT short-term composite outcome of stroke, death, or procedural myocardial infarction differed across various patient groups. Interaction tests were done with Cox proportional hazard models. All analyses were done with Stata release 11, apart from the meta-analysis, which was done with ReviewManager version 5.0. This study is registered, number ISRCTN25337470.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Figure 1 shows the trial profile. Between May, 2001, and October, 2008, 1713 patients from 50 academic centres in Europe, Australia, New Zealand, and Canada were enrolled and randomised. Three patients (stenting group, two; endarterectomy group, one) withdrew consent immediately after randomisation and were excluded from the ITT analysis. 751 (88%) of 853 patients assigned to carotid stenting and 760 (89%) of 857 patients assigned to endarterectomy were randomised at centres classified as experienced. Table 1 shows baseline characteristics of study participants.

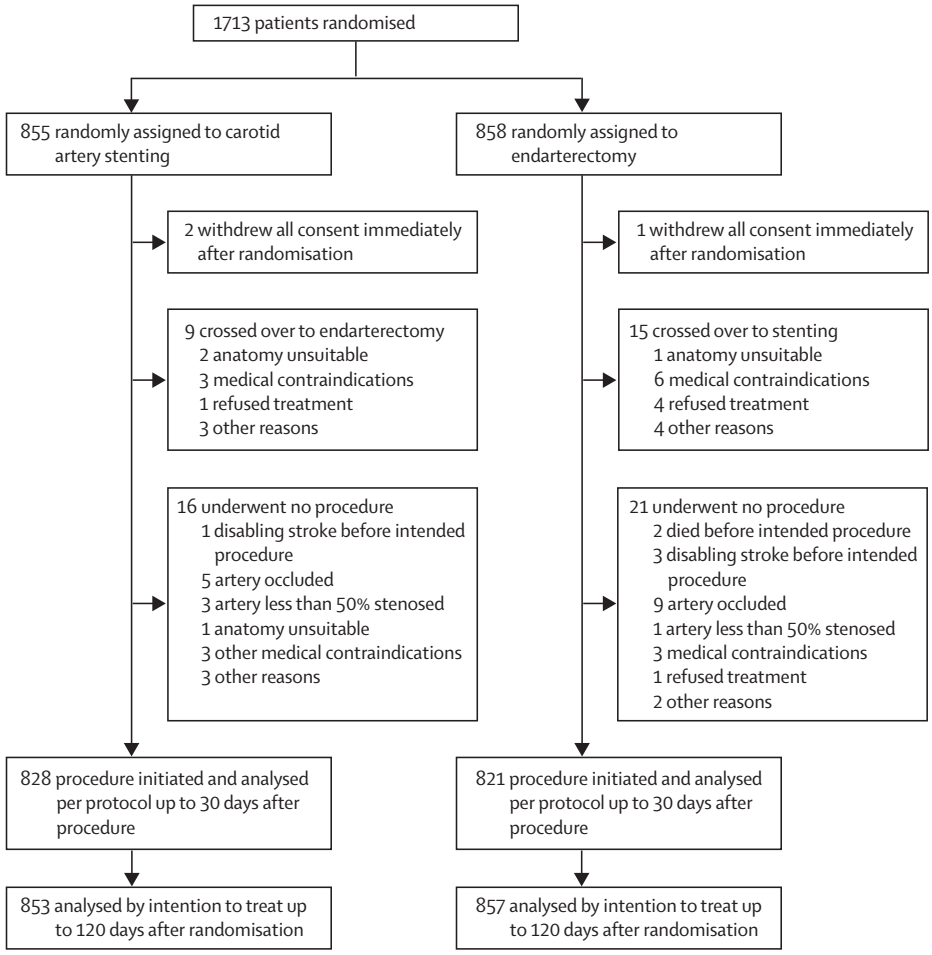


Figure 1. Trial profile
Data for the number of patients screened for eligibility were not recorded.

Most patients had their allocated treatment initiated (stenting group, n=828; endarterectomy group, n=821). Nine patients allocated to stenting crossed over to surgery without an attempt at the procedure and a further 16 had no attempted ipsilateral endarterectomy or stenting procedure (figure 1). 15 patients allocated to endarterectomy crossed over to stenting without an attempt at endarterectomy and 21 had no attempted ipsilateral procedure.

Monitoring of adverse events led to concern about the stenting results of two investigators at supervised centres. These investigators were stopped from treating further patients within the trial and their centres were suspended from randomisation. All the patients allocated to stenting (n=11, five with disabling stroke or death) or endarterectomy during the same time period (n=9, one with fatal stroke) at these centres were included in the analyses. One of the two centres subsequently restarted randomisation with a different investigator performing stenting.

Table 1. Baseline characteristics of patients

	Stenting (n=853)	Endarterectomy (n=857)
Age (years)	70 (9)	70 (9)
Sex		
Women	252 (30%)	251 (29%)
Men	601 (70%)	606 (71%)
Vascular risk factors		
Treated hypertension	587 (69%)	595 (69%)
Systolic blood pressure (mm Hg)	148·4 (24·2)	146.0 (23·6)
Diastolic blood pressure (mm Hg)	79·2 (11·7)	78.3 (12·7)
Cardiac Failure	23 (3%)	47 (5%)
Angina in last 6 months	83 (10%)	77 (9%)
Previous myocardial infarction	151 (18%)	156 (18%)
Previous CABG	109 (13%)	116 (14%)
Atrial Fibrillation	57 (7%)	59 (7%)
Other cardiac embolic source	19 (2%)	16 (2%)
Diabetes mellitus, non-insulin dependent	134 (16%)	147 (17%)
Diabetes mellitus, insulin dependent	50 (6%)	40 (5%)
Peripheral artery disease	139 (16%)	136 (16%)
Current Smoker	205 (24%)	198 (23%)
Ex-smoker	408 (48%)	424 (49%)
Treated hyperlipidaemia	522 (61%)	562 (66%)
Cholesterol (mmol/L)	4·8 (1.3)	4·9 (1.3)
Degree of symptomatic carotid stenosis*		
50-69%	92 (11%)	76 (9%)
70-99%	761 (89%)	781 (91%)

Table 1 (continued)

Degree of contralateral stenosis*		
<50%	565 (66%)	561 (65%)
50-69%	128 (15%)	142 (17%)
70-99%	105 (12%)	110 (13%)
Occluded	49 (6%)	37 (4%)
Unknown	6 (1%)	7 (1%)
Most recent ipsilateral event†		
Amaurosis fugax	148 (17%)	142 (17%)
Transient ischaemic attack	273 (32%)	303 (35%)
Ischaemic hemispheric stroke	393 (46%)	376 (44%)
Retinal infarct	26 (3%)	23 (3%)
Multiple ipsilateral symptoms prior to randomisation	330 (39%)	317 (37%)
Ipsilateral stroke prior to most recent ipsilateral event	131 (15%)	106 (12%)
Modified Rankin Score at Randomisation		
0-2	756 (89%)	744 (87%)
3-5‡	81 (10%)	99 (12%)
Unknown	16 (2%)	14 (2%)

Data are number (%) or mean (SD). CABG=coronary artery bypass graft.
* Degree of stenosis measured by North American Symptomatic Carotid Endarterectomy Trial[2] method at randomisation centre.
† If two events were reported on the same day, the more serious of the two was counted (stroke>retinal infarction>transient ischaemic attack>amaurosis fugax).
‡ In three patients the event was more than 12 months before randomisation and in two the date was unknown.
§ Some Rankin scores of 3 or more were caused by non-stroke disability.

Figure 2 shows the delay from randomisation to first initiated ipsilateral treatment in the per-protocol analysis. Median delay from randomisation to treatment was shorter in the stenting group than in the endarterectomy group, as was the delay from most recent ipsilateral event to treatment (table 2).

Of the 828 patients in whom stenting was initiated as allocated, 64 (8%) had their procedure aborted before the insertion of a stent (38 procedures were aborted because of difficulty gaining access to the stenosis, 15 were aborted because of the finding of an occluded artery, one patient had a fatal stroke, one patient had fatal myocardial infarction before completion of treatment, two had other medical complications, and further investigation in seven patients showed the artery to be <50% stenosed). Of the 62 patients whose stenting procedure was aborted after initiation and who did not have a fatal event, 37 went on to have an ipsilateral endarterectomy, whereas 25 continued with best medical care only. Only two of the 821 patients whose allocated endarterectomy was initiated had their procedure aborted (one

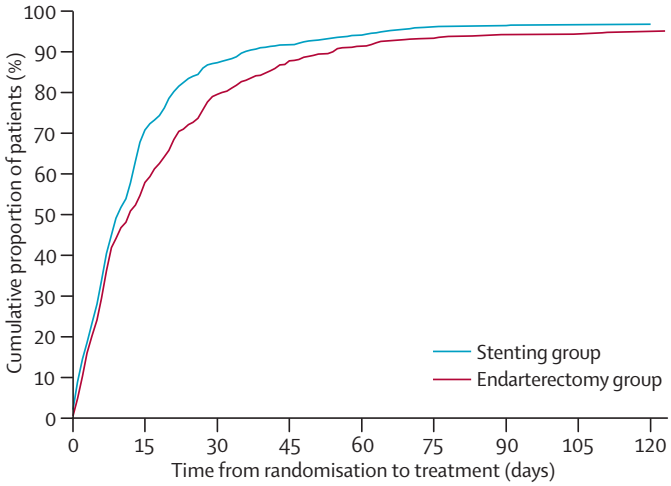


Figure 2. Time between randomization and treatment
Cumulative number of patients in whom allocated treatment was initiated per protocol plotted as a proportion of the total number randomised in each group (vertical axis), against the delay between the dates of randomisation and the treatment (horizontal axis). Only allocated per-protocol treatment dates were counted.

Table 2. Time from randomisation and from most recent ipsilateral event to allocated treatment

Baseline characteristics	Stenting (n=828)	Endarterectomy (n=821)	P-value*
Time from randomisation to treatment (days)	9 (5, 17)	11 (5, 24)	<0·001
≤ 14 days	578 (70%)	469 (57%)	
> 14 days	250 (30%)	352 (43%)	
Time from most recent event to treatment (days)	35 (15, 82)	40 (18, 87)	0·013
≤ 14 days	205 (25%)	151 (18%)	
> 14 days	623 (75%)	668 (81%)	

Data are number (%) or median (IQR) in the per-protocol analysis. Three patients in the endarterectomy group were randomised more than 12 months after onset of symptoms. The date of the most recent event was unknown in two patients (endarterectomy group).
* Mann-Whitney *U* test.

patient had an allergic reaction during general anaesthesia; the other became distressed and the endarterectomy had to be abandoned). Both patients subsequently had ipsilateral stenting.

The following stents were each used in 10% or more of the 764 patients in whom stents were inserted: Carotid Wallstent (Boston Scientific), Precision (Cordis), and Protégé (EV3). The following were each used in less than 10% of patients: Acculink (Guidant), Xact (Abbott), Smart (Cordis), Cristallo Ideale (Invatec), Exponent (Medtronic), Next Stent (Boston Scientific). Protection devices were known to have been used in 593 (72%) of 828 patients. The following protection devices were each used in 10% or more of the patients in whom stenting was attempted:

FilterWire EZ (Boston Scientific), Angioguard (Cordis), Spider FX (EV3), and Emboshield (Abbott). A range of other protection devices were each used in less than 5% of patients. In 27 patients, it was not clear whether or not a protection device was used.

In the ITT analysis, between randomisation and 120 days, there was no significant difference in the rate of disabling stroke or death between groups (stenting group, 4·0% *vs* endarterectomy group, 3·2%; table 3).

Table 3. Outcome measures within 120 days of randomisation (intention-to-treat population)

	CAS n=853	CEA n=857	HR (95% CI)	RD (95% CI)	P-value*
Primary outcome					
Stroke, death or procedural MI	72 (8·5%)	43 (5·1%)	1·73 (1·18, 2·52)	3·4 (1·0, 5·8)	0·004
Secondary outcomes					
Any stroke	65 (7·7%)	34 (4·0%)	1·97 (1·30, 2·99)	3·6 (1·4, 5·9)	0·001
Any stroke or death	72 (8·5%)	39 (4·6%)	1·91 (1·29, 2·82)	3·9 (1·5, 6·2)	0·001
Any stroke or procedural death	68 (8·0%)	35 (4·1%)	2·01 (1·33, 3·02)	3·9 (1·6, 6·1)	0·0006
Disabling stroke or death	34 (4·0%)	26 (3·1%)	1·33 (0·80, 2·21)	0·9 (-0·8, 2·7)	0·28
All cause death	19 (2·3%)	7 (0·8%)	2·76 (1·16, 6·56)	1·4 (0·3, 2·6)	0·017

Data are number of first events (Kaplan-Meier estimate at 120 days). Risk differences are calculated from Kaplan-Meier estimates at 120 days.
* Log-rank test.

The risk of stroke, death, or procedural myocardial infarction 120 days after randomisation was significantly higher in patients in the stenting group than in patients in the endarterectomy group (8·5% *vs* 5·2%), representing an estimated 120-day absolute risk difference of 3·3% (95% CI 0·9–5·7) with an HR in favour of surgery of 1·69 (1·16–2·45, log-rank p=0·006; figure 3, table 3). Most outcome events in the stent and endarterectomy groups occurred within 30 days of the first ipsilateral procedure (61 of 72 events *vs* 31 of 44 events). A few events occurred after randomisation but before the date of treatment (two patients *vs* one patient), or in patients who had no attempted ipsilateral procedure (three patients *vs* six patients), or more than 30 days after treatment but within 120 days of randomisation (six patients *vs* six patients).

Compared with endarterectomy, allocation to stenting had a greater 120-day risk of the outcome measures of any stroke, any stroke or death, any stroke or procedural death, and all-cause death (table 3). Most strokes within 120 days of randomisation were ipsilateral to the treated carotid artery and most were ischaemic (table 4). There were very few haemorrhagic strokes with only two patients in whom the cause of the stroke was uncertain. The observed treatment effect was largely driven by the higher number of non-disabling strokes in the stenting group, most of which had symptoms lasting for more than 7 days. There was an excess of fatal strokes

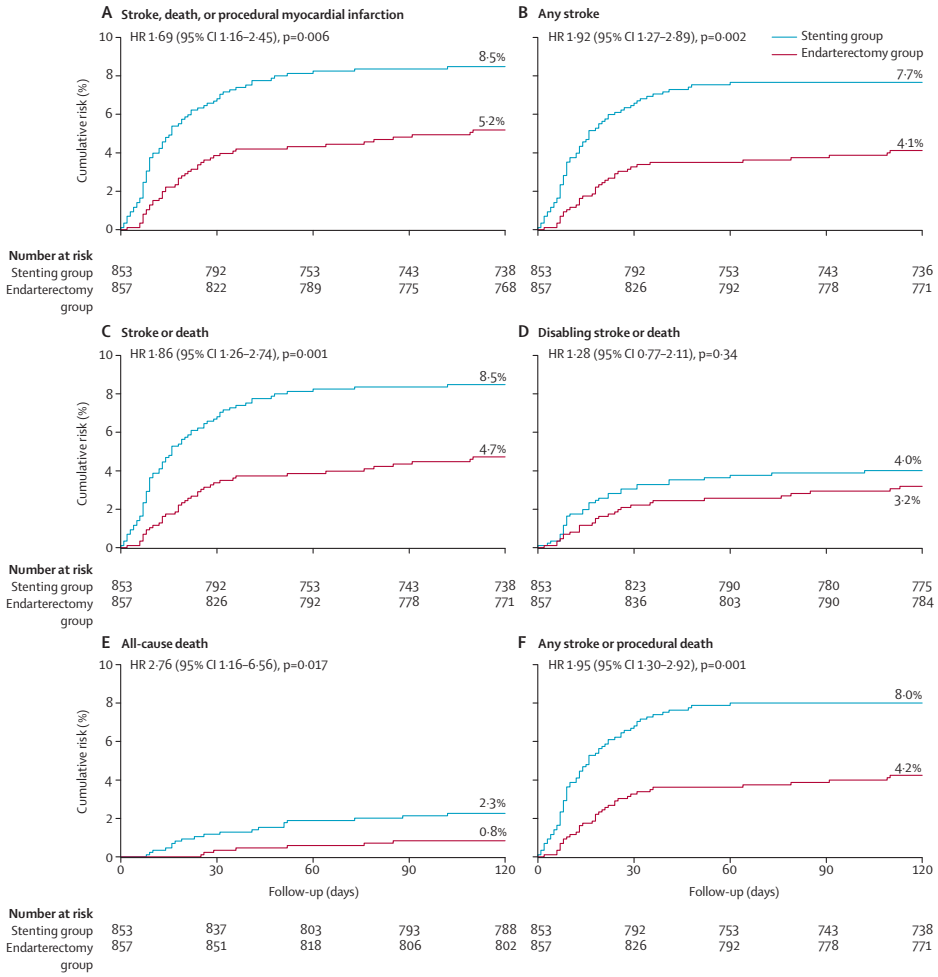


Figure 3. Kaplan-Meier estimates of cumulative incidence of various outcome measures
Data were analysed by intention to treat. The numbers above the end of the lines are the incidence estimates at 120 days after randomisation. HR=hazard ratio.

in the stenting group compared with the surgery group, but little difference in the number of patients with disabling stroke within 120 days of randomisation.

The per-protocol analysis included 1649 patients (stenting group, n=828; endarterectomy group, n=821). Results for 30-day procedural risk mirrored the results of the intention-to-treat analysis. Risk of stroke, death, or procedural myocardial infarction was higher in the stenting group than in the endarterectomy group (30-day risk 7·4% *vs* 4·0%; risk difference [RD] 3·3%, 95% CI 1·1–5·6; risk ratio [RR] 1·83, 1·21–2·77, χ^2 p=0·003; table 5). Risk of any stroke or death up to 30 days after treatment remained significantly higher in patients in whom stenting was initiated than in patients with surgery initiated, but there was no significant difference in the risk of disabling stroke or death between treatment groups. There were more fatal strokes in the

stenting group than in the endarterectomy group (eight *vs* three), but difference in the risk of death alone was no longer significant (table 5). 43 (74%) of 58 strokes in the stenting group and 12 (44%) of 27 in the endarterectomy group occurred on the day of the procedure.

Table 4. Number of outcome events recorded between randomisation and 120 days in the intention-to-treat (ITT) analysis and between initiation of treatment and 30 days after treatment in the per-protocol analysis.

	ITT analysis		Per-protocol analysis	
	Stenting n=853	Endarterectomy n=857	Stenting n=828	Endarterectomy n=821
Any stroke	65*	34	58*	27
Ipsilateral stroke	58	29	52	21
Ischaemic stroke	63	27	56	21
Haemorrhagic stroke	3	5	2	5
Uncertain pathology	0	2	0	1
Non-disabling stroke	39	14	36	11
Lasting fewer than 7 days	9	5	8	5
Lasting more than 7 days	31†	9‖	29†	6‖
Disabling stroke	17‡	19	14	14
Fatal stroke	9	2	8	3
Procedural MI	3	4	3	5
Non-fatal MI	0	4	0	5
Fatal MI	3	0	3	0
Non-stroke, Non-MI death	7	5	1	1
Cranial nerve palsy	1¶	44	1¶	44
Disabling cranial nerve palsy	1¶	1	1¶	1
Haematoma	31	50	30	50
Severe haematoma**	9	28	8	28

Data are number of first events of each type. See text for definition of per protocol.

* In two patients this was a retinal infarction. One patient had both an ischaemic and a haemorrhagic stroke.

† One patient had a subsequent fatal myocardial infarction and one patient also had a non-disabling stroke that lasted for more than 7 days.

‡ One patient had a subsequent disabling stroke.

§ Two patients subsequently died of a cause unrelated to stroke or myocardial infarction.

¶ One patient had a non-fatal myocardial infarction within 30 days of the first procedure, which was undertaken more than 120 days after randomisation. This myocardial infarction was therefore excluded from the ITT analysis (which stopped at 120 days) but was included in the per-protocol 30-day analysis that included all first ipsilateral allocated procedures.

‖ The cranial nerve palsy in this patient in the stenting group, which was initiated but aborted, occurred after endarterectomy done within 30 days of the stenting procedure.

** Severe haematoma was defined as one that required surgical evacuation or blood transfusion, or resulted in extended hospital stay.

Table 5. Outcome measures between initiation of treatment and 30 days after treatment (per-protocol analysis)

	CAS n=828	CEA n=821	Risk ratio (95% CI)	RD (95% CI)	P-value*
Primary outcome					
Stroke, death or MI	61 (7·4%)	33 (4·0%)	1·83 (1·21, 2·77)	3·3 (1·1, 5·6)	0·003
Secondary outcomes					
Any stroke	58 (7·0%)	27 (3·3%)	2·13 (1·36, 3·33)	3·7 (1·6, 5·8)	0·001
Any stroke or death	61 (7·4%)	28 (3·4%)	2·16 (1·40, 3·34)	4·0 (1·8, 6·1)	0·0004
Disabling stroke or death	26 (3·1%)	18 (2·2%)	1·43 (0·79, 2·59)	0·9 (-0·6, 2·5)	0·23
All cause death	11† (1·3%)	4 (0·5%)	2·73 (0·87, 8·53)	0·8 (-0·1, 1·8)	0·072

Data are number of first events (%). See text for definition of per protocol.

* χ^2 test.

† One patient had a fatal stroke but died more than 30 days after the procedure. The event is therefore counted in the fatal stroke outcome but not in the procedural death outcome.

Few procedural myocardial infarctions were recorded (three in the stenting group, all of which were fatal, compared with five in the endarterectomy group). Cranial nerve palsies were almost completely avoided by stenting (table 4; RR 0·02, 95% CI 0·00–0·16, p<0·0001). The one cranial nerve palsy recorded in the stenting group occurred as a complication of an endarterectomy done within 30 days of stenting. This patient and one additional patient in the endarterectomy group required percutaneous endoscopic gastrostomy feeding as a result of the cranial nerve palsies, which were classified as disabling. There were also fewer haematomas of any severity in the stenting group than in the endarterectomy group (table 4; RR 0·59, 0·38–0·93, p=0·0197), and fewer severe haematomas requiring surgical intervention, blood transfusion, or extended hospital stay (table 4; RR 0·28, 0·13–0·62, p=0·0007).

A post-hoc sensitivity analysis was undertaken to examine if the results of the per-protocol analysis were affected by inclusion of patients in whom the allocated procedure was initiated but not completed. Exclusion of the 64 patients allocated to stenting and two patients allocated to endarterectomy in whom the procedures were aborted after initiation—ie, including only patients in whom the allocated procedure was completed as planned—made little difference to the results (30-day risk of stroke, death, or procedural myocardial infarction 7·6% in the stenting group *vs* 4·0% in the endarterectomy group; RD 3·6%, 95% CI 1·3–5·9; RR 1·88, 1·24–2·86, p=0·002).

We undertook exploratory analyses of the composite outcome of stroke, death, or procedural myocardial infarction for predefined subgroups (figure 4). These analyses suggested that carotid stenting might have a similar risk to endarterectomy in women, but that the intervention was more hazardous than endarterectomy in men. The difference was mainly caused by a higher risk of stroke, death, or procedural myocardial infarction in women assigned to endarterectomy than in men (7·6% *vs* 4·2%). However, the difference between the hazard ratios comparing the risk of stenting with endarterectomy in men and women only reached borderline significance

(interaction p=0·071). Stenting was more hazardous, and endarterectomy less hazardous, in patients without treated hypertension at baseline than in patients with treated hypertension (figure 4).

There was also a suggestion that patients allocated to the stenting group had a similar risk of stroke, death, or procedural myocardial infarction to those allocated to endarterectomy after multiple ipsilateral symptoms, but compared with patients with only one event before randomisation, the difference in the hazard ratios only reached borderline significance (interaction p=0·055). There was no evidence that the relative increase in the hazard of an event in the stenting group compared with the endarterectomy group differed significantly

across any other subgroups.

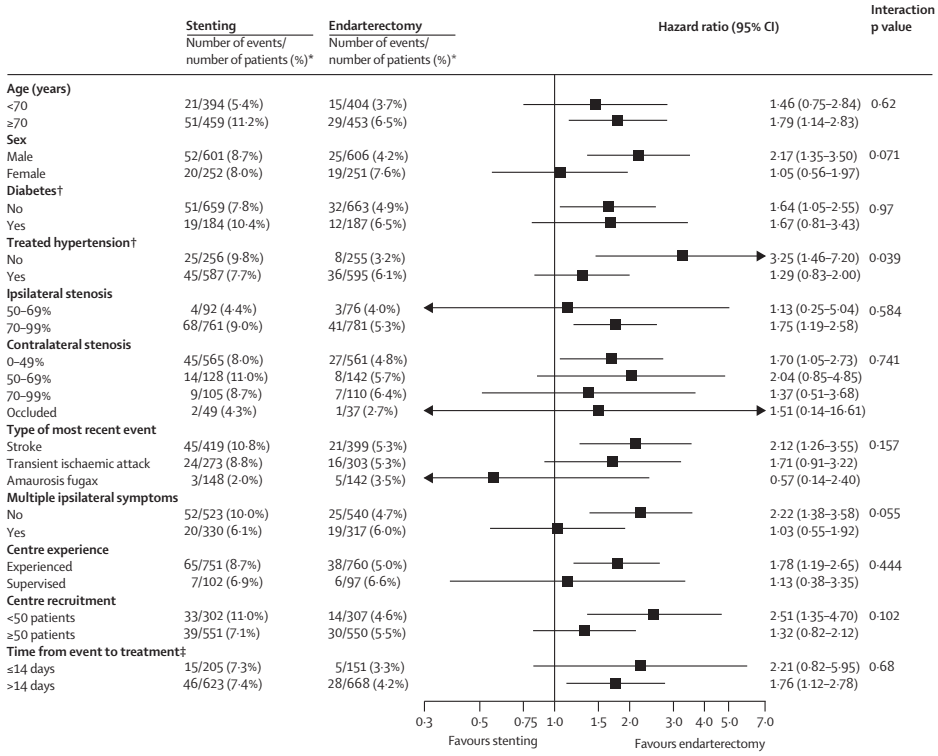


Figure 4. Subgroup analysis to compare the rates of stroke, death, or procedural myocardial infarction in different subgroups

Subgroups are defined according to baseline characteristics and analysed by intention to treat up to 120 days after randomisation, apart from time from event to treatment, which is analysed per protocol. p values are associated with treatment-covariate interaction tests. *Data are number of events of first stroke, death, or procedural myocardial infarction within 120 days of randomisation/number of patients (Kaplan-Meier estimate at 120 days). †Patients with missing information were excluded from the analysis. ‡Time from the most recent ipsilateral event before randomisation to the date of treatment, analysed per protocol for 30-day procedural events only (results are relative risk and 95% CI at 30 days after treatment).

DISCUSSION

Short-term results from this randomised controlled trial show that carotid endarterectomy is safer than carotid stenting for treatment of patients with symptomatic carotid artery stenosis. Patients allocated to stenting had a 3·3% higher risk of stroke, death, or procedural myocardial infarction within 120 days of randomisation in the ITT analysis. In the per-protocol analysis, the rate of any stroke or death within 30 days of treatment in the stenting group was more than twice the rate recorded in the endarterectomy group. The difference between groups in the per-protocol analysis was mainly attributable to an excess of non-disabling stroke in the stenting group compared with the endarterectomy group, but there were also more fatal strokes and fatal myocardial infarctions in the stenting group. By contrast, the numbers of disabling strokes in the two groups were identical and the rate of disabling stroke or death was not significantly different between groups.

Most strokes within 30 days of treatment were ipsilateral to the treated artery and most were ischaemic. Despite the recommended use of combined antiplatelet therapy with aspirin and clopidogrel before stenting and for 1 month afterwards, plus use of heparin during the procedure, there were only two haemorrhagic strokes within 30 days of stenting compared with five after endarterectomy, suggesting that dual antiplatelet therapy in this setting is safe. However, this antithrombotic regimen did not reduce ischaemic stroke sufficiently in the stenting group.

The balance of risk in favour of surgery caused by an excess of non-disabling stroke in the stenting group might be seen as partly offset by the fact that endarterectomy was associated with more cranial nerve injuries and more severe haematomas than was stenting. However, the long-term outcome of non-disabling stroke might be worse than that of non-disabling cranial nerve palsy. A recent systematic review has highlighted the increased risk of dementia associated with recurrent stroke[10] and the long-term consequences of the non-disabling strokes in our study might only become evident with further follow-up, which will include measures of disability and quality of life.

Patients who received a stent had a shorter wait from most recent stroke or transient ischaemic attack to treatment than did those who received endarterectomy, but even so only 25% of patients in the stenting group were treated within 14 days of symptoms, compared with 18% of those in the endarterectomy group. However, there was no difference in the risks of stenting compared with endarterectomy whether or not patients were treated within 14 days of symptoms or later. Several strokes occurred before treatment was initiated (five *vs* seven) and several patients developed asymptomatic carotid artery occlusion before treatment (five *vs* nine), emphasising the importance of treating carotid stenosis as soon as possible after symptoms.

The results of our study are consistent with those seen in previous randomised trials.[11] A new analysis of events occurring within 30 days of treatment in CAVATAS also showed an excess of minor strokes in patients assigned to endovascular treatment compared with those assigned

to endarterectomy, with no difference in rates of disabling stroke or death.[12] CAVATAS used outdated techniques and few patients had stents inserted. The first multicentre randomised trial of carotid stenting with modern devices designed for the carotid artery, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, mostly recruited patients with asymptomatic stenosis at high risk for endarterectomy.[13] Therefore, the trial's findings, which suggested that stenting was not inferior to endarterectomy, cannot be directly compared with our results. The EVA-3S and SPACE trials recruited only symptomatic patients and had similar protocols to our trial.[5] and [6] We have therefore combined the published 30-day safety data from EVA-3S, SPACE, and ICSS in a meta-analysis (figure 5). The summary statistic strongly favours carotid endarterectomy (odds ratio for stroke, death, or myocardial infarction within 30 days after the procedure 1·73, 95% CI 1·29–2·32). One further large randomised trial, the Carotid Revascularization Endarterectomy *vs* Stenting Trial (CREST), has completed recruitment, but has not yet published any safety data.[14]

Since CAVATAS was completed, there has been a reduction in risk of adverse outcomes associated with endovascular treatment, but the risk associated with endarterectomy has reduced to a greater extent. The risk of stroke, death, or procedural myocardial infarction in the stenting group of our trial is similar to the risk associated with carotid endarterectomy that was reported in the European Carotid Surgery Trial (ECST) in 1998.[1] By contrast, the risk of stroke, death, or procedural myocardial infarction after endarterectomy in our trial and in EVA-3S was approximately half that reported in ECST. This reduction in risk probably reflects improved anaesthetic and surgical techniques, and improved medical treatment before surgery. The low rate of myocardial infarction in our trial is consistent with improved medical treatment before surgery.

Our results are applicable to the current practice of carotid stenting at most vascular centres. The participating centres were representative of academic centres with substantial experience of treating carotid stenosis and needed to show a high standard of practice before they could join the trial. Our results could be criticised in that the experience of the interventionists in carotid stenting was less than that of the surgeons in carotid endarterectomy. However, the risk of outcome events associated with stenting was lower in inexperienced, supervised centres than in more experienced centres (figure 4) and there was no significant difference in the excess hazard of stenting compared with endarterectomy between supervised and experienced centres or between centres recruiting more or less than 50 patients; therefore, inexperience cannot explain our results. The EVA-3S trial also showed no differences in the outcomes favouring endarterectomy related to the experience of the interventionists or the number of procedures done within the trial.[5]

There are several possible explanations for the excess of non-disabling stroke seen in the stenting group compared with the endarterectomy group. Investigators who undertook follow-up assessments were not masked to treatment allocation, leading to the possibility of ascertainment bias of minor events. A post-analysis audit has confirmed that all but 77 patients were seen for follow-up by a neurologist or stroke physician, or by research nurses

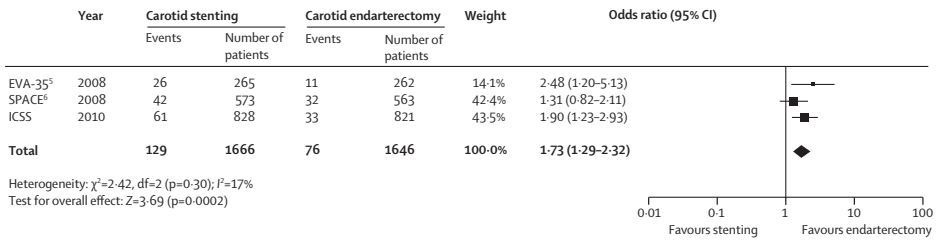


Figure 5. Meta-analysis comparing safety of carotid artery stenting with endarterectomy in the recent trials
Odds ratio for any stroke, death, or procedural myocardial infarction within 30 days of treatment in the three recent trials of carotid artery stenting versus endarterectomy including only symptomatic patients. Analysis is based on published results of per-protocol data. The large diamond represents the odds ratio and 95% CI of the combined data. The summary estimate statistic was calculated by use of a Mantel-Haenszel fixed-effect model; the centre of the diamond is the point estimate, and its width the 95% CI. EVA-3S=Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis. SPACE=Stent-Protected Angioplasty versus Carotid Endarterectomy. ICSS=International Carotid Stenting Study.

or practitioners supervised by a neurologist, not directly involved in the revascularisation procedures. A sensitivity analysis excluding the 77 patients seen for follow-up by a surgeon only, provided similar results to those of the full analysis (data not shown), making it unlikely that biased reporting affected the results. We were concerned that some short-lived events might be missed in surgical patients operated on under general anaesthesia and returned to surgical wards, whereas these events might not be missed in endovascular patients treated under local anaesthesia. However, this hypothesis is an unlikely explanation of our results, since most of the excess non-disabling strokes associated with stents lasted for more than 7 days. The conclusion that the excess in non-disabling stroke cannot be explained by bias is supported by the results of a blinded MRI subanalysis of this trial.[15] This subanalysis showed a significantly higher proportion of patients with new ischaemic lesions on MRI in the stenting group than in the endarterectomy group (50% *vs* 17%, adjusted odds ratio 5·21, 95% CI 2·78–9·79, p<0·0001).

The most likely explanation for the excess risk of non-disabling stroke associated with stenting is that it is related to instrumentation of the carotid stenosis, given that most strokes occurred on the day of treatment. Selection of patients could be important in keeping the risks of instrumentation to a minimum. Future analyses of our trial will investigate anatomical and clinical risk factors for procedural stroke, as well as the effects of stent design and protection devices.

Our exploratory analyses suggested that carotid stenting might have a similar risk to endarterectomy in women, but that the intervention was more hazardous than endarterectomy in men. However, the difference between the hazard ratios comparing stenting with endarterectomy in women and men did not reach statistical significance. The difference seemed to be largely explained by a higher risk of outcome events associated with endarterectomy in women than in men. The increased risk associated with endarterectomy in women is a consistent feature of most large studies and was also seen in the EVA-3S trial,[8] in the pooled analysis of the major carotid endarterectomy trials,[16] and in a systematic review of the published series.[17] Stenting seemed to be more hazardous, and endarterectomy less hazardous, in patients

without treated hypertension at baseline than in patients with treated hypertension, but the reasons remain unclear. However, a systematic review of predictors of stroke and death caused by carotid endarterectomy showed a similar increase in risk of stroke or death associated with hypertension (HR 1·82, 95% CI 1·37–2·41, p<0·0001) in accordance with our findings.[18]

Our results suggest that carotid endarterectomy should remain the treatment of choice for symptomatic patients with severe carotid stenosis suitable for surgery. Most patients had no complications from either procedure. Thus, some patients might still opt for stenting after being presented with the available evidence, especially if they have a strong preference for avoiding surgery. Since outcomes in the stenting group were similar to those reported after carotid endarterectomy in previous trials that compared surgery with best medical treatment alone, stenting is also likely to be better than no revascularisation in patients unwilling or unable to have surgery because of medical or anatomical contraindications.

The aim of treatment for carotid stenosis is long-term prevention of stroke. The EVA-3S and SPACE studies showed little difference between carotid stenting and endarterectomy groups in the rates of ipsilateral non-perioperative stroke occurring more than 30 days after treatment, but the length of follow-up in these studies was restricted to a maximum of 4 years and 2 years, respectively.[7] and [8] CAVATAS had a longer follow-up period and reported a higher 8-year rate of non-perioperative stroke in patients who received endovascular treatment (21·1%) than in patients who received surgery (15·4%; HR 1·66, 95% CI 0·99–2·80).[12] Most of the divergence occurred more than 2 years after randomisation, which might be partly explained by a higher incidence of restenosis after endovascular treatment than after endarterectomy.[19] However, CAVATAS included only a small proportion of patients treated by use of a stent, and the long-term rate of restenosis after stent insertion remains uncertain. Follow-up is therefore continuing in ICSS and further data will become available from the trial in due course.

CONTRIBUTORS

JE wrote the first draft of the manuscript. JD undertook the statistical analyses. RLF maintained the database and undertook database queries. LHB contributed to the analysis. All the authors listed in the writing committee made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; and also contributed to drafting the article or revising it critically for important intellectual content. The committee members and the remaining investigators listed at participating centres made contributions to the conception and design or acquisition of data. MMB had the final responsibility for the analyses and the manuscript content as the chief investigator of ICSS.

INTERNATIONAL CAROTID STENTING STUDY INVESTIGATORS

Writing committee: Jörg Ederle (Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, UK) Joanna Dobson (Medical Statistics Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK), Roland L Featherstone (Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, UK), Leo H Bonati (Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, UK), H Bart van der Worp (Department of Neurology, Rudolf

Magnus Institute of Neuroscience, University Medical Centre Utrecht, Netherlands), Gert J de Borst (Department of Vascular Surgery, University Medical Centre Utrecht, Netherlands), T Hauw Lo (Department of Radiology, University Medical Centre Utrecht, Netherlands), Peter Gaines (Sheffield Vascular Institute, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK), Paul J Dorman (Department of Neurology, Newcastle General Hospital, Newcastle upon Tyne, UK), Sumaira Macdonald (Department of Radiology, Freeman Hospital, Newcastle upon Tyne, UK), Philippe A Lyrer (Department of Neurology and Stroke Unit, University Hospital Basel, Basel University, Switzerland), Johanna M Hendriks (Department of Vascular Surgery, Erasmus Medical Center, Rotterdam, Netherlands), Charles McCollum (Cardiovascular Medicine, School of Biomedicine, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK), Paul J Nederkoorn (Department of Neurology, Academic Medical Centre, University of Amsterdam, Netherlands), Martin M Brown (Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, University College London, UK). *Steering Committee:* A Algra, J Bamford (chair), J Beard, M Bland, A W Bradbury, M M Brown (chief investigator), A Clifton, P Gaines, W Hacke, A Halliday, I Malik, J L Mas, A J McGuire, P Sidhu, G Venables. *Credential committee:* A Bradbury, M M Brown, A Clifton, P Gaines. *Data Monitoring Committee:* R Collins, A Molyneux, R Naylor, C Warlow (chair). *Outcome Event Adjudication Committee:* J M Ferro, D Thomas. *Central office staff at UCL Institute of Neurology:* L H Bonati, L Coward, J Dobson (trial statistician), J Ederle, R F Featherstone (trial manager), H Tindall, D J H McCabe, A Wallis. *Participating centres (number of enrolled patients per centre; local investigators): Australia* Austin Health, Heidelberg (46; M Brooks, B Chambers [principal investigator], A Chan, P Chu, D Clark, H Dewey, G Donnan, G Fell, M Hoare, M Molan, A Roberts, N Roberts). Box Hill Hospital (Monash University), Melbourne (25; B Beiles, C Bladin [principal investigator], C Clifford, G Fell, M Grigg, G New). Monash Medical Centre, Clayton (26; R Bell, S Bower, W Chong, M Holt, A Saunder, P G Than [principal investigator]). Princess Alexandra Hospital, Brisbane (48; S Gett, D Leggett, T McGahan [principal investigator], J Quinn, M Ray, A Wong, P Woodruff). Repatriation General Hospital, Daw Park, Adelaide (6; R Foreman, D Schultz [principal investigator], R Scroop, B Stanley). Royal Melbourne Hospital, Melbourne (57; B Allard, N Atkinson, W Cambell, S Davies [principal investigator], P Field, P Milne, P Mitchell, B Tress, B Yan). Royal Hobart Hospital, Hobart (18; A Beasley, D Dunbabin, D Stary, S Walker [principal investigator]). *Belgium* Antwerp University Hospital, Antwerp (10; P Cras, O d'Archambeau, J M H Hendriks [principal investigator], P Van Schil). A Z St Blasius, Dendermonde (5; M Bosiers [principal investigator], K Deloose, E van Buggenhout). A Z Sint Jan Brugge-Oostende, Campus Brugge, Brugges (18; J De Letter, V Devos, J Ghekiere, G Vanhooren [principal investigator]). Cliniques Universitaires St Luc, Bruxelles (1; P Astarci, F Hammer, V Lacroix, A Peeters [principal investigator], R Verhelst). Imelda Ziekenhuis, Bonheiden (3; L DeJaegher [principal investigator], A Peeters, J Verbist). *Canada* CHUM Notre-Dame Hospital, Montreal (30; J-F Blair, J L Caron, N Daneault, M-F Giroux, F Guilbert, S Lanthier, L-H Lebrun, V Oliva, J Raymond, D Roy [principal investigator], G Soulez, A Weill). Foothills Medical Centre, Calgary (4; M Hill [principal investigator], W Hu, M Hudion, W Morrish, G Sutherland, J Wong). *Finland* Helsinki University Central Hospital, Helsinki (33; A Albäck, H Harno, P Ijäs, M Kaste [principal investigator], M Lepäntalo, S Mustanoja, T Paananen, M Porras, J Putaala, M Railo, T Sairanen, L Soinne, A Vehmas, P Vikatmaa). *Germany* Otto von Guericke University, Magdeburg (9; M Goertler [principal investigator], Z Halloul, M Skalej). *Ireland* Beaumont Hospital, Dublin (4; P Brennan, C Kelly, A Leahy, J Moroney [principal investigator], J Thornton). *Netherlands* Academic Medical Centre, Amsterdam (56; M J W Koelemay, P J Nederkoorn [principal investigator], J A A Reekers, Y B W E M Roos). Erasmus Medical Centre, Rotterdam (75; J M Hendriks, P J Koudstaal [principal investigator], P M T Pattynama, A van der Lugt, L C van Dijk, M R H M van Sambeek, H van Urk, H J M Verhagen). Haga Teaching Hospitals, The Hague (45; C M A Bruijninckx, S F de Bruijn, R Keunen, B Knippenberg, A Mosch [principal investigator], F Treurniet, L van Dijk, H van Overhagen, J Wever). Isala Klinieken, Zwolle (14; F C de Beer, J S P van den Berg [principal investigator], B A A M van Hasselt, D J Zeilstra). Medical Centre Haaglanden, The Hague (3; J Boiten [principal investigator], J C A de Mol van Otterloo, A C de Vries, G J Lycklama a Nijeholt, B F W van der Kallen). UMC St Radboud, Nijmegen (13; J D Blankensteijn, F E De Leeuw, L J Schultze Kool [principal investigator], J A van der Vliet). University Medical Centre, Utrecht (270; G J de Borst, G A P de Kort, L J Kapelle [principal investigator], T H Lo, W P Th M Mali, F Moll, HB van der Worp, H Verhagen). *New Zealand* Auckland City Hospital, Auckland (40; P A Barber, R Bourchier, A Hill, A Holden, J Stewart [principal investigator]). *Norway* Rikshospitalet

University Hospital, Oslo (16; S J Bakke [principal investigator], K Krohg-Sørensen, M Skjelland, B Tennøe). *Poland* Institute of Psychiatry and Neurology (2nd Department of Neurology & Department of Neuroradiology) and Medical University of Warsaw (2nd Department of General, Vascular and Oncological Surgery), Warsaw (20; P Bialek, Z Biejat, W Czepiel, A Czlonkowska [principal investigator], A Dowzenko, J Jedrzejewska, A Kobayashi, M Lelek, J Polanski). *Slovenia* University Medical Centre, Ljubljana (12; J Kirbis, Z Milosevic, B Zvan [principal investigator]). *Spain* Hospital Clinic, Barcelona (18; J Blasco, A Chamorro [principal investigator], J Macho, V Obach, V Riambau, L San Roman). Parc Taulí Sabadell Hospital, Barcelona (33; J Branera, D Canovas [principal investigator], Jordi Estela, A Gimenez Gaibar, J Perendreu). *Sweden* Malmö University Hospital, Malmö (67; K Björses, A Gottsater [principal investigator], K Ivancev, T Maetzsch, B Sonesson). Sodersjukhuset, Stockholm (55; B Berg, M Delle, J Formgren, P Gillgren, T-B Kall, P Konrad [principal investigator], N Nyman, R Takolander). The Karolinska Institute, Stockholm (5; T Andersson, J Malmstedt, M Soderman, C Wahlgren, N Wahlgren [principal investigator]). *Switzerland* Centre Hospitalier Universitaire Vaudois, Lausanne (12; S Binaghi, L Hirt, P Michel [principal investigator], P Ruchat). University Hospital Basel, Basel (94; L H Bonati, S T Engelter, F Fluri, L Guerke, A L Jacob, E Kirsch, P A Lyrer [principal investigator], E-W Radue, P Stierli, M Wasner, S Wetzel). University Hospital of Geneva, Geneva (16; C Bonvin, A Kalangos, K Lovblad, N Murith, D Ruefenacht, R Sztajzel [principal investigator]). *UK* Addenbrookes Hospital, Cambridge (5; N Higgins, P J Kirkpatrick, P Martin [principal investigator]). K Varty Birmingham Heartlands Hospital, Birmingham (11; D Adam, J Bell, A W Bradbury, P Crowe, M Gannon, M J Henderson, D Sandler, R A Shinton [principal investigator], J M Scriven, T Wilmink). Lancashire Teaching Hospitals NHS Trust, Preston (2; S D'Souza, A Egun, R Guta, S Punekar, D M Seriki [principal investigator], G Thomson). Liverpool Royal Infirmary (21) and the Walton Centre, Liverpool (7; J A Brennan, T P Enevoldson, G Gilling-Smith [principal investigator], D A Gould, P L Harris, R G McWilliams, H-C Nasser, R White). Manchester Royal Infirmary, Manchester (2; K G Prakash, F Serracino-Inglott, G Subramanian [principal investigator], J V Symth, M G Walker). Newcastle Acute Hospitals NHS Foundation Trust, Newcastle upon Tyne (108; M Clarke, M Davis, S A Dixit, P Dorman [principal investigator], A Dyker, G Ford, A Golkar, R Jackson, V Jayakrishnan, D Lambert, T Lees, S Louw, S Macdonald, A D Mendelow, H Rodgers, J Rose, G Stansby, M Wyatt). North Bristol NHS Trust, Frenchay Hospital, Bristol (13; T Baker, N Baldwin [principal investigator], L Jones, D Mitchell, E Munro, M Thornton). Royal Free Hospital, London (1; D Baker, N Davis, G Hamilton [principal investigator], D McCabe, A Platts, J Tibballs). Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield (151; J Beard, T Cleveland, D Dodd, P Gaines, R Lonsdale, R Nair, A Nassef, S Nawaz, G Venables [principal investigator]). St George's University of London and St George's NHS Healthcare Trust, London (58; A Belli, A Clifton, G Cloud, A Halliday, H Markus [principal investigator], R McFarland, R Morgan, A Pereira, A Thompson). St Mary's Hospital, Imperial College Healthcare NHS Trust, London (13; J Chataway [principal investigator], N Cheshire, R Gibbs, M Hammady, M Jenkins, I Malik, J Wolfe). University College London Hospitals NHS FoundationTrust, London (51; M Adiseshiah, C Bishop, S Brew, J Brookes, M M Brown [principal investigator], R Jäger, N Kitchen). University Hospital of South Manchester, Wythenshawe, Manchester (58; R Ashleigh, S Butterfield, G E Gamble, C McCollum [principal investigator], A Nasim, P O'Neill, J Wong). Western Infirmary, Glasgow (5; R D Edwards, K R Lees, A J MacKay, J Moss [principal investigator], P Rogers).

CONFLICTS OF INTEREST

PG holds a research grant from Gore Medical and has a consultant and proctorship agreement with Boston Scientific. SM holds consultancy agreements with CR Bard and WL Gore. All other authors have no relevant conflicts of interest to declare.

Correspondence to: Prof Martin M Brown, Institute of Neurology, University College London, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK m.brown@ion.ucl.ac.uk

ACKNOWLEDGMENTS

This study was funded by grants from the Medical Research Council, the Stroke Association, Sanofi-Synthélabo, and the European Union. MMB's Chair in Stroke Medicine is supported by the Reta Lila Weston Trust for Medical Research. JE and RLF are supported by a grant from Medical Research Council. LHB was supported by grants from the Swiss National Science Foundation (PBBSB-116873) and the University of Basel. This work was undertaken at University College London Hospital/University College London, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

REFERENCES

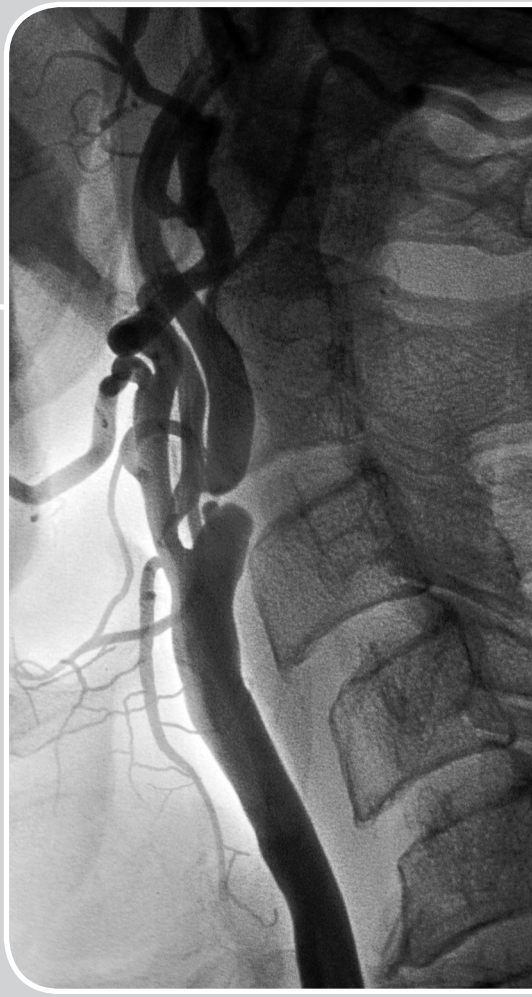
1. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379–1387.
2. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998; 339: 1415-1425.
3. Rothwell PM, Eliasziw M, Gutnikov SA, et al, for the Carotid Endarterectomy Trialists' Collaboration, Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003; 361: 107–116.
4. CAVATAS investigators, Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357: 1729–1737.
5. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355: 1660–1671.
6. The SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368: 1239–1247.
7. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurol 2008; 7: 893–902.
8. Mas JL, Trinquart L, Leys D, et al, for the EVA-3S investigators. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. Lancet Neurol 2008; 7: 885–892.
9. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004; 18: 69–74.
10. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol 2009; 8: 1006–1018.
11. Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev 2007; 4: CD000515.
12. Ederle J, Bonati LH, Dobson J, et al, on behalf of the CAVATAS investigators. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol 2009; 8: 898–907.
13. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004; 351: 493–501.
14. Lal BK, Brott TG. The Carotid Revascularization Endarterectomy vs Stenting Trial completes randomization: lessons learned and anticipated results. J Vasc Surg 2009; 50: 1224–1231.
15. Bonati LH, Jongen LM, Haller S, et al, for the ICSS-MRI study group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol 2010; 9: 353-362.
16. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ, for the Carotid Endarterectomy Trialists Collaboration, Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004; 363: 915–924.
17. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. Cerebrovasc Dis 2005; 20: 69–77.
18. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. BMJ 1997; 315: 1571–1577.

19. Bonati LH, Ederle J, McCabe DJ, et al, on behalf of the CAVATAS investigators, Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol 2009; 8: 908–917.

Chapter 12

Summary

Samenvatting



SUMMARY

This thesis evaluates the results of carotid artery stenting versus surgery in patients with a symptomatic carotid artery stenosis. In **chapter 1** a review of literature is given.

In **chapter 2** the use of Transcranial Doppler sonography before and during CAS is discussed. We concluded that it is a safe, non invasive and inexpensive technique. It gives a good impression of the collateral circulation before the intervention and can delineate a group of patients who are at risk for ischemic complications. During the angioplasty blood flow velocity and the occurrence of microemboli (HITS) can be monitored continuously. This provides the ability to compare different cerebral protection devices and to have some quality control during the procedure.

Chapter 3 gives an overview of the three different types of cerebral protection devices which are used during carotid artery stenting. A stenosis with thrombus is probably best treated with a proximal occlusion device. In patients with critical perfusion of the brain a filter device might be better tolerated. A 90-99% stenosis may be difficult to pass with a filter device and in these cases a distal occlusion device could be preferable. Another option is to perform an unprotected predilation so that afterwards a filter can be placed. However, if we should use a cerebral protection device and which device is best in which situation still remains to be determined.

In **chapter 4** we discuss that DW-MRI revealed ischemic lesions are more often after protected CAS than after CEA and that most of these lesions do not cause focal neurological deficits. More research has to be done to find out what these lesions mean for the patient. Another interesting subject would be the amount of ischemic lesions after protected versus unprotected CAS. **Chapter 5** shows that filters can be a cause of complications. Depending on the design, distal filters may cause a pressure gradient and may seriously reduce antegrade flow. This effect is marked in perforated membrane filters and almost absent in the wire mesh filter. Whenever a filter is in place during a phase of bradycardia and hypotension, it is reasonable to suppose that the cerebral blood flow may fall below a critical level. It seems reasonable to include potential flow obstruction of the filter as a criterion when selecting a particular protection device, among other recognized characteristics, such as emboli capture rate, ease of placement, and utility of the filter in various grades of ICA tortuosity.

In **chapter 6** we investigate the relationship between fluctuations in plasma adrenaline and noradrenaline in patients undergoing CEA or CAS. Although the numbers are small in this study, CAS is associated with a significantly less marked catecholamine response than CEA, likely due to differing sympathetic nervous system reactions to carotid artery clamping compared to carotid sinus stretching during CAS.

Hemodynamic instability after CEA has been linked to surgical mortality and morbidity, especially the occurrence of stroke and cardiac complications. Hemodynamic instability has also been described after CAS and may have clinical implications. Particular hypotension during

CAS is a likely contributing factor in the development of peri- and post-procedural cardiac and neurological complications. Therefore there is a need to eliminate hemodynamic instability during CAS. Our study in **chapter 7** suggests that the prophylactic use of isoprenaline, a ß-adrenergic agonist, may help to prevent hemodynamic instability during carotid stenting. Future, larger studies are needed to definitively demonstrate the value of this treatment.

In **chapter 8** the results of this contemporary study showed that patients with CAS have a lower incidence of perioperative myocardial ischemia and troponin T release, compared to carotid endarterectomy. More invasive surgery and surgical stress may be associated with increased perioperative myocardial ischemia due to a mismatch in myocardial oxygen supply and demand. Prolonged myocardial ischemia may lead to myocardial injury that poses the patient at subsequent increased risk of cardiovascular events. Therefore, CAS may be superior to carotid endarterectomy in the prevention of cardiovascular events.

In **chapter 9** the single center results of carotid stenting from 1999-2004 in the Erasmus MC were demonstrated. Thirty days after treatment the severe morbidity and mortality was 3.1%, which is similar to the results of endarterectomy in the same period. The study also showed on obvious learning curve.

In **chapter 10** we evaluated the mid-term outcome of carotid stenting in the Erasmus Medical Center. During follow-up, the annual risk of mid-term stroke was 0.9%. Four patients developed late stroke: two fatal strokes (one haemorrhagic, one unknown origin), one ischemic ipsilateral minor stroke on base of in-stent restenosis and one ischemic contralateral minor stroke. Three reported a TIA during follow-up. In this selected group of symptomatic patients the annual incidence of late stroke was in agreement with other carotid stent studies. Ongoing randomised trials will clarify if the incidence of late stroke after carotid stenting is competitive to the incidence of late stroke after carotid endarterectomy in symptomatic patients.

In **chapter 11** we discussed the results of the International Carotid Stenting Study. Short-term results show that carotid endarterectomy is safer than carotid stenting in patients with symptomatic carotid artery stenosis. Carotid artery stenting is a technique which is continually developing. Until today, major improvements have been made in technique and materials, which make carotid artery stenting safer. From the randomised clinical trials it can be concluded that stenting carries a higher risk than surgery. However, the majority of patients had no complications from either procedure. Carotid endarterectomy should be the treatment of choice for symptomatic carotid stenosis suitable for either procedure, but in patients willing to accept the increased risk of stenting or patients not suitable for carotid surgery due to medical or anatomical contraindications stenting may still be a viable option. Stenting and endarterectomy both have their place as different treatment options for carotid stenosis and should preferably complement each other, with advantages of either technique in certain patient subgroups, which need to be further identified. Better understanding of the pathophysiology of the cerebral perfusion, the plaque morphology, patient selection and the onset of neurological events should guide us to better and safer patient care. The use of CEA and CAS as complementary

therapies, while optimising medical treatment, will provide the greatest likelihood of minimising poor patient outcome.

SAMENVATTING

Dit proefschrift evalueert de resultaten van carotis stenting (CAS) versus carotis endarterïectomie (CEA) bij patiënten met een symptomatische carotisstenose. In **hoofdstuk 1** wordt een overzicht gegeven van de literatuur.

In **hoofdstuk 2** wordt het gebruik van Transcraniële Doppler Ultrasonografie (TCD) voorafgaande aan en gedurende de carotisstent procedure besproken. De techniek is veilig, niet invasief en goedkoop. Het geeft een goed beeld van de collaterale circulatie en kan patiënten identificeren die een risico hebben op ischemische complicaties. Gedurende de procedure kunnen zowel stroomsnelheden als het aantal microemboliën worden gemeten. Dit geeft de mogelijkheid om verschillende cerebrale protectie devices met elkaar te vergelijken en is het een indirecte maat voor de kwaliteit van de techniek.

Hoofdstuk 3 geeft een beschrijving van de kenmerken van de drie verschillende typen cerebrale protectie devices die gebruikt worden tijdens een carotisstent procedure. Een carotisstenose met verse thrombus kan mogelijk het beste behandeld worden met proximale occlusie. Bij patiënten met een kritische perfusie van het brein zal waarschijnlijk een filter beter worden verdragen. Maar een 90-99% stenose kan weer lastig te passeren zijn met een filter device zodat in deze gevallen een distale occlusie misschien weer de voorkeur heeft. Een andere mogelijkheid is om eerst een predilatatie te verrichten zonder bescherming waarna alsnog een filter kan worden geplaatst. Echter internationaal bestaat er nog steeds geen consensus of het gebruik van een protectie device werkelijk geïndiceerd is bij carotis stenting en welk device het meest geschikt is voor een specifieke laesie.

In **hoofdstuk 4** wordt besproken dat er na CAS meer ischemische laesies zichtbaar zijn op de DW-MRI dan na CEA. Het merendeel van deze laesies veroorzaakten geen focale neurologische uitval. Verder onderzoek zal moeten worden verricht naar wat deze laesies precies betekenen en welke gevolgen deze afwijkingen hebben voor de patiënt. Daarbij kan het interessant zijn om het aantal ischemische laesies te vergelijken bij CAS met en zonder een protectie device.

In **hoofdstuk 5** bespreken we dat filters ook een oorzaak kunnen zijn van complicaties. Afhankelijk van het ontwerp kan er een drukverval ontstaan over de filter omdat de flow door de filter wordt gereduceerd. Dit effect is het meest aanwezig bij de membraan filters en vrijwel afwezig bij een draad filter. Bij het uitkiezen van een protectie device is het te overwegen om flow obstructie als selectie criterium toe te voegen aan de al bestaande criteria, zoals permeabiliteit, gemak van positioneren en bruikbaarheid in tortueuze vaten.

In **hoofdstuk 6** onderzoeken we het verschil in adrenaline, noradrenaline en renine productie tijdens CEA en CAS. Ook al zijn de getallen klein, tijdens CAS lijkt de catecholamine productie duidelijk verminderd. Dit wordt mogelijk veroorzaakt door een verschil in reactie van het sympathische zenuwstelsel tussen het afklemmen van de halsslagader en het overstrekken van de sinus caroticum tijdens CAS.

Hemodynamische instabiliteit na CEA is gecorreleerd met morbiditeit en mortaliteit, in het bijzonder met het ontstaan van een herseninfarct of cardiale complicaties. Ook bij CAS wordt hemodynamische instabiliteit beschreven en dit heeft klinische implicaties. Onze studie in **hoofdstuk 7** suggereert dat het profylactisch toedienen van isoprenaline, een ß-adrenerge agonist, het ontstaan van hemodynamische instabiliteit mogelijk voorkomt. Grotere studies moeten de definitieve waarde van deze therapie echter nog aantonen.

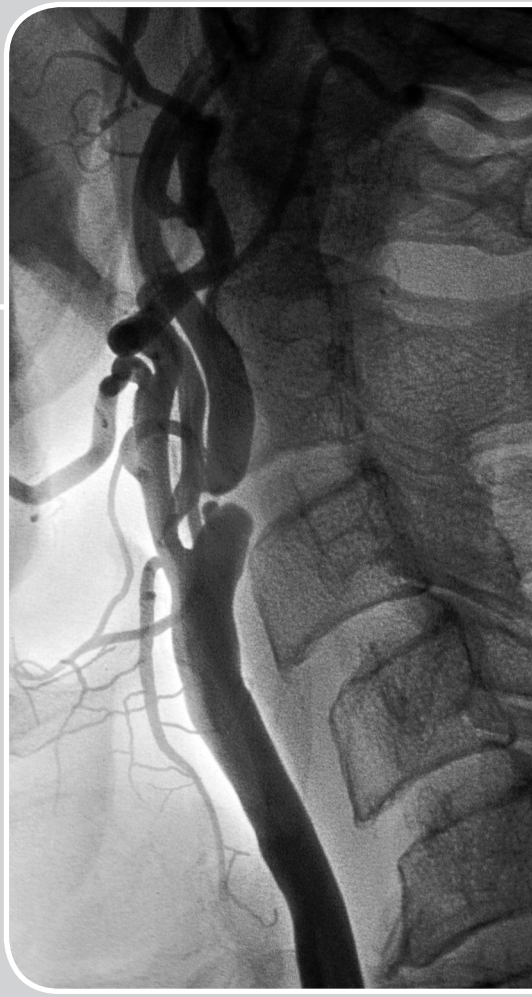
In **hoofdstuk 8** laten de resultaten zien dat patiënten na CAS een lagere incidentie hebben van perioperatieve cardiale ischemie en troponine T release in vergelijking met CEA patiënten. Invasive chirurgie en chirurgische stress zijn mogelijk geassocieerd met toegenomen perioperatieve cardiale ischemie, door een mismatch in zuurstof vraag en aanbod. Langdurige cardiale ischemie kan leiden tot myocard schade waardoor de patiënt een toegenomen risico heeft op cardiovasculaire events. Mogelijk is CAS superieur ten opzichte van CEA in het voorkomen van cardiovasculaire events.

In **hoofdstuk 9** worden de resultaten van carotisstenting van 1999 tot 2004 in het Erasmus MC getoond. De ernstige morbiditeit en mortaliteit was 3.1%, wat vergelijkbaar is met de resultaten van de operatie in dezelfde periode. De studie laat echter ook een zeer duidelijke learning curve zien.

In **hoofdstuk 10** worden de middellange termijn resultaten van het Erasmus MC besproken. Het risico op het krijgen van een herseninfarct was 0.9% per jaar. Vier patiënten ontwikkelden een infarct: twee fatale beroertes (een bloeding, en een onbekende herkomst), een ipsilateraal ischemisch klein herseninfarct op basis van een in-stent restenose en een ischemisch contralateraal klein herseninfarct. Drie patiënten kregen een TIA gedurende follow-up. Deze resultaten zijn in overeenstemming met de literatuur. Lopende gerandomiseerde studies zullen moeten laten zien of carotis stenting op de lange termijn net zulke goede resultaten heeft als een endarteriëctomie in symptomatische patiënten.

In **Hoofdstuk 11** worden de resultaten van de International Carotid Stent Study gepresenteerd. Geconcludeerd kan worden dat voor patiënten met een symptomatische carotisstenose op de korte termijn een operatie veiliger is dan een stentplaatsing. Dit is in overeenstemming met andere gerandomiseerde studies. Daarbij moet worden opgemerkt dat bij beide procedures maar weinig patiënten complicaties hadden. Op dit moment is een carotis endarterïectomie de behandeling van keuze bij een symptomatische carotisstenose die geschikt is voor beide technieken. Maar indien een patiënt zelf bereid is een hoger risico te accepteren of indien de patiënt niet geschikt is voor chirurgie vanwege ernstige comorbiditeit of anatomische contra-indicaties, dan is carotisstenting nog steeds een valide keuze. CEA en CAS zijn therapieën die elkaar aanvullen, waarbij elke techniek zijn voordelen heeft bij bepaalde patiëntengroepen. Beter begrip van de pathofysiologie van de hersenperfusie, plaque morfologie, patiënten selectie en het ontstaan van neurologische uitval zal de verdere behandeling van patiënten met een carotisstenose moeten verbeteren. Het gebruik van CAS en CEA als complementaire therapieën, met daarbij een optimalisering van de secundaire preventie, zal een slechte uitkomst van de behandeling van deze patiëntengroep verminderen.

Dankwoord



Dit proefschrift is ontstaan dankzij de steun en inzet van vele mensen. Enkele personen wil ik in het bijzonder noemen.

Professor Hero van Urk, mijn promotor en opleider. Jouw structuur rond de patiënt was zijn tijd ver vooruit en jouw chirurgische techniek een fundament voor altijd. Veel dank voor het vertrouwen en alle mogelijkheden die je mij hebt geboden.

Professor Peter Pattynama, mijn tweede promotor. Als geen ander kun jij complexe vraagstukken reduceren tot een relatief eenvoudig probleem. Jouw scherpe analyses, je grote kennis en kwaliteiten als interventieradioloog zijn altijd zeer waardevol voor mij geweest.

Marc van Sambeek, mijn co-promotor. Jouw enthousiasme en positieve instelling zijn ongekend. Jarenlang hebben wij intensief samengewerkt en lief en leed gedeeld. Nu werken we meer op afstand, maar het voelt nog steeds hetzelfde. Ik bewaar hele goede herinneringen aan die periode en ik weet dat onze vriendschap nooit zal verdwijnen.

Lukas van Dijk. Jij bent één van de grondleggers van het carotissstent programma in het Erasmus MC en wat hebben we samen veel stents geplaatst. Altijd op zoek naar het beste resultaat, altijd bereid voor overleg of om even langs te komen. Ook al zijn we nu geen directe collega's meer, je bent en blijft een goede, soms wat dromerige, vriend.

Professor Kieje Bruining. Als studentonderzoeker heb jij mij enthousiast gemaakt voor de chirurgie. We hadden een geweldig team waardoor onze eindeloze experimenten in het laboratorium gewoon een feestje werden. Als opleider streng, maar ik zie je nog steeds zoals ik je heb toegezongen bij je afscheid: "hij is gewoon van goud"!

Professor Don Poldermans, jouw energie is indrukwekkend en als geen ander kun jij de puntjes op de i zetten. Dank voor de vele adviezen.

Professor Peter Koudstaal, veel dank voor het kritisch lezen van het manuscript. Door de uitstekende structuur en de prettige communicatie tussen onze afdelingen zijn wij als Erasmus MC in staat kwaliteit te leveren.

Nico du Bois. Ook al heb je voor je gevoel niets aan dit boekje bijgedragen, het is ontstaan in een periode waarin jij een belangrijke rol hebt gespeeld. Ik heb zeer goede herinneringen aan onze vele gezamenlijke operaties en regelmatig vraag ik me af: "wat zou Nico hebben gedaan"? Mijn chirurgische leermeester voor altijd.

Mijn huidige collega's Hence, Mark, Ellen, Roderik en Sander wil ik bedanken voor de prettige samenwerking. Ik hoop dit nog vele jaren op deze manier te kunnen blijven doen.

Ook wil ik alle verpleegkundigen en medewerkers van de unit 9 zuid bedanken voor de goede zorg rond de patiënt. Jullie inzet is ongekend en ik heb veel respect voor het zware werk wat jullie dagelijks moeten verrichten. Hierbij wil ik ook alle secretaresses van de afdeling Heelkunde betrekken.

Interventieradiologen en laboranten. Dank voor jullie onuitputtelijke inzet. Zonder al die stents was dit boekje er niet geweest!

Jaap Zindler. Als student was je al betrokken bij dit onderwerp. Vele uren hebben we doorgebracht. Misschien moeten we toch nog eens een keer emboliën tellen!

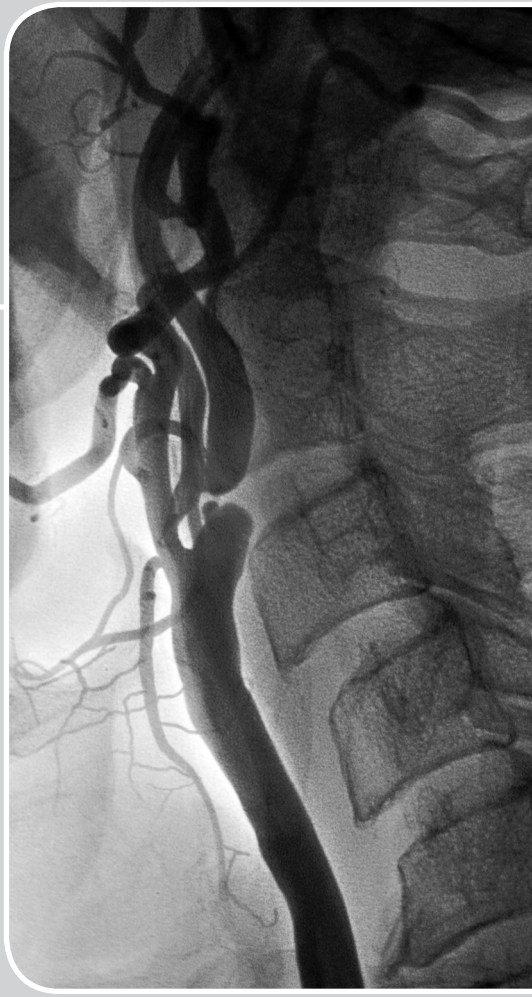
Ellen Rouwet, mijn paranimf en collega. Meer dan een jaar geleden kwam jij ons team versterken en dat hebben we gemerkt. Jouw enthousiasme en inzet zijn fenomenaal en met veel gevoel voor humor. Ik hoop nog lang met je te kunnen samenwerken en misschien moet ik ook gewoon wat vaker op mijn hoofd (letterlijk) gaan staan.

Khê Tran, mijn paranimf en goede vriendin. In een andere regio opgeleid, maar altijd mijn "slapie" op de CASH cursus. Je moest daarna wel naar Rotterdam komen en sindsdien is onze vriendschap alleen maar groter geworden. Ik bewaar hele goede herinneringen aan onze weekendjes weg en samen met Larissa en Martijne zullen er nog meerdere volgen.

Lieve Pa en Ma, jullie hebben dit allemaal voor mij mogelijk gemaakt. Zonder jullie jarenlange inzet en vertrouwen had ik hier niet gestaan. Veel dank voor alle onvoorwaardelijke liefde en steun.

Lieve Peter-Paul. Jij geloofde er al heel lang niet meer in, maar het boekje is er toch gekomen. Je bent mijn grote liefde, mijn maatje en sparringpartner. Het leven met jou is een grote uitdaging en een spannend avontuur. Samen hebben wij een prachtige dochter en jullie zijn het belangrijkste in mijn leven. Ik hoop nog heel lang van jou en je kookkunsten te kunnen genieten in ons "stilthouse"!
Lieve Katelijne, jij bent het allermooiste wat ik ooit heb gekregen!

Publications



Arnold J, Hendriks J, Bruining H.A. The role of tonometry in routine intensive care monitoring. Brit J Intensive Care 1993; 3 (12): 433-436.

Arnold J, Hendriks J, Ince J, Bruining HA. Tonometry to assess the adequacy of splanchnic oxygenation in the critically ill. Intensive Care Med 1994; 20 (6): 452-456.

Sambeek van MRHM, Hagenaars T, Tongeren van RBM, Dijk van LC, Hendriks JM, Coen VLMA. Peripheral vascular brachytherapie: An introduction. J Cardiovasc Surg 2000; 41 (6): 891-895.

Sambeek van RHM, Dijk van LC, Hendriks JM, Grotel van M, Kuiper JW, Pattynama PMT, Urk van H. Endovascular treatment of acute abdominal aortic aneurysm: feasibility and preliminary results. J Endovasc Ther 2002; 9: 443-448.

Hendriks JM, Sambeek van MRHM, Dijk van LC, Urk van H. Carotid Artery Stenting: An Introduction. Indian Journal of Surgery Vol 64, No3, May-June 2002.

Barry MC, Hendriks JM Alberts G, Boomsma F, Dijk van LC, Pattynama PMT, Poldermans D, Bouchier Hayes D, van Urk H, van Sambeek MRHM. Comparison of catecholamine hormone release in patients undergoing carotid artery stenting or carotid endarterectomy. J Endovasc Ther 2004; 11: 240-250.

Flach HZ, van der Lugt A, Ouhlous M, Hendriks JM, van Sambeek MRHM, Koudstaal PJ, van Dijk LC. Cerebral ischemia after carotid intervention. J Endovasc Ther 2004; 11: 251-257.

Hendriks JM, Zindler JD, Dijk van LC, Sambeek van MRHM. Cerebral protection during percutaneous carotid intervention, which device should be used? Acta Chir Belg 2004 Jun; 104(3): 300-303.

Van Sambeek MRHM, Hendriks JM, Tseng L, van Dijk LC, van Urk H. Sac enlargement without endoleak: When and how to convert and technical considerations. Sem Vasc Surg 2004 Dec; 17(4): 284-287.

De Weert TT, Ouhlous M, Zondervan PE, Hendriks JM, Dippel DWJ, van Sambeek MRHM, van der Lugt. In vitro characterization of atherosclerotic carotid plaque with multidetector computed tomography and histopathological corelation. Eur Radiol 2005; 15(9): 1906-1914.

Ouhlous M, Flach HZ, de Weert TT, Hendriks JM, Sambeek van MRHM, Dippel DWJ, Pattynama PMT, van der Lugt A. Carotid plaque composition and cerebral infarction: MR imaging study. AJNR. Am J Neuroradiol 2005 May; 26(5):1044-1049.

Hendriks JM, van Sambeek MRHM. Carotid Stenting. J Cardiovasc Surg 2005; 46(4): 327-332.

van Nes, Hendriks JM, Tseng LN, van Dijk LC, van Sambeek MRHM. Endoscopic aneurysm sac fenestration as a treatment option for growing aneurysms due to type 2 endoleak or endotension. J Endovasc Ther 2005; 12(4): 430-434.

Hendriks JM, Zindler JD, van der Lugt A, Pattynama PM, van Sambeek Mr, Bosch JL, van Dijk LC. Embolic protection filters for carotid stenting: difference in flow obstruction depending on filterconstruction. J Endovasc Ther 2006 Feb; 13(1): 47-50.

Zindler JD, Hendriks JM, Koudstaal PJ, Pattynama PM, vasn Sambeek MR, van Dijk LC. Complications within 30 days following placement of a carotid stent with cerebral protection in patients with considerable symptomatic carotid stenosis; Erasmus MC, Rotterdam, 1999-2004. Ned Tijdschr Geneeskd 2006 Apr 1; 150(13): 730-734.

Visser JJ, van Sambeek MR, Hunink MG, Redekop WK, van Dijk LC, Hendriks JM, Bosch JL. Acute Abdominal Aortic Aneurysm: Cost analysis of endovascular repair and open surgery in hemodynamically stable patients with 1-year follow-up. Radiology 2006; 240(3): 681-689.

de Weert TT, Ouhlous M, Meijering E, Zondervan PE, Hendriks JM, van Sambeek MR, Dippel DW, van der Lugt A. In vivo characterization and quantification of atherosclerotic carotid plaque components with multidetector computd tomography and histopathological correlation. Arterioscler Thromb Vasc Biol 2006; 26(10): 2366-2372.

Sier MF, van Sambeek MR, Hendriks JM, van Grotel M, van Dijk LC, Pattynama PM, van Urk, H, Bosch JL. Shrinkage of abdominal aortic aneurysm after succesful endovasculair repair: results from singel center study. J Cardiovasc Surg 2006; 47(5):557-561.

Visser JJ, Bosch JL, Hunink MG, van Dijk LC, Hendriks JM, Poldermans D, Van Sambeek MR. Endovasculair repair versus open surgery in patients with ruptured abdominal aortic aneurysm: clinical outcomes with 1-year follow-up. J Vasc Surg. 2006; 44(6): 1148-1155.

Feringa HH, Hendriks JM, Karagiannis S, Schouten O, Vidakovic R, van Sambeek MR, Klein J, Noordzij P, Bax JJ, Poldermans D. Carotid artery stenting versus endarterectomy in relation to perioperative myocardial ischemia, troponin T release and major cardiac events. Coron Artery Dis 2007; 18(6): 483-487.

NFM Kok, SC de Jong, JM Hendriks. Een man met een aneurysma van de arteria carotis interna. Nederlands Tijdschrift voor Heelkunde. 2006; 15 (8): 242-245.

Van Laanen J, Hendriks JM, Van Sambeek MR. Carotid artery stenting 2008. Panminerva med 2008 Jun; 50(2): 153-159. Review

Alexander S Bosch JL, Hendriks JM, Visser JJ, Van Sambeek MR. The 30-day mortality of ruptured abdominal aortic aneurysms: influence of gender, age, diameter and comorbidities. J Cardiovasc Surg 2008 Oct; 49(5): 633-637.

Van Laanen J, Hendriks JM, van Sambeek MR. Factors influencing restenosis after CAS. J Cardiovasc Surg 2008; 49(6): 743-747.

Grootenboer N, Bosch JL, Hendriks JM, van Sambeek MR. Epidemiology, Aetiology, Risk of Rupture and Treatment of Abdominal Aneurysms: Does sex Matter? Eur J Vasc Endovasc Surg. 2009 Sep; 38(3): 278-294.

Barry MC, Hendriks JM, van Dijk LC, Pattynama P, Poldermans D, Boucher Hayes D, van Urk H, van Sambeel MR. A comparative study of myocardial injury during conventional and endovascular aortic aneurysm repair: measurement of cardiac troponin T and plasma cytokine release. Ir J Med Sci 2010; 179(1): 35-42.

International Carotid Stenting Study investigators, Elderle J, Dobson J. Featherstone RL, Bonati LH, van der Worp HB, de Bordt GJ, LO TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010 Mar 20; 375: 985-997.

New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic stenosis: a substudy of the International Carotid Stenting Study (ICSS). Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, Macdonald S, Gaines PA, Waaijer A, Stierli P, Jäger HR, Lyrer PA, Kapelle LJ, Wetzel SG, vander Lugt A, Mali WP, Brown MM, vander Worp HB, Engelter ST; ICSS-MRI study group. Lancet Neurol 2010 Apr; 9(4): 353-363.

Systematic review and meta-analysis of sex differences in outcome after intervention for abdominal aortic aneurysm. Grootenboer N, van Sambeek MR, Arends LR, Hendriks JM, Hunink MG, Bosch JL. Br J Surg 2010 Aug; 97(8): 1169-1179.

Device specific outcomes after endovascular abdominal aortic aneurysm repair. Bastos Gonçalves F, Rouwet EV, Metz R, Hendriks JM, Vrancken Peeters MP, Muhs BE, Verhagen HJ. J Cardiovasc Surg 2010 Aug; 51(4): 515-531.

Decision-making in type-B dissection: current evidence and future perspectives. Bastos Gonçalves F, Metz R, Hendriks JM, Rouwet EV, Muhs BE, Poldermans D, Verhagen HJ. J Cardiovasc Surg. 2010 Oct; 51(5): 657-667.

Chapters

Hendriks JM, Visser GH, Dijk van LC, Pattynama, PMT, Koudstaal P, Urk van H, Sambeek van MRHM. The use of TCD before and during CAS. In: Carotid artery angioplasty and stenting. Minerva Medica Torino 2002; 174-177 ISBN 88-7711-422-3.
Sambeek van MRHM, Hendriks JM, Bouvy ND, Tseng LNL, Urk van H. Endoscopic fenestration of AAA for hygroma and growing AAA after endovascular repair In: Controversies and updates in vascular and cardiac surgery. Minerva Medica Torino 2004; 241 –245, ISBN 88-7711-457-6.
Sambeek van MRHM, Dijk van LC, Hendriks JM. Abdominal Aneurysm – EVAR. In: Comprehensive Vascular and Endovascular Surgery. Mosby, Edinburgh 2004; 409-425, ISBN 0 7234 3232 5.

van Sambeek MRHM, van Dijk LC, Hendriks JM, Pattynama PMT, van Urk H. Mortality reduction by EVAR. In: Vascular and Endovascular Challenges. Greenhalgh (Ed). ISBN 0-9544687-1-6. Biba Publishing, London 2004; 190-196.

Van Sambeek MRHM, van Dijk LC, Pattynama PMT, Hendriks JM. Endovascular treatment of abdominal aortic aneurysm. In: The Paris Course On Revascularisation. Marco J, Serruys P, Biamino, et al (Eds). ISBN 2- 913628-16-8. Fournie Imprimeur, Toulouse 2004; 373-385.

van Sambeek MRHM, Hendriks JM, van Dijk LC. Management of complications during carotid artery stenting. In: Endovascular Interventions for Vascular Disease: Principles and Practice. Thomson M, Sappoval M, Matsumura J, Morgan R, Loftus I (Eds). ISBN 10-0849339790 Taylor and Francis Books INC, New York 2007; Chapter 18, 185-192.

Voute M, Akkersdijk G, Hendriks JM, Vrancken Peeters M, Pattynama PMT, Verhagen H. Thrombolysis for acute and chronic arterial occlusion. Chapter in BranchereauA, Jacobs MJHM, ed. Innovative Cardiovascular Procedures. Turin: Edizioni Minerva Medica; 2009; 201-209. ISBN 13: 978-88-7711-637-6.

Marc R.H.M. van Sambeek, Philippe Cuypers, Johanna M. Hendriks, Jaap Buth. Abdominal Aneurysm: Endovascular Aneurysm Repair. Chapter in Comprehensive Vascular and Endovascular Surgery, 2^{e}, edited by Drs. Hallett, Mills, Earnshaw, Reekers and Rooke. Mosby 2009; 480-494, ISBN 978-0-323-05726-4.