CAROTID ARTERY REVASCULARIZATION

Hemodynamic and cognitive implications

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CAROTID ARTERY REVASCULARIZATION

Hemodynamic and cognitive implications

Revascularisatie van de arteria carotis
Effecten op hemodynamiek en cognitie

(met een samenvatting in het Nederlands)

Proefschrift

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ANNEM'E VE BABAM'A

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1

Introduction

BACKGROUND

Stroke is one of the leading causes of mortality and morbidity worldwide.[1] About 80% of strokes are due to cerebral ischemia and in circa 20% of these patients the cause of ischemic stroke is caused carotid artery stenosis >50%.[2] Patients who have suffered from transient ischemic attack (TIA) or ischemic stroke and have ipsilateral carotid stenosis are at particular increased risk of subsequent stroke.[3]

Carotid endarterectomy

Carotid endarterectomy (CEA) has been performed since the 1950s and the benefit of surgery has been shown unambiguously with the results of large clinical trials in the 1990s.[4-7] CEA reduces the risk of stroke in patients with recently symptomatic internal carotid stenosis of more than 50%, with increasing benefit of surgery with higher degree of stenosis.[4,5,7] In patients with 50–69% stenosis surgery leads to a 5-year an absolute risk reduction (ARR) of 7.8% (confidence interval (CI) 3.1 to 12.5), however with 70–99% stenosis surgery leads to ARR in the 5-year risk of stroke or operative death of 15.3% (95% CI, 9.8 to 20.7).[7] After these findings, carotid surgery had become the established standard treatment for severe symptomatic carotid artery stenosis.[8]

Carotid artery stenting

In the last decade of the 20th century endovascular treatment of the carotid artery came progressively more into use. This technique appeared advantageous because it does not require surgical incision, hereby preventing cranial nerve damage and necessitates only local anesthesia for insertion of a catheter in the groin, enabling continuous neurological monitoring of the patient.[9] Treatment of carotid stenosis by carotid angioplasty with stent placement (CAS) could also be cost-effective because of a shorter hospital stay. Endovascular treatment and CEA have been compared in the randomized Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). In this trial, endovascular treatment (initially only percutaneous transluminal angioplasty (PTA) and later during the study also with stenting when believed necessary) had similar major risks and effectiveness at prevention of stroke during a follow-up period of 3 years compared with CEA, but with wide confidence intervals.[9] Mainly because of this lack of precision, the results were not sufficient for general introduction of endovascular techniques as an alternative to CEA. In addition, information about thromboembolic and other complications had remained inadequate.

CAS versus CEA

The interventional technique used to treat carotid stenosis had progressed remarkably since the start of CAVATAS, from simple inflatable balloon catheters at the start of the trial to the use of stenting at the end. The large clinical trials comparing endarterectomy with stenting were still recruiting patients at the time the studies described in this thesis were conducted. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), that also included asymptomatic patients, did not find CAS inferior to CEA.[10] However, during the periprocedural period there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy.[10] Furthermore, randomized trials for the treatment of symptomatic carotid stenosis have failed to establish the equivalence of stenting with endarterectomy in the majority of patients.[11-14] In fact these studies show that the periprocedural (30 day) stroke or death rate is higher with stenting than with endarterectomy. Moreover, in subgroup analysis in patients ≥ 70 years of age the increased periprocedural stroke or death risk was higher in patients treated with stenting compared with those treated with surgery.[14] There was no significant difference in periprocedural stroke or death in patients younger than 70 years treated with CAS or CEA.[14] Current guidelines recommend CEA for patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70–99%) carotid artery stenosis if preoperative morbidity and mortality risk is estimated to be below 6%.[15] CAS as an alternative to CEA is recommended in patients with > 70% stenosis at average to low risk of complications and in certain circumstances, e.g. surgically difficult accessibility of stenosis, medical conditions that greatly increase surgery risk or to undergo anesthesia, or in case of radiation-induced stenosis or restenosis after CEA.[15]

Complications after carotid revascularization

Periprocedural morbidity of carotid revascularization procedures is mainly caused by cerebral ischemia, myocardial infarction, hyperperfusion syndrome and cranial nerve palsies. In addition to these complications, observational studies have found hemodynamic changes to complicate these treatments. Hypotension after CAS has been attributed to manipulation of the carotid sinus and baroreceptor dysfunction.[16-18] The arterial baroreceptors are stretch receptors located in the carotid sinuses, and play a key role in short-term adjustments of blood pressure.[19] Early postprocedural decreases in blood pressure have been observed after CAS,[16,17,20-23] and varying degrees of hypotension have also been reported in the early postoperative period after CEA as well.[24-27]

Controlled but non-randomized studies have suggested that arterial hypotension is a more frequent complication after CAS than after CEA.[28,29] Only one of the recent randomized trials of CAS versus CEA quantified the risk of early blood pressure changes: the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Stenosis (EVA-3S) trial reported that bradycardia or hypotension was observed during the first 30 days of treatment in 11 (4.2%) of the 261 patients treated with CAS and in none of the 259 patients treated with CEA.[12]

Although postprocedural hypotension might not seem hazardous, in some observational studies, hemodynamic depression or a greater change in blood pressure after CAS was associated with an increased risk of stroke, myocardial infarction (MI), or death.[16,17,29,30] Randomized trials have consistently shown that CAS is associated with a significantly higher rate of stroke or death within 30 days of treatment than CEA.[14] The extent to which this excess is attributable to hemodynamic depression after CAS is uncertain. Arterial hypertension after CEA and CAS has been associated with the cerebral hyperperfusion syndrome, stroke, or death.[25,31,32] Observational studies suggested that hypertension and the cerebral hyperperfusion syndrome may occur more frequently after CEA.[31-36]

Thromboembolism after carotid revascularization

One of the key risks of CAS is dislodgement and distal embolization of plaque and thrombotic debris, leading to stroke or retinal ischemia. Several studies have suggested that CAS is associated with an increase in clinically "silent" thromboembolic events as compared with CEA. A small, randomized substudy of CAVATAS detected, by use of transcranial Doppler ultrasound, four times more often microembolism to the brain after angioplasty than after surgery.[37] Moreover, non-randomized studies had suggested that on diffusion-weighted imaging (DWI), new ischemic lesions are found about three times as often after CAS than after CEA.[38] This observation has recently been confirmed in a randomized study.[39]

DWI lesions and effects on clinical outcome

The majority of these DWI lesions were not associated with symptoms of transient ischemic attack or stroke.[40-42] However, there has been concern that ischemic brain lesions without correlating focal neurological deficit may have an impact on cognitive functioning.[38,43-44] In elderly people free of dementia and stroke at baseline, the presence of "silent" ischemic lesions more than doubled the risk of dementia and was related to a steeper decline in cognitive functioning.[45] Neuropsychological deficit may not be as apparent as neurological

deficit but can be similarly disruptive to the life of an individual. On the other hand previous non-randomized studies have described improvement after carotid revascularization as well, however it remains unknown why some patients decline in cognitive performance and why others improve.[46] Yet, the effects on cognition of new ischemic lesions after CAS and CEA had remained unclear at the time of the studies reported in this thesis.

OBJECTIVE

The purpose of this thesis is to study the effects of hemodynamic complications after carotid revascularization procedures, in order to gain more insight in the clinical consequences thereof. In general, the results of large clinical trials do not incorporate effects on blood pressure or cognition in their main research questions. Another aim was to assess the cognitive consequences of carotid revascularization. The effects of silent brain infarcts after CAS and CEA on cognition have never been compared in a randomized manner. Therefore, at study initiation we believed that widespread introduction of carotid artery stenting as an alternative to surgery would be inappropriate without knowing the consequences of hemodynamic compromise or neuropsychological outcome.

The studies in this thesis are part of the International Carotid Stenting Study (ICSS), the ICSS-MRI substudy and the cognition substudy. The cognition substudy enrolled patients participating in ICSS at the University Medical Center Utrecht and the Academic Medical Center in Amsterdam from February 2006 onwards till the end of the recruitment in December 2008.

OUTLINE OF THE THESIS

1. Hemodynamic complications

In this part we focused on the hemodynamic effects of CAS and CEA. In chapter 2 we described the effects of both treatments on blood pressure up to one-year follow-up. In chapter 3 we compared the rate of periprocedural hemodynamic depression (defined as severe bradycardia, asystole or hypotension requiring treatment) and hypertension requiring treatment between CAS or CEA. In addition we determined independent predictors thereof and assessed whether these complications were related with clinical outcome at 30 days. In chapter 4 we investigated whether the occurrence of postprocedural hemodynamic depression was associated with the amount of new ischemic brain lesions, because of reports that both occurred more frequently after CAS.

2. Cognition

The main emphasis of this section is on cognitive functioning after CAS and CEA. In chapter 5 we compared the effects on cognition in patients treated within the ICSS cognition substudy. We also compared the occurrence of new cerebral ischemic lesions on DWI-MRI in a subpopulation of these patients. In chapter 6 we studied what the impact of cerebral white matter lesions was on cognitive functioning in patients with mild, moderate and severe lesion burden at baseline.

In patients with a fetal-type posterior cerebral artery the blood supply is mainly or exclusively by the internal carotid artery. In patients with ipsilateral carotid artery stenosis this is likely to result in a larger area with hypoperfusion than in case of a normal posterior cerebral artery. Patients with a fetal-type posterior cerebral artery could therefore benefit more from revascularization. Therefore we compared the effects of carotid revascularization on cognition between patients with a fetal-type posterior cerebral artery and those with a normal posterior cerebral artery in chapter 7. In chapter 8 we summarize the results and we discuss in detail the strengths and weaknesses of the study. Finally, we give suggestions for future research.

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SECTION 1

Hemodynamic complications

2

Effects of carotid endarterectomy or stenting on blood pressure in the International Carotid Stenting Study (ICSS)

Stroke 2011;42:3491-3496.

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ABSTRACT

Background and purpose Arterial hypotension is more frequently observed early after carotid artery stenting (CAS) than after carotid endarterectomy (CEA), but their long-term effects on blood pressure (BP) are unclear. We compared the effects of CAS and CEA on BP up to one year after treatment in the International Carotid Stenting Study.

Methods Patients with symptomatic carotid stenosis were randomly allocated to CAS or CEA. Systolic and diastolic BP were recorded at baseline, at discharge, and at 1, 6, and 12 months. Antihypertensive medication use was recorded. A per-protocol analysis was performed. Patients with missing BP records were excluded. Between-group BP changes were compared and adjusted for baseline covariates with linear regression. Within-group BP changes were compared with the paired t test.

Results CAS (N = 587) and CEA (N = 637) were both associated with a decrease in BP at discharge, which was greater after CAS (mean difference in systolic BP between groups, 10.3 mm Hg; 95% CI, 7.3 to 13.3; $P < 0.0001$; in diastolic BP, 4.1 mm Hg; 95% CI, 2.4 to 5.7; $P < 0.0001$). During follow-up, BP changes were not different between groups. Adjustment for differences in baseline characteristics did not change the results. Fewer patients undergoing CAS used antihypertensive medication during follow-up than patients undergoing CEA (relative risk at 12 months, 0.91; 95% CI, 0.85 to 0.97; $P = 0.0073$).

Conclusions CAS leads to a larger early decrease in BP than CEA, but this effect does not persist over time. CAS may lessen the requirement for antihypertensive medication more than CEA.

Clinical Trial Registration - URL http://www.controlled-trials.com. Unique identifier: ISRCTN25337470.

INTRODUCTION

Arterial hypotension is a frequent complication after carotid artery stenting (CAS), and has been attributed to manipulation of the carotid sinus and baroreceptor dysfunction.[1-3] The arterial baroreceptors are stretch receptors located in the carotid sinuses, and play a key role in short-term adjustments of blood pressure.[4] In case series of CAS, hypotension or hemodynamic depression has been observed in up to half of cases.[1,2,5] Hypertension and the related cerebral hyperperfusion syndrome are well-known complications after carotid endarterectomy (CEA).[6] However, previous studies have reported varying degrees of hypotension in the early postoperative period after CEA as well.[7-9] The long-term effects of CAS and CEA on blood pressure (BP) are unclear. Systolic blood pressures (SBP) remained lower than at baseline after CEA but not after endovascular treatment up to six months follow-up in one small trial.[10] However, an older study found no BP lowering effect of CEA.[11]

We hypothesized that lower BPs would persist longer after CAS than after CEA, and that this would affect the use of antihypertensive drugs. Therefore, we compared the change in BP after CAS and CEA up to 12 months of follow-up from baseline, and compared the use of antihypertensive drugs between these groups during follow-up.

METHODS

Subjects

All patients in this study were participants in the International Carotid Stenting Study (ICSS, ISRCTN25337470). ICSS is an international, randomized controlled trial comparing the risks, benefits, and cost-effectiveness of CAS and CEA in patients with a recently symptomatic carotid artery stenosis greater than 50%. Patient criteria, randomization, and the results of an interim safety analysis have been described elsewhere.[12] Patients were followed up at 30 days after treatment, and at 6 and 12 months and each subsequent year after randomization. BPs were recorded according to center policy at randomization (baseline), at discharge after treatment, and at one, six, and 12 months follow-up. Single measurements were made without distinctions about which arm had to be used, and mercury sphygmomanometers as well as electronic devices were allowed for BP measurement. Records were kept on whether patients used any antihypertensive medication and for the use of any antithrombotic medication or a statin during follow-up visits. Patients with missing BP records were excluded from the analysis.

Study approval

ICSS was approved by local ethics committees for non-UK centers and by the Northwest Multicentre Research Committee in the UK. Each patient provided written informed consent.

Outcome measures

The primary outcome measure of the present study was the changes in SBP and diastolic BP (DBP) between baseline and follow-up. The use of antihypertensive medication during follow-up was a secondary outcome measure.

Statistical analysis

A per-protocol analysis was performed for the primary and secondary outcome measures. Because of the explanatory character of this study, analysis was restricted to the patients who received the allocated treatment as their first and only treatment, thus patients with an abandoned treatment were excluded from the analyses.

SBP and DBP changes were defined as the BP at randomization subtracted from the measurement at discharge after treatment, and at one, six, and 12 months. Negative values therefore represent a decline in BP from the first measurement. Mean differences between the two treatment groups in SBP and DBP changes with corresponding 95% confidence intervals (CI) were calculated. The relation between treatment and BP changes was analyzed with linear regression and was adjusted for age and sex and for imbalances in other baseline characteristics. Risk ratios were calculated for the use of antihypertensive medication at one, six, and 12 months follow-up between the two treatment groups, and for the use of any antithrombotic medication or a statin during follow-up. For within-group (CAS or CEA) changes of BP, 95% CIs based on the paired t-test were calculated. Because a history of hypertension and the use of antihypertensive drug at baseline might affect the outcomes, we performed additional analyses in patients with treated hypertension at baseline.

RESULTS

Patient flow

Figure 2.1 illustrates the flow of the 1,713 enrolled patients in ICSS and provides reasons for exclusion from analysis. The present study population consists of the 766 CAS and 819 CEA patients with a single initiated and completed intervention.

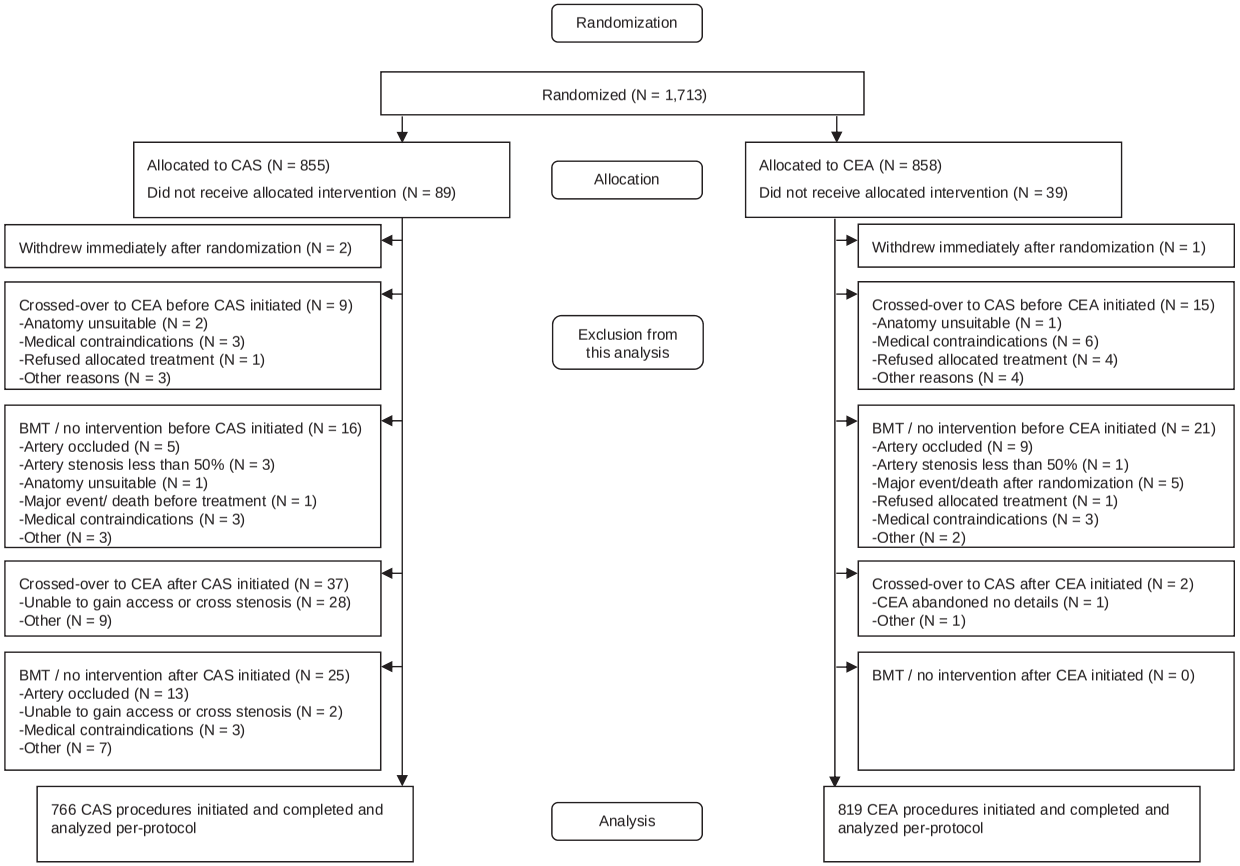


Figure 2.1 BMT indicates best medical treatment; CAS, carotid artery stenting; CEA, carotid endarterectomy. In ICSS, randomization was stratified by center with minimization for sex, age, contralateral occlusion, and side of the randomized artery. No record was kept of patients screened who were ineligible or treated outside the trial.[12]

Baseline characteristics

Baseline SBP and DBP did not differ between the two groups, and there was no difference in the percentage of patients with treated hypertension. Fewer patients randomized to CAS had a history of cardiac failure at randomization; there were no other differences in baseline characteristics between the groups (Table 2.1).

Follow-up

The mean length of post-procedural hospitalization did not differ between both groups (CAS, 3.2 days; CEA, 3.6 days; mean difference (MD), 0.4 days; 95% CI, -0.3 to 1.2; P = 0.272). Patients without follow-up BP measurement at 1 month were 2.6 years older (95% CI, 0.5 to 4.6; P = 0.015) and had 1.4 times more often a TIA as a presenting symptom (95% CI, 1.1 to 1.8; P = 0.017). The patients who did not have a follow-up BP measurement at 12 months were 2.7 years older (95% CI, 1.4 to 4.1; P < 0.0001), had lower baseline SBP

Table 2.1 Patient characteristics at baseline

	CAS (N = 766)	CEA (N = 819)
Age (years)	70 (9)	70 (9)
Sex (male)	534 (70%)	577 (71%)
Vascular risk factors		
Treated hypertension	523 (69%)	571 (70%)
Systolic blood pressure (mmHg)	147 (24)	146 (24)
Diastolic blood pressure (mmHg)	79 (12)	78 (12)
Cardiac failure	21 (3%)	44 (6%)
Angina pectoris in past 6 months	74 (10%)	72 (9%)
Previous myocardial infarction	133 (18%)	150 (19%)
Previous CABG	99 (13%)	111 (14%)
Atrial fibrillation	47 (6%)	53 (7%)
Other cardiac embolic source	16 (2%)	16 (2%)
Type 2 diabetes mellitus	121 (16%)	135 (17%)
Type 1 diabetes mellitus	47 (6%)	38 (5%)
Peripheral arterial disease	128 (17%)	131 (16%)
Current smoker	186 (25%)	190 (23%)
Ex-smoker	364 (48%)	404 (50%)
Treated hyperlipidemia	474 (63%)	537 (66%)
Cholesterol (mmol/L)	4.9 (1.3)	4.9 (1.3)

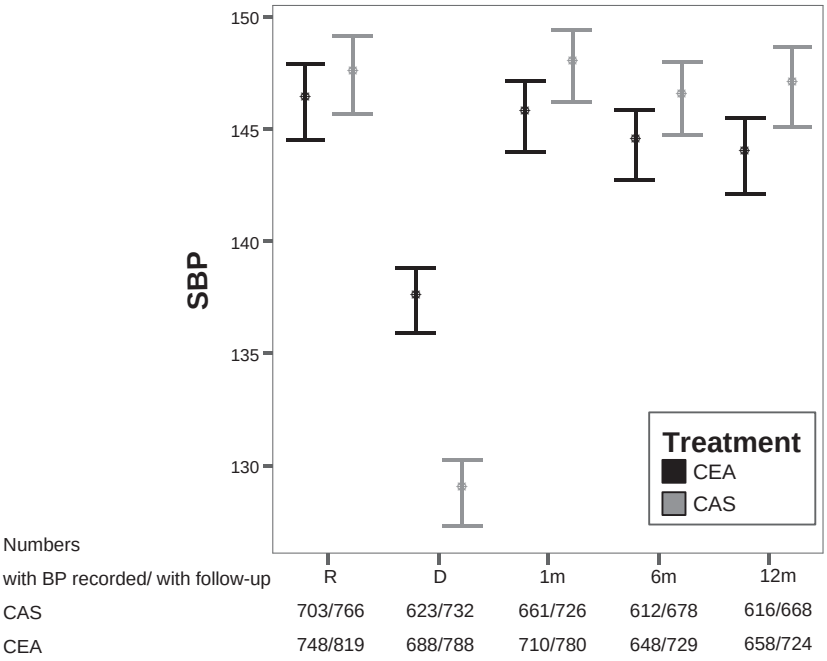
Table 2.1 continues on next page

Table 2.1 *Continued*

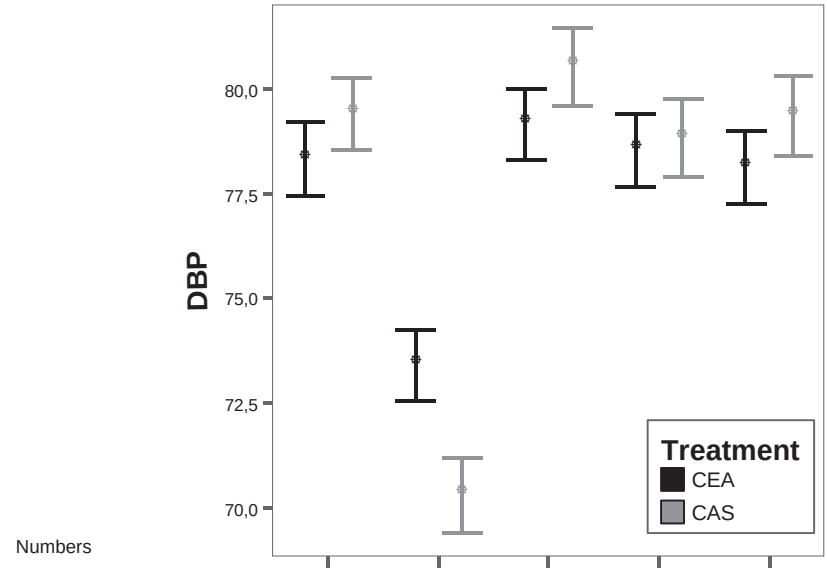
	CAS (N = 766)	CEA (N = 819)
Degree of symptomatic carotid stenosis[a]		
50–69%	81 (11%)	72 (9%)
70–99%	685 (89%)	747 (91%)
Degree of contralateral stenosis[a]		
< 50%	510 (67%)	538 (66%)
50–69%	111 (15%)	135 (17%)
70–99%	97 (13%)	104 (13%)
Occluded	45 (6%)	35 (4%)
Unknown	3 (0%)	7 (1%)
Most recent ipsilateral event[b]		
Amaurosis fugax	138 (18%)	134 (16%)
Transient ischemic attack	247 (32%)	291 (36%)
Ischemic stroke	349 (46%)	359 (44%)
Retinal infarction	23 (3%)	22 (3%)
Unknown	9 (1%)	13 (2%)
Event < 6 months before randomization	741 (97%)	779 (95%)
Event 6–12 months before randomization[c]	25 (3%)	38 (5%)
Multiple events before randomization	303 (40%)	307 (38%)
Stroke before index event	115 (15%)	103 (13%)
Score on mRS at randomization		
0–2	686 (90%)	711 (87%)
3–5[d]	66 (9%)	94 (12%)
Unknown	14 (2%)	14 (2%)

Data are number (%) or mean (SD). CABG indicates coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy; mRS, modified Rankin scale. [a] Degree of stenosis measured by North American Symptomatic Carotid Endarterectomy Trial method at randomization center.[13]
[b] If two events were reported on the same day, the more serious was counted (stroke > retinal infarction > transient ischemic attack > amaurosis fugax). [c] In two patients, the event was more than 12 months before randomization and in two the date was unknown. [d] Some Rankin scores of 3 or more were caused by non-stroke disability.

(-5.2 mmHg; 95% CI, -9.1 to -1.3; $P = 0.008$), and had 1.47 times more often a history of myocardial infarction (95% CI, 1.12 to 1.95; $P = 0.006$). The baseline characteristics between CAS and CEA patients who were not seen for follow-up examination did not differ at 1 month, but CAS patients who did not have BP measurements at 12 months had 0.87 times less often treated hypertension at baseline (95% CI, 0.75 to 1.00; $P = 0.047$).



Numbers with BP recorded/ with follow-up	R	D	1m	6m	12m
CAS	703/766	623/732	661/726	612/678	616/668
CEA	748/819	688/788	710/780	648/729	658/724



Numbers with BP recorded/ with follow-up	R	D	1m	6m	12m
CAS	703/766	622/732	661/726	612/678	615/668
CEA	748/819	688/788	709/780	648/729	657/724

Figure 2.2 Systolic and diastolic blood pressures at all time points.

Blood pressure changes in primary and secondary outcomes

SBPs and DBPs at baseline and during follow-up in both groups are shown in Figure 2.2. At discharge after treatment, the decrease in SBP and DBP was larger in the CAS group than after CEA (MD in SBP between groups, -10.3; 95% CI, -13.3 to -7.3; $P < 0.0001$; MD in DBP between groups: -4.1; 95% CI: -5.7 to -2.4, $P < 0.0001$). In both groups, DBP decreased significantly between baseline and discharge after treatment. There were no differences between the groups at subsequent follow-up visits up to 12 months after randomization (Table 2.2). The differences between BP changes after CAS or CEA did not alter substantively after adjustment for age, sex, and history of cardiac failure.

At one month from randomization, DBP was about 1 mmHg higher than at baseline after each of the procedures, but this change was only significant after CAS. At six months, SBP was slightly lower than at baseline in both groups (MD SBP CAS, -2.5; 95% CI, -4.7 to -0.4; $P = 0.022$, and MD SBP CEA, -3.0; 95% CI, -5.0 to -0.9; $P = 0.005$), but at 12 months only in patients treated with CEA (MD SBP, -4.4; 95% CI, -6.5 to -2.2; $P < 0.0001$). There were no differences between SBP at baseline and after 12 months follow-up in patients treated with CAS. Significantly fewer CAS patients were using antihypertensive medication than patients treated with CEA at all the follow-up appointments up to one year after randomization (Table 2.3). The numbers of patients treated with any antithrombotic medication or a statin during follow-up were similar between the two groups, with the exception of a slightly less frequent use of any antithrombotic treatment in patients treated with CEA at six months (Supplementary Table S2.1).

Blood pressure changes in patients with treated hypertension at baseline

In a sensitivity analysis of patients with treated hypertension at baseline, the difference between both groups stayed evident for the decrease in BP at discharge (MDs between CAS and CEA in SBP, -9.2 mmHg; 95% CI, -12.8 to -5.6; $P < 0.0001$; and DBP, -3.8; 95% CI, -5.8 to -1.9; $P = 0.0001$). The differences between the changes between CAS and CEA during follow-up were largely of the same magnitude as in the overall analysis.

DISCUSSION

The present study shows that both CAS and CEA are associated with a decrease in BP in the first days after treatment, and that this decrease is larger after CAS than after CEA. The difference in BP between CAS and CEA disappeared at one month after treatment and was not seen during follow-up up to one year after randomization. Patients in both groups had slightly lower SBP at 12 months than at baseline, but the difference was only

Table 2.2 Change in blood pressures from baseline to follow-up

No. (CAS, CEA)	CAS	95% CI	*P*	CEA	95% CI	*P*	MD (95% CI)[a]	*P*
Change discharge – baseline								
SBP[b] (587–637)	-19.1	-21.3 to -16.9	< 0.0001	-8.8	-10.9 to -6.8	< 0.0001	-10.3 (-13.3 to -7.3)	< 0.0001
DBP[b] (586–637)	-9.0	-10.2 to -7.9	< 0.0001	-5.0	-6.1 to -3.8	< 0.0001	-4.1 (-5.7 to -2.4)	< 0.0001
Change 1-month follow-up – baseline								
SBP[b] (612–656)	-0.4	-2.4 to 1.7	0.734	-1.6	-3.4 to 0.2	0.084	1.3 (-1.5 to 4.0)	0.370
DBP[b] (612–655)	1.1	0.0 to 2.1	0.048	0.8	-0.2 to 1.9	0.117	0.2 (-1.3 to 1.7)	0.775
Change 6-months follow-up – baseline								
SBP[b] (567–601)	-2.5	-4.7 to -0.4	0.022	-3.0	-5.0 to -0.9	0.005	0.4 (-2.5 to 3.4)	0.772
DBP[b] (567–601)	-0.9	-2.1 to 0.2	0.106	-0.3	-1.4 to 0.9	0.632	-0.7 (-2.3 to 1.0)	0.430
Change 12-months follow-up – baseline								
SBP[b] (567–606)	-2.1	-4.3 to 0.2	0.077	-4.4	-6.5 to -2.2	<0.0001	2.3 (-0.8 to 5.4)	0.147
DBP[b] (566–605)	-0.5	-1.7 to 0.6	0.382	-0.7	-1.9 to 0.4	0.208	0.2 (-1.4 to 1.8)	0.793

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; DBP; diastolic blood pressure; MD, mean difference between CAS and CEA; SBP, systolic blood pressure. Baseline measurement is at randomization. Negative within-group scores mean a decrease from baseline. [a] Effect estimates remained essentially the same after adjustment for age, sex, and cardiac failure. [b] Measurement in mmHg.
Numbers represent patients with blood pressure records both at baseline and at follow-up.

Table 2.3 Antihypertensive treatment at follow-up

N (CAS, CEA)	CAS	CEA	RR	95% CI	*P*
1 Month follow-up					
Antihypertensive use 1 month (720–770)	413 (57%)	514 (67%)	0.86	0.79 to 0.93	0.0002
6 Months follow-up					
Antihypertensive use 6 months (671–720)	440 (67%)	508 (71%)	0.93	0.86 to 1.00	0.0472
12 Months follow-up					
Antihypertensive use 12 months (660–720)	441 (67%)	529 (74%)	0.91	0.85 to 0.97	0.0073

Data are number (%). CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; RR, risk ratio.

significant in the CEA patients. However, patients treated with CAS used antihypertensive drugs less frequently during the complete period of follow-up whereas there were no major differences in the use of any antithrombotic medication or statins.

In observational studies, early postprocedural decreases in BP have been observed after both CEA[7-9,11] and CAS.[1,3,14-16] Controlled but non-randomized studies have suggested that arterial hypotension is a more frequent complication after CAS than after CEA.[17,18] In the randomized Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial of CAS versus CEA in patients with symptomatic carotid artery stenosis, bradycardia or hypotension was observed during the first 30 days of treatment in 11 (4.2%) of the 261 patients treated with CAS and in none of the 259 patients treated with CEA.[19] None of the other recent randomized trials of CAS versus CEA reported on early BP changes.[12,20,21]

Arterial hypotension during or after CAS has been explained by the stretching of the carotid sinus baroreceptors by the stent.[5] CEA impairs blood pressure homeostasis through ipsilateral carotid baroreceptor denervation. Some drugs used in the perioperative period, such as opioids, affect cardiovascular function by attenuation of sympathetic afferent and efferent activity, direct central or peripheral vagal stimulation, and direct and indirect effects on the myocardium and vascular smooth muscle.[22]

The effects of CEA and endovascular treatment on BP during a longer period of follow-up have been compared in a single-center substudy of the randomized Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and in the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial.[10] Of the 55 patients randomized to endovascular treatment in CAVATAS, 31 received percutaneous transluminal angioplasty (PTA) alone, and 24 were treated by stenting. At six-months follow-up, SBP was 4.9 mmHg lower compared with baseline in surgically treated patients, whereas

there was a non-significant decrease of 1.9 mmHg in patients treated with PTA or stenting. In the EVA 3-S trial, no statistically significant differences between patients treated with CEA and those treated with CAS were found in SBP and the use of antihypertensive drugs at one and four years follow-up. At one year, 82% of the patients randomized to stenting used antihypertensive medication, as compared with 87% of the patients randomized to CEA.[23] This difference may have missed statistical significance because of the smaller group sizes than in our study. In a substudy of the randomized North American Symptomatic Carotid Endarterectomy Trial (NASCET), no difference in SBP at two years was observed between patients treated with CEA and patients who received best medical care alone.[24]

More stringent BP control could further reduce the long-term risk of stroke in patients treated with CAS or CEA. Randomized trials have shown that the use of antihypertensive medication reduces the risk of recurrent stroke after stroke or TIA.[25] Guidelines for the prevention of stroke in patients with TIA or stroke therefore recommend the use of antihypertensive medication for the large majority of patients.[26,27] We consider overall BP control in ICSS unsatisfactory, because the majority of patients had SBPs above target levels in guidelines current at the time (Figure 2.2). The use of any antihypertensive medication at one year was just 67% of patients after CAS and 74% after CEA. This could be seen as indicating a reduced requirement for antihypertensive medication after CAS. However, the data also indicate considerable undertreatment of hypertension in both arms. In ICSS, medical care during follow-up was at the discretion of the treating physician, and at one year this is most likely to have been the patient's general practitioner.

Our study has limitations. First, there was no predefined BP measurement protocol in ICSS. However, we do not expect this to have a large effect on our findings, because we calculated BP difference scores per patient, and because BP measurements were done according to the same policy in each center for patients treated with CAS or CEA. Second, no records were kept why BP measurements were missing, which could have caused selection bias. However, baseline characteristics of patients excluded from the analyses because of missing data did not differ greatly from those of the included patients. Excluded patients were older, which could have a caused an underestimation of BP changes. In the present study, BP changes between baseline and follow-up at one, six, and 12 months were similar between CAS and CEA. The interpretation of this finding is hampered by the substantially more frequent use of any antihypertensive drug in patients treated with CEA, despite a similar frequency of treated hypertension at baseline. In addition, no records were kept of the type of antihypertensive medication and dosages in both groups. It appears plausible that because of the larger early BP reduction after CAS than after CEA, antihypertensive medication was stopped and not resumed more frequently after CAS than after CEA. The absence of a difference in BP

between CAS and CEA during follow-up after discharge despite lower use of antihypertensive medication, suggests that CAS may have a long-term hypotensive effect compared to CEA. The analysis of data from further follow-up in ICSS beyond one year, which will be available after completion of the trial, may provide further insights into this effect.

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SUPPLEMENTARY MATERIAL

Supplementary Table S2.1 Treatment with antithrombotic or statin during follow-up

N (CAS, CEA)	CAS	CEA	RR	95% CI	*P*
1 Month follow-up					
Antithrombotic medication (722–770)	705 (98%)	745 (97%)	1.01	0.99 to 1.03	0.295
6 Months follow-up					
Antithrombotic medication (672–722)	660 (98%)	692 (96%)	1.03	1.01 to 1.04	0.009
12 Months follow-up					
Antithrombotic medication (661–720)	632 (96%)	687 (95%)	1.00	0.98 to 1.03	0.860
1 Month follow-up					
Statin/lipid lowering medication (722–770)	556 (77%)	619 (80%)	0.96	0.91 to 1.01	0.112
6 Months follow-up					
Statin/lipid lowering medication (672–722)	531 (79%)	595 (79%)	0.96	0.91 to 1.01	0.110
12 Months follow-up					
Statin/lipid lowering medication (661–720)	537 (81%)	601 (84%)	0.97	0.93 to 1.02	0.278

Data are number (%). CAS = carotid artery stenting; CEA = carotid endarterectomy; RR = risk ratio.

3

Effects of carotid endarterectomy or stenting on hemodynamic complications in the International Carotid Stenting Study: a randomized comparison

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ABSTRACT

Background Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are frequently complicated by hemodynamic instability.

Aims The study aims to compare the incidence of hemodynamic complications between carotid artery stenting (CAS) and carotid endarterectomy (CEA) in the International Carotid Stenting Study (ICSS; ISRCTN25337470).

Methods Patients with symptomatic carotid stenosis were randomly allocated to CAS or CEA. The occurrence of periprocedural hemodynamic depression (severe bradycardia, asystole, or hypotension requiring treatment) and hypertension requiring treatment was assessed in a per-protocol analysis. We compared the rate of hemodynamic complications, determined independent predictors thereof, and assessed their relation with the composite outcome of all-cause death, stroke, and myocardial infarction within 30 days of treatment.

Results A number of 766 CAS and 819 CEA patients had a single completed intervention. Hemodynamic depression occurred in 13.8% after CAS and in 7.2% after CEA (relative risk (RR), 1.9; 95% CI, 1.4 to 2.6; $P < 0.0001$). Hypertension requiring treatment occurred less often after CAS than after CEA (RR, 0.2; 95% CI, 0.1 to 0.4; $P < 0.0001$). In CAS patients, a history of cardiac failure was the strongest independent predictor of hemodynamic depression (RR, 2.4; 95% CI, 1.3 to 4.8; $P = 0.009$). There was no statistically significant association between hemodynamic complications and the occurrence of the composite outcome.

Conclusion Hemodynamic depression occurs more often after CAS and severe hypertension more often after CEA, but these complications are not responsible for the excess of major perioperative events after CAS.

INTRODUCTION

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are frequently complicated by hemodynamic instability due to manipulation of the carotid sinus. In some observational studies, hemodynamic depression after CAS has been associated with an increased risk of stroke, myocardial infarction (MI), or death.[1-4] Randomized trials have consistently shown that CAS is associated with a significantly higher rate of stroke or death within 30 days of treatment than CEA.[5] The extent to which this excess is attributable to hemodynamic depression after CAS is uncertain. Arterial hypertension after CEA and CAS has also been associated with the cerebral hyperperfusion syndrome (CHS), stroke, or death.[6-8]

Based on observational studies, hemodynamic depression appears to occur more frequently after CAS,[4,9-11] whereas hypertension and CHS may occur more frequently after CEA.[6,8-12] However, evidence from randomized trials for a difference in type and frequency of hemodynamic complications after CAS and CEA is limited.[13-15] The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial reported hypotension or bradycardia in the first 30 days after treatment in 11 (4.2%) CAS patients and in none of the CEA patients; no information is available on the rate of hypertension or CHS.[15] Early effects on blood pressure were not reported for the randomized trials Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), or Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[16-18]

Aims

Our primary aim was to compare the incidence of hemodynamic complications in patients who were treated with CAS or CEA in the randomized International Carotid Stenting Study (ICSS). We also determined independent predictors for the occurrence of hemodynamic complications and related this to outcome at 30 days after treatment.

METHODS

Subjects

All patients in this study were participants in the ICSS, an international, randomized, controlled trial comparing the risks, benefits, and cost-effectiveness of CAS and CEA in patients with a recently symptomatic carotid artery stenosis greater than 50%. Patient criteria, randomization, and results of an interim safety analysis have been described elsewhere.[19]

Stenting and surgery procedures

The ICSS study protocol prescribed that all patients should receive best medical care throughout the entire study period. The combination of aspirin and clopidogrel was recommended to cover stenting procedures. Intraprocedural heparin was mandatory at a dose determined by the operator. The protocol recommended the use of approved cerebral protection devices during stenting where it was feasible and safe to deploy them, as well as intravenous administration of atropine or a similar agent just before balloon dilatation or stent placement. Endarterectomy procedures included the use of local or general anesthesia, and shunts or patches as determined by the operating surgeon.[20]

Data collection and definitions of events

At study inclusion, data were collected on the patients' presenting symptoms, demographic characteristics, and cardiovascular risk factors. The primary outcome measure of this study was the occurrence of hemodynamic complications, defined as peri- and postprocedural bradycardia (defined as a heart rate less than 40 bpm), asystole, any new arrhythmia, and any hypotension or hypertension requiring treatment. In the ICSS protocol, no fixed cut-off blood pressure value was set to define hypotension or hypertension requiring treatment, and treatment of any hemodynamic complication was at the discretion of the treating physician. It was not mandatory to provide information on the exact timing and duration of hemodynamic changes after revascularization, and this information is therefore not available. The physiologically related symptoms bradycardia, asystole, and hypotension were combined as 'hemodynamic depression.' Diagnosis of a CHS required at least one of the following symptoms: epilepsy, headache, or confusion in the perioperative period. We related the occurrence of hemodynamic complications to the composite of all-cause death, stroke, and MI in the first 30 days after the intervention.

Study approval

ICSS (ISRCTN25337470) was approved by local ethics committees for non-UK centers and by the Northwest Multicentre Research Committee in the UK. Each patient provided written informed consent.

Statistical analysis

A per-protocol analysis was performed for the primary and secondary outcome measures. Because of the explanatory character of the study, analyses were restricted to the patients in

whom the allocated treatment was completed and a stent was deployed or endarterectomy achieved as their first and only treatment, thus patients with an abandoned treatment were excluded from the analyses.

We compared the occurrence of hemodynamic complications between patients treated with CAS or CEA with Poisson regression and calculated crude risk ratios (RR) with corresponding 95% confidence intervals (CIs). For each of the two treatments, potential predictors for hemodynamic complications were selected with univariable Poisson regression analyses, using a significance level of $P < 0.10$. We performed backward elimination analyses with hemodynamic depression or hypertension as an outcome to determine independent baseline predictors in the peri-procedural period. Predictors with $P < 0.05$ were retained in the final model. In each of the two treatment groups, outcome was compared between patients with or without hemodynamic complications by means of hazard ratios (HR) and corresponding 95% CIs with Cox-regression analysis. We additionally calculated age and sex-adjusted HRs. Similar analyses were performed for the occurrence of all strokes and that of non-disabling strokes.

RESULTS

Patient flow and baseline characteristics

Figure 3.1 illustrates the flow of the 1,713 patients enrolled in ICSS and provides reasons for exclusion from analysis in the present study. Seven hundred and sixty-six CAS and 819 CEA patients had a single initiated and completed intervention. Fewer patients randomized to CAS had a history of cardiac failure at randomization; there were no other differences in baseline characteristics between the groups (Supplementary Table S3.1). Of the patients randomized to CEA, 482 (58.9%) had a standard endarterectomy and 35 (4.3%) eversion endarterectomy. A description of the surgical technique was missing in 301 (36.7%) patients. The mean length of post-procedural hospital stay did not differ between the groups (CAS, 3.2 days; CEA, 3.6 days; MD 0.4 days; 95% CI, -0.3 to 1.2; $P = 0.272$).

Incidence of hemodynamic complications

Hemodynamic depression occurred in 105 (13.8%) of the patients treated with CAS and in 59 (7.2%) of the patients treated with CEA (RR, 1.9; 95% CI, 1.4 to 2.6; $P < 0.0001$; Table 3.1). All of the individual components of hemodynamic compromise, i.e. hypotension, asystole and severe bradycardia, were individually significantly more common after CAS

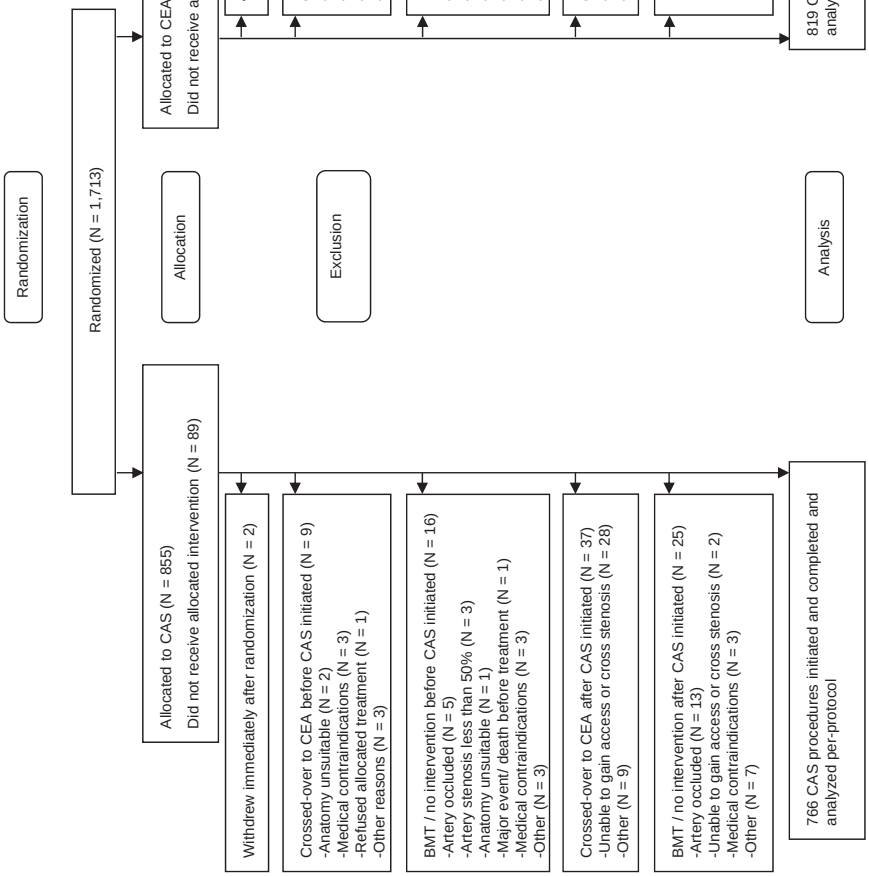

Figure 3.1 BMT indicates best medical treatment; CAS, carotid artery stenting; CEA, carotid endarterectomy. In ICSS, randomization was stratified by center with minimization for sex, age, contralateral occlusion and side of the randomized artery. No record was kept of patients screened who were ineligible or treated outside the trial.[19]

Table 3.1 Frequencies of postprocedural hemodynamic complications

N	CAS (761)	CEA (815)	RR	95% CI	*P*
Composite HD	105 (13.8%)	59 (7.2%)	1.91	1.41 to 2.58	< 0.0001
Hypotension	92 (12.1%)	56 (6.9%)	1.76	1.28 to 2.42	0.0005
Asystole	10 (1.3%)	2 (0.2%)	5.36	1.18 to 24.36	0.030
Severe bradycardia	16 (2.1%)	5 (0.6%)	3.43	1.26 to 9.31	0.016
New arrhythmia	1 (0.1%)	7 (0.9%)	0.15	0.02 to 1.24	0.079
Hypertension	12 (1.6%)	67 (8.3%)	0.19	0.11 to 0.35	< 0.0001
Cerebral hyperperfusion syndrome	4 (0.5%)	3 (0.4%)	1.42	0.32 to 6.31	0.648

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval HD, hemodynamic depression (hypotension, severe bradycardia, asystole); RR, risk ratio.

than CEA. Twelve (1.6%) patients treated with CAS and 67 (8.3%) of those treated with CEA developed hypertension requiring treatment (RR, 0.2; 95% CI, 0.1 to 0.4; $P < 0.0001$). There were only four (0.5%) and three patients (0.4%) who developed CHS after CAS and CEA, respectively. The mean length of hospital stay did not differ between patients who developed hemodynamic depression and those who did not: 5.5 days vs. 6.3 days, respectively; MD 0.7 days; 95% CI, -1.3 to 2.7; $P = 0.483$). The mean duration of hospital stay also did not differ between patients with or without postprocedural hypertension: 7.2 days vs. 6.1 days, MD -1.1 days; 95% CI -3.8 to 1.7, $P = 0.447$).

Predictors of hemodynamic complications

In patients treated with CAS, a history of cardiac failure was an independent risk factor for hemodynamic depression. A higher baseline systolic blood pressure (SBP) was associated with a lower risk of hemodynamic depression after CEA, and with a higher risk of hypertension requiring treatment in both groups. In patients treated with CAS, TIA or stroke as the presenting event was related to a lower risk of hypertension than retinal ischemia (Table 3.2). Supplementary Table S3.2 shows the RRs in the univariable analysis. Because too many data were missing on the type of CEA, we could not perform reliable analyses of this parameter.

Effect of hemodynamic complications on vascular outcomes

In the first 30 days after treatment, the composite outcome of stroke, MI, or death occurred in 60 (7.8%) of the patients treated with CAS and in 33 (4.0%) of the patients treated with

Table 3.2 Independent predictors of hemodynamic complications according to treatment

	Hemodynamic depression						Hypertension					
	CAS			CEA			CAS			CEA		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Independent predictors												
Cardiac failure	2.44	1.25 to 4.76	0.009									
Stroke before index event	0.41	0.20 to 0.87	0.019									
Systolic blood pressure (per 10 mmHg)				0.90	0.81 to 1.00	0.047	1.21	1.06 to 1.39	0.006	1.19	1.08 to 1.32	0.001
Presenting index event												
Retinal ischemia							1.00					
TIA							0.15	0.03 to 0.81	0.027			
Stroke							0.16	0.03 to 0.84	0.030			

Hemodynamic depression indicates hypotension requiring treatment, severe bradycardia, and asystole.

Table 3.3 Hazard ratios for 30-day neurological outcome after revascularization according to treatment

	CAS						CEA					
Outcome	cHR	95% CI	*P*	aHR	95% CI	*P*	cHR	95% CI	*P*	aHR	95% CI	*P*
Stroke, MI, or death												
Composite HD	1.61	0.85 to 3.03	0.141	1.53	0.81 to 2.90	0.188	0.40	0.05 to 2.89	0.361	0.40	0.06 to 2.94	0.369
Hypertension	1.08	0.15 to 7.79	0.940	0.94	0.13 to 6.82	0.953	1.57	0.55 to 4.47	0.398	1.44	0.50 to 4.11	0.496
All stroke												
Composite HD	1.54	0.79 to 2.97	0.202	1.47	0.76 to 2.84	0.255	0.49	0.07 to 3.60	0.482	0.50	0.07 to 3.72	0.501
Hypertension	1.14	0.16 to 8.22	0.899	1.01	0.14 to 7.28	0.996	1.99	0.69 to 5.74	0.206	1.85	0.64 to 5.38	0.257
Non-disabling stroke												
Composite HD	2.09	0.98 to 4.45	0.055	2.10	0.99 to 4.47	0.055	1.28	0.16 to 9.99	0.815	1.32	0.17 to 10.35	0.793
Hypertension	1.79	0.25 to 13.07	0.566	1.75	0.24 to 12.83	0.581	1.13	0.14 to 8.82	0.908	1.10	0.14 to 8.64	0.928

aHR indicates adjusted hazard ratio; CAS, carotid artery stenting; CEA, carotid endarterectomy; cHR, crude hazard ratio; HD, hemodynamic depression; MI, myocardial infarction.

CEA. There was no significant association between hemodynamic complications and the occurrence of stroke, MI, or death (Figure 3.2). Adjustment for age and sex did not alter these results substantially (Table 3.3).

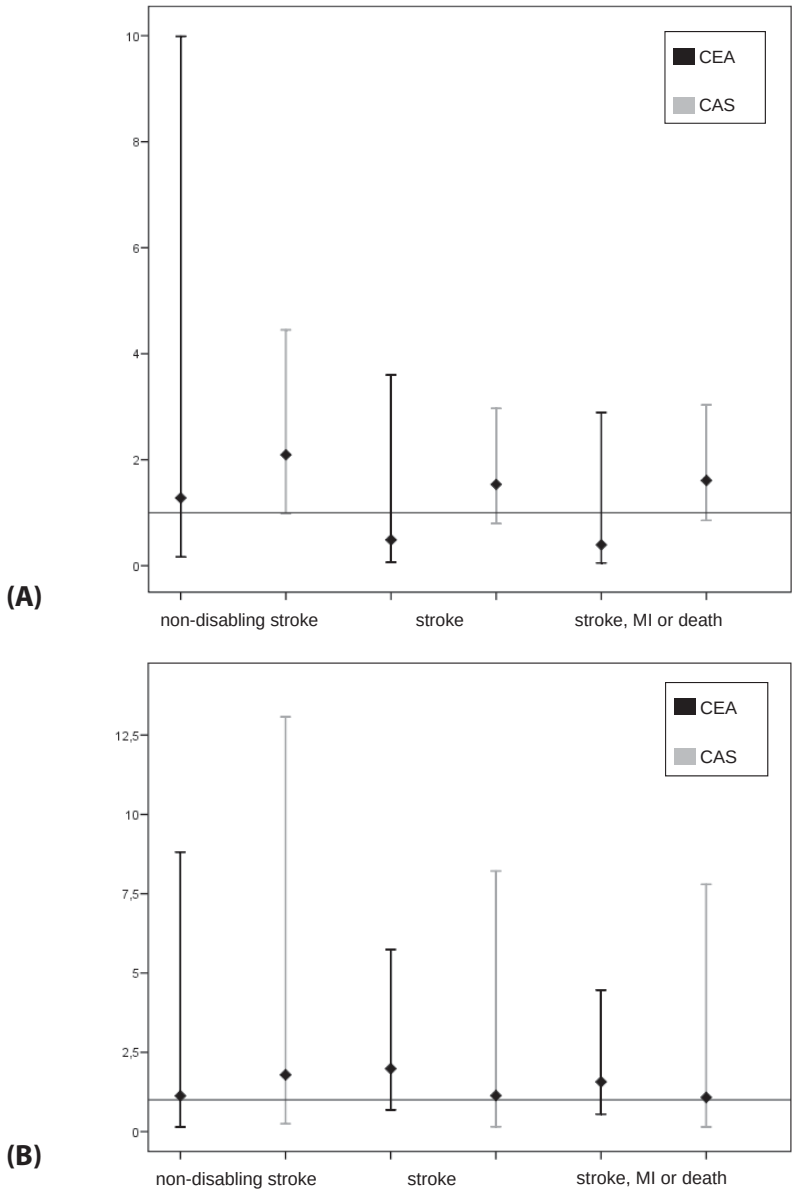

Figure 3.2 **(A)** Hazard ratios for 30-day neurological outcome after revascularization according to treatment in patients with postprocedural hemodynamic depression. **(B)** Hazard ratios for 30-day neurological outcome after revascularization according to treatment in patients with postprocedural hypertension.

DISCUSSION

In ICSS, patients had an almost twofold higher risk of developing any type of hemodynamic depression after CAS than after CEA. By contrast, severe hypertension developed five times as often after CEA than after CAS. Cerebral hyperperfusion syndrome occurred infrequently in both groups.

Information on the occurrence of hemodynamic complications after CAS and CEA in previous randomized trials is limited and not unambiguous. In a single-center substudy of 104 patients included in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), no differences were found in the frequency of episodes with hypotension (76% and 75%) or hypertension (13% and 11%) immediately after endovascular treatment or CEA, respectively.[13] In a single-center randomized trial comparing CAS and CEA in 85 patients with asymptomatic carotid artery stenosis, hypotension or bradycardia occurred in 12% of the CAS patients and in none of the patients treated with CEA.[14] In EVA-3S, bradycardia and hypotension also only occurred in patients treated with CAS.[15]

Although the rate of hemodynamic depression of 13.8% observed in patients treated with CAS in ICSS is considerably higher than the 4.2% rate of bradycardia or hypotension in EVA-3S, this is substantially lower than the frequency of these complications in uncontrolled series of patients treated with CAS. In these studies, the frequency of hypotension or hemodynamic depression ranged from 19 to 51%.[1,3,4,21,22] This difference may be explained by the use of different definitions for hypotension or hemodynamic depression as a composite measure. For example, most observational studies defined arterial hypotension as a SBP below a fixed value,[3,11,23-25] or a specific fall in blood pressure,[22,24] whereas in ICSS hypotension was only reported if this required treatment and we therefore could have missed less severe episodes of hypotension. Recent large clinical trials did not report the development of early hypotension after CEA.[15,17,18] However, non-randomized and retrospective studies have reported hypotension in the early postoperative period after CEA in 12 to 41% of the cases.[4,7,26,27] The more frequent occurrence of hemodynamic depression after CAS than after CEA can be explained by stretching of the carotid sinus baroreceptors. These receptors play a key role in short-term adjustments of blood pressure,[28] by providing a tonic inhibitory influence on sympathetic tone, thus controlling peripheral vasoconstriction and cardiac output.[29] Increased impulse frequency, as can be triggered by CAS, inhibits sympathetic action, resulting in peripheral vasodilation and blood pressure lowering. Bradycardia, by activation of cardiac branches of vagus nerves, contributes to blood pressure lowering.[30]

As expected, severe hypertension occurred more frequently after CEA than after CAS. However, even in patients treated with CEA, the incidence of hypertension was lower than

in most previous observational studies of CEA, in which post-operative hypertension was observed in 9 to 66% of the cases.[7,27,31-34] "Severe postoperative hypertension" occurred in 19% of the cases in a recent systematic review on the CHS.[12] The lower rate of hypertension requiring treatment in ICSS may reflect improvement in the control of blood pressure prior to revascularization in recent years.

After carotid surgery, hypertension can occur due to sectioning of the sinus nerves.[28] Carotid baroreceptor denervation also causes increased arterial pressure variability, because of decreased vagal and sympathetic baroreflex sensitivity.[29] However, deformation of the adventitial tissue after CEA or CAS, in which the baroreceptors are located, causes baroreceptor stimulation.[35] Several studies have suggested that the occurrence of postprocedural hypertension or hypotension after CEA is affected by the surgical technique. Sparing of the intercarotid nerve may reduce the risk of severe postoperative hypertension.[32] In an observational study, eversion endarterectomy reduced baroreceptor sensitivity and was associated with higher postoperative blood pressures and the need for more additional antihypertensive therapy in the postoperative period compared with compared to conventional CEA.[36,37] Next to dissection, clamping of the carotid sinus during carotid surgery probably damages its innervation.[28] Most severe symptoms occur when the interruption in the baroreflex is sudden, as is the case after surgery.[38]

In this study, CHS was equally rare after both procedures. The frequency of CHS in ICSS is in line with that in earlier studies, reporting an incidence of 0 to 3%.[8,12,39]

In the present study, a history of cardiac failure was the only independent risk factor for hemodynamic depression. Previous studies have associated the presence of the stenosis at the carotid bifurcation and calcification of the plaque with hemodynamic depression,[3,22,23,25] but these factors were not evaluated in ICSS. Increasing age,[24] and contralateral carotid artery stenosis,[25] which have also been related to the occurrence of hypotension and bradycardia were not found to be independent predictors of hemodynamic depression in ICSS. Higher SBP at baseline was the single most important and modifiable predictor of severe hypertension after CAS or CEA, and was also related to a lower risk of hemodynamic depression in CEA patients.

In some uncontrolled studies of patients treated with CAS, periprocedural hemodynamic depression was associated with increased rates of stroke or death,[1-3,24] but this was not confirmed by others.[11,23,25] In the current study, we found no significant association between the occurrence of either hemodynamic compromise or hypertension requiring treatment and the risk of stroke, MI, or death within 30 days. It is therefore unlikely that hemodynamic changes explain the excess of stroke and death which we reported in ICSS after CAS compared to CEA.[18]

According to current guidelines, CAS should be offered to patients considered at high surgical risk because of cardiac problems.[40] Because of the increased occurrence of hemodynamic depression after CAS in patients with cardiac failure observed in the present study, we suggest this recommendation should be treated with caution in patients with cardiac failure.

A limitation of our study was that actual blood pressure values after CAS and CEA were not noted, and that our analyses were based on episodes of hypotension or hypotension that required an intervention according to the judgment of the treating physician. This may have led to ascertainment bias, because in many centers physicians taking care of CAS patients will have been different from those responsible for CEA patients. However, a previous study has shown that at discharge after treatment, blood pressures were still considerably lower after CAS than after CEA,[41] suggesting that the increased occurrence of hypotension after CAS is real. Second, we were not able to assess the effects of specific antihypertensive drugs on hemodynamic changes after carotid revascularization, because information on the type of drug was not available. Finally, since we have insufficient information about the surgical techniques that have been used, and because ICSS was not a randomized trial comparing one surgical technique to the other, the present study cannot be used to recommend a specific technique for CEA.

In conclusion, severe hypotension and bradycardia occur more often after CAS and severe hypertension more often after CEA. Clinicians should pay careful attention to baseline SBP, since this is the only modifiable determinant for hemodynamic complications.

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SUPPLEMENTARY MATERIAL

Supplementary Table S3.1 Patient characteristics at baseline

	CAS (N = 766)	CEA (N = 819)
Age (years)	70 (9)	70 (9)
Sex (male)	534 (70%)	577 (71%)
Vascular risk factors		
Treated hypertension	523 (69%)	571 (70%)
Systolic blood pressure (mmHg)	147 (24)	146 (24)
Systolic blood pressure > 180 mmHg	83 (11%)	86 (11%)
Diastolic blood pressure (mmHg)	79 (12)	78 (12)
Cardiac failure	21 (3%)	44 (6%)
Angina pectoris in past 6 months	74 (10%)	72 (9%)
Previous myocardial infarction	133 (18%)	150 (19%)
Previous CABG	99 (13%)	111 (14%)
Atrial fibrillation	47 (6%)	53 (7%)
Other cardiac embolic source	16 (2%)	16 (2%)
Type 2 diabetes mellitus	121 (16%)	135 (17%)
Type 1 diabetes mellitus	47 (6%)	38 (5%)
Peripheral arterial disease	128 (17%)	131 (16%)
Current smoker	186 (25%)	190 (23%)
Ex-smoker	364 (48%)	404 (50%)
Treated hyperlipidemia	474 (63%)	537 (66%)
Cholesterol (mmol/L)	4.9 (1.3)	4.9 (1.3)
Degree of symptomatic carotid stenosis[a]		
50–69%	81 (11%)	72 (9%)
70–99%	685 (89%)	747 (91%)
Degree of contralateral stenosis[a]		
< 50%	510 (67%)	538 (66%)
50–69%	111 (15%)	135 (17%)
70–99%	97 (13%)	104 (13%)
Occluded	45 (6%)	35 (4%)
Unknown	3 (0%)	7 (1%)
Most recent ipsilateral event[b]		
Amaurosis fugax	138 (18%)	134 (16%)
Transient ischemic attack	247 (32%)	291 (36%)
Ischemic hemispheric stroke	349 (46%)	359 (44%)
Retinal infarction	23 (3%)	22 (3%)
Unknown	9 (1%)	13 (2%)

Supplementary Table S3.1 continues on next page

Supplementary Table S3.1 *Continued*

	CAS (N = 766)	CEA (N = 819)
Event < 6 months before randomization	741 (97%)	779 (95%)
Event 6–12 months before randomization[c]	25 (3%)	38 (5%)
Multiple events before randomization	303 (40%)	307 (38%)
Stroke before index event	115 (15%)	103 (13%)
Modified Rankin score at randomization[d]		
0–2	686 (90%)	711 (87%)
3–5[d]	66 (9%)	94 (12%)
Unknown	14 (2%)	14 (2%)

Data are number (%) or mean (SD). CABG indicates coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy; mRS, modified Rankin scale.

[a] Degree of stenosis measured by North American Symptomatic Carotid Endarterectomy Trial method at randomization center.[1]

[b] If two events were reported on the same day, the more serious was counted (stroke > retinal infarction > transient ischemic attack > amaurosis fugax).

[c] In two patients the event was more than 12 months before randomization and in two the date was unknown.

[d] Some Rankin scores of 3 or more were caused by non-stroke disability.

Supplementary Table S3.2 Predictors of hemodynamic complications according to treatment

	Composite hemodynamic depression						Hypertension					
	CAS			CEA			CAS			CEA		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
Age	1.01	0.99 to 1.03	0.485	1.02	0.99 to 1.05	0.154	1.05	0.99 to 1.11	0.125	1.01	0.99 to 1.03	0.468
Female sex	1.11	0.76 to 1.61	0.603	0.81	0.46 to 1.42	0.459	1.15	0.35 to 3.80	0.813	1.60	1.00 to 2.54	0.048
Vascular risk factors												
Treated hypertension	1.13	0.76 to 1.68	0.545	1.14	0.65 to 1.98	0.653	1.36	0.37 to 4.96	0.646	1.15	0.69 to 1.93	0.597
Systolic blood pressure (10 mmHg)	1.05	0.98 to 1.13	0.202	0.90	0.82 to 1.00	0.049	1.24	1.07 to 1.43	0.005	1.25	1.15 to 1.37	0.000
Diastolic blood pressure (10 mmHg)	1.05	0.91 to 1.20	0.522	0.93	0.78 to 1.10	0.387	1.26	0.89 to 1.79	0.194	1.30	1.11 to 1.54	0.001
Cardiac failure	2.11	1.05 to 4.25	0.037	1.26	0.48 to 3.33	0.637	3.17	0.43 to 23.40	0.259	1.10	0.42 to 2.89	0.843
Angina pectoris in past 6 months	0.86	0.45 to 1.63	0.641	0.74	0.28 to 1.99	0.556	0.83	0.11 to 6.36	0.860	0.83	0.34 to 1.98	0.667
Previous myocardial infarction	1.23	0.80 to 1.90	0.340	1.24	0.69to 2.24	0.475	2.33	0.71 to 7.62	0.163	1.38	0.81 to 2.35	0.240
Previous CABG	0.85	0.49 to 1.49	0.574	1.44	0.77 to 2.69	0.253	2.20	0.61 to 7.98	0.231	1.23	0.67 to 2.28	0.503
Atrial fibrillation	0.91	0.42 to 1.96	0.808	0.76	0.25 to 2.36	0.638	1.36	0.18 to 10.34	0.764	0.67	0.22 to 2.05	0.481
Other cardiac embolic source	1.35	0.48 to 3.81	0.567	1.74	0.46 to 6.50	0.412	4.18	0.57 to 30.48	0.158	1.52	0.41 to 5.69	0.531
Type 2 diabetes mellitus	1.09	0.68 to 1.74	0.719	1.02	0.53 to 1.96	0.959	2.63	0.81 to 8.61	0.109	0.68	0.33 to 1.38	0.283
Type 1 diabetes mellitus	0.75	0.32 to 1.75	0.506	1.09	0.36 to 3.31	0.885	1.36	0.18 to 10.34	0.764	0.62	0.16 to 2.45	0.499
Peripheral arterial disease	0.75	0.44 to 1.27	0.287	0.82	0.40 to 1.68	0.585	0.44	0.06 to 3.40	0.434	1.64	0.96 to 2.78	0.068
Current smoker	0.67	0.42 to 1.07	0.097	0.75	0.40 to 1.42	0.375	0.61	0.14 to 2.75	0.519	0.87	0.49 to 1.52	0.616
Ex-smoker	1.27	0.89 to 1.82	0.185	1.57	0.95 to 2.61	0.079	1.07	0.35 to 3.29	0.904	1.04	0.66 to 1.64	0.882
Treated hyperlipidemia	0.90	0.62 to 1.28	0.547	0.93	0.56 to 1.55	0.777	0.60	0.19 to 1.83	0.367	1.05	0.64 to 1.71	0.846
Cholesterol (mmol/L)	0.87	0.76 to 1.01	0.070	1.05	0.86 to 1.28	0.633	1.01	0.63 to 1.61	0.982	1.21	1.01 to 1.46	0.039

Supplementary Table S3.2 continues on next page

Supplementary Table S3.2 *Continued*

	Composite hemodynamic depression						Hypertension					
	CAS			CEA			CAS			CEA		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
70–99% degree symptomatic carotid stenosis	1.13	0.62 to 2.08	0.691	1.81	0.58 to 5.63	0.307	0.36	0.99 to 1.29	0.117	1.53	0.57 to 4.07	0.398
Degree of contralateral stenosis												
50–69% stenosis	0.86	0.49 to 1.49	0.588	1.15	0.60 to 2.19	0.672	0.66	0.08 to 5.31	0.696	1.13	0.61 to 2.09	0.687
70–99% stenosis	1.21	0.74 to 1.99	0.453	1.37	0.71 to 2.66	0.353	2.27	0.60 to 8.61	0.229	1.24	0.64 to 2.39	0.522
contralateral occlusion	0.83	0.35 to 1.94	0.658				1.65	0.21 to 13.10	0.636	1.09	0.36 to 3.35	0.875
Most recent ipsilateral event												
Amaurosis fugax	0.96	0.37 to 2.52	0.931	1.97	0.27 to 14.41	0.504	0.17	0.03 to 1.13	0.066	1.64	0.22 to 12.20	0.628
Transient ischemic attack	0.68	0.26 to 1.77	0.429	1.90	0.27 to 13.35	0.520	0.14	0.03 to 0.80	0.026	2.28	0.33 to 15.91	0.407
Stroke	0.80	0.32 to 2.02	0.798	1.23	0.17 to 8.77	0.835	0.17	0.03 to 0.81	0.026	1.60	0.23 to 11.27	0.636
Unknown	0.64	0.08 to 4.97	0.669	1.83	0.13 to 26.77	0.658						
Multiple events before randomization	0.73	0.50 to 1.07	0.109	0.79	0.47 to 1.34	0.381	1.09	0.35 to 3.41	0.880	1.61	1.02 to 2.55	0.040
Stroke before index event	0.41	0.20 to 0.86	0.018	0.37	0.12to 1.17	0.092	1.91	0.53 to 6.95	0.325	1.68	0.95 to 2.97	0.073
Modified Rankin score at randomization	0.89	0.45 to 1.75	0.733	1.03	0.48 to 2.21	0.935	1.07	0.14 to 8.20	0.950	0.36	0.12 to 1.12	0.077

CAS indicates carotid artery stenting; CEA, carotid endarterectomy. Hemodynamic depression indicates the composite of hypotension needing treatment, severe bradycardia, and asystole.

SUPPLEMENTARY REFERENCES

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Periprocedural hemodynamic depression is associated with a higher number of new ischemic brain lesions after stenting in the International Carotid Stenting Study-MRI Substudy

Stroke [Accepted for publication].

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ABSTRACT

Background and purpose Carotid artery stenting (CAS) is associated with a higher risk of both hemodynamic depression and new ischemic brain lesions on diffusion-weighted imaging (DWI) than carotid endarterectomy (CEA). We assessed whether the occurrence of hemodynamic depression is associated with these lesions in patients with symptomatic carotid stenosis treated by CAS or CEA in the randomized International Carotid Stenting Study (ICSS) MRI Substudy.

Methods The numbers and total volumes of new ischemic lesions on DWI one to three days after CAS or CEA were measured in the ICSS-MRI substudy. Hemodynamic depression was defined as periprocedural bradycardia, asystole, or hypotension requiring treatment. The number of new ischemic lesions was the primary outcome measure. We calculated risk ratios (RR) and 95% confidence intervals (CI) per treatment with Poisson regression comparing the number of lesions in patients with or without hemodynamic depression.

Results A total of 229 patients were included (122 allocated CAS, 107 CEA). After CAS, patients with hemodynamic depression had a mean of 13 new DWI lesions, compared with a mean of 4 in those without hemodynamic depression (RR, 3.36: 95% CI, 1.73 to 6.50). The number of lesions after CEA was too small for reliable analyses. Lesion volumes did not differ between patients with or without hemodynamic depression.

Conclusions In patients treated by CAS, periprocedural hemodynamic depression is associated with an excess of new ischemic lesions on DWI. The findings support the hypothesis that hypoperfusion increases the susceptibility of the brain to embolism.

Clinical Trial Registration - URL : http://www.controlled-trials.com. Unique identifier: ISRCTN25337470.

INTRODUCTION

In patients with symptomatic carotid artery stenosis, stenting (CAS) is associated with a higher risk of periprocedural stroke than endarterectomy (CEA).[1] Patients treated by CAS also more frequently have new ischemic lesions on post-treatment MRI scans with diffusion-weighted imaging (DWI).[2] The cause of the higher risk of new cerebral ischemia early after CAS as compared to CEA is uncertain.

Embolism from the carotid artery plaque during stent deployment or arterial dissection is generally held responsible for the majority of new ischemic lesions during carotid revascularization. During CAS and CEA, cerebral microembolic signals are often detected with transcranial Doppler.[3] A high frequency of these signals has been associated with a higher risk of stroke,[4] but the large majority of the underlying emboli do not lead to cerebral ischemia.[5] It has been proposed that under circumstances of a normal cerebral perfusion, most of these emboli are cleared by the cerebral circulation, and that hypoperfusion increases the risk of a focal ischemic lesion.[6] This is supported by a study that showed that patients with impaired perfusion in the hemisphere ipsilateral to the carotid artery stenosis before stenting had more ischemic lesions on DWI after the intervention than patients with a normal perfusion.[7]

Both CAS and CEA may be accompanied by periprocedural hemodynamic depression or other cardiovascular symptoms.[8] In the International Carotid Stenting study (ICSS),[9] severe arterial hypotension, bradycardia or asystole occurred twice as often in patients treated by CAS than by CEA.[10] Such hemodynamic depression may lead to a temporary reduction in cerebral perfusion.[11,12]

We hypothesized that hemodynamic depression during CAS or CEA will impair the washout of emboli during revascularization and will therefore be associated with a higher risk of new DWI lesions on MRI performed soon after revascularization. Therefore, we compared the number and volume of new DWI lesions after CAS or CEA in patients who experienced hemodynamic depression with the number and volume of lesions in those without hemodynamic depression.

METHODS

Subjects

All patients in this study were participants in the ICSS-MRI substudy,[2] a prospective multicenter substudy in seven centers within ICSS (ISRCTN25337470).[13] ICSS is an

international, randomized controlled trial comparing the risks and benefits of CAS versus CEA in patients with recently symptomatic carotid artery stenosis greater than 50%. The design of both studies, patient eligibility criteria, the results of an interim safety analysis of ICSS, and the main results of the MRI substudy have been reported previously.[2,9]

Study approval

ICSS (ISRCTN25337470) and the MRI substudy were approved by local ethics committees for non-UK centers and by the Northwest Multicentre Research Committee in the UK. All patients provided written informed consent.

Stenting and surgery procedures

The ICSS study protocol prescribed that all patients should receive best medical care throughout the entire study period. The combination of aspirin and clopidogrel was recommended to cover stenting procedures. Intraprocedural heparin was mandatory at a dose determined by the operator. Approved cerebral protection devices were recommended for use during stenting where it was feasible and safe to deploy them, as well as the intravenous administration of atropine or a similar agent just before balloon dilatation or stent placement. Endarterectomy procedures included the use of local or general anesthesia, and shunts or patches as determined by the operating surgeon.[13]

Data collection and definitions of hemodynamic events

At study inclusion, data were collected on the patients' presenting symptoms, demographic characteristics, and cardiovascular risk factors. Hemodynamic depression was defined as the occurrence during or soon after revascularization of one or more of the physiologically related symptoms bradycardia (defined as a heart rate of < 40 BPM), asystole, or hypotension requiring treatment.[10] In ICSS, no fixed cut-off blood pressure value was set to define 'hypotension requiring treatment.' Treatment of any hemodynamic complication was at the discretion of the treating physician. Investigators were asked to complete the forms as soon as possible after the revascularization procedure, but it was not mandatory to provide information on the exact timing and duration of hemodynamic changes after revascularization. Therefore hemodynamic depression could occur any time between the start of the intervention to discharge.

Imaging

MRI scans at field strengths of 1.5 T or 3.0 T were performed 1 to 7 days before treatment (pretreatment MRI), and 1 to 3 days after treatment (post-treatment MRI). Sixty-six patients were studied with 3-T scanners (CAS, N = 37; CEA, N = 29) and 165 were studied with 1.5-T scanners (CAS, N = 87; CEA, N = 78). Pre- and post-treatment scans included DWI sequences. On each scan, the number and volume of hyperintense lesions on DWI was measured. New periprocedural ischemic brain lesions were defined as hyperintense DWI lesions on post-treatment MRI that were not present on pretreatment MRI. In each patient, the total number of new DWI lesions (lesion count) and the total lesion volume were assessed. White matter lesions, or age-related white matter changes (ARWMC) are correlates of small vessel disease on imaging of brain parenchyma.[14] Quantification of these lesions was done on the pretreatment fluid-attenuated inversion recovery sequences with the ARWMC scale.[15]

Outcome measures

The primary outcome measure of the present study was the total count of new hyperintense DWI lesions on the post-treatment scan that were not present on the pretreatment scan. The total volume of these lesions was a secondary outcome measure.

Statistical analysis

For this study, we carried out a per-protocol analysis including only patients who completed the allocated treatment as their first and only ipsilateral treatment. Patients who received the alternative revascularization procedure (cross-overs) or received no revascularization were therefore excluded from the analyses.

Because of the differences in the occurrence of hemodynamic depression and in the risk of new ischemic lesions between CAS and CEA, we performed all analyses separately for each of the two treatment groups. We compared the number of new DWI lesions between patients with or without hemodynamic depression with Poisson regression and calculated crude risk ratios (RR) with corresponding 95% confidence intervals (CIs). To accommodate the large variance in the lesion count data, we adapted the scale parameter of the Poisson model. We adjusted crude RR estimates for the five largest imbalances in baseline characteristics per treatment. In a post-hoc analysis we also adjusted for the use of a cerebral protection device or atropine during stenting.

For log-transformed DWI total lesion volumes, we calculated mean differences with corresponding 95% CIs between the patients with and without hemodynamic depression with linear regression and adjusted for imbalances in baseline characteristics.

RESULTS

Baseline characteristics

There were 231 patients included in the ICSS-MRI substudy.2 Two CAS patients with missing information on hemodynamic complications were excluded from the current analyses. Therefore, this study included a total of 229 patients, of whom 122 were treated by CAS and 107 by CEA. Fifteen patients (12%) treated by CAS and 9 (8%) treated by CEA had hemodynamic depression requiring treatment. Baseline characteristics of the patients are shown in Table 4.1. In patients treated by CAS relevant baseline differences in the patients with and those without hemodynamic depression comprised baseline ARWMC score, sex, smoking history, the index ischemic event, and a history of multiple ischemic events before randomization. In patients treated by CEA these were baseline ARWMC score, age, sex, smoking history, and systolic blood pressure at randomization.

The mean patient stay was 3.5 days in the hospital after the intervention, without differences according to treatment or the occurrence of hemodynamic depression (data not shown). In 44 (36%) CAS procedures a cerebral protection device was used. In 12 (10%) CAS patients information on the use of cerebral protection devices was missing. Hemodynamic depression occurred in 6 (14%) CAS patients treated with such a device, and in 9 (14%) CAS patients treated without cerebral protection (RR, 1.0; 95% CI, 0.4 to 2.6). Atropine was administered during stenting in 75 (61%) CAS patients; information on atropine use was not available in 21 (17%) of patients. Thirteen (17%) patients treated with atropine had periprocedural hemodynamic depression, and two (8%) patients not treated with atropine (RR, 2.3; 95% CI, 0.5 to 9.3).

DWI lesions

In both patient groups, there was no difference in the proportion of patients with at least one new DWI lesion between patients who had hemodynamic depression compared with those without hemodynamic depression (Table 4.2). After CAS, patients with hemodynamic depression had a mean of 13 new DWI lesions, versus a mean of 4 in those without hemodynamic depression: RR, 3.36; 95% CI, 1.73 to 6.50. Adjustments for the potentially

Table 4.1 Patient characteristics at baseline

	CAS (N = 122)		CEA (N = 107)	
	HD+ (N = 15)	HD- (N = 107)	HD+ (N = 9)	HD- (N = 98)
Age (years)	70 (8.7)	70 (9.4)	67 (6.8)	70 (8.9)
Sex (male)	13 (87%)	72 (67%)	7 (78%)	69(70%)
Vascular risk factors				
Treated hypertension	10 (67%)	73 (68%)	6 (67%)	68 (69%)
Systolic blood pressure (mm Hg)	159 (24)	156 (26)	147 (22)	158 (24)
Diastolic blood pressure (mm Hg)	84 (11)	82 (13)	75 (9)	84 (13)
Cardiac failure	2 (13%)	1 (1%)	0 (0%)	6 (6.7%)
Previous myocardial infarction	4 (27%)	14 (14%)	0 (0%)	12 (14%)
Previous CABG	1 (7%)	10 (10%)	2 (22%)	6 (7%)
Atrial fibrillation	1 (7%)	4 (4%)	0 (0%)	5 (6%)
Diabetes mellitus type II	2 (13%)	9 (9%)	4 (44%)	13 (15%)
Peripheral arterial disease	1 (7%)	21 (20%)	1 (11%)	14 (14%)
Current smoker	3 (20%)	35 (36%)	2 (22%)	23 (26%)
Ex-smoker	8 (53%)	40 (41%)	7 (78%)	44 (49%)
Treated hyperlipidemia	9 (60%)	68 (64%)	8 (89%)	64 (65%)
Degree of symptomatic carotid stenosis[a]				
50–69%	1 (7%)	14 (13%)	0 (0%)	8 (8%)
70–99%	14 (93%)	93 (87%)	9 (100%)	90 (92%)
Degree of contralateral stenosis[a]				
< 50%	9 (60%)	70 (65%)	4 (44%)	71 (72%)
50–69%	1 (7%)	11 (10%)	2 (22%)	14 (14.3%)
70–99%	3 (20%)	20 (19%)	3 (33%)	11 (11%)
Occluded	2 (13%)	6 (6%)	0 (0%)	2 (2%)
ARWMC at baseline	4.7 (5.1)	5.5 (4.7)	4.0 (3.4)	5.3 (4.4)
Most recent ipsilateral event[b]				
Amaurosis fugax	4 (27%)	19 (18%)	2 (22%)	18 (19%)
Transient ischemic event	4 (27%)	37 (35%)	3 (33%)	42 (44%)
Ischemic hemispheric stroke	5 (33%)	48 (45%)	2 (22%)	36 (38%)
Retinal infarction	2 (13%)	2 (2%)	1 (11%)	0 (0%)
Unknown	0 (0%)	1 (1%)	1 (11%)	0 (0%)
Multiple events before randomization	6 (40%)	49 (50%)	2 (22%)	40 (45%)
Stroke before index event	1 (7%)	20 (20%)	1 (11%)	12 (14%)
Modified Rankin score at randomization				
0–2[c]	14 (93%)	88 (92%)	8 (89%)	79 (90%)

Data are number (%) or mean (SD). ARWMC indicates age-related white matter changes; CAS, carotid artery stenting; CEA, carotid endarterectomy; CABG, coronary artery bypass grafting; HD (hemodynamic depression = hypotension requiring treatment, severe bradycardia and asystole) and mRS, modified Rankin scale. [a] Degree of stenosis measured by North American Symptomatic Carotid Endarterectomy Trial[16] method at randomization center. [b] If two events were reported on the same day, the more serious was counted (stroke > retinal infarction > transient ischemic attack > amaurosis fugax). [c] Some Rankin scores of 3 or more were caused by non-stroke disability.

Table 4.2 Hemodynamic depression and new ischemic brain lesions

	CAS (N = 122)			CEA (N = 107)		
	HD+ (N = 15)	HD- (N = 107)	RR 95% CI	HD+ (N = 9)	HD- (N = 98)	RR 95% CI
At least one new DWI lesion	8 (53%)	52 (49%)	1.10 (0.66 to 1.83)	3 (33%)	15 (15%)	2.18 (0.77 to 6.13)
Count DWI lesions Mean (SD)	13 (30)	4 (10)	3.36 (1.73 to 6.50)	0.4 (0.7)	0.6 (2.2)	0.71 (0.13 to 3.86)
Adjustment						
ARWMC			3.41 (1.77 to 6.59)			0.82 (0.15 to 4.40)
Age						0.76 (0.14 to 4.14)
Sex			3.13 (1.60 to 6.13)			0.71 (0.13 to 3.87)
Smoking (present and past)			3.29 (1.71 to 6.35)			0.83 (0.15 to 4.63)
Ipsilateral index event			4.08 (2.12 to 7.85)			
Multiple events before index event			3.28 (1.71 to 6.30)			
SBP						1.08 (0.22 to 5.32)
Cerebral protection device use			3.48 (1.75 to 6.92)			
Atropine use			3.83 (1.89 to 7.73)			

	CAS (N = 122)			CEA (N = 107)		
	HD+ (N = 15)	HD- (N = 107)	MD[a] 95% CI	HD+ (N = 9)	HD- (N = 98)	MD[a] 95% CI
Total Volume Median (Q1–Q3)	0.0425 (0.000–1.930)	0 (0.000–0.137)	0.54 (-0.10 to 1.17)	0 (0.00–0.09)	0 (0.00–0.00)	0.08 (-0.48 to 0.64)
Adjustment						
ARWMC			0.57 (-0.06 to 1.20)			0.10 (-0.47 to 0.67)
Age						0.09 (-0.48 to 0.65)
Sex			0.53 (-0.12 to 1.17)			0.07 (-0.49 to 0.63)
Smoking (present and past)			0.53 (-0.11 to 1.16)			0.11 (-0.46 to 0.68)
Ipsilateral index event			0.60 (-0.05 to 1.24)			
Multiple events before index event			0.55 (-0.10 to 1.21)			
SBP						0.17 (-0.38 to 0.73)
Cerebral protection device use			0.55 (-0.12 to 1.21)			
Atropine use			0.57 (-0.12 to 1.26)			

ARWMC indicates age-related white matter changes; CAS: carotid artery stenting; CEA: carotid endarterectomy; HD: hemodynamic depression (hypotension requiring treatment, severe bradycardia, and asystole); MD: mean difference; Q1–Q3; interquartile range; RR: risk ratio; SBP: systolic blood pressure. [a] Mean difference after log transformation; a positive difference indicates larger volumes with HD+.

confounding baseline factors (ARWMC score, sex, smoking history, the index ischemic event, and history of multiple ischemic events) had no major influence on the crude effect estimate (Table 4.2). The occurrence of hemodynamic depression had no effect on lesion count after CEA: RR, 0.71; 95% CI, 0.13 to 3.86 (Table 4.2). This did not change after adjustment for the baseline ARWMC score, age, sex, smoking history, or systolic blood pressure. Most patients had their postprocedural MRI within one day of the intervention. Supplementary Table S4.1 shows the distribution of lesions in patients with or without hemodynamic depression based on the timing of the postprocedural scan. Post-hoc adjustments for the use of a cerebral protection device or atropine during stenting did not affect the outcomes (Table 4.2).

For both CAS and CEA, there were no differences in total DWI lesion volume between patients with hemodynamic depression and those without hemodynamic depression after log-transformation. The mean differences did not change essentially after adjustment (Table 4.2). Supplementary Table S4.2 shows the data of the combined treatment groups.

DISCUSSION

We found that in patients who were treated by CAS, the occurrence of peri-procedural hemodynamic depression was associated with an over three times higher number of new ischemic brain lesions on DWI compared with patients without this complication. This effect was not observed in patients who had hemodynamic depression after CEA.

Our finding of an increased occurrence of new ischemic lesions on DWI in patients with hemodynamic depression after CAS is in line with earlier observations in uncontrolled studies, in which periprocedural hemodynamic depression was associated with increased rates of stroke or death after CAS.[17-20] However, this association has not been found in every study.[21-23]

In the current study, 12% of the patients treated by CAS had periprocedural hemodynamic depression requiring treatment, whereas uncontrolled series of patients treated by CAS have reported frequencies of arterial hypotension or hemodynamic depression ranging from 19 to 51%.1[7,19,24-26] This difference may be explained by ascertainment bias, because the assessment of hemodynamic depression was a primary aim of some of the observational studies, but not of ICSS. In addition, definitions for hypotension or hemodynamic depression as a composite measure differed between ICSS and the observational studies. Most of the last defined arterial hypotension as a drop in systolic blood pressure below a fixed value, or as a specific absolute fall in blood pressure, whereas in ICSS hypotension was only reported if this required treatment.[10] We therefore could have missed less severe

episodes of hypotension.

In ICSS, hemodynamic depression requiring treatment occurred in 13.8% of the patients treated by CAS and in 7.2% of the patients treated by CEA.[10] In the ICSS-MRI substudy, 35% of the patients treated by CAS and 9% of those treated by CEA had two or more new ischemic lesions on DWI.[27] Because the number of patients with two or more new DWI lesions after CAS was substantially higher than the number with hemodynamic depression requiring treatment, it is clear that the difference in the risk of hemodynamic depression requiring treatment between CAS and CEA is not the only determinant of the difference in the occurrence of new ischemic lesions between the two treatments. However, smaller reductions in blood pressure that did not require treatment were not reported in ICSS, and it is possible that these may have contributed to the development of new lesions in some patients not fulfilling our definition of hemodynamic depression. Our assumption that in ICSS reductions in blood pressure after CAS did occur more frequently than reported is supported by the fact that at discharge, systolic blood pressures were about 10 mm Hg lower after CAS than after CEA.[28] Moreover, in the present study, hemodynamic depression remained strongly associated with an increased number of new ischemic lesions after adjustments for potentially confounding baseline factors.

The main source for periprocedural ischemia after CEA or CAS is thromboembolism.[29] Our findings are consistent with the hypothesis that hypoperfusion increases the susceptibility of the brain to infarction from emboli by impairing washout of emboli from the cerebral circulation.[6,30] Hemodynamic depression after carotid revascularization procedures occurs when carotid sinus stimulation leads to bradycardia, by affecting the sinus and atrioventricular nodes, and to hypotension, by peripheral vasodilatation.[31] In ICSS as a whole, we found no evidence that the increased rate of hemodynamic depression after CAS explained the excess of stroke and death within 30 days of CAS versus CEA.[9,10] However, the number of clinical outcome events was relatively small. MRI increases the number of ischemic insults detected as a result of revascularization, increasing the sensitivity to differences between patients.[2] Using ischemic lesions on DWI as a surrogate marker for ischemic stroke after carotid revascularization,[2] we have now been able to correlate hemodynamic depression with postprocedural cerebral ischemia.

Our study suggests that prevention of severe hypotension and bradycardia might reduce the number of new DWI lesions after CAS, but this can only be tested in a new randomized trial. It has been proposed that in case of hemodynamic depression after stenting, patients should be treated with intravenous fluids, atropine and alpha-agonists, and that any oral antihypertensive medication should be discontinued.[32] However, treatment options may vary based on patient characteristics and on the severity of hemodynamic symptoms.

In contrast to patients treated by CAS, we found no evidence that hemodynamic depression was associated with a higher number of new ischemic lesions in patients treated by CEA. However, the number of new ischemic lesions in patients treated by CEA was very low, and we therefore lacked statistical power to detect any association. Total lesion volumes did not differ between patients with or without hemodynamic depression, our data, however, suggests that the individual lesions were smaller in patients who had hemodynamic depression

Strengths of this study are the prospective assessment of hemodynamic depression and of new ischemic lesions on DWI, in addition to its relatively large sample size. A limitation is the lack of direct periprocedural cerebral perfusion measures. We therefore cannot confirm that hemodynamic depression resulted in compromised cerebral perfusion. Secondly, in ICSS it was not mandatory to report the exact timing of periprocedural hemodynamic complications, although the investigators were asked to complete the form as soon as possible after the procedure. It is therefore possible that these could have occurred at any time between the start of the revascularization and discharge. However, based on observations in uncontrolled series,[17,19,24-26] we expect that the large majority of hemodynamic events will have occurred during or immediately following CAS or CEA. For this reason, most if not all MRI scans will have been performed after the development of hemodynamic depression. Moreover, we do not have data on the duration of hemodynamic depression, therefore we cannot refute the possibility that duration of hemodynamic compromise influences the amount of new ischemic lesions. In the ICSS-MRI substudy the interval to the postprocedural MRI was longer after CEA than after CAS, median 1 day (interquartile range (IQR) 1-2) and 1[IQR 1-1], respectively $P = 0.008$.[2] And we could therefore have missed additional new ischemic lesions after CAS. Finally, apart from the severity of the stenosis, we do not have information on plaque characteristics.

Conclusion

In patients treated by CAS, hemodynamic depression was associated with a higher number of new ischemic lesions on postprocedural DWI MRI. This finding suggests that avoidance of periprocedural hypotension and bradycardia may reduce the risk of DWI lesions occurring during CAS.

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SUPPLEMENTARY MATERIAL

Supplementary Table S4.1 Timing of new lesions between patients with or without hemodynamic depression

Postprocedural MRI N total = 229	HD+ N = 24	HD- N = 205	RR 95% CI
At same day or day 1			
≥ 1 lesion	8 (40%)	50 (34%)	1.18 (0.66 to 2.10)
≥ 2 lesions	5 (25%)	31 (21%)	1.19 (0.52 to 2.69)
Total 167 (73%)	20	147	
After day 1			
≥ 1 lesion	3 (75%)	17 (29%)	2.56 (1.28 to 5.12)
≥ 2 lesions	3 (75%)	12 (21%)	3.63 (1.70 to 7.73)
Total 167 (73%)	4	58	

CI indicates confidence interval; HD, hemodynamic depression; RR, risk ratio.

Supplementary Table S4.2 Hemodynamic depression and new ischemic brain lesion in total population

	HD+ N = 24	HD- N = 205	RR 95% CI
Any new DWI lesion (yes/no)	11 (46%)	67 (33%)	1.40 (0.87 to 2.26)
Count DWI lesions Mean (SD)	8.46 (24.4)	2.36 (7.4)	3.58 (2.07 to 6.22)
Adjustment			
ARWMC			3.71 (2.14 to 6.42)
Age			4.02 (2.36 to 6.84)
Sex			3.41 (1.96 to 5.95)
Smoking (present and past)			3.82 (2.21 to 6.62)
Ipsilateral index event			3.63 (2.10 to 6.28)
Multiple events before index event			3.37 (1.94 to 5.87)
SBP			3.54 (2.03 to 6.18)
Treatment			3.10 (1.87 to 5.15)
			MD[a] 95% CI
Median volume (Q1–Q3)	0 (0.00–0.26)	0 (0.00–0.05)	0.40 (-0.04 to 0.84)
Adjustment			
ARWMC			0.43 (-0.00 to 0.87)
Age			0.42 (-0.01 to 0.86)
Sex			0.39 (-0.05 to 0.83)
Smoking (present and past)			0.43 (-0.01 to 0.87)
Ipsilateral index event			0.41 (-0.03 to 0.86)
Multiple events before index event			0.40 (-0.06 to 0.85)
SBP			0.41 (-0.03 to 0.85)
Treatment			0.36 (-0.07 to 0.79)

ARWMC indicates age-related white matter changes; CAS: carotid artery stenting; CEA: carotid endarterectomy; HD: hemodynamic depression (hypotension requiring treatment, severe bradycardia, and asystole); MD: mean difference; Q1–Q3; interquartile range; RR: risk ratio; SBP: systolic blood pressure. [a] Mean difference after log transformation; a positive difference indicates larger volumes with HD+.

SECTION 2

Cognition

5

Cognition after carotid endarterectomy or stenting: a randomized comparison

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ABSTRACT

Objective To compare the effect on cognition of carotid artery stenting (CAS) and carotid endarterectomy (CEA) for symptomatic carotid artery stenosis.

Methods Patients randomized to CAS or CEA in the International Carotid Stenting Study (ICSS; ISRCTN25337470) at two participating centers underwent detailed neuropsychological examinations (NPE) before and six months after revascularization. Ischemic brain lesions were assessed with diffusion-weighted imaging before and within three days after revascularization. Cognitive test results were standardized into z-scores, from which a cognitive sum score was calculated. The primary outcome was the change in cognitive sum score between baseline and follow-up.

Results Of the 1,713 patients included in ICSS, 177 were enrolled in the two centers during the substudy period, of whom 140 had an NPE at baseline and 120 at follow-up. One patient with an unreliable baseline NPE was excluded. CAS was associated with a larger decrease in cognition than CEA, but the between-group difference was not statistically significant: -0.17 (95% CI, -0.38 to 0.03; $P = 0.092$). Eighty-nine patients had a pre-treatment MRI and 64 within three days after revascularization. New ischemic lesions were found twice as often after CAS than after CEA (relative risk, 2.1; 95% CI, 1.0 to 4.4, $P = 0.041$).

Conclusions Differences between CAS and CEA in effect on cognition were not statistically significant, despite a substantially higher rate of new ischemic lesions after CAS than after CEA.

Classification of evidence This study provides Class III evidence that any difference between the effects of CAS and CEA on cognition at six months after revascularization is small.

INTRODUCTION

Carotid endarterectomy (CEA) reduces the risk of stroke in patients with recently symptomatic internal carotid artery (ICA) stenosis.[1] Carotid artery stenting (CAS) has been considered an alternative to CEA, but to date the equivalence of stenting and endarterectomy for the treatment of symptomatic carotid stenosis has not been established.[2-5] In addition, on diffusion-weighted imaging (DWI), new ischemic lesions are found about three times as often after CAS than after CEA.[6,7] The majority of these lesions did not cause focal neurological deficits, but there has been concern that these may have a negative impact on cognition.[6,8] In elderly people free of dementia and stroke at baseline, the presence of "silent" infarcts more than doubled the risk of dementia and was related to a steeper decline in cognitive functioning.[9] Our primary aim was to compare the effects on cognition of CAS and CEA in patients with symptomatic carotid artery stenosis. A secondary aim was to compare the occurrence of new cerebral ischemic lesions on DWI-MRI in a subpopulation of these patients.

METHODS

The present study is a prospective substudy of the International Carotid Stenting Study (ICSS) performed in two of the participating centers.[4] All ICSS patients at the University Medical Center Utrecht (UMCU) and the Academic Medical Center in Amsterdam (AMC), the Netherlands, enrolled in ICSS between February 2006 and December 2008, could participate in this substudy.

Center and investigator requirements for participating in the ICSS, patient eligibility criteria, procedures, and clinical follow-up examinations have been described elsewhere.[4] Randomization in the ICSS was stratified by center with minimization for sex, age, contralateral occlusion and side of the randomized artery.[4] MRI results were interpreted by two independent observers (LMJ, LHB) who were blinded to treatment assignment and to clinical and cognitive outcomes. Neuropsychological examinations (NPEs) were administered by trained researchers and took about 90 minutes to complete. Essentially, the test battery did not rely on motor responses. When a test was not considered reliable due to a focal neurological deficit, the results of this test were excluded from the analyses. NPEs were rated by a single observer (AA) and were screened for accuracy by an experienced clinical neuropsychologist (MJEvZ).

Standard protocol approvals and patient consent

The institutional review boards of the two centers approved both the ICSS (ISRCTN25337470) and this substudy, and written informed consent was obtained from each patient.

Study sample and assessments

Patients

Patients with recently symptomatic ICA stenosis of > 50%, measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria or its non-invasive equivalent,[1] were randomly assigned to CAS or CEA. At inclusion, data were collected on presenting symptoms, demographic characteristics, and cardiovascular risk factors. The score on the National Institutes of Health Stroke Scale (NIHSS)[10] was assessed at baseline and at one day after the procedure, and the score on the modified Rankin Scale (mRS)[11] at baseline and at one and six months after the procedure.

Cognition

Cognition was assessed in the week preceding the procedure and after six months. The neuropsychological examination comprised eight cognitive domains, including 16 tasks (Table 5.1). Mood was assessed by the Beck Depression Inventory II,[12] and anxiety by the Spielberger State-Trait Anxiety Inventory.[13] Premorbid verbal intelligence was estimated by the National Adult Reading Test (NART; Dutch version),[14] pre-existent cognitive decline with the Informant Questionnaire on Cognitive Decline in the Elderly,[15] and current signs of general cognitive decline with the Mini-Mental State Examination.[16] Supplementary Table S5.1 provides a short description of these assessments.

Raw NPE scores per individual at baseline and at follow-up were expressed as SD units; the so-called z-scores. These z-scores were calculated using the mean and SD of a control group,[17] in which healthy individuals performed the same NPE at baseline and at 6-month follow-up, hereby controlling for potential practice effects in our patients. The z-score for each domain represents the mean of the z-scores comprising that domain. As a measure of overall cognitive functioning, a cognitive sum score was calculated, representing the mean z-score over the eight domains.[18] Negative cognitive scores express a score below the mean of the reference group.

Table 5.1 Cognitive functioning at baseline

	CAS (N = 71)	CEA (N = 69)
Cognitive sum z-score[a]	-0.05 (0.71)	-0.35 (1.08)
Baseline domain z-scores and raw test scores		
Abstract Reasoning z-score	-0.26 (0.75)	-0.49 (0.90)
Raven Advanced Progressive Matrices, short form	5.9 (2.7)	5.8 (2.7)
WAIS similarities	19.8 (5.7)	17.6 (7.1)
Attention z-score	0.91 (1.26)	0.50 (0.69)
WAIS III Digit Span Forward	8.2 (2.2)	7.6 (2.2)
Visual Elevator of the Test of Everyday Attention[b]	7.0 (1.9)	7.6 (2.9)
Executive Functioning z-score	-0.41 (0.59)	-0.61 (0.69)
Brixton Spatial Anticipation Task	21.7 (6.5)	22.0 (7.2)
Letter Fluency[c]	9.7 (3.9)	7.6 (2.9)
Language z-score	-0.39 (0.83)	-0.61 (1.20)
Token Test, short form	16.6 (3.2)	15.5 (4.4)
Boston Naming Test, short form	77.4 (10.9)	75.9 (12.7)
Verbal Memory z-score	0.11 (1.08)	-0.34 (1.02)
WAIS III Digit Span backward	5.2 (2.3)	4.7 (2.0)
Rey Auditory Verbal Learning Test[d]	20.4 (5.1)	18.4 (5.4)
Semantic Fluency	26.7 (9.9)	24.6 (9.5)
Visual Memory z-score	-0.15 (1.08)	-0.23 (0.85)
Rey-Osterrieth Complex Figure-delay	15.2 (7.2)	14.6 (5.7)
Visual Perception z-score	-0.35 (0.90)	-0.47 (0.98)
Benton Judgment of Line Orientation, short form	22.1 (6.4)	22.2 (6.2)
Facial Recognition Task, short form	42.6 (5.2)	42.9 (4.7)
Rey-Osterrieth Complex Figure-copy	31.7 (5.4)	30.4 (5.8)
Neglect z-score	1.18 (1.79)	0.44 (3.56)
Star Cancellation of the Behavioral Inattention Task	54.7 (1.9)	53.9 (3.7)
Premorbid and current cognition		
Informant Questionnaire of Cognitive Decline	3.1 (0.2)	2.9 (0.5)
Estimated premorbid Intelligent Quotient (NART)	111.8 (23.1)	105.1 (28.1)
MMSE	27 [19–30]	25 [20–29]
Premorbid anxiety/depression		
STAI	40.9 (13.1)	39.8 (11.4)
STAT	34.6 (10.1)	33.1 (9.1)
BDI	7.1 (6.3)	7.2 (6.4)

Data are mean (SD) or median [range]. Abbreviations: CAS = carotid artery stenting, CEA = carotid endarterectomy, WAIS = Wechsler adult intelligence scale, NART = national adult reading test, MMSE = mini mental state examination, STAI = state-trait anxiety inventory (state), STAT = state-trait anxiety inventory (trait), BDI = Beck's depression inventory. [a] Cognitive scores are expressed as SD units (z-scores) from the mean in a normal reference population, with negative values expressing scores below the reference mean. [b] The mean of the visual elevator accuracy and timing score. [c] The mean of total words produced beginning with letter "N" or "A". [d] The mean of the total direct, delayed, and recognized word count [range 5.0 to 36.6]. Neuropsychological test battery.[18]

MRI

MRI with DWI was performed one to three days before revascularization and within three days thereafter. The number and volume of new ischemic lesions were assessed as part of the previously reported ICSS-MRI study.[7] A new ischemic lesion was defined as a new hyperintensity on the post-treatment DWI that was not present on the pre-treatment MRI. Lesions were silent if there was no new correlating focal neurological deficit.

Outcome measures

Our primary aim was to compare the effects on cognition between CAS and CEA in patients with symptomatic carotid artery stenosis. Previous controlled studies have provided class III evidence that neither procedure has an effect on cognition.[19-21] Our primary outcome measure was the change in cognitive sum z-score between baseline and follow-up. A decrease in z-score means a worsening of cognition from baseline to follow-up. Secondary outcome measures were the changes in individual cognitive domain scores, and the number and volumes of new DWI lesions after treatment.

Sample size calculation and statistical analysis

The original target sample size was 200 patients, enabling detection of an assumed 20% difference between CAS and CEA in the occurrence of cognitive impairment at six months follow-up, with a significance of 5% and a power of 80%. Data were analyzed per treatment received, i.e. the analysis included all patients who received either procedure, irrespective of cross–over from allocated treatment. This implies that patients without any treatment were excluded.

We performed T-tests for continuous and normally distributed data, Mann-Whitney U tests for ordinal and non-parametric data, and χ^2 analyses for categorical data on baseline characteristics to determine whether any selection had occurred between patients who were re-examined at follow-up and those who were not. We calculated the mean difference in the change of the cognitive sum z-score between baseline and follow-up between the two groups with corresponding 95% CIs, and adjusted for age, sex, and education with linear regression. Similar calculations were done for domain scores.

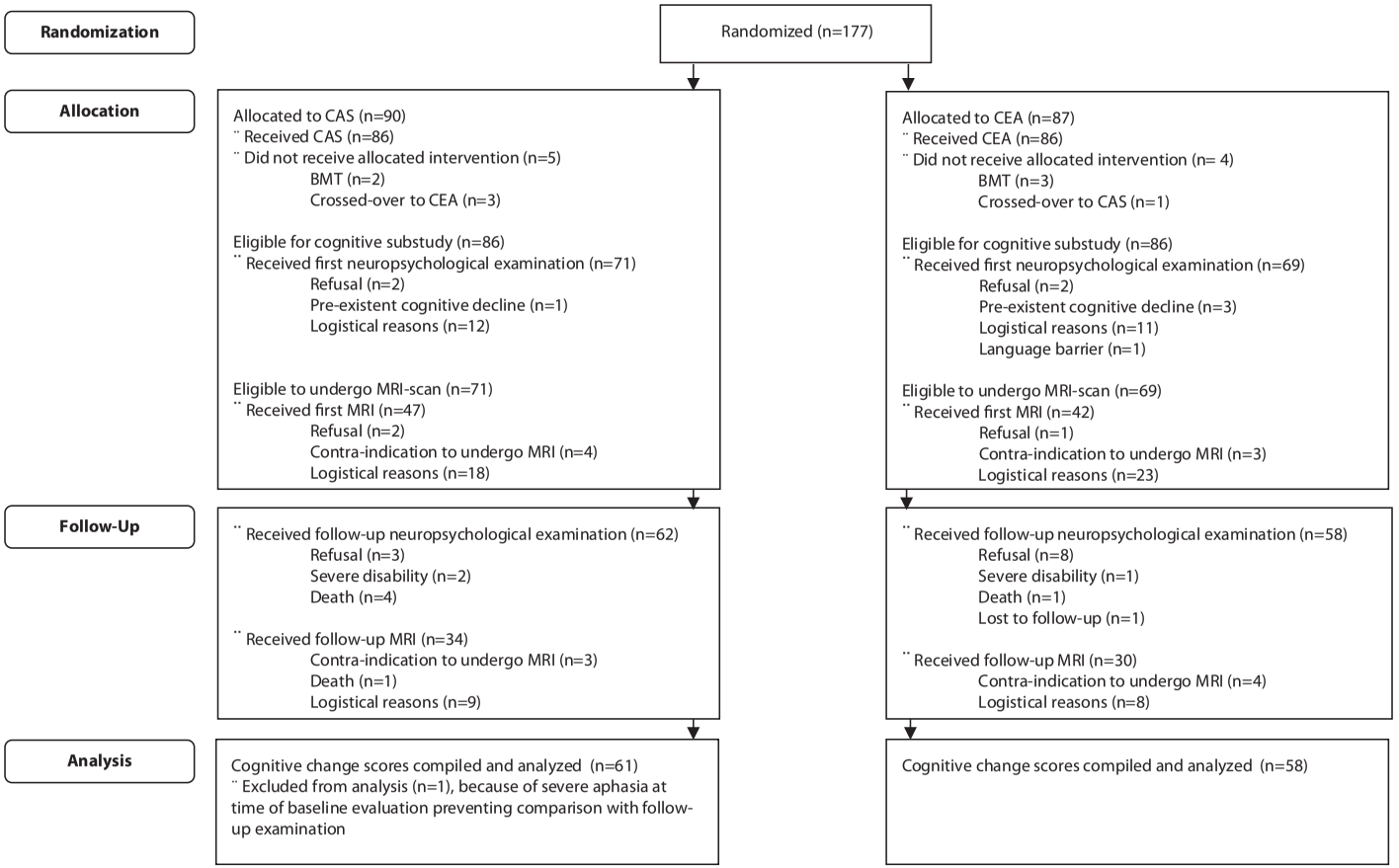

Figure 5.1 Flowchart of cognitive substudy population. Abbreviations: CAS = carotid angioplasty and stenting, CEA = carotid endarterectomy, BMT = best medical treatment. In ICSS, randomization was stratified by center with minimization for sex, age, contralateral occlusion and side of the randomized artery. No record was kept of patients screened who were ineligible or treated outside the trial.[4]

RESULTS

The current study was terminated before the target of 200 patients had been reached when inclusion into the ICSS was stopped. During the study period, 177 patients were included in the ICSS at the two participating centers (Figure 5.1). Seventy-one of the 88 patients (81%) randomized to CAS, and 69 of 89 patients (76%) randomized to CEA were enrolled in this study and underwent the baseline NPE. Of these 140 patients, 120 (86%) were seen for follow-up NPE and included in the analyses (Figure 5.1). One patient with an unreliable baseline NPE was excluded from analysis. The pre-treatment MRI scan was performed in 89 of the 140 patients (64%) and the post-treatment scan in 64 (46%). The patients in the two groups did not differ with regard to baseline characteristics, anxiety and depression levels, educational level, and estimated premorbid intelligence, but patients in the CAS group had a slightly higher MMSE at baseline (Table 5.2). Patients who did not have follow-up NPE were 6.2 years older (95% CI, 1.2 to 11.3; $P = 0.016$), but they did not differ with regard to other demographic, clinical, or baseline cognitive characteristics. The drop-out rate was 9 after CAS and 11 after CEA.

There was a significant decrease in the cognitive sum score after CAS of 0.19 (95% CI, 0.10 to 0.29; $P < 0.0001$) from baseline to six-months follow-up, but there was no significant decrease in the score after CEA, which fell by 0.02 (95% CI, -0.16 to 0.21; $P = 0.825$). The mean difference of -0.17 (95% CI, -0.38 to 0.03, $P = 0.092$) between the changes was not statistically significant (Table 5.3). This did not change after a post-hoc adjustment for baseline depression and anxiety. Within the individual domains, the unadjusted change in the cognitive domain 'abstract reasoning' was significantly worse after CAS (difference between changes -0.22; 95% CI, -0.44 to 0.00; $P = 0.046$), but after adjustment for age, sex and education this did not stay statistically significant. There were no statistically significant differences between the groups in the change in any of the other domains either before or after adjustment (data not shown).

New ischemic DWI lesions were found in 17 (50%) of 34 patients after CAS and 7 (23%) of 30 patients after CEA (risk ratio 2.1; 95% CI, 1.0 to 4.4; $P = 0.041$). There were no statistically significant differences in baseline characteristics between patients with and those without new DWI lesions (data not shown). DWI lesions were associated with new focal neurological deficits in two patients with ischemic strokes after CAS and one ischemic stroke after CEA. In the patients with new DWI lesions on the post treatment MRI, there were no differences between CAS and CEA in number or volumes of these lesions. The median number of lesions in patients after CAS was 3 (interquartile range (IQR), 1 to 9.5) compared with 1 (IQR 1 to 6) after CEA ($P = 0.236$). Median total lesion volume was 0.30 mL (IQR, 0.22

to 1.47) after CAS and 0.13mL (IQR, 0.06 to 0.49) after CEA ($P = 0.340$). There were no significant differences between CAS and CEA in the post-procedural score on the NIHSS, the 6-month stroke rate, and the mRS score at 1 and 6 months follow-up (data not shown).

Table 5.2 Patient characteristics at baseline

	CAS (N = 71)	CEA (N = 69)
Demographics		
Age (years)	69.4 (8.9)	67.9 (12.5)
Education	5 [1–7]	4 [2–7]
Sex (male)	50 (70%)	51 (74%)
Vascular Risk Profile		
History of hypertension	50 (70%)	48 (71%)
Cardiac failure	1 (1%)	3 (4%)
History of diabetes	14 (19%)	16 (23%)
Angina pectoris in last 6 months	6 (9%)	3 (4%)
Myocardial infarction	7 (10%)	15 (22%)
CABG	8 (11%)	12 (17%)
Peripheral arterial disease	9 (13%)	13 (19%)
Atrial fibrillation	2 (3%)	3 (5%)
Other cardiac embolic source	2 (3%)	2 (3%)
Current smoker	27 (38%)	18 (27%)
History of hyperlipidemia	47 (67%)	51 (75%)
Systolic blood pressure (mmHg)	169 (28)	166 (27)
Diastolic blood pressure (mmHg)	86 (13)	87 (14)
Presenting symptomatology		
Amaurosis fugax or retinal infarct	27 (38%)	17 (25%)
Transient ischemic attack	34 (48%)	35 (51%)
Hemispheric ischemic stroke	30 (42%)	35 (51%)
Time intervals (days)		
Last event to randomization	31 (34)	25 (30)
Last event to neuropsychological evaluation	39 (36)	36 (34)
Last event to treatment	41 (36)	38 (34)
Artery characteristics		
Symptomatic artery, L	37 (52%)	37 (54%)
Severe (70–99%) stenosis symptomatic artery	63 (89%)	60 (87%)
Clinical assessment		
NIHSS	0 [0–9]	0 [0–11]
mRS	1 [0–4]	1 [0–3]

Data are mean (SD), number (%), or median [range]. Abbreviations: CAS = carotid artery stenting, CEA = carotid endarterectomy, CABG = coronary artery bypass grafting, NIHSS = national institutes of health stroke scale, mRS = modified Rankin scale.

Table 5.3 Change in cognitive functioning between baseline and follow-up

Domain (N CAS, N CEA)	CAS	CEA	Mean difference	95% CI
Change in cognitive sum z-score[a] (61,58)	-0.19 (0.38)	-0.02 (0.71)	-0.17	-0.38 to 0.03
Change in cognition domain z-scores				
Abstract Reasoning (43,34)	-0.17 (0.48)	0.04 (0.45)	-0.22	-0.44 to 0.00
Attention (59,57)	-0.09 (1.05)	-0.13 (1.60)	0.04	-0.46 to 0.53
Executive Functioning (55,45)	0.13 (0.36)	0.17 (0.48)	-0.05	-0.21 to 0.12
Language (59,58)	-0.25 (0.68)	-0.18 (0.70)	-0.07	-0.32 to 0.18
Verbal Memory (59,56)	-0.16 (0.76)	-0.09 (1.00)	-0.07	-0.39 to 0.26
Visual Memory (53,52)	0.24 (0.72)	0.24 (0.66)	0.00	-0.27 to 0.26
Visual Perception (54,50)	-0.14 (0.54)	-0.17 (0.73)	0.04	-0.21 to 0.28
Neglect (49,42)	-1.75 (1.70)	-0.61 (3.57)	-1.13	-2.27 to 0.01

Data are mean (SD). [a] Change measured as the cognitive sum z-score at follow-up minus the sum z-score at baseline (negative values indicate a decrease in z-score). After adjustment for age, sex, and education these results did not change essentially. Abbreviations: CAS = carotid artery stenting, CEA = carotid endarterectomy.

DISCUSSION

In this study, no statistically significant difference in the change in cognition after six months follow-up was detected between CAS and CEA for symptomatic carotid artery stenosis. Because recruitment into the ICSS was terminated earlier than expected, inclusion in this substudy was stopped before the target sample size of 200 patients had been reached. The lack of a difference in cognition between CAS with CEA may therefore be explained by insufficient statistical power. However, our study strongly suggests that any difference between the effects of CAS and CEA on cognition at six months after revascularization is small. Unfortunately, given the recent completion of the ICSS and the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST),[5] it appears inconceivable that another and larger randomized trial will address this issue shortly.

In contrast to CEA, CAS was associated with a small but statistically significant detrimental effect on cognition at six months after treatment. The effect of worse cognitive functioning in patients treated with CAS is consistent with the substantially higher rate of new ischemic DWI lesions after CAS than after CEA. However, this finding should be interpreted with caution because the evaluation of within-group changes in cognition was not the primary aim of our study and may also have been affected by the premature termination of this study.

The effects of CAS and CEA on cognition have previously been compared in a single randomized study that included 48 patients.[21] No difference in cognition was observed

between the groups at six and 30 days after treatment. Two older randomized studies have compared the effects on cognition of CEA with those of percutaneous transluminal angioplasty without stenting, including 46 and 116 patients, respectively.[19,20] At six months there was no difference in cognition between the groups. The first two studies were underpowered to detect small differences, and the last has only been published as an abstract.[19] An apparent observation is that patients in these studies as well as in ours had a relatively good cognition at baseline free of focal neuropsychological impairments at the group level. Previous non-randomized studies have reported conflicting effects of CAS or CEA on cognition.[22] These results may be attributed to differences in patient characteristics and in methodological aspects. We used an extensive neuropsychological test battery and controlled for potential practice effects by use of a reference group that was re-assessed after an identical time interval. Therefore, we confidently conclude that the observed effects of CAS and CEA on cognition are real.

Consistent with earlier studies, the incidence of new DWI lesions in the population examined in this study was significantly higher after CAS than after CEA.[6,7] Several authors have expressed concerns that new and clinically 'silent' ischemic lesions after CAS or CEA could lead to new cognitive impairment.[6-9] However, in two recent studies of 22 and 41 patients with asymptomatic ICA stenosis treated with stenting, no relation was found between the number of new DWI lesions and cognitive functioning at six weeks or three months, but these studies were severely underpowered.[23,24] A similar observation was made in another small and non-randomized study of CAS or CEA for symptomatic or asymptomatic stenosis.[25]

The clinical significance of new ischemic lesions on early DWI has been questioned because of their partial reversibility: in the ICSS-MRI study, just 17% of patients with new DWI lesions detected after CAS and 53% of those with new lesions after CEA had corresponding new hyperintensity on fluid attenuated inversion recovery (FLAIR) images at the site of at least one lesion after one-month.[7] In addition, most lesions may be too small to lead to cognitive impairment. However, the deterioration in cognitive functioning that we found after CAS supports concerns that even small and partly reversible lesions may affect cognition in a population at risk of cognitive decline.

There are important strengths to our study. First, this is the largest randomized study on the effects on cognition in patients treated for symptomatic carotid stenosis. Second, we had an MRI scan in a large sub-set of patients, and it appears unlikely that the occurrence of new ischemic lesions differed substantially between patients who were scanned and those who were not. Third, in a large percentage of patients neuropsychological follow-up (86%) was performed. Fourth, a very comprehensive neuropsychological test battery,

which covered all essential cognitive domains, was used; furthermore the potential effects of mood and anxiety were taken into account.

In addition to the premature termination of patient inclusion, our study has other limitations. Not all patients enrolled in ICSS in our two centers were included in the current study. This might have caused selection bias. In addition, patients who did not have follow-up NPE were 6.2 years older. Although these patients did not differ from the 120 patients who did have follow-up with regard to other demographic, clinical or cognitive characteristics at baseline, we cannot exclude that the cognitive effects of revascularization in these patients could have been different. Furthermore, we could not prevent that the NPEs were performed unblinded to treatment allocation. Finally, our data concern the first six months after revascularization only. If during longer follow-up new ischemic lesions add additional brain damage to those induced by CAS or CEA, differences between the groups may become more pronounced.

With the present sample size, differences in cognition between CAS and CEA for symptomatic carotid stenosis at six months after treatment were just not statistically significant. In a secondary analysis, CAS had a small but statistically significant detrimental effect on cognitive functioning at six months after treatment for symptomatic carotid stenosis, an effect not observed with CEA. Given the more than two-fold higher rate of new ischemic lesions on DWI after CAS than after CEA, this study lends support to concerns that such lesions may have a harmful effect on cognition.

However, our study provides Class III evidence that any difference between the effects of CAS and CEA on cognition at six months after revascularization is small.

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SUPPLEMENTARY MATERIAL

Supplementary Table S5.1 Contents of assessments

	Content
Beck's Depression Inventory	Measures depressive symptoms. It consists of a 21 question survey, with each answer scored on a scale of 0 to 3. A score of < 15 denotes mild, from 15–30 moderate, and > 30 severe depression.[1]
National Adult Reading Test, Dutch version	Estimates premorbid verbal intelligence level. It requires reading of 50 irregular words. The score is the number of correctly pronounced words. The NART score is transposed into an IQ (Intelligent Quotient) score.[2]
Modified Rankin Score	Measures the degree of disability or dependence in daily activities. The scale consists of 6 points, with 0 meaning no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; and 5, severe disability.[3]
Informant Questionnaire on Cognitive Decline in the Elderly	Determines the decline in cognitive functioning. The short form enlists 16 everyday situations, and is rated by a relative for amount of change over the past 10 years. The following scale is used: 1. Much improved, 2. A bit improved, 3. Not much change, 4. A bit worse, 5. Much worse. A score above 3.3 to 3.6 is likely to be related to dementia.[4]
Mini Mental State Examination	Screens for general cognitive decay. It consists of a 30-point questionnaire; a score of ≥ 25 denotes no symptoms of cognitive decay and 21–24, mild; 10–20, moderate; and ≤ 9, severe cognitive impairment.[5]
National Institutes of Health Stroke Scale	A 42 point scale with 11 categories to assess stroke related neurological deficit. Ratings for each item are between 0 and 4 with 0 as normal. There is allowance for untestable items.[6]
Spielberger State Trait Anxiety Inventory	A self-report assessment including separate measures of state and trait anxiety. There are 20 statements on each questionnaire, each with 4 possible responses. Each response option has a weighted score of 1 to 4. The scores can vary from 20 to 80. High scores on the scales mean more anxiety.[7]
Education	Dutch classification system, according to Verhage, including 7 categories. 1 = did not finish primary school, 2 = finished primary school, 3 = did not finish secondary school, 4 = finished secondary school, low level, 5 = finished secondary school, medium level, 6 = finished secondary school, highest level, and/or college degree, 7 = university degree.[8]

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6

The effect of white matter lesions on cognition after carotid revascularization

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ABSTRACT

Background Cerebral white matter lesions (WML) are associated with cognitive impairment, and carotid revascularization with cognitive worsening or improvement. We assessed the relation between WML severity and changes in cognition after carotid endarterectomy or stenting.

Methods Patients with symptomatic carotid artery stenosis, enrolled in the International Carotid Stenting Study (ISRCTN25337470), underwent detailed neuropsychological examinations (NPE) before and after 6 months. Cognitive results were standardized into z-scores, from which a sumscore was calculated. The primary outcome was the mean difference (MD) in sumscore between baseline and follow-up. Changes in sumscore were related to WML severity with the 'age-related white matter changes' score, assessed on baseline MRI-FLAIR. Three groups were formed based on this score.

Results Eighty-nine patients had both baseline MRI and NPE, of these 77 had a calculable cognitive difference score. The cognitive sumscore at six months was worse than at baseline: MD,-0.21; 95% CI, -0.32 to -0.09). The change in sumscore did not depend on WML load: MD for no-to-mild WML, -0.15; 95% CI, -0.39 to 0.09, for moderate WML, -0.27; 95% CI, -0.48 to -0.06; and for severe WML, -0.21; 95% CI, -0.40 to -0.04. This did not change essentially after adjustment for baseline factors.

Conclusion Cognitive functioning deteriorated after carotid revascularization, regardless of baseline WML burden.

INTRODUCTION

Cerebral white matter lesions (WML) have been associated with cognitive deficits,[1-4] particularly with disturbances in executive functioning, attention, naming, and visuoconstructional praxis,[2,5] but also in mental speed and on global measures of cognition.[2,4,5] The prevalence and severity of WML increase with age[6-8] and with the presence of hypertension[6,9] or diabetes.[10] WML are correlates of small vessel disease on imaging of brain parenchyma, encompassing ischemic and hemorrhagic lesions.[11] One probable pathophysiological mechanism is that a decrease in vessel lumen leads to chronic hypoperfusion of the white matter, eventually resulting in cell degeneration and cell death.[11]

In some studies, the severity of WML has been associated with the extent of atherosclerosis in the carotid artery,[3,12,13] but others did not find this association.[8] Internal carotid artery stenosis has also been associated with cognitive impairment,[3] and some authors have reported improvement in cognition after carotid revascularization.[14] However, such improvement was not observed in all studies,[14] and in a recent substudy of the randomized International Carotid Stenting Study (ICSS),[15] carotid artery stenting (CAS) had a small detrimental effect on cognitive functioning at six months after treatment, whereas carotid endarterectomy (CEA) had no effect on cognition.[16]

Because of the reported interrelation between carotid artery stenosis, WML, and cognitive impairment, we tested the hypothesis that the severity of WML at the time of carotid revascularization might influence cognitive performance at six months, with an improvement in patients with no or minor WML at baseline and no improvement or worsening in patients with a higher WML load, due to a reduced "cognitive reserve" in these patients.

METHODS

The study population consisted of participants who were recruited simultaneously in the cognition substudy[16] and in the MRI substudy[17] of ICSS (ISRCTN25337470)[15,18] between February 2006 and December 2008 at the University Medical Center Utrecht (UMCU) and the Academic Medical Center in Amsterdam (AMC), the Netherlands. Patients were considered eligible for neuropsychological examination (NPE) if there was neither a language barrier nor pre-existent cognitive decline. Patients were excluded if they did not have any revascularization procedure after randomization. The institutional review boards of these centers had approved both studies, and written informed consent was obtained from each patient.

Patients and procedures

Patient criteria and procedures in ICSS have been reported earlier.[15,18] In short, patients with recently symptomatic ICA stenosis of at least 50%[19] were randomly assigned to CAS or CEA. Data on presenting symptoms, demographic characteristics, and cardiovascular risk factors were collected. The National Institutes of Health Stroke Scale (NIHSS)[20] was assessed at baseline and at one day after treatment, and the modified Rankin Scale (mRS)[21] at baseline and at one and six months after treatment.

Neuropsychological assessment

The neuropsychological tests used to assess cognition in this study have been reported previously.[16] Cognition was assessed in the week preceding treatment and after six months by means of an extensive NPE that consisted of 15 tests, resulting in 20 test measures representative for the major cognitive domains according to Lezak, i.e. abstract reasoning, attention, executive functioning, language, verbal memory, visual memory, visual perception, and neglect.[22] By combining performance over tasks and cognitive domains, we also assessed cognitive integrity or 'mental effort' by means of tasks that go beyond the scope of the corresponding cognitive domain itself.[23] That is, evaluation of functions where many different cognitive abilities are needed for optimal performance including mental speed, attention, executive functioning, planning, and overview capacity and cognitive flexibility. This construct of 'mental effort' consisted of the following tasks: Boston naming task, Verbal fluency (Letters 'N' and 'A' in 1 minute), the Visual Elevator subtest of the Test of Everyday Attention, the Rey-Osterrieth complex figure (copy and delayed recall trial) and the Benton Judgment of Line Orientation test.

Measures of mood states for depression were tested with the Beck's Depression Inventory (2nd Ed.),[24] and of anxiety with the State and Trait Anxiety Inventory.[25] Higher assessment scores indicate a higher measure of anxiety or depression. Pre-existent cognitive decline was assessed by means of the Informant Questionnaire of Cognitive Decline;[26] where everyday situations are rated by a relative for amount of cognitive change over the past 10 years and a score above 3.6 is likely to be related to dementia. Furthermore, estimates for current general cognitive functioning (Mini Mental State Examination) were obtained.[27]

Test results transformation

Individual test scores were transformed into standard deviation (SD) units – z-scores – based on the mean and SD of a control group.[28] The control group consisted of healthy

individuals who had performed the same NPE and were retested after an identical time interval, hereby controlling for potential practice effects in our patients. Control subjects were free from pre-existent neurological, psychiatric or cognitive abnormalities. The z-score for each domain was derived by calculating the mean of the z-scores comprising that domain. Also, as a measure of overall cognition, a cognitive sum score was calculated, representing the mean over the eight major cognitive domains.[22] Negative domain scores at baseline express a score below the mean of the control group. To assess the cognitive change over time, difference scores were calculated by subtracting the baseline values from the scores at follow-up. Therefore, negative domain or sum change scores indicate a decrease from baseline.

Imaging

Magnetic Resonance Imaging (MRI) was performed one to three days before treatment. MRI parameters, WML data, and lesion measurements have been reported earlier.[17] Baseline WML were semiquantitatively assessed on fluid-attenuated inversion recovery (FLAIR) sequences using the Age-Related White Matter Change (ARWMC) score, which has a good intra- and interrater reliability.[29,30] An ARWMC sum score was calculated afterwards (range 0–30). Based on the sum ARWMC score, patients were divided into groups according to tertiles in the current patient group: no-to-mild ARWMC ≤ 3 (WML-), moderate ARWMC = 4–5 (WML+), and severe ARWMC ≥ 6 (WML++).

Outcome measures

The primary outcome measure of this study was the change in cognitive sum z-score between baseline and follow-up, expressed as a mean difference (MD). Secondary outcome measures were the change(s) per cognitive domain z-scores.

Statistical analysis

Descriptive statistics were performed on patient characteristics at baseline in the three WML categories. We compared cognitive change between baseline and follow-up between the three WML groups with linear regression in which we used two dummy variables for the non-normally distributed WML classes. Differences between the WML groups were calculated with accompanying 95% confidence intervals (CIs) and were adjusted for age, sex, and education. In a separate model we additionally adjusted for baseline imbalances between the groups (history of coronary artery bypass grafting, presenting TIAs or

symptoms involving an eye). Negative difference scores between the groups indicate a worse performance in comparison with the reference group, i.e. the "no-to-mild WML" category. We calculated the unadjusted change within the different WML groups with the paired t-test.

RESULTS

Patient flow

Figure 6.1 shows the patient flow, and provides reasons for exclusion. A total of 151 patients were eligible to participate during the study period. Eventually, 78 patients had both MRI imaging and a follow-up NPE. The study population consisted of the 77 patients with a calculable cognitive difference score, because in one subject the baseline examination was found unreliable due to symptoms of the presenting stroke. Patients without follow-up NPE were 8.2 years older compared with those who were tested at follow-up (95% CI, 3.1 to 13.2), but they did not differ with regard to the ARWMC sum score (mean difference (MD) 2.1, 95% CI -1.1 to 5.4) and other demographic, clinical, and cognitive characteristics (data not shown). The two raters agreed on the ARWMC score in 197 of 231 (85.3%) cases.

WML categories

The no-to-mild 'WML–' group consisted of 28 patients, the moderate 'WML+' group of 17 patients and the severe 'WML++' of 32 patients. The WML+ patients were 4.2 years older and WML++ patients were 9.7 years older than WML– patients. The groups did not differ with regard to hemispheric ischemic events at presentation. Retinal ischemia or amaurosis fugax had occurred less often in WML++ patients. WML+ patients more often had had TIA than WML- patients. Patients in the WML+ group more often had a history of coronary artery bypass grafting. Otherwise the groups did not differ with regard to other baseline characteristics (Supplementary Tables).

Unadjusted cognitive change within the different WML categories

Between baseline and 6-months follow-up, the cognitive sumscore at six months after revascularization was worse than at baseline; MD: -0.21; 95% CI, -0.32 to -0.09. The cognitive sumscore decreased by 0.15 (95% CI, -0.39 to 0.09) in the WML- group, by 0.27 (95% CI, -0.48 to -0.06) in the WML+ group; and by 0.21 (95% CI, -0.40 to -0.04) in the WML++ group. In the WML- group, the domain visual memory improved by 0.28 (95%

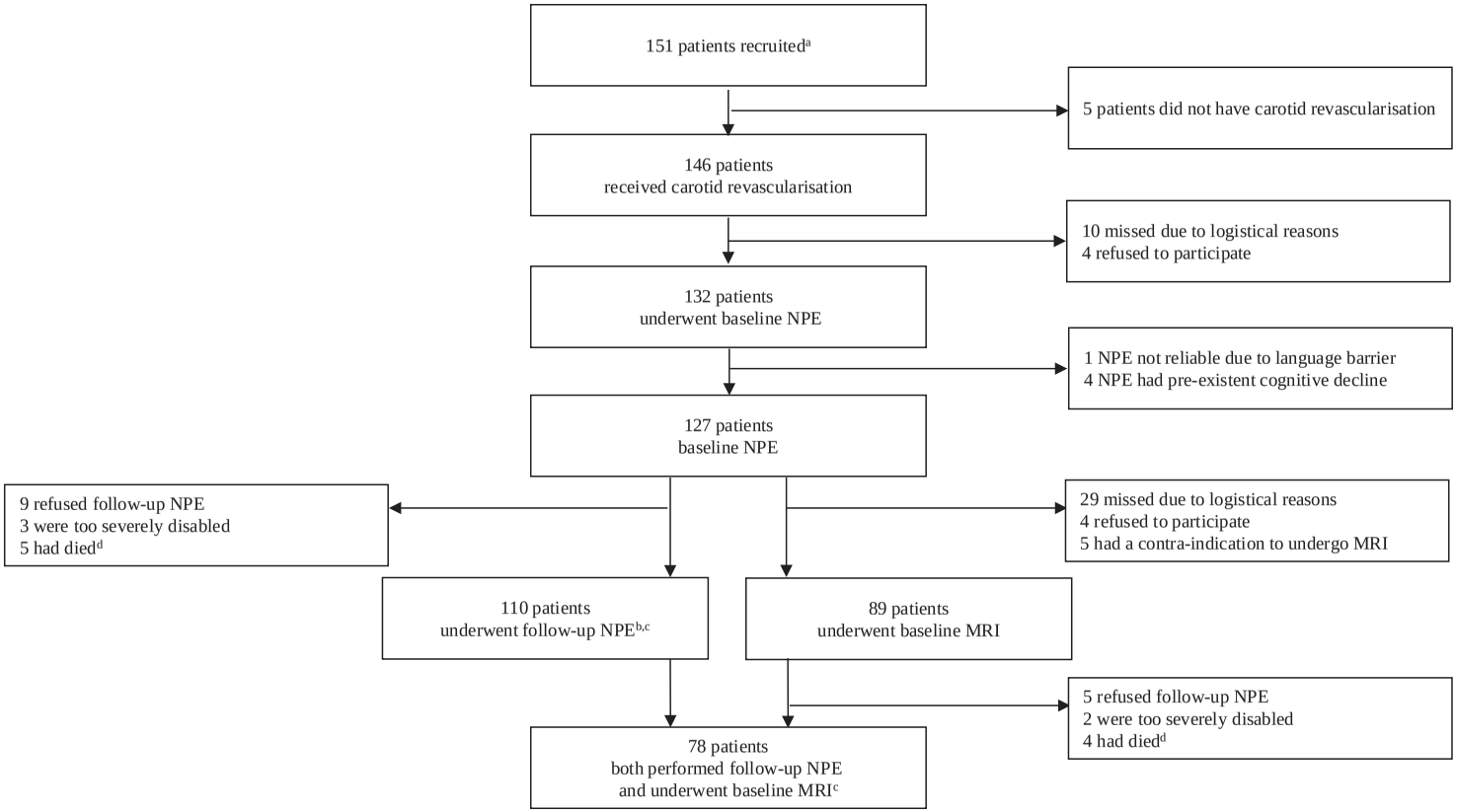

Figure 6.1 Flowchart of substudy population. [a] Eligible participants during recruitment period when NPE and MRI were feasible simultaneously. [b] Cognitive difference scores were calculated of these patients. [c] In one patient the baseline examination was not considered reliable due to complications after presenting stroke, therefore cognitive change scores of this patient could not be compiled. [d] These complications belong to the same patients. NPE = neuropsychological examination; MRI = magnetic resonance imaging.

CI, 0.02 to 0.54); in the WML+ group, the domain neglect decreased by -0.95 (95% CI, -1.52 to -0.38); and in the WML++ group, language decreased by 0.26 (95% CI, -0.51 to -0.01), verbal memory by 0.32 (95% CI, -0.64 to -0.01), and visual perception by 0.37 (95% CI, -0.61 to -0.13). There were no significant changes in the other domain scores within the WML groups.

Cognitive unadjusted and adjusted mean difference between the WML categories

There was no statistically significant difference in the cognitive sum score change from baseline to follow-up between the categories WML-, and WML+ (MD -0.12, 95% CI, -0.44 to 0.20), respectively WML++ (MD -0.06; 95% CI, -0.34 to 0.21) (Table 6.1). This did not change after adjustment for age, sex and education, nor after additional adjustment for baseline imbalances (previous CABG, presenting TIAs, and eye symptoms). In the domain attention, there was a larger change in the WML++ group than in the WML- group (improvement by 0.89 (95% CI, 0.08 to 1.71), after additional adjustment for baseline imbalances). There were no significant differences between the groups in the other cognitive domain score changes, and adjustment did not affect this importantly. The change over time in the composite score 'mental effort' was also similar across groups, both before and after adjustment for baseline imbalances. Figure 6.2 shows that there is no linear relationship of cognition with baseline ARWMC score in a post-hoc analysis.

Table 6.1 Change in cognition between baseline and follow-up between moderate WML and severe WML compared with mild WML

Change	Between WML- and WML+		Between WML- and WML++	
Domain	MD[a] of the changes	95% CI	MD of the changes	95% CI
Change in cognitive sum z-score[b]				
Crude	-0.12	-0.44 to 0.20	-0.06	-0.34 to 0.21
Model 1	-0.15	-0.48 to 0.19	-0.12	-0.45 to 0.20
Model 2	-0.19	-0.55 to 0.16	-0.18	-0.51 to 0.16
Change in composite score				
Mental Effort				
Crude	0.04	-0.24 to 0.32	-0.08	-0.31 to 0.16
Model 1	0.04	-0.24 to 0.33	-0.04	-0.32 to 0.25
Model 2	0.03	-0.28 to 0.34	-0.06	-0.35 to 0.23

Table 6.1 continues on next page

Table 6.1 *Continued*

Change	Between WML- and WML+		Between WML- and WML++	
Domain	MD[a] of the changes	95% CI	MD of the changes	95% CI
Change in cognition domain z-scores				
Abstract Reasoning				
Crude	-0.01	-0.36 to 0.35	0.14	-0.16 to 0.44
Model 1	-0.06	-0.43 to 0.31	0.01	-0.36 to 0.38
Model 2	-0.22	-0.61 to 0.18	-0.03	-0.40 to 0.34
Attention				
Crude	0.78	-0.13 to 1.68	0.16	-0.60 to 0.91
Model 1	0.88	-0.05 to 1.80	0.39	-0.50 to 1.28
Model 2	0.64	-0.33 to 1.61	0.39	-0.50 to 1.27
Executive Functioning				
Crude	0.02	-0.33 to 0.38	0.03	-0.27 to 0.33
Model 1	0.03	-0.33 to 0.40	0.05	-0.32 to 0.41
Model 2	0.11	-0.29 to 0.51	0.06	-0.32 to 0.44
Language				
Crude	-0.16	-0.57 to 0.24	-0.09	-0.43 to 0.25
Model 1	-0.13	-0.54 to 0.29	-0.01	-0.42 to 0.40
Model 2	-0.10	-0.55 to 0.35	-0.00	-0.42 to 0.42
Verbal Memory				
Crude	-0.00	-0.44 to 0.44	-0.16	-0.53 to 0.20
Model 1	0.01	-0.45 to 0.47	-0.13	-0.57 to 0.31
Model 2	0.04	-0.47 to 0.54	-0.14	-0.60 to 0.32
Visual Memory				
Crude	0.03	-0.39 to 0.45	-0.11	-0.45 to 0.24
Model 1	-0.04	-0.47 to 0.39	-0.26	-0.66 to 0.14
Model 2	-0.08	-0.54 to 0.39	-0.31	-0.73 to 0.11
Visual Perception				
Crude	-0.17	-0.60 to 0.26	-0.27	-0.63 to 0.09
Model 1	-0.13	-0.58 to 0.31	-0.16	-0.59 to 0.26
Model 2	-0.06	-0.53 to 0.42	-0.17	-0.61 to 0.26
Neglect				
Crude	-0.32	-2.55 to 1.91	-0.17	-2.03 to 1.69
Model 1	-0.49	-2.74 to 1.76	-0.76	-2.96 to 1.43
Model 2	-0.71	-3.12 to 1.69	-1.10	-3.31 to 1.11

Data are mean (SD). [a] Negative values indicate a worsening ([b] cognitive sumscore at follow-up minus the score at baseline) in cognition in WML+ and WML++ patients compared with WML-. Crude model indicates unadjusted analyses. In model 1 mean differences (95% CI) between the WML+ and WML- and WML++ and WML- are adjusted for age, sex and education. Model 2 includes additional adjustment for history of coronary artery bypass grafting, presenting TIAs or symptoms involving the eye.

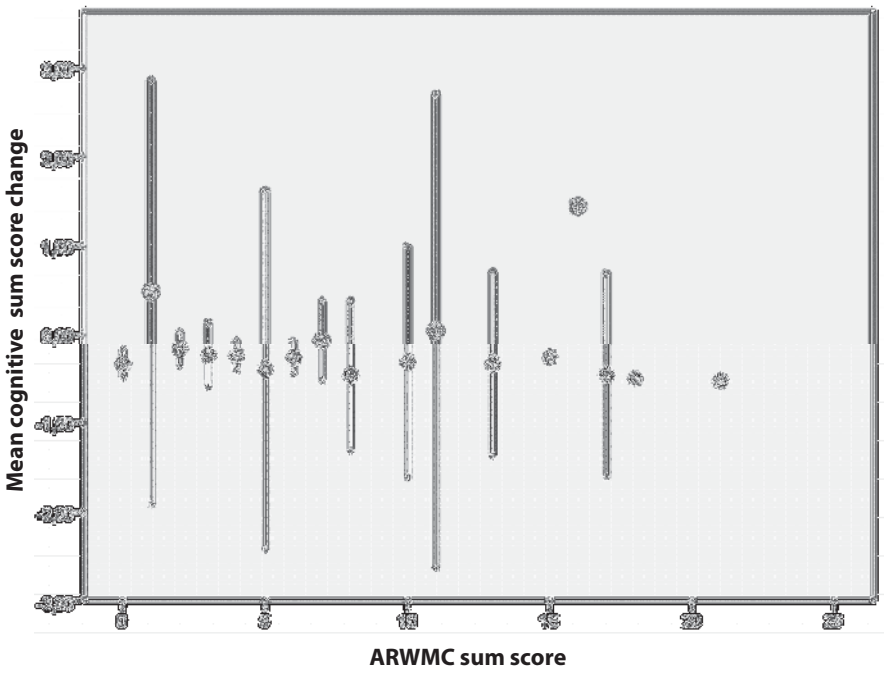

Figure 6.2 Relation between baseline ARMWC score and cognitive change over time. ARWMC represents age-related white matter changes score; error bars show 95% confidence intervals.

Mood states

Anxiety and depression scores between the groups did not differ at baseline (Supplementary Table S6.2). In all three WML categories, the state anxiety level decreased significantly over time (WML-: -8.9, 95% CI, -13.1 to -4.6; WML+: -8.2, 95% CI, -16.1 to -0.5; WML++: -9.1, 95% CI, -12.6 to -5.5), but no change in trait anxiety or depression levels was observed. The change in mood states was not different between the WML+ and WML++ group in comparison with the reference group WML- (data not shown).

Clinical outcomes

There were no relevant differences in post-procedural NIHSS or mRS at 6 months between the three groups (data not shown).

DISCUSSION

In this study, we found a worsening of overall cognition at six months after CEA or CAS for symptomatic carotid artery stenosis, which was independent of the severity of WML before revascularization. However, patients with the highest WML load declined in one or more cognitive domains (neglect and language, verbal memory, and visual perception, respectively) whereas the patients with the least WML burden improved in the domain visual memory.

For two reasons, we had expected that if carotid revascularization would have a beneficial effect on cognition as suggested by several studies,[14] the benefit would be greatest in patients with the least severe WML. First, these patients might have benefited most of an increase in cerebral perfusion, because they have the least permanent brain damage. Secondly, clinically 'silent' ischemic lesions caused by CEA or CAS might have the largest negative impact on cognition in patients with the most severe WML because of their limited reserve capacity. Because of the observed overall decline in cognition, we had to reject both hypotheses. In a randomized comparison of patients treated with CAS or CEA, we found that CAS was associated with a larger decrease in cognition at six months than CEA, but the between-group difference was just not statistically significant, most likely due to a small sample size. New ischemic lesions were found twice as often after CAS than after CEA.[16] This suggests that new and mostly 'clinically silent' ischemic lesions contribute to cognitive decline after the intervention,[31] but strong evidence supporting this relation is lacking.

Many studies have shown an association between the presence and severity of WML and cognitive decline.[2,32-34] The cognitive deficits affected included psychomotor function,[11] attention,[2,5,11] executive functioning,[2,5,11,34] mental processing speed,[2,5,32,34] visuoconstructional praxis,[2,5] naming,[5] memory,[34] and concentration.[2] In this study, we could not find an association of WML severity with cognitive decline after carotid revascularization, despite the use of an extensive test battery that assessed the most consistently affected domains and tasks. In contrast to earlier studies, we report on the effect of WML on cognitive change in relation to an intervention, i.e. carotid revascularization. Moreover, our patients all had recent TIA or ischemic stroke, whereas this was not the case in most previous studies that investigated elderly subjects who had non-specific neurological events.[5] The fact that our patients had recent stroke (or amaurosis fugax, retinal ischemia, TIA) did not bias our findings, because the distribution of ischemic strokes was similar in all groups. Moreover in patients with recent ischemic stroke, the overall degree of WML has been related to cognitive decline.[35]

The relation of white matter lesions to large artery disease remains controversial. Although small vessel disease is broadly affected by the same risk factors,[11] the relation with large vessel disease is not clear however. Large population-based studies found a relationship

with carotid atherosclerosis with WML, a finding that was true only for periventricular but not for subcortical WML.[13] In a longitudinal follow-up study in patients with recent symptomatic carotid stenosis of 30–69% degree, total plaque volume was significantly correlated with baseline ipsilateral WML, whereas carotid artery stenosis was not.[36] And a recent study, combining the data of two large cohorts of ischemic stroke patients, found no association between carotid stenosis and ipsi- or contralateral WML. These findings suggest that atherothromboemboli are unlikely to cause most WML or other forms of cerebral small vessel lesions.[8]

Strengths of our study are the comprehensive data collection, and the use of the ARWMC rating scale for scoring WML on MRI, in accordance with the Vascular Cognitive Impairment Harmonization standards.[37] Cognitive functioning was assessed with an extensive neuropsychological test battery (comprising the same or very similar tests as the VCI harmonization standards),[37] and premorbid cognitive decline and mood states were taken into account.

This study has limitations. First, a small number of patients did not have a follow-up NPE. These patients were significantly older and may have shown a greater decline in cognition. Secondly, WML were scored with a semiquantitative ordinal rating scale,[30] which is a frequently used method, but has ceiling effects and is less precise, in contrast to automated volumetric measurements. In patients with subjective memory complaints, volumetric measurements of WML were found to be more sensitive than visual scoring methods with respect to memory symptoms.[38] However, as there is no ideal rating scale yet visual rating scales will stay mandatory in clinical practice and in studies involving large amounts of subjects.[39] However, the ARWMC rating scale has been shown to correlate well with cognitive impairment in patients with stroke (mainly executive functioning).[40] In future studies of cognition in patients treated with CEA or CAS, diffusion tensor MRI (DTI) may quantify structural changes better and map these with the relevant cognitive networks.[41] Moreover, this has shown to be better correlated with cognition than conventional MRI techniques.[42] However, for the time being the use of the ARWMC rating scale is correct.[37] Thirdly, we assessed the relation between the total ARWMC score and cognition, and did not take the different WML locations into account. Some earlier studies have reported that the volume of periventricular but not of deep WML was associated with impairment in mental processing speed.[33] However, recently WML were found to be associated with frontal hypometabolism and executive function regardless its location.[43] This shows that many not adjacent areas are involved in large-scale distributed cognitive networks.[44] Fourthly, although the sample size of our study was comparable with that of previous studies of cognition after carotid revascularization, this was too small to perform adequate

subgroup analyses based on the type of carotid revascularization. For the same reason, the presence of a type II error cannot be excluded. A recent study found (with volumetric measurements) that after taking atrophy into account, WML was no longer associated with cognition (mainly executive functioning).[45] Given these findings, it would be wise to take cortical or hippocampal atrophy into account in future studies. Our study concerns merely the short term after revascularization, a longer follow-up duration would probably create a greater distinction in cognitive functioning between the different WML categories, for example due to lesion progression.

In the present study, cognitive functioning after carotid revascularization deteriorated within all WML categories. This cognitive decline was not related to the severity of WML.

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SUPPLEMENTARY MATERIAL

Supplementary Table S6.1 Baseline characteristics

	WML-	WML+	WML++
	Mild ARWMC	Moderate ARWMC	Severe ARWMC
	N = 28	N = 17	N = 32
Demographics			
Age (years)	64 (8)	68 (6)	74 (6)
Education[1]	4 [4–5]	4 [3–6]	5 [3–5]
Male sex	22 (79%)	14 (82%)	24 (75%)
Vascular Risk Profile			
History of hypertension	22 (79%)	11 (69%)	22 (69%)
Cardiac failure	0 (0%)	1 (6%)	2 (6%)
History of diabetes	6 (21%)	3 (18%)	10 (31%)
Angina pectoris in last 6 months	0 (0%)	0 (0%)	2 (6%)
Myocardial infarction	5 (18%)	6 (38%)	4 (13%)
CABG	2 (7%)	6 (35%)	5 (16%)
Peripheral arterial disease	7 (25%)	2 (13%)	7 (22%)
Atrial fibrillation	1 (4%)	0 (0%)	1 (3%)
Other cardiac embolic source	1 (4%)	1 (7%)	0 (0%)
Current smoker	8 (28%)	4 (25%)	12 (38%)
Treated hyperlipidemia	21 (75%)	14 (88%)	19 (59%)
Systolic blood pressure (mmHg)	169 (29)	167 (35)	168 (26)
Diastolic blood pressure (mmHg)	88 (11)	85 (14)	84 (17)
Presenting symptomatology			
Amaurosis fugax or retinal infarct	14 (50%)	4 (24%)	7 (22%)
Transient ischemic attack	14 (50%)	14 (82%)	16 (50%)
Hemispheric ischemic stroke	13 (46%)	6 (35%)	16 (50%)
Time intervals (days)			
Last event to neuropsychological evaluation	31 (23)	43 (44)	42 (39)
Last event to treatment	33 (23)	45 (44)	44 (39)
Artery characteristics			
Symptomatic artery, L	14 (50%)	8 (47%)	16 (50%)
Severe (70–99%) stenosis symptomatic artery	23 (82%)	16 (94%)	28 (88%)
Procedure, CEA	13 (46%)	11 (65%)	14 (44%)
Clinical assessment			
NIHSS	0 [0–1]	0 [0–1]	1 [0–1]
mRS	1 [0–2]	1 [0–1.5]	2 [0–2]

Data are mean (SD), number (%), or median [interquartile range IQR]. CABG = coronary artery bypass grafting; CEA = carotid endarterectomy; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin scale. Missing data < 5%.

Supplementary Table S6.2 Cognitive functioning at baseline

	WML-	WML+	WML++
	Mild ARWMC	Moderate ARWMC	Severe ARWMC
Cognitive sum z-score[a] (N = 77)	-0.04	-0.33	-0.28
Mental Effort score[b]	-0.38	-0.67	-0.52
Baseline domain z-scores and raw test scores			
Abstract Reasoning z-score (N = 57)	-0.47	-0.51	-0.41
Raven Advanced Progressive Matrices Short form (20-13-24)	5.6 (3.2)	5.7 (2.9)	5.4 (2.2)
WAIS similarities (20-13-24)	17.9 (5.2)	17.3 (7.3)	19.2 (7.6)
Attention z-score (N = 77)	0.84	0.21	0.57
WAIS III Digit Span Forward (28-17-32)	5.6 (1.5)	5.4 (1.5)	5.4 (1.0)
Visual Elevator of the Test of Everyday Attention[c] (22-13-25)	7.1 (1.6)	7.4 (3.1)	7.6 (3.2)
Executive Functioning z-score (N = 73)	-0.49	-0.74	-0.62
Brixton Spatial Anticipation Task (26-16-27)	21.2 (6.2)	21.8 (8.3)	23.4 (7.1)
Letter Fluency[d] (26-16-28)	9.1 (4.8)	8.0 (4.5)	8.6 (3.7)
Language z-score (N = 77)	-0.41	-0.71	-0.45
Token Test, short form (26-16-30)	16.9 (3.1)	15.3 (4.1)	15.6 (4.1)
Boston Naming Test, short form (28-16-32)	75.7 (10.9)	77.6 (9.9)	79.3 (7.6)
Verbal Memory z-score (N = 77)	-0.02	-0.31	-0.24
WAIS III Digit Span Backward (28-17-32)	4.0 (1.5)	3.6 (1.1)	3.8 (1.5)
Rey Auditory Verbal Learning Test[e] (25-16-32)	18.6 (5.0)	19.4 (3.9)	18.2 (5.5)
Semantic Fluency (26-16-28)	26.5 (9.2)	25.2 (5.9)	25.1 (9.0)
Visual Memory z-score (N = 72)	0.15	-0.30	-0.35[c]
Rey-Osterrieth Complex Figure-delay (27-16-29)	17.2 (6.3)	14.2 (5.7)	13.9 (5.1)
Visual Perception z-score (N = 76)	-0.37	-0.48	-0.58
Benton Judgment of Line Orientation, short form (27-16-29)	22.0 (5.2)	22.5 (7.7)	21.9 (5.2)
Benton Facial Recognition Task, short form (27-15-30)	43.1 (4.6)	43.6 (4.1)	41.8 (4.5)
Rey-Osterrieth Complex Figure-copy (27-16-30)	31.6 (5.1)	30.8 (6.1)	30.5 (5.9)
Neglect z-score (N = 64)	0.68	0.72	0.10
Star Cancellation of the Behavioural Inattention Task (22-14-28)	54.2 (4.4)	54.2 (1.7)	53.6 (3.2)
Premorbid and current cognition			
Informant Questionnaire of Cognitive Decline (23-14-24)	2.9 (0.4)	2.7 (0.7)	3.0 (0.3)
Estimated premorbid Intelligent Quotient (11-12-18)	84.7 (10.6)	96.2 (31.3)	117.3 (21.3)
MMSE (15-11-18)	26 [19–30]	26 [23–30]	27 [21–29]

Supplementary Table S6.2 continues on next page

Supplementary Table S6.2 *Continued*

	WML-	WML+	WML++
	Mild ARWMC	Moderate ARWMC	Severe ARWMC
Premorbid anxiety/depression			
STAI (22-15-30)	41.5 (14.3)	38.5 (10.1)	42.0 (12.7)
STAT (22-15-29)	31.3 (8.6)	34.3 (8.9)	35.1 (9.1)
BDI (20-14-25)	7.0 (7.3)	5.3 (5.2)	7.1 (5.4)

Data are mean (SD) or median [range]. [a] Cognitive scores are expressed as units of standard deviations (z-scores) from the mean in a normal reference population, with negative values expressing scores below the normal population mean. [b] Mental effort score is a composite of the following tasks: Boston naming task, Visual elevator accuracy, Verbal fluency ("N" and "A"), Rey-Osterrieth Complex Figure, Benton Judgment of Line Orientation. [c] Mean of the visual elevator accuracy and timing score. [d] Mean of total words produced beginning with letter "N" or "A". [e] Mean of the total direct, delayed, and recognition trials. WAIS = Wechsler adult intelligence scale; MMSE = mini mental state examination; STAI = state-trait anxiety inventory (state); STAT = state trait anxiety inventory (trait); BDI = Beck's depression inventory. Neuropsychological test battery.[2]

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Ipsilateral fetal-type posterior cerebral artery is associated with cognitive decline after carotid revascularization

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ABSTRACT

Background Stenosis of the internal carotid artery has been associated with cognitive impairment and decline. However, studies testing the effect of carotid revascularization on cognition have had conflicting results. This may in part be explained by variation in the flow territory of the carotid artery. In 12 to 36% of the patients, the posterior cerebral artery is mainly or exclusively supplied by the internal carotid artery via a fetal-type posterior cerebral artery. In these patients, ipsilateral carotid artery stenosis is likely to result in a larger area with hypoperfusion than in case of a normal posterior cerebral artery. Patients with a fetal-type posterior cerebral artery could therefore benefit more from revascularization. We compared the effects of carotid revascularization on cognition between patients with a fetal-type and those with a normal posterior cerebral artery.

Methods Patients with symptomatic internal carotid artery stenosis ≥ 50%, enrolled in the International Carotid Stenting Study at our center, underwent detailed neuropsychological examinations before and 6 months after revascularization. Cognitive test results were standardized into z-scores, from which a cognitive sumscore was calculated. The primary outcome was the change in cognitive sumscore between baseline and follow-up. Changes in cognitive sumscore were compared between patients with an ipsilateral fetal-type and those with a normal posterior cerebral artery, as assessed with CT or MR angiography.

Results Of 145 patients enrolled at our center during the study period, 98 had both angiography at baseline and neuropsychological examination at baseline and at 6-months follow-up. The cognitive sum score decreased by 0.28 (95% confidence interval [CI], 0.10 to 0.45) in 13 patients with an ipsilateral fetal-type posterior cerebral artery and by 0.07 (95% CI, 0.002 to 0.15) in 85 patients with a normal posterior cerebral artery (mean difference, -0.20; 95% CI, -0.40 to -0.01). This did not change essentially after adjustment for baseline factors.

Conclusion An ipsilateral fetal-type posterior cerebral artery appears to increase cognitive decline after carotid revascularization. Until our finding has been reproduced in an independent study, we think that the presence of an ipsilateral fetal-type posterior cerebral artery should not affect the decision to perform carotid endarterectomy or stenting.

INTRODUCTION

In population-based studies, internal carotid artery (ICA) stenosis has been associated with cognitive impairment and decline.[1,2] Although convincing evidence supporting a causal relationship is lacking, this has been attributed to cerebral hypoperfusion or to the occurrence of 'silent' brain infarcts.[3] In patients with symptomatic ICA stenosis, perfusion of the ipsilateral territory of the middle cerebral artery is inversely related to the degree of the stenosis.[4] Several authors have therefore suggested that in these patients, carotid revascularization could improve cognition. However, studies assessing the effect of carotid revascularization on cognition have not been able to demonstrate a convincing benefit.[5] A recent substudy of the randomized International Carotid Stenting Study (ICSS)[6] even found that carotid artery stenting (CAS) was associated with a small decrease in cognition at 6 months after the procedure. In this study, carotid endarterectomy (CEA) had no effect on cognition.[7]

The conflicting results of studies testing the relation between carotid revascularization and changes in cognition have been ascribed to differences between the studies in sample size, type of patients, duration of follow-up, and type of neuropsychological assessment.[5] Differences in effect of revascularization on cognition might also be explained by variation in the flow territory of the carotid artery. Considerable variation of the circle of Willis has been described in healthy individuals,[8] as well as in patients with symptomatic ICA stenosis.[9] A fetal-type configuration of the posterior part of the circle of Willis (FTP) has been found in 12 to 36% of the cases. In these cases, the posterior cerebral artery is mainly or exclusively supplied by the ICA via the posterior communicating artery (PCoA).[10] In patients with a fetal-type PCoA, an ipsilateral ICA stenosis may result in a larger volume with hypoperfusion than in patients with a normal variant of the circle of Willis. If cerebral perfusion is related to cognition, this may result in more severe cognitive impairment. Alternatively, emboli from ipsilateral ICA stenosis might cause damage in areas supplied by a fetal-type PCoA, contributing to cognitive dysfunction.

The (infero)medial temporal lobe and occipital two thirds of the hippocampus are commonly supplied by posterior cerebral artery (PCA) branches,[11] and are therefore dependent on the ICA in case of a fetal-type PCoA. This part of the hippocampus is critical for cognition, especially for memory and spatial navigation.[12] A recent study assessing cognitive function during intracarotid amobarbital infusion in epilepsy patients found that the presence of an FTP was associated with lower memory scores.[13]

We hypothesized that the benefit of carotid revascularization with regard to cognition would be larger in patients with an ipsilateral fetal-type circle of Willis than in patients

with the normal variant. Therefore, we compared changes in cognition 6 months after CEA or CAS for symptomatic ICA stenosis between patients with a fetal-type FTP and those with a normal PCA.

METHODS

The present study is a single-center prospective substudy of the randomized International Carotid Stenting Study (ICSS).[6] All patients enrolled in ICSS at the University Medical Center Utrecht, the Netherlands, between February 2006 and December 2008, could participate in this substudy. ICSS was an international, randomized, controlled, clinical trial comparing CAS and CEA in patients with a recently symptomatic carotid artery stenosis ≥ 50%. Center and investigator requirements for participating in ICSS, patient eligibility criteria, study procedures, clinical follow-up examinations, and an interim safety analysis have been described elsewhere.[6] We have earlier reported the effects on cognition of CAS and CEA in this substudy of ICSS.[7] Patients were excluded from the present study in case of pre-existent cognitive decline, a language barrier, when a neuropsychological evaluation was not done or not informative because of severe aphasia or other severe focal neurological deficit, or when the intracranial arteries were not visualized with CT or MR angiography.

Study approval

Our institutional review board approved both ICSS (ISRCTN25337470) and the cognitive substudy, and each patient provided written informed consent.

Study sample and assessments

Patients with recently symptomatic ICA stenosis of at least 50%, measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria or its non-invasive equivalent,[14] were randomly assigned to CAS or CEA. At inclusion, data were collected on presenting symptoms, demographic characteristics, and cardiovascular risk factors. The score on the National Institutes of Health Stroke Scale (NIHSS) was assessed at baseline, and the score on the modified Rankin Scale (mRS) at baseline and at 1 and 6 months after the procedure.

Neuropsychological assessment and test transformation

Cognition was assessed in the week preceding the procedure and after 6 months. The neuropsychological examination (NPE) comprised 7 cognitive domains, including 15 tasks, as described previously.[7] In addition, mood was assessed by the Beck Depression Inventory II,[15] and anxiety by the Spielberger State and Trait Anxiety Inventory.[16] Premorbid verbal intelligence was estimated with the National Adult Reading Test (NART, Dutch version),[17] pre-existent cognitive decline with the Informant Questionnaire of Cognitive Decline in the Elderly,[18] and current general cognitive functioning with the Mini Mental State Examination.[19]

Individual raw test scores at baseline and at follow-up were expressed as standard deviation (SD) units; the so-called z-scores. Z-score transformation was based on the mean and SD of a control group,[20] in which healthy individuals performed the same NPE at similar time intervals, thus controlling for potential practice effects in our patients. Each z-domain score represents the mean of the z-scores in that domain. As a measure of overall cognitive functioning, a cognitive sumscore was calculated, representing the mean z score over the 7 domains.[21] NPEs were rated by a single observer (Ay.A) and were screened for accuracy by an experienced clinical neuropsychologist (MJEvZ). Both were blinded to the anatomy of the circle of Willis in the patients.

Imaging parameters

CT angiography (CTA) or MR angiography (MRA) was performed in the week before revascularization (Supplementary Methods).

All CT- and MR-angiograms were evaluated by a neuroradiologist (JH) who was blinded to treatment assignment and to clinical and cognitive outcomes. In each patient, all segments of the circle of Willis were evaluated: anterior communicating artery (ACoA, present or absent); A1 segment of the anterior cerebral artery (ACA; normal, hypoplastic, or absent), P1 segment of the PCA (present or absent), and the PCoA (absent, or diameter < P1, = P1, or > P1).[9] Fetal-type PCA (FTP) was defined as a PCoA with a diameter greater than that of the ipsilateral P1, or when the ipsilateral P1 was absent.[22]

Diffusion imaging

MRI with DWI was performed 1 to 3 days before revascularization and within 3 days thereafter. The number and volume of new ischemic lesions were assessed as part of the previously reported ICSS-MRI study.[23] A new ischemic lesion was defined as a new

hyperintensity on the post-treatment DWI that was not present on the pretreatment MRI. Lesions were silent if there was no new corresponding focal neurologic deficit.

Outcome measures

The primary outcome measure of this study was the change in cognitive sum z-score between baseline and follow-up. A decrease in z-score means a worsening of cognition from baseline to follow-up. Secondary outcome measures were the changes in individual cognitive domain scores.

Statistical analysis

We performed t-tests for continuous and normally distributed data, Mann-Whitney U tests for non-parametric data, and χ^2 analyses for categorical data on baseline characteristics to determine whether selection bias had occurred between patients who were re-examined at follow-up and those who were not.

We calculated the mean difference in the change of the cognitive sum z-score between baseline and follow-up between the patients with and without FTP with corresponding 95% confidence intervals (CIs) with linear regression. Adjusted mean differences were calculated and are reported for those factors that changed the point estimate with at least 10%. Similar calculations were done for domain scores.

RESULTS

Patient flow and baseline characteristics

During the study period, 145 patients were randomized in ICSS at our center. Five of these patients had no revascularization because of medical reasons (severe disability (3) or carotid occlusion (2)), four had pre-existent cognitive decline, four refused to participate, one had a language barrier, one had an unreliable baseline NPE, 10 had no cranial CTA or MRA, and 8 had logistical reasons for exclusion. Consequently, this study consists of 112 patients with both baseline NPE and angiography, of whom 54 were treated with CEA and 58 with CAS. Sixteen patients had an ipsilateral FTP and 96 patients a normal ipsilateral PCA. Baseline clinical characteristics and patency of the anterior part of the circle of Willis did not differ between the two groups (Table 7.1).

Table 7.1 Baseline characteristics

	Normal PCA (N = 96)	Foetal-type PCA (N = 16)
Age (years)	69 (9)	68 (9)
Sex (male)	72 (75%)	10 (63%)
Education[a]	5.0 [4.0–6.0]	4.0 [3.3–4.8]
Vascular risk factors		
Treated hypertension	71 (75%)	10 (65%)
Systolic blood pressure (mm Hg)	168 (27)	174 (28)
Diastolic blood pressure (mm Hg)	86 (13)	87 (13)
Cardiac failure	3 (3%)	1 (6%)
Angina pectoris in past 6 months	7 (7%)	0 (0%)
Previous myocardial infarction	19 (20%)	3 (19%)
Previous CABG	17 (18%)	2 (13%)
Atrial fibrillation	4 (4%)	0 (0%)
Other cardiac embolic source	4 (4%)	0 (0%)
Type 2 diabetes mellitus	16 (17%)	2 (13%)
Type 1 diabetes mellitus	4 (4%)	1 (6%)
Peripheral arterial disease	17 (18%)	3 (19%)
Current smoker	32 (34%)	3 (19%)
Ex-smoker	55 (59%)	9 (56%)
Treated hyperlipidemia	72 (76%)	13 (81%)
Cholesterol (mmol/L)	4.7 (1.1)	4.9 (1.4)
Imaging		
MRA	68 (71%)	11 (69%)
CTA	28 (29%)	5 (31%)
Treatment		
CEA	44 (46%)	10 (63%)
CAS	52 (54%)	6 (38%)
Symptomatic side		
Left carotid artery	44 (46%)	10 (63%)
Degree of symptomatic carotid artery stenosis[b]		
50–69%	13 (14%)	2 (13%)
70–99%	83 (87%)	14 (88%)
Degree of contralateral carotid artery stenosis[b]		
< 50%	58 (60%)	13 (81%)
50–69%	12 (13%)	0 (0%)
70–99%	15 (16%)	2 (13%)
Occluded	7 (7%)	1 (6%)
Unknown	4 (4%)	0 (0%)

Table 7.1 continues on next page

Table 7.1 *Continued*

	Normal PCA (N = 96)	Foetal-type PCA (N = 16)
Anatomy anterior part circle of Willis		
Ipsilateral A1 present	80 (83%)	15 (94%)
Anterior communicating artery present	95 (99%)	15 (94%)
Contralateral A1 present	86 (90%)	15 (94%)
Most recent ipsilateral event[c]		
Amaurosis fugax	24 (26%)	2 (13%)
Transient ischemic attack	34 (37%)	4 (25%)
Ischemic stroke	29 (32%)	9 (56%)
Retinal infarction	3 (3%)	1 (6%)
Unknown	2 (2%)	0 (0%)
NIHSS at randomization	0 (0–1)	0.5(0–1)
Modified Rankin score at randomization		
0–2	85 (90%)	15 (94%)
3–5[d]	10 (11%)	1 (6%)
Unknown	1 (0%)	0 (0%)

Data are number (%), mean (SD), or median (IQR). CABG indicates coronary artery bypass grafting; CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; MRA; magnetic resonance angiography; NIHSS, national institutes of health stroke scale. [a] Education levels according to Verhage. [b] Degree of stenosis measured by NASCET method. [c] If two events were reported on the same day, the more serious was counted (stroke > retinal infarction > transient ischaemic attack > amaurosis fugax). [d] Some Rankin scores of 3 or more were caused by non-stroke disability.

Ninety-eight patients (88%) had a follow-up NPE at six months. Missing follow-up examinations were due to patient refusal (N = 8), severe disability (N = 2), and death (N = 4). Of these patients, three had an ipsilateral FTP. Patients without follow-up NPE were 5.9 years older (95% CI, 0.9 to 10.9), more often had treated hyperlipidemia at baseline (relative risk (RR), 1.35; 95% CI, 1.20 to 1.52), and performed worse on the domain 'visual memory' (mean difference (MD), -0.55; 95% CI, -1.09 to -0.01). They did not differ with regard to other demographic, clinical, or baseline cognitive characteristics.

Cognition

There were no major differences in cognitive sum scores at baseline between the two groups, but patients with an FTP tended to perform worse in each of the cognitive domains and had lower scores for two tasks in the cognitive domains 'executive functioning' and 'visual perception' (Supplementary Table S7.1).

There was a significant decrease in the cognitive sumscore of 0.28 (95% CI, 0.10 to 0.45) in patients with an FTP from baseline to 6 months follow-up, and of 0.07 (95% CI, 0.002 to 0.15) in patients with a normal variant. The mean difference in sumscore change between patients with and patients without FTP was -0.20 (95% CI, -0.40 to -0.01). After adjustment for potential confounders the results remained essentially the same (Supplementary Table S7.2). Within the individual cognitive domains, there were no statistically significant differences in change from baseline to 6-months follow-up between patients with an FTP and patients with a normal PCA, both before and after adjustment. However, patients with an FTP tended to perform worse in 6 of the 7 domains (Table 7.2).

Clinical and DWI outcomes

Fifty-four patients (55%) with follow-up NPE had an MRI within 3 days after the procedure. New ischemic lesions were found in 17 (35%) of 48 patients with a normal PCA and in 2 (33%) of 6 with an FTP (RR, 0.9; 95% CI, 0.3 to 3.1). Of these lesions, 15 (88%) and 1

Table 7.2 Change in cognitive functioning at 6-months follow-up

Domain (N normal PCA, N fetal-type PCA)	Normal PCA (95% CI)	Fetal-type PCA (95% CI)	MD (95% CI)	MD (95% CI)
			Unadjusted	Adjusted[a]
Cognitive sum z-score (85,13)	-0.07 (-0.15 to -0.002)	-0.28 (-0.45 to -0.10)	-0.20 (-0.40 to -0.01)	-0.19 (-0.38 to 0.01)
Cognitive domain z-scores				
Abstract Reasoning (57,9)	-0.05 (-0.18 to 0.09)	0.01 (-0.29 to 0.31)	0.06 (-0.30 to 0.41)	0.07 (-0.28 to 0.42)
Attention (83,12)	-0.14 (-0.44 to 0.17)	-0.72 (-1.32 to -0.11)	-0.58 (-1.40 to 0.24)	-0.66 (-1.33 to 0.00)
Executive Functioning (79,12)	0.06 (-0.06 to 0.18)	0.05 (-0.35 to 0.45)	-0.01 (-0.35 to 0.33)	-0.14 (-0.56 to 0.27)
Language (85,13)	-0.20 (-0.35 to -0.06)	-0.24 (-0.55 to 0.08)	-0.03 (-0.42 to 0.36)	0.13 (-0.28 to 0.54)
Verbal Memory (84,12)	-0.21 (-0.36 to -0.06)	-0.47 (-0.88 to -0.05)	-0.26 (-0.68 to 0.17)	-0.12 (-0.60 to 0.37)
Visual Memory (78,12)	0.22 (0.06 to 0.38)	0.11 (-0.38 to 0.61)	-0.11 (-0.54 to 0.33)	-0.05 (-0.56 to 0.47)
Visual Perception (83,12)	-0.20 (-0.33 to -0.06)	-0.21 (-0.62 to 0.20)	-0.01 (-0.40 to 0.37)	-0.05 (-0.47 to 0.37)

[a] Values reflect scores adjusted for side stenosis, time interval between symptom onset and treatment, BDI (Beck's depression inventory) and STAI, state-trait anxiety inventory. CI indicates confidence interval; MD, mean difference; PCA, posterior cerebral artery. The adjusted scores are calculated on fewer patients than described in the first column due to missing values.

(50%) respectively were not associated with stroke or a transient ischemic attack. There were no differences between the two groups in the median scores on the mRS at one and six months.

2 patients with a normal PCA and 3 patients with an FTP had a stroke within 30 days after the intervention. Excluding these patients from the analyses had no relevant effect on the changes in cognitive sum score and individual domain scores between baseline and 6-months follow-up.

DISCUSSION

In contrast to our expectations, we found that in patients with a symptomatic ICA stenosis and a fetal-type posterior cerebral artery (FTP), carotid revascularization was associated with a larger decline in cognition than in patients with a normal PCA. This finding could not be explained by differences in the anterior part of the circle of Willis, by a worse functional outcome at six months after revascularization, or by a more frequent occurrence of new 'silent' ischemic lesions on DWI within the first 3 days.

In patients with an FTP, the ipsilateral postcommunicating part of the PCA is supplied in whole or in part by the ICA. In these cases, the supply territory of the ICA therefore also includes the posterior part of the thalamus, the posterior two thirds of the hippocampus, the medial-inferior part of the temporal lobe, and the occipital lobe.[25] In patients with an ICA stenosis and an ipsilateral FTP, cerebral perfusion is therefore likely to be compromised in a considerably larger area of the brain than in patients with a normal PCA.

In patients with carotid artery stenosis, perfusion in the territory of the middle cerebral artery is inversely related to the degree of the stenosis,[4] and carotid revascularization has been shown to improve perfusion.[26] Small studies have suggested that an increase in cerebral perfusion after carotid revascularization is associated with cognitive improvement.[27,28] Because of the larger perfusion territory of the ICA in patients with an ipsilateral FTP, we had hypothesized that any improvement in cognition after carotid revascularization would be larger in patients with an FTP than in patients with a normal PCA. Our observation of a larger decline in cognition in patients with an FTP is therefore difficult to explain. We found no evidence of a higher rate of new ischemic brain lesions in patients with an FTP, and there were no differences between the groups in patency of the anterior part of the circle of Willis.

The relation between cerebral perfusion and cognition has remained controversial. In several studies, a lower total cerebral blood flow has been related with worse information-

processing speed, executive function, and global cognition.[29-31] However, in one of these studies, these associations disappeared after correcting total cerebral blood flow for brain volume.[31] Still, even if there is no relation between cerebral perfusion and cognition, this would not explain the larger decrease in cognition after revascularization in patients with an FTP than in those with a normal PCA.

The present study has limitations. The small number of patients with an FTP was in line with rates of FTP reported in the literature, but this may have led to imprecision of effect estimates. Secondly, only about half of patients had postprocedural imaging, for which reason we could not reliably assess the effects of number and location of new lesions on cognitive function. Finally, we did not assess differences in perfusion of the ipsilateral hemisphere between patients with an FTP and patients with a normal PCA, and do therefore not know whether perfusion in patients with an FTP was indeed more compromised before revascularization, nor whether this improved more after the procedure.

In conclusion, an ipsilateral FTP appears to be associated with cognitive decline after carotid revascularization. The cause of this decline is uncertain, and seems not to be related to the occurrence of periprocedural cerebral ischemia. Until our finding has been reproduced in an independent study, we think that the presence of an ipsilateral FTP should not affect the decision to perform carotid endarterectomy or stenting.

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SUPPLEMENTARY MATERIAL

METHODS

Imaging parameters

CTA was performed with a 16- or 64 row scanner (Philips Medical Systems, Best, the Netherlands) after injection of 50 mL contrast material at 5 mL/s, followed by a saline chaser bolus of 50 mL injected at the same flow rate. A 64x0.625 mm collimation was used, with a pitch of 0.672 and a rotation time of 0.40 seconds. Exposure settings were 80/120 kVp and 300/95 mAs. Overlapping sections of 1.0 mm (16- slice) or 0.9 mm slice thickness (40 or 64- slice) were reconstructed at a reconstruction interval of 0.5 mm and a field of view of 160 mm.

MRA was performed on 1.5 or 3.0 Tesla scanners (Philips Medical Systems, Best, the Netherlands) with a quadrature head coil for signal-intensity reception. The imaging protocol consisted of a 2D phase-contrast sagittal localizer survey through the circle of Willis, followed by a 3D-TOF MRA sequence with the following parameters: TR, 23 ms; TE, 3.5 ms; flip angle, 18°; sensitivity encoding factor, 2; FOV, 200 x 200 x 100 mm; matrix, 304 x 200 with 100 sections; reconstructed voxel size, 0.39 x 0.39 x 1.00 mm; and acquisition time, 2 minutes 57 seconds.

Supplementary Table S7.1 Cognitive functioning at baseline

Test (N normal PCA, N fetal-type PCA)	Normal PCA (N = 96)	Fetal-type PCA (N = 16)
Cognitive sum z-score[a] (96,16)	-0.19 (0.83)	-0.42 (0.72)
Baseline domain z-scores and raw test scores		
Abstract Reasoning z-score (64,13)	-0.33 (0.79)	-0.62 (1.07)
Raven Advanced Progressive Matrices, short form (63,13)	6.1 (2.5)	4.9 (3.4)
WAIS similarities (64,13)	18.8 (6.4)	17.5 (7.6)
Attention z-score (95,16)	0.68 (1.33)	0.19 (1.24)
WAIS III Digit Span Forward (95,16)	8.0 (2.2)	6.9 (1.8)
Visual Elevator of the Test of Everyday Attention[a] (75,11)	7.1 (2.8)	6.1 (3.1)
Executive Functioning z-score (90,16)	-0.48 (0.70)	-0.73 (0.60)
Brixton Spatial Anticipation Task (86,16)	20.9 (6.7)	24.8 (5.9)
Letter Fluency[b] (87,16)	9.2 (4.3)	8.2 (3.5)
Language z-score (96,16)	-0.47 (1.11)	-0.67 (0.90)
Token Test, short form (89,16)	16.4 (3.8)	15.4 (3.9)
Boston Naming Test, short form (95,16)	76.9 (12.5)	75.9 (9.3)
Verbal Memory z-score (94,16)	-0.03 (1.15)	-0.17 (0.76)
WAIS III Digit Span backward (94,16)	5.1 (2.2)	4.6 (2.3)
Rey Auditory Verbal Learning Test[c] (93,16)	19.8 (5.9)	19.8 (5.0)
Semantic Fluency (86,16)	26.3 (10.3)	23.9 (5.7)
Visual Memory z-score (89,16)	-0.11 (0.90)	-0.16 (1.13)
Rey-Osterrieth Complex Figure-delay (89,16)	15.5 (6.0)	15.2 (7.6)
Visual Perception z-score (94,16)	-0.33 (0.93)	-0.70 (0.97)
Benton Judgment of Line Orientation, short form (88,15)	22.6 (5.9)	21.9 (7.3)
Facial Recognition Task, short form (89,16)	43.2 (4.7)	42.8 (3.8)
Rey-Osterrieth Complex Figure-copy (91,16)	32.1 (5.0)	29.0 (5.3)
Premorbid and current cognition		
Informant Questionnaire of Cognitive Decline	2.96 (0.36)	3.02 (0.20)
Estimated premorbid Intelligent Quotient (NART)	76.1 (21.4)	71.2 (14.8)
MMSE	26 [25–28]	26 [24–27]
Premorbid anxiety/depression		
STAI	40.2 (12.5)	38.9 (11.5)
STAT	34.4 (9.8)	30.2 (10.8)
BDI	7.2 (6.5)	6.2 (5.2)

Data are mean (SD) or median [range]. *Cognitive scores are expressed as units of standard deviations (z-scores) from the mean in a normal reference population, with negative values expressing scores below the normal population mean. [a] Mean of the visual elevator accuracy and timing score. [b] Mean of total words produced beginning with letter "N" or "A". [c] Mean of the total direct, delayed, and recognized word count. CAS, carotid artery stenting; CEA, carotid endarterectomy; WAIS, Wechsler adult intelligence scale; NART, national adult reading test; MMSE, mini mental state examination; STAI, state-trait anxiety inventory (state); STAT, state trait anxiety inventory (trait); BDI, Beck's depression inventory.

Supplementary Table S7.2 Adjusted change in cognitive functioning in patients with normal variant versus fetal variant

	Mean difference	(95% CI)
Unadjusted cognitive sum z-score	-0.20	(-0.40 to -0.01)
Additional adjustment		
Age (years)	-0.20	(-0.40 to -0.01)
Sex	-0.20	(-0.40 to -0.01)
Education	-0.20	(-0.39 to 0.00)
Side stenosis[a]	-0.22	(-0.41 to -0.02)
Treatment	-0.20	(-0.39 to -0.00)
Treated hypertension	-0.20	(-0.40 to -0.00)
CABG	-0.20	(-0.40 to -0.01)
Diabetes Mellitus	-0.20	(-0.40 to -0.01)
Peripheral artery disease	-0.20	(-0.39 to 0.00)
Smoker	-0.21	(-0.40 to -0.01)
Degree symptomatic stenosis	-0.20	(-0.40 to -0.01)
Contralateral degree of stenosis	-0.20	(-0.39 to -0.01)
Presenting symptoms	-0.19	(-0.39 to 0.01)
NIHSS	-0.20	(-0.40 to -0.01)
Time interval[a]	-0.17	(-0.38 to 0.03)
STAI[a]	-0.22	(-0.41 to -0.03)
STAT	-0.21	(-0.40 to -0.01)
BDI[a]	-0.22	(-0.41 to -0.02)
3 factors (age, sex, education)	-0.20	(-0.40 to 0.00)
4 factors[a]	-0.19	(-0.38 to 0.01)

[a] Time interval represent the days between symptoms and treatment.
BDI indicates Beck's depression inventory; CABG, coronary artery bypass grafting; CI, confidence interval; NIHSS, national institutes of health stroke scale; STAI, state-trait anxiety inventory (state); STAT, state trait anxiety inventory (trait).

8

General discussion

In part 8.1 I will hold our major findings with regard to hemodynamic changes in perspective. In part 8.2, I will summarize the main findings of our cognitive studies and I will try to integrate them with reference to other studies. Further, I will discuss methodological shortcomings. And finally in part 8.3 I will give conclusions, provide possible implications for patient care and make recommendations for future studies.

8.1 MAIN FINDINGS SECTION 1

This thesis describes the effect of carotid revascularization on hemodynamic and cognitive function in patients treated for symptomatic carotid stenosis. The patients participated in the International Carotid Stenting Study (ICSS),[1] a randomized comparison of carotid artery stenting (CAS) with carotid endarterectomy (CEA). At study initiation, the other large clinical trials of CAS versus CEA were still recruiting patients.[2-4]

General issues

Patients who have suffered from transient ischemic attack (TIA) or ischemic stroke and have ipsilateral carotid stenosis are at particular increased risk of subsequent stroke.[5] After landmark clinical trials, carotid surgery had become the established standard treatment for severe symptomatic carotid artery stenosis to prevent recurrent cerebral ischemia.[6-10] In the 1990s endovascular treatment of the carotid artery emerged as a promising alternative to surgery. However, equivalence of this treatment was still not established at that time.[11]

In recent years, large clinical trials comparing CEA with CAS have shown that CEA remains the treatment of choice for treatment of symptomatic carotid stenosis. However, in certain circumstances CAS can be an alternative to CEA.

Revascularization

Surgical or endovascular carotid revascularization procedures restore perfusion, i.e. blood supply, to the brain. In case of surgery the atherosclerotic plaque, which mainly resides at the carotid bifurcation, is removed. Endovascular procedures use a balloon to flatten the plaque and widen the lumen (percutaneous transluminal angioplasty with predilatation); and additionally insert a stent to prevent the artery from narrowing again (CAS). The stent exerts a continuous radial pressure on the arterial walls and sometimes postdilatation is also performed after stent placement. The radial force that the stent produces differs between stent designs and is also dependent on the length of the stenosis as well.[12]

Autoregulation

The carotid sinus, that contains the baroreceptors, is located just distal to the bifurcation of the common carotid artery and measures approximately 7 mm in diameter.[13] The baroreceptors are mechanoreceptors and sense changes in blood pressure by stretch on the blood vessel wall in order to maintain normal blood pressure. To this end, the carotid sinus reflex, as first described by Hering in 1923,[14] acts via two routes: a chronotropic component that affects the sinus and atrioventricular nodes that leads to bradycardia and a vasodilatory component that leads to hypotension.[13] CAS increases the impulse frequency due to the mounted pressure on the mechanoreceptors, ultimately resulting in peripheral vasodilation and arterial hypotension; the bradycardia that ensues contributes to the hypotension.[15] On the other hand, hypotension occurs after CEA as well. As a result, the actual stimulus to the baroreceptors to fire may be any circumferential stress or deformation of the sinus wall and not merely the intrasinus pressure itself.[16,17]

Definition hemodynamic events

Hemodynamics is the mechanics of pulsatile blood flow in the cardiovascular system.[18] In this section we focus on hemodynamic depression or hypertension that occurs after carotid revascularization. The cerebral hyperperfusion syndrome (CHS) has been associated with hypertension. Because hypotension, bradycardia and asystole are related pathophysiologically we joined them together as "hemodynamic depression." The ICSS was not a trial that primarily intended for blood pressure comparisons between patients treated with surgery or stenting. It had a rather pragmatic approach to these issues; both hypotensive and hypertensive episodes were registered if they had required any kind of therapy. Treatment of these episodes was left at the discretion of the treating physician. CHS had to cover at least one of the symptoms: epilepsy, headache, or confusion in the perioperative period.

Hemodynamic depression

Observational and underpowered studies had suggested that hypotension occurred more frequently after CAS,[19-22] and hypertension and CHS more after CEA.[20-22,23-25] Hemodynamic depression after CAS has been associated with an increased risk of stroke, myocardial infarction (MI), or death.[19,26-28] The consistent finding of higher rates of 30-day morbidity and mortality after CAS than after CEA prompted the question to which extent hemodynamic depression after CAS could be attributable to this.

Long-term hemodynamic effects

It would be a pleasant by-effect if prevention of recurrent cerebral ischemia by carotid revascularization also led to long-term blood pressure lowering, thus rendering a lessened need for medication.

The carotid sinus segment is the main site that causes saturation of the carotid sinus reflex.[16] So any intervention to alter this reflex should focus on this part of the pathway. The idea of treating severe hypertension, refractory to medical therapy, by surgically implantable devices seems promising,[29] and observational studies have shown that mechanical stimulation of carotid baroreceptors is feasible and in the short term can reduce hypertension.[30] However, this treatment strategy is rather invasive, has obvious disadvantages and information on large groups of patients and long-term consequences is lacking.

> *Will continuous stimulation of the baroreceptors, like in the case of CAS, result in lowering of blood pressure in the long term?*

Previous studies have shown that the long-term role in the regulation of the baroreflex is minimized by the ability of arterial baroreceptors to reset their threshold value to any sustained new level of blood pressure.[31] This means that any initial effect would be mitigated over time when a new equilibrium has been reached. In addition, others have suggested that carotid sinus baroreceptors reset when exposed to static pressure, but that resetting is prevented or attenuated when the baroreceptors are exposed to pulsatile pressure.[32] So pulsatile pressure might be necessary to prevent resetting and sustain central and peripheral nervous system responses in the baroreflex pathway.[33] It should be noted however, that adaptation occurs also through central resetting; which mainly occurs in case of continuous static pressure. The peripheral resetting means that discharge will be less at any given level of pressure.[16]

In chapter 2 we have seen that both procedures were associated with blood pressure decrease in the first days after treatment and that at one year blood pressures were similar in patients treated with CAS or CEA, however the use of antihypertensive medication was lower in patients treated with CAS. This finding suggests that there is some long-term BP lowering effect of CAS. How much as this might look promising, as there is robust evidence that blood pressure lowering after ischemic cerebral events further prevents vascular events,[34] blood pressure control for secondary stroke prevention was suboptimal in our whole population. After the further than one-year results of ICSS are published, more will be clear about any sustained effect on use of lesser antihypertensive medication used.

The other side of the coin

After carotid surgery, hypertension can occur due to sectioning of the sinus nerves.[35] Carotid baroreceptor denervation also causes increased arterial pressure variability, because of decreased vagal and sympathetic baroreflex sensitivity.[36] Several studies have suggested that the occurrence of postprocedural hypertension or hypotension after CEA is affected by the surgical technique. Eversion endarterectomy requires division of the carotid artery, which transects the carotid sinus nerve, ultimately followed by higher postoperative blood pressures.[37] Unfortunately, we have insufficient information about the surgical techniques that have been used during CEA in ICSS.

As expected, we found that severe hypertension occurred more frequently after CEA than after CAS (Chapter 3). However, even after CEA, the incidence of postprocedural hypertension was lower than in most previous observational studies of CEA.[38-41] Moreover, the occurrence of CHS was lower than expected after both procedures.[24,25] It might be that these findings reflect the heightened awareness of CHS and preventive measures that are taken after revascularization. Otherwise the post-surgical blood pressure control regimens might have been stricter in the last years.

Outcome after hemodynamic compromise

> *What is the relation of hemodynamic compromise with morbidity and mortality after carotid revascularization? And are there ways to prevent hemodynamic complications?*

In chapter 3 we did not find a significant association between either hemodynamic depression or severe hypertension and the risk of stroke, myocardial infarction or death within 30 days. And therefore we cannot offer an explanation for the excess of stroke and death after CAS in ICSS as a whole. We found that baseline systolic blood pressure was the only modifiable determinant for hemodynamic complications. In clinical practice, patients with cardiac disease are often considered at high risk to undergo carotid endarterectomy and therefore are treated by CAS instead. However, on the basis of our findings these patients will experience hemodynamic depression more often. Physicians should be aware of these complications, because fluid challenge can be unsafe in these patients.

Hemodynamic depression and silent cerebral ischemia

In chapter 3 we could not relate the occurrence of hemodynamic depression with postprocedural ischemic stroke. However, carotid artery stenting is related with a higher amount of new ischemic brain lesions on post-treatment diffusion-weighted imaging (DWI). In chapter 4 we tried to relate hemodynamic depression to the higher occurrence of DWI lesions, with the assumption that hemodynamic depression will lead to impaired cerebral perfusion by a compromised washout of emboli. After CAS we found that peri-procedural hemodynamic depression was associated with an over three times higher number of new ischemic brain lesions on DWI compared with patients without this complication. Our results are consistent with the hypothesis that hypoperfusion makes the brain more prone to infarction from emboli by impairing their washout from the cerebral circulation.[42-43] By means of ischemic lesions on DWI as a surrogate marker for ischemic stroke after carotid revascularization,[44] we have now been able to correlate hemodynamic depression with postprocedural cerebral ischemia.

8.2 MAIN FINDINGS SECTION 2

The ICSS enrolled 1,713 patients, of which 177 from the Academic Medical Center Amsterdam and the University Medical Center Utrecht during the cognition substudy period. A total of 140 patients participated in the cognition substudy and performed a baseline neuropsychological examination at these two centers. This section of the thesis describes the studies of patients that participated in the cognition substudy and ICSS-MRI substudy within ICSS, a randomized controlled trial of carotid artery stenting (CAS) or carotid endarterectomy (CEA) for symptomatic carotid stenosis. Prospective data collection was done comprehensively by repeated neuropsychological examinations and with pre- and postprocedural MRI with diffusion-weighted imaging (DWI). Baseline white matter lesions were semiquantitatively assessed using the Age-Related White Matter Change (ARWMC) score.[45]

General issues

This study was initiated because of the observed higher rate of ischemic DWI lesions after CAS compared with CEA in observational and small randomized studies.[46] Most of these lesions do not cause neurological deficits and are therefore considered silent. However, there were concerns that silent lesions might negatively affect cognition,[46-48] also because in healthy elderly people free from stroke or dementia at baseline, new and clinically

silent ischemic lesions more than doubled the risk of dementia and led to steeper decline in cognitive functioning.[49] In this way, carotid revascularization might impair cognitive function, especially in case of new (silent) ischemic lesions. On the other hand, it had also been suggested that carotid revascularization could result in cognitive improvement as well.[50] Thus the debate over the consequences of carotid revascularization on cognition continued. In this respect the severity of white matter lesions that patients have at time of treatment might be relevant. White matter lesions (WML) are related with cognition and some studies have also found an association of WML with the extent of atherosclerosis in the carotid artery.[51-53]

Does the higher amount of small DWI lesions after stenting matter? In other words, will stenting harm patients' cognitive performance more than surgery?

Will the presence of white matter lesions at baseline affect neuropsychological outcomes? I.e. do patients with more white matter lesions have a lesser "cognitive reserve" capacity and will they therefore deteriorate more cognitively?

We further extended our search for factors that might influence postprocedural cognition. For this purpose, we investigated the contribution of a fetal type posterior cerebral artery (FTP) to cognition.

An FTP is an embryonic variant of the posterior cerebral artery that receives its blood supply mainly or exclusively via the internal carotid artery (ICA).[54] In case of an FTP, the supply territory of the ICA is extended to other parts of the brain normally not supplied by the ICA (parts of the thalamus, hippocampus, temporal lobe, and the occipital lobe).[55] This way, impaired cerebral circulation could be more harmful to patients with an FTP. For it has been shown that perfusion in the territory of the middle cerebral artery is inversely related to the degree of carotid artery stenosis.[56] However, carotid revascularization has shown to improve perfusion.[57] Furthermore, it has been suggested that an increase in cerebral perfusion after carotid revascularization is associated with cognitive improvement.[58,59]

In patients with an internal carotid stenosis and an ipsilateral fetal-type posterior cerebral artery, cerebral perfusion is likely to be compromised in a considerably larger area of the brain than in patients with a normal posterior cerebral artery. Will these patients benefit more from carotid revascularization?

INTEGRATION OF MAIN FINDINGS SECTION 2

Randomized comparison of CAS vs CEA; relation of new ischemic lesions with cognition

The only three earlier randomized studies of endovascular treatment versus endarterectomy could not detect cognitive differences between the treatments, however these studies had methodological shortcomings.[60-62] The between-group difference in the cognitive sumscore between CAS and CEA in our study was -0.17 (95% CI -0.38 to 0.03), despite a doubled rate of new ischemic lesions after CAS than after CEA (95 % CI 1.0 to 4.4), which was consistent with other studies that found a higher rate of ischemic lesions after CAS than after CEA.[44,46]

There was also no association between total lesion volume and global cognitive functioning. However, patients who were treated by CAS showed a significant decrease in cognition of -0.19 (95% CI 0.10 to 0.29), while cognitive functioning fell by 0.02 in patients treated by CEA (95% CI -0.16 to 0.21) (chapter 5).

How strong is the link between new ischemic brain lesions and cognition?

In patients undergoing intracardiac surgery, cognitive decline has been associated with the presence of new ischemic lesions on postoperative MRI and this was more severe with greater ischemic load.[63] However, in studies of patients undergoing coronary artery bypass grafting no such relation was found.[64,65] The absence of a difference in cognitive functioning after CAS or CEA observed in the present study, despite the substantially higher rate of new ischemic lesions after CAS, is comparable with observations in randomized trials of off-pump versus on-pump coronary artery bypass graft surgery. In these trials, no sustained difference in post-operative cognition between the two treatment groups was found, despite a 200-fold reduction of the number of intraoperative cerebral emboli during off-pump surgery in one of these studies.[66,67]

The lack of, or us not being able to find, an association between new ischemic lesions and cognitive functioning between patients treated with CAS or CEA may in part be explained by the reversibility of these lesions. In the ICSS-MRI study, only 17% of the DWI lesions detected in the first three days after CAS and 53% of those after CEA showed a corresponding new hyperintensity on the FLAIR sequence at one-month follow-up. In another study, only 2 of 64 (3%) early DWI lesions were visible on T2-weighted MR images at 6 months.[68] In addition, most lesions may be just too small to lead to cognitive

impairment on the short term. Furthermore, we also did not find an association between total lesion volume and global cognitive functioning. Then again, after stenting patients did deteriorate in cognitive functioning, hereby lending support to concerns that even small and partly reversible lesions may affect cognition. Additionally, our follow-up period may have been just too short to detect cognitive worsening between the two procedures. The mean follow-up duration per patient in the longitudinal Rotterdam Scan study was 3.6 years and when participants with silent brain infarcts at baseline were subdivided into those with and those without additional infarcts at follow-up, the decline in cognitive function was restricted to those with additional silent infarcts.[49] So we cannot rule out that the patients who had suffered from silent ischemic lesions in our study are at increased risk of cognitive decline, particularly if they would face new ischemic events in the future.

White matter lesions and cognition

Cerebral white matter lesions (WML) have been associated with cognitive deficits.[69-72] In chapter 6 we have shown that patients had a decrease of -0.21 in cognitive sum score (95% CI -0.32 to -0.09) after carotid revascularization. Unexpectedly, the decline in cognition was not dependent on white matter lesion load at baseline.

Our hypothesis was that patients with the largest white matter lesions would have the least cognitive reserve capacity,[73-75] and that the reverse would be true for patients with the least white matter lesions. These patients would have shown an improvement after carotid revascularization, because they might benefit most of an increase in cerebral perfusion. Because of the observed overall decline in cognition, we had to reject our assumptions. One possible explanation for the cognitive worsening is that new ischemic lesions contribute to cognitive decline after the intervention,[63] but we lack strong evidence to support this hypothesis. That said, it is not clear whether the small decline in cognitive performance has any clinical value (at least for the short term). When compared with generally used classifications of cognitive decline, our patients' cognitive performance did not approximate this cut-off value at all. An accepted definition of any new deficit in a cognitive domain is a drop of ≥ 1 SD, and new cognitive impairment in case of a new deficit in two or more domains after the procedure.[60]

Fetal-type posterior cerebral circulation and cognition

The cognitive sum score decreased by 0.28 (95% confidence interval, 0.10 to 0.45) in 13 patients with an ipsilateral fetal-type posterior cerebral artery (FTP) and by 0.07 (95%

CI, 0.002 to 0.15) in 85 patients with a normal posterior cerebral artery (PCA) (mean difference, -0.20; 95% CI, -0.40 to -0.01) (chapter 7).

"The barren land gets overflown."

In contrast to our expectations, we found that in patients with a symptomatic ICA stenosis and an FTP, carotid revascularization was associated with a larger decline in cognition than in patients with a normal PCA. This finding could not be explained by differences in the anterior part of the circle of Willis, by a worse functional outcome at six months after revascularization, or by a more frequent occurrence of new 'silent' ischemic lesions on DWI within the first 3 days.

The relation between cerebral perfusion and cognition has remained controversial. In several studies, a lower total cerebral blood flow has been related with worse information-processing speed, executive function, and global cognition.[76-78] However, in one of these studies, these associations disappeared after correcting total cerebral blood flow for brain volume.[78] Still, even if no genuine relation between cerebral perfusion and cognition existed, this would not explain the larger decrease in cognition after revascularization in patients with an FTP than in those with a normal PCA.

In a metaphorical sense, I would like to make the comparison of watering arid land; this course of action will not make the ground more fertile. However, this is perhaps a rather disproportionate assumption, since our patients did not have major cognitive problems to begin with. On the other hand, it maybe just possible that, patients with an embryonic variant of the cerebral circulation, such as an FTP, have less ability to develop new or compensating responses to disabling effects or pathophysiological changes. This theory of neural compensation refers to the utilization of brain structures or networks that are not normally used by healthy individuals.[74]

METHODOLOGICAL CONSIDERATIONS

At this point some comments on the methodological aspects of this work are relevant.

Sample size calculation and bias

Sample-size calculations before the start of this study were hampered by conflicting data on cognitive outcome after CEA and scarcity of information on cognition after CAS.[50] Unfortunately, the target sample of 200 patients had not been reached, because recruitment

into ICSS was terminated earlier than expected, therefore presence of a type II error cannot be excluded. Of the 177 patients that were enrolled in ICSS, 172 were potential candidates to participate in the cognition substudy. However, only 140 patients had undergone the first neuropsychological examination, possibly leading to *ascertainment bias*. However, reasons for non-participation were similar in patients treated with CAS and CEA (chapter 5).

Furthermore, only about half of our study population had an MRI after the procedure, for which reason we could not reliably assess the effects of number and location of new lesions on cognitive function. Although, it appears unlikely that the occurrence of new ischemic lesions differed substantially between patients who were scanned and those who were not, we cannot rule out that *selection bias* may have occurred. Mainly, in chapter 6 and 7 this could have been a major issue, because patients had to be able to undergo both neuropsychological examination and radiological imaging to participate in these studies. This reduced the number of patients to a little more than the half of the total of patients that were enrolled during the substudy period. The small number of patients with an FTP was in line with rates of FTP reported in the literature (chapter 7), but the small number of patients may have led to imprecision of effect estimates. The *attrition rate* at follow-up was considered reasonable (more than 85% for all studies). However, patients without follow-up neuropsychological examination or who did not have a second MRI were significantly older. These patients may have had a greater decline in cognition; again this could have led to an underestimation of the effect of CAS or CEA on cognition.

Neuropsychological test battery, cognitive domains

Some psychometric tests may be insensitive to identify abnormalities,[79] for example because of ceiling effects, and subtle cognitive changes can therefore not be ruled out. To reduce the chance of failing to detect subtle cognitive changes, we assessed cognitive functioning comprehensively with a neuropsychological test battery (comprising the same or very similar tests proposed by the Vascular Cognitive Impairment (VCI) harmonization standards).[80] The test battery comprised the eight major cognitive domains; abstract reasoning, attention, executive functioning, language, verbal memory, visual memory, visual perception, and neglect. Mood, anxiety and premorbid intelligence levels were taken into account. Patients with signs of pre-existent cognitive decline were excluded. By these means we have tried to raise the precision of our cognitive measurements.

The neuropsychological test scores were standardized based on a historical control group of healthy individuals, who had been tested at similar time intervals.[81] However, these persons were not properly matched to our patients and differed with regard to age (younger) and sex

(more females). This is a potential cause of *misclassification bias*, which results in an incorrect estimation of effect. However, because the misclassification was consistent in all patients; i.e. regardless of therapy, baseline white matter lesions, or type of intracranial vasculature, this bias was non-differential and this would have caused our results to converge to one another. This might be an explanation as to why the differences between our study groups were small.

Variation test performance; re-test variability

The substantial variation in test performance when subjects undergo the same neuropsy chological test twice has recently been proposed as an additional factor to explain the absence of differences in cognition between groups in coronary bypass studies.[82] Although we cannot exclude that intra-subject variation may have contributed to the negative findings in our study, we have tried to minimize this by transforming raw neuropsychological test scores into z-scores based on the results of two examinations of a control group that had undergone the neuropsychological test battery at the same time interval, thereby also controlling for potential practice effects.

MRI assessments

Two researchers who were masked to treatment and were not involved with the statistical analyses examined all scans. The intra- and interrater reliability of semiquantitave assessed DWI lesion volumes is considered good.[83] White matter lesions (WML) were scored with a semiquantitative ordinal rating scale,[45] which is a frequently used method with good intra- and interrater reliability,[45,84] but has ceiling effects and is less precise, in contrast to automated volumetric measurements. However, we tried to minimize the possibility of bias by the aggregation of lesion burden into tertiles. In patients with subjective memory complaints, volumetric measurements of WML were found to be more sensitive than visual scoring methods with respect to memory symptoms.[85] However, as there is no ideal rating scale yet visual rating scales will stay mandatory in clinical practice and in studies involving large amounts of subjects.[86]

Blinding

Another concern is that as part of this clinical trial it was not possible to blind test assessors to treatment assignment, as the baseline assessments took place when the patients already knew their assignment and were admitted to either the neurological or surgical ward before stenting or CEA, respectively. The postoperative scar did not make it feasible for

observers to stay blinded at follow-up. However, we tried to overcome this partly by two independent observers who were blinded to treatment assignment and to clinical and cognitive outcomes that interpreted the MRI results.

8.3 EVALUATION OF THIS THESIS & IMPLICATIONS FOR CLINICAL CARE AND FUTURE PERSPECTIVES

Given the recent results of the large clinical trials comparing CAS with CEA, the standard treatment for symptomatic carotid stenosis remains CEA. Nevertheless, carotid artery stenting will still remain an option in certain patient categories. Therefore, awareness of possible complications after carotid revascularization is important and improvement of patient care in daily clinical practice indispensable.

Conclusions

- CAS leads to a larger early decrease in blood pressure than CEA, but this effect does not persist over time. CAS may reduce the need for antihypertensive medication more than CEA.
- Hemodynamic depression occurs more often after CAS and severe hypertension more often after CEA, but these complications are not responsible for the excess of major perioperative events after CAS. Baseline systolic blood pressure is the only modifiable determinant for hemodynamic complications.
- After CAS, periprocedural hemodynamic depression is associated with an excess of new ischemic lesions on DWI.
- There is a substantially higher rate of new ischemic lesions after CAS than after CEA. In contrast to CEA, CAS has a small detrimental effect on cognition at six months after treatment, but differences between CAS and CEA in effect on cognition are not statistically significant.
- We provided evidence that any difference between the effects of stenting and surgery 6 months after revascularization is small.
- Cognitive functioning may deteriorate after carotid revascularization, regardless of baseline white matter lesion burden.
- An ipsilateral fetal-type posterior cerebral artery appears to increase cognitive decline after carotid revascularisation.

Implications for patient care

- Blood pressure control should be more stringent before and after carotid revascularization, as recommended by guidelines for secondary stroke prevention.
- Avoidance of periprocedural hypotension and bradycardia may reduce the risk of DWI lesions occurring during CAS.
- The long-term cognitive effects of the higher 'silent' lesion burden after CAS are unclear. If more ischemic lesions add up, cognitive impairment could become more pronounced.
- Patients with the least white matter lesion load at baseline are not protected against cognitive decline after carotid revascularization.
- Presence of an ipsilateral fetal-type posterior cerebral artery should not affect the decision to perform carotid endarterectomy or stenting, until our findings have been reproduced by a larger study.

Future perspectives

- In randomized studies comparing carotid revascularization procedures care should be taken to improve *best medical treatment*.
- Procedural characteristics should be as uniform as possible, or should be accounted for.
- In future studies of cognition in patients treated with carotid revascularization diffusion tensor MRI may quantify structural changes better and map these with the relevant cognitive networks.
- In cognition studies it would be wise to take cortical or hippocampal atrophy into account.
- The power to detect differences in cognition between CAS and CEA might increase with longer follow-up.

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Synopsis

About a fifth of ischemic stroke is caused by carotid artery stenosis. Revascularization of the carotid artery prevents subsequent ischemic stroke. Carotid endarterectomy (CEA) remains the standard treatment, however in certain cases carotid artery stenting (CAS) can be an adequate alternative. Physicians treating patients with carotid artery stenosis should be aware of the short and long term consequences of complications that arise after these procedures.

Chapter 1 provides a general introduction to the background of carotid revascularization. The central topic of section 1 concerns hemodynamic changes in the short and long-term and the effect of periprocedural hemodynamic compromise on the development of new cerebral ischemic lesions, and clinical outcome. In section 2 the main objective is to gain more insight in cognitive consequences of carotid artery revascularization. The role of CAS vs. CEA – and silent cerebral ischemia in a subset of patients –, baseline white matter lesions and the presence of an embryonic variant of the circle of Willis on cognition is assessed.

SECTION 1

The results of **chapter 2** show that both CAS and CEA were associated with a decrease in blood pressure at discharge after treatment. Blood pressure (BP) decreased more after CAS (mean difference (MD) between groups in systolic BP 10.3 mmHg, 95% CI, 7.3 to 13.3). But during follow-up BP changes were not different between the groups. However, fewer patients undergoing CAS used antihypertensive medication during follow-up than after CEA. Therefore, CAS may lessen the need for antihypertensive medication more than CEA. The emphasis of **chapter 3** is to compare the incidence of hemodynamic complications between CAS and CEA. The occurrence of periprocedural hemodynamic depression (the combination of severe bradycardia, asystole, or hypotension requiring treatment) and hypertension requiring treatment was assessed. Hemodynamic depression occurred in 13.8% after CAS and in 7.2% after CEA (relative risk (RR), 1.9; 95% CI 1.4 to 2.6). Hypertension requiring treatment occurred less often after CAS (RR, 0.2; 95% CI, 0.1 to 0.4). In CAS patients, a history of cardiac failure was the strongest independent predictor of hemodynamic depression (RR, 2.4; 95% CI, 1.3 to 4.8). In the first 30 days after treatment, the composite outcome of stroke, myocardial infarction (MI), or death occurred in 60 (7.8%) of the patients treated with CAS and in 33 (4.0%) of the patients treated with CEA. There was no significant association between hemodynamic complications and the occurrence of stroke, MI, or death. We conclude that, hemodynamic depression occurs more often after CAS and severe hypertension more often after CEA, but that these complications are not responsible for the excess of major perioperative events after

CAS. In **chapter 4** we assessed whether the occurrence of hemodynamic depression is associated with the occurrence of new ischemic brain lesions as assessed with diffusion-weighted imaging. After CAS, patients with hemodynamic depression had a mean of 13 new DWI lesions, compared with a mean of 4 in those without hemodynamic depression (RR, 3.36: 95% CI, 1.73 to 6.50). The number of lesions after CEA was too small for reliable analyses. We have determined that, in patients treated by CAS, periprocedural hemodynamic depression is associated with an excess of new ischemic lesions on DWI. The findings support the hypothesis that hypoperfusion increases the susceptibility of the brain to embolism.

SECTION 2

The objective of **chapter 5** was to compare the cognitive effects of carotid artery stenting (CAS) and carotid endarterectomy (CEA) for symptomatic carotid artery stenosis. Patients underwent detailed neuropsychological examinations in the week before and after 6 months after the procedure. CAS was associated with a larger decrease in cognition than CEA, but the between-group difference was not statistically significant: -0.17 (95% CI, -0.38 to 0.03). Ischemic brain lesions were assessed with diffusion-weighted imaging before and within 3 days after revascularization in a subset of patients. New ischemic lesions were found twice as often after CAS than after CEA (RR, 2.1; 95% CI, 1.0 to 4.4, $P = 0.041$). Thus, differences between CAS and CEA in effect on cognition were not statistically significant, despite a substantially higher rate of new ischemic lesions after CAS than after CEA. With this study we provided Class III evidence that any difference between the effects op CAS and CEA on cognition at six months after revascularization is small.

Cerebral white matter lesions (WML) are associated with cognitive impairment, and carotid revascularization has been associated with cognitive worsening or improvement. In **chapter 6** we assessed the relation between WML severity and changes in cognition after CEA or CAS. All patients showed a decline in cognitive performance at six months: mean difference -0.21 (95% CI, -0.32 to -0.09). However, the change in sumscore did not depend on WML load: MD for patients with no-to-mild WML, -0.15 (95% CI, -0.39 to 0.09), for moderate WML, -0.27 (95% CI, -0.48 to -0.06); and for severe WML, -0.21 (95% CI, -0.40 to -0.04).

In 12 to 36% of the patients, the posterior cerebral artery (PCA) is mainly or exclusively supplied by the internal carotid artery via a fetal-type posterior cerebral artery (FTP). In these patients, ipsilateral carotid artery stenosis is likely to result in a larger area with hypoperfusion than in case of a normal PCA. Patients with an FTP could therefore

benefit more from revascularization. In **chapter 7** we compared the effects of carotid revascularization on cognition between patients with an FTP and those with a normal PCA. The cognitive sum score decreased by 0.28 (95% CI, 0.10 to 0.45) in 13 patients with an ipsilateral FTP and by 0.07 (95% CI, 0.002 to 0.15) in 85 patients with a normal PCA (MD, -0.20; 95% CI, -0.40 to -0.01). We find that, an ipsilateral fetal-type posterior cerebral artery appears to increase cognitive decline after carotid revascularization. We concluded that, this finding should be reproduced in an independent study.

To conclude, the studies presented in this thesis indicate that CAS leads to a larger early decrease in blood pressure than CEA, but this effect does not persist over time. The occurrence of hemodynamic depression after CAS does not explain the excess of major perioperative events after CAS. However, after CAS periprocedural hemodynamic depression is associated with an excess of new ischemic brain lesions.

CAS has a small detrimental effect on cognition at six months after treatment, but compared with CEA there is no statistically significant difference. Baseline white matter lesion burden does not affect the decline in cognition after carotid revascularization. And the presence of an ipsilateral fetal-type posterior cerebral artery seems to increase cognitive decline. The challenge for further studies assessing outcome after carotid revascularization is to identify the patients at risk of postprocedural major adverse events and cognitive decline.

Nederlandse samenvatting

Een beroerte is een van de meest voorkomende oorzaken van invaliditeit en overlijden. In ongeveer 80% van de gevallen wordt een beroerte veroorzaakt door een herseninfarct of een TIA. In ongeveer een vijfde van deze gevallen betreft de oorzaak van het infarct een ernstige vernauwing van de halsslagader, in medische terminologie ook wel stenose van de a. carotis. Patiënten die een TIA of een herseninfarct hebben doorgemaakt hebben een groter risico om opnieuw een beroerte door te maken. Vanaf de jaren '50 van vorige eeuw werd een ernstige vernauwing van de halsslagader behandeld middels operatie. Gedurende deze ingreep wordt de vernauwing-veroorzakende aderverkalking verwijderd. Dit wordt ook wel endarteriëctomie van de arteria carotis genoemd.

Inmiddels was vanuit meerdere grote wetenschappelijke onderzoeken gebleken dat een operatie een recidiefberoerte kan voorkomen. Vanaf de negentiger jaren werd echter steeds vaker een alternatieve behandeling gebezigd, waarbij de stenose werd behandeld door middel van een dotterprocedure, waarbij er soms ook een stent achtergelaten werd. Een stent is een metalen spiraal die het verstopte bloedvat ervan weerhoudt weer dicht te slibben. Een soortgelijke behandeling werd al langer bij patiënten met een hartinfarct toegepast. Er leken veel positieve kanten aan deze behandeling; er behoefde namelijk geen operatie onder narcose verricht te worden, patiënten hadden geen ontsierende littekens en het verblijf in het ziekenhuis kon danig worden verkort. Het was alleen niet bekend of deze behandeling net zo'n goed effect had om een beroerte in de toekomst te voorkomen. Bovendien was er nog weinig bekend over de complicaties die door deze behandeling veroorzaakt werden.

In recente jaren is hieromtrent meer duidelijkheid gekomen. Gebleken is, dat patiënten met een ernstige vernauwing van de arteria carotis nog steeds de standaardbehandeling, namelijk operatie (ofwel carotis endarteriëctomie), dienen te ondergaan. Gerandomiseerde (door het lot bepaalde) studies waarbij de operatieve behandeling werd vergeleken met stentplaatsing hebben laten zien dat na de laatste behandeling patiënten duidelijk vaker een beroerte of overlijden van de patiënt in de eerste 30 dagen na de behandeling tot gevolg had. In bepaalde gevallen echter is de behandeling middels een dotterprocedure met stentachterlating een goed alternatief. Dit is het geval wanneer de stenose moeilijk door de chirurg benaderd kan worden of wanneer er een contra-indicatie bestaat om een operatie onder narcose te ondergaan, als de vernauwing het gevolg is van eerdere bestraling in de nek of als de vernauwing een recidief is na eerdere operatie.

Ten tijde van de uitvoering van de onderzoeken in dit proefschrift waren de studies die de beide behandelingen met elkaar vergeleken nog gaande. Onze studies werden verricht omdat er bepaalde zorgen waren omtrent stentplaatsing. Bepaalde studies meldden namelijk dat de endovasculaire (binnen in een bloedvat) behandeling, die we ook wel dotteren met

stentplaatsing noemen, vaker leidde tot problemen met de bloeddruk na de behandeling en dat er vaker kleine stolsels (thrombi) naar de hersenen losschoten.

Deel 1 van dit proefschrift gaat over de complicaties die te maken hebben met de bloeddrukveranderingen rondom de behandeling die kunnen leiden tot doorbloedingsproblemen van de hersenen (ofwel hemodynamische veranderingen). Wij hebben onderzocht of het voorkomen van hemodynamische veranderingen ook vaker leidde tot een beroerte of een andere ernstige complicatie. Deel 2 beschrijft de effecten van operatie en stentplaatsing van de halsslagader op de cognitie, waarbij wij tevens hebben gekeken of het hebben van wittestofafwijkingen van de hersenen (hiervan is bekend dat ze leiden tot cognitief verval) de cognitie na operatie of stentplaatsing ook beïnvloedde. Tevens hebben wij onderzocht wat de cognitieve gevolgen zijn van behandeling van de halsslagader indien er sprake is van een bepaalde variant van de intracraniële bloedvoorziening.

Deel 1

In **hoofdstuk 2** hebben wij laten zien dat zowel endovasculaire als de operatieve benadering van de ernstig vernauwde halsslagader is geassocieerd met een bloeddrukdaling op moment van ontslag na de procedure. De bloeddrukdaling was groter na endovasculaire behandeling (het gemiddeld systolisch bloeddrukverschil tussen de groepen betrof 10.3 mmHg, 95% betrouwbaarheidsinterval (BI) 7.3 tot 13.3). Tijdens het verdere vervolg was er geen verschil meer tussen de beide behandelingen, maar de patiënten die de stentplaatsing hadden ondergaan gebruikten minder bloeddrukverlagers. Deze bevinding zou kunnen betekenen dat na stentplaatsing patiënten minder medicatie tegen hoge bloeddruk nodig hebben.

In **hoofdstuk 3** wordt vergeleken hoe vaak hemodynamische complicaties ontstaan na beide behandelingen. We hebben onderzocht hoe vaak hemodynamische depressie (te weten ernstige daling van de hartslag, wegvallen van de hartslag of ernstige bloeddrukdaling) en een ernstige verhoging van de bloeddruk ontstaat na beide behandelingen. Hemodynamische depressie ontstond in 13.8% van de gevallen na stentplaatsing en in 7.2% van de geopereerde patiënten (relatief risico (RR), 1.9; 95% BI 1.4 tot 2.6). Ernstige hypertensie ontstond minder vaak na stentplaatsing (RR, 0.2; 95% BI 0.1 tot 0.4). Een medisch verleden met hartfalen was de belangrijkste onafhankelijke voorspeller voor het ontwikkelen van hemodynamische depressie (RR, 2.4; 95% BI, 1.3 tot 4.8). In de eerste 30 dagen na de behandeling trad de samengevoegde uitkomstmaat van beroerte, hartinfarct en overlijden op in 60 (7.8%) van de patiënten die werden gestent en in 33 (4.0%) van de patiënten die werden geopereerd. Er was geen significante associatie van hemodynamische complicaties

en de samengestelde uitkomstmaat. Wij veronderstelden hierdoor dat het vaker voorkomen van ernstige complicaties na stentplaatsing niet het gevolg zijn van hemodynamische complicaties. In **hoofdstuk 4** hebben we onderzocht of hemodynamische depressie geassocieerd is met het ontstaan van nieuwe ischemische herseninfarcten die worden gezien op diffusie-gewogen opnames met MRI-onderzoek. Na stentplaatsing hadden patiënten met hemodynamische depressie een gemiddeld aantal van 13 nieuwe ischemische laesies, vergeleken met 4 in patiënten zonder hemodynamische depressie (RR, 3.36: 95% BI, 1.73 tot 6.50). Over de geopereerde patiënten konden we geen betrouwbare uitspraken doen. We concludeerden dat na stenten, doorgemaakte hemodynamische depressie rondom de behandeling is geassocieerd met een verhoogd aantal nieuwe ischemische hersenlaesies. Dit zou kunnen betekenen dat een verstoorde doorbloeding de hersenen vatbaar maakt voor embolisatie (losgeschoten thrombi).

Deel 2

In **hoofdstuk 5** worden de effecten van de endovasculaire en operatieve behandeling op de cognitie vergeleken. Patiënten ondergingen voor de behandeling een uitgebreid neuropsychologisch onderzoek en dit werd na 6 maanden herhaald. Stenten was geassocieerd met een grotere achteruitgang in cognitie dan operatie, maar het verschil tussen de behandeling was niet significant (-0.17 (95% BI, -0.38 tot 0.03). In een kleinere groep patiënten werd ook middels MRI-onderzoek gekeken naar het ontstaan van nieuwe hersenlaesies. Nieuwe laesies werden twee keer vaker na stentplaatsing gevonden dan na operatie (RR, 2.1; 95% BI, 1.0 tot 4.4, $P = 0.041$). Dit wil zeggen dat ondanks het substantieel vaker voorkomen van nieuwe laesies na stentplaatsing, dit niet leidde tot een groter verschil in cognitie in vergelijking met patiënten die werden geopereerd.

Wittestofafwijkingen van de hersenen zijn geassocieerd met cognitieve disfunctie en achteruitgang. In **hoofdstuk 6** hebben we onderzocht of patiënten met de kleinste hoeveelheid wittestofafwijkingen voor de behandeling (dus de minste schade aan de hersenen vooraf) het cognitief beter zouden doen dan patiënten die meer wittestofafwijkingen hadden. Onze resultaten lieten echter zien dat alle patiënten het cognitief slechter deden, onafhankelijk van de hoeveelheid witte stofafwijkingen die ze vooraf hadden.

De hersenen worden van bloed voorzien via een netwerk van bloedvaten; dit netwerk krijgt zijn bloed via de 2 halsslagaders en 2 slagaders achter in de hals die langs de wervelkolom zijn gelegen. Zij komen binnen de schedel samen en vormen een soort *rotonde*; de cirkel van Willis. Bij een bepaalde variant in deze circulatie, in medische termen een foetale variant van de a. cerebri posterior, wordt een groter gedeelte van de hersenen van bloed voorzien

via de aan dezelfde zijde gelegen halsslagader. Wij hebben in **hoofdstuk 7** onderzocht of het hebben van zo'n variant wellicht leidt tot een verbetering van de cognitieve vermogens, aangezien na de behandeling de bloedtoevoer in een groter gedeelte wordt hersteld. Onze resultaten lieten echter zien dat het hebben van een foetale variant er juist voor zorgt dat de cognitie achteruitgaat.

Samenvattend kunnen wij stellen dat er vroeg na stentplaatsing een grotere bloeddrukdaling ontstaat in vergelijking met na operatie, echter dit verschil houdt geen stand bij verder vervolg. Het voorkomen van hemodynamische depressie na stentplaatsing geeft geen verklaring voor vaker gemelde complicaties na deze procedure. Echter, hemodynamische depressie rondom stentplaatsing is wel geassocieerd met een grotere hoeveelheid nieuwe ischemische hersenlaesies.

Stentplaatsing veroorzaakt een kleine achteruitgang in cognitie 6 maanden na behandeling, echter bij vergelijk met operatie is er geen statistisch significant verschil.

De hoeveelheid wittestofafwijkingen voor de behandeling heeft geen invloed op de cognitieve veranderingen na behandeling. De aanwezigheid van een foetale variant van de arteria cerebri posterior lijkt een verslechtering van cognitie te veroorzaken.

Toekomstige studies zullen moeten proberen patiënten te identificeren met een verhoogd risico op het oplopen van ernstige complicaties en/of cognitief verval.

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"Alleen ben je nergens…"
PANC

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Curriculum vitae

Aysun Altınbaş was born on the 28th of January 1980 in Enschede, the Netherlands. At secondary school she participated in the bilingual education program and graduated in 1998 (Atheneum β, Stedelijk Lyceum Zuid, Enschede, the Netherlands). In the same year she started her medical training at Utrecht University, the Netherlands. As a medical student she completed a traineeship Pediatrics at Rio University Hospital, Patras, Greece. Before finishing her medical training, she worked on a research project entitled "Integrative regulation of anxiety and pathophysiological processes of self-starvation" at the Rudolf Magnus Institute of Neuroscience under supervision of M.J.H. Kas, PhD. Until her practical rotations in Neurology she believed she would become a psychiatrist. At which point she realized that Neurology was the best combination of the brain and the body. After obtaining her medical degree in 2004, she started her training in Neurology in 2005 (prof. J. van Gijn, MD, PhD and prof. J.H.J. Wokke, MD, PhD). In July 2006 she started to work on the research described in this thesis at the department of Neurology, Rudolf Magnus Institute of Neuroscience under supervision of M.J.E. van Zandvoort, PhD, H.B. van der Worp, MD, PhD and professor L.J.K. Kappelle, MD, PhD. On the 31st of October 2013 – the same day this thesis will be defended – she hopes to qualify as a neurologist. She will continue with a traineeship in Pediatrics at the Wilhemina Children's Hospital (J. Frenkel, MD, PhD) within the context of her traineeship in Child Neurology (prof. K.P.J. Braun, MD, PhD), her new fascination.