The Safety of Carotid Artery Surgery and Stenting

Submitted for the degree of MD (Res), UCL 2015

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1. Personal declaration

I, David Doig, confirm that the work presented in this thesis is my own, and has not previously been submitted for a higher degree. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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1.1.1 Funding declaration

ICSS was funded by the UK Medical Research Council (MRC) and managed by the UK National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. The views and opinions expressed herein are those of the author and do not necessarily reflect those of the NIHR Health Services Research programme of the Department of Health. Additional funding was supplied by grants from the Stroke Association, Sanofi-Synthelabo and the European Union. This work was undertaken at University College London, which received a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The funders of ICSS had no role in trial design, data collection, analysis, or the writing of this thesis.

2. Acknowledgements

I would like to acknowledge the huge contribution of the patients who enrolled in the International Carotid Stenting Study, without whom none of our research would have been possible. Their involvement with the trial will benefit countless other patients with carotid artery stenosis.

This work was carried out at UCL under the supervision of Professor Martin Brown and Dr Rolf Jäger. I thank them both for the opportunity to carry out this work and for their advice throughout. Dr Leo Bonati of Universitätsspital Basel and Mr Toby Richards of UCL provided academic support and critical comments on the work. Dr Stefan Brew and Dr Matt Adams of UCLH NHS Trust provided training in radiological image analysis. I am grateful to Dr Mark White of UCLH NHS Trust for technical support in maintaining an imaging database for ICSS analyses. Ben Hobson at UCL collaborated on several analyses and patiently evaluated hundreds of sets of vascular imaging. Other ICSS investigators are listed in Appendix II and collaborated on publications based on this work.

Roland Featherstone is the trial manager for ICSS and assisted with data cleaning and preparation for analysis. Adrienne Wallis entered trial data. I am grateful to Joanna Dobson and Liz Turner from the London School of Hygiene and Tropical Medicine who provided statistical support and advice and helped to produce figures for this thesis. Helen Tindall organized us all and provided encouragement. Fiona Kennedy gave a second opinion on analysis results and kept us motivated.

3. Personal contribution

The work presented in this thesis is my own, and is based on data from the International Carotid Stenting Study, a multicentre international trial. A list of trial investigators and trial centres is given in Chapter 24 (Appendix III). As a UCL Research Associate I worked in the central trial office from December 2009 to December 2012 cleaning data and designing and performing the analyses set out in Chapters 15, 18 and 19. The analyses in Chapters 14, 16 and 17 were carried out with the practical assistance and advice of statisticians at the London School of Hygiene and Tropical Medicine who also helped prepare the forest plots of results as acknowledged in Chapter 2. While clinical follow-up in ICSS continued I followed up our local trial patients in person – taking clinical measurements, arranging further investigation and adjusting their secondary prevention therapy as necessary.

A list of publications and presentations derived from this work is given in Chapters 10-11.

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4. Abstract

4.1.1 Introduction

Carotid endarterectomy (CEA) remains the standard of care for patients with greater than 50% symptomatic carotid artery stenosis to prevent recurrent stroke. The International Carotid Stenting Study (ICSS) compared the safety and efficacy of carotid angioplasty and stenting (CAS), with CEA. This thesis aims to determine which baseline patient characteristics, processes of care or vascular anatomical variants are associated with risk of stroke, myocardial infarction (MI) or death within 30 days of either procedure, and whether existing models to predict the risk of these complications performed well in ICSS patients.

4.1.2 Methods

ICSS was a multicentre international randomized controlled open trial. Medically stable patients with >50% symptomatic carotid artery stenosis due to atherosclerosis were randomized to either CAS or CEA. Procedures were carried out by accredited operators according to trial protocol.

4.1.3 Results

Women in ICSS experienced a higher risk of stroke, (MI) or death within 30 days of CEA, although sex was not an independent risk factor for this endpoint. They also experienced a significantly higher risk of haematoma and cranial nerve palsy after surgery. The risk of surgery was not significantly influenced by type of anaesthesia, surgical reconstruction or shunt use.

The risk of stroke, MI or death following CAS rose with increasing age and was higher with open-cell design stents. The risk of CAS was not influenced by vascular anatomical variation seen on pre-stenting catheter angiography. Cerebral protection devices (CPDs), designed to prevent debris causing stroke, did not protect against periprocedural stroke.

Existing risk scores for CEA and CAS tested in ICSS had insufficient power to discriminate between low- and high-risk groups.

4.1.4 Conclusions

New methods of predicting the risk of carotid revascularization are needed to allow patients and clinicians to make informed choices about treatment for symptomatic carotid artery stenosis.

5. Table of contents

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8. Abbreviations

ACAS	the Asymptomatic Carotid Atherosclerosis Study
ACST(-2)	the Asymptomatic Carotid Surgery Trial (2)
ARWMC	age-related white matter change score
BACASS	the Basel Carotid Artery Stenting Study
(s)(d)BP	(systolic) (diastolic) blood pressure
CAS	carotid artery stenting / carotid angioplasty and stenting
CAVATAS	the Carotid and Vertebral Artery Transluminal Angioplasty Study
CCA	common carotid artery
CE	symbol / mark declaring manufacturer's product or device meets the requirement of applicable European Community directives
CEA	carotid endarterectomy
(95%) CI	(95%) confidence interval
CONSORT	Consolidated Standard of Reporting Trials
CREST	the Carotid Revascularization Endarterectomy vs Stenting Trial
CT(A)	computed tomography (angiogram)
DICOM	Digital Imaging and Communications in Medicine
DMC	data monitoring committee
DSA	digital subtraction angiogram
DWI(-MR)	diffusion-weighted imaging (magnetic resonance scan)
ECA	external carotid artery
ECG	electrocardiogram
ECST(-2)	the European Carotid Surgery Trial (2)
EDV	end-diastolic velocity (of blood flow)
EU	European Union
EVA-3S	the Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis trial
FBC	full blood count
FLAIR	fluid-attenuated inversion recovery
HR	hazard ratio
ICA	internal carotid artery

ICH	intracranial haemorrhage
ICSS	the International Carotid Stenting Study
ICU	intensive care unit
ISRCTN	International Standard Randomized Controlled Trial Number
ITT	intention-to-treat
MeSH	Medical Subject Headings
MI	myocardial infarction
mmHg	millimetre of mercury
(CE)MR(A)	(contrast-enhanced) magnetic resonance (angiogram)
MRC	the UK Medical Research Council
MREC	Multicentre Research Ethics Committee
mRS	modified Rankin Score
N/A	not applicable
NASCET	the North American Symptomatic Carotid Endarterectomy Trial
OR	odds ratio
PP	per protocol
PSV	peak systolic velocity (of blood flow)
PTA	percutaneous transluminal angioplasty
QALY	quality-adjusted life year
RR	risk ratio
SAPPHIRE	the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial
SPACE(-2)	the Stent-Protected Angioplasty versus Carotid Endarterectomy trial (2)
TESCAS-C	the Treatment of Carotid Atherosclerotic Stenosis in China trial
TIA	transient ischaemic attack
UK	United Kingdom of Great Britain and Northern Ireland
US(A)	United States (of America)
VA	the Veterans' Administration Symptomatic Trial
WHO	the World Health Organization
XA	catheter / intra-arterial angiogram

9. MeSH Keywords

Carotid artery stenosis

Carotid atherosclerosis

Carotid artery ulcerating plaque

Carotid endarterectomy

Stents

Brain ischemia

Stroke

Myocardial infarction

Cranial nerves

Haematoma

10. List of original publications derived from this work

10.1.1 Chapter 12 (Introduction and literature review)

Doig D, Brown M M. "Carotid stenting versus endarterectomy". *Annu Rev Med* 2012;63:259-276 – work adapted for presentation in this thesis with permission from the Annual Review of Medicine, Volume 63 © 2012 by Annual Reviews, http://annualreviews.org

Doig D, Brown M M. "Acute stroke care and management of carotid artery stenosis". *Pathy's Principles and Practice of Geriatric Medicine.* John Wiley & Sons (2012). pp 655-674

Doig D, Brown M M. "Acute stroke care and management of carotid artery stenosis". *Cardiovascular disease and health in the older patient.* John Wiley and Sons (2012), pp 261-298

10.1.2 Chapter 14 (Risk factors for stroke, myocardial infarction or death following carotid endarterectomy)

"Risk factors for stroke, myocardial infarction, or death following carotid endarterectomy: results from the International Carotid Stenting Study" *accepted for publication*

10.1.3 Chapter 16 (Risk factors for, and impact of, cranial nerve palsy and haematoma following carotid endarterectomy)

Doig D, Turner EL, Dobson J, Featherstone RL, de Borst GJ, Brown MM, Richards T. "Incidence, impact and predictors of cranial nerve palsy and haematoma following carotid endarterectomy in the International Carotid Stenting Study" *Eur J Vasc Endovasc Surg* 2014;48:498-504

10.1.4 Chapter 13 (Risk factors for stroke, myocardial infarction or death following carotid stenting)

"Predictors of stroke, myocardial infarction, or death within 30 days of carotid artery stenting: results from the International Carotid Stenting Study" *accepted for publication*

10.1.5 Chapter 18 (Vascular anatomical factors influencing the risk of new ischaemic brain lesions on diffusion-weighted MRI following carotid stenting)

“Carotid anatomy does not predict the risk of new ischaemic brain lesions on diffusion-weighted imaging after carotid artery stenting in the ICSS-MRI Substudy” *accepted for publication*

11. List of original presentations derived from this work

11.1.1 2013

Featherstone, R. L., Kennedy, F., Doig, D., Dobson, J., & Brown, M. M. “Proportion of patients treated by carotid endarterectomy or stenting who might have had as good an outcome with optimised medical treatment: a modelling study using the Carotid Artery Risk Score”. *Cerebrovasc Dis* 2013;35:63-63

11.1.2 2012

Doig, D., Featherstone, R. L., Richards, T., Brown, M. M. “Performance of risk prediction scores for carotid endarterectomy”. *Presented at UK Vascular Society AGM, Manchester, 2012.*

Kennedy, F. L., Featherstone, R. L., Doig, D., & Brown, M. M. “Compliance and durability of blood pressure control for secondary stroke prevention in the International Carotid Stenting Study”. *Cerebrovascular Diseases, 33 (Suppl 2)*, 1-2. Karger. doi:10.1159/000339538

Brown, M. M., Dobson, J., Doig, D., Featherstone, R. L., & Turner, E. L. (2012). “Primary analysis of the International Carotid Stenting Study: a randomised comparison of the effectiveness of carotid stenting and endarterectomy in preventing long-term stroke in patients with symptomatic carotid stenosis”. *Cerebrovascular Diseases, 33 (Suppl 2)*, 1-2. doi:10.1159/000339538

Doig, D. A., Featherstone, R. L., Turner, E. L., Dobson, J., Richards, T., & Brown, M. M. (2012). “The influence of surgical technique and patient characteristics on the outcome of carotid endarterectomy (CEA): data from the International Carotid Stenting Study (ICSS). *Cerebrovascular Diseases, 33 (Suppl 2)*, 1-2. Karger. doi:10.1159/000339538

Doig, D. A., van der Worp, H. B., Featherstone, R. L., & Brown, M. M. “Timing of periprocedural major events associated with revascularisation in the International Carotid Stenting Study (ICSS)”. *Cerebrovascular Diseases, 33 (Suppl 2)*, 1-2. Karger. doi:10.1159/000339538

11.1.3 2011

Doig, D. A., Brew, S., Richards, T., Featherstone, R. L., & Brown, M. M. (2011). "Does intensive peri-procedural management prevent complications of carotid revascularization?". *International Journal of Stroke, 6 (s2)*, 1-65. Wiley. doi:10.1111/j.1747-4949.2011.00684.x

Featherstone, R. L., Doig, D., Altinbas, A., van der Worp, H. B., & Brown, M. M. (n.d.). "Impact of 30-day outcomes in the International Carotid Stenting Study (ICSS) on disability at one year". *International Journal of Stroke, 6 (s2)*, 1-65. Wiley. doi:10.1111/j.1747-4949.2011.00684.x

Doig, D. A., Dobson, J., Featherstone, R. L., & Brown, M. M. "Short-term predictors of stroke after carotid stenting and carotid endarterectomy: data from the International Carotid Stenting Study (ICSS)*". Cerevrovascular Diseases,* Karger. doi:10.1159/000329448

11.1.4 2010

Doig, D. A., Featherstone, R. L., & Brown, M. M. (2010). Cerebral protection devices do not protect against peri-procedural stroke: data from the International Carotid Stenting Study. *Cerebrovascular Diseases, 29 ((Suppl 2))*, 1-341. Karger. doi:10.1159/000321266

Doig, D., Featherstone, R. L., & Brown, M. M. "Short-term predictors of risk of stenting for symptomatic carotid stenosis - data from the International Carotid Stenting Study (ICSS)". *Journal of Neurology, Neurosurgery and Psychiatry, 82 (3)*, e1. UK: Highwire Press British Medical Journal Publishing Group. doi:10.1136/jnnp.2010.235572.11

Featherstone, R. L., Doig, D. A., Altinbas, A., van der Worp, H. B., & Brown, M. M. "The results of the European Carotid Surgery Trial no longer predict outcome of carotid endarterectomy: a comparison with results of the International Carotid Stenting Study". *Cerebrovascular Diseases, 29 (Suppl 2)*, 1-341. Karger. doi:10.1159/000321266

12. Introduction and literature review

12.1 Stroke and vascular disease

12.1.1 Background

Stroke is one of the leading causes of death and disability throughout the world [1]. Most commonly-defined as “rapidly-developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until earlier death, with no apparent non-vascular cause” [2], the term “stroke” therefore describes the presentation of the patient rather than the underlying pathophysiology, and is distinct from a Transient Ischaemic Attack (TIA) in which the signs and symptoms of focal cerebral dysfunction resolve within 24 hours. As brain imaging becomes more accessible, TIA has more recently been defined as “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia without acute infarction” [3]. Stroke syndromes affect all age groups, becoming increasingly prevalent in later life. Data from the United States suggest that nearly 800,000 residents in that country alone suffered a new or recurrent stroke each year [4]. In the United Kingdom the equivalent figure is estimated to be 152,000 new patients experiencing a stroke each year [5].

Early treatment and identification of risk factors for recurrent disease is important – mortality following a stroke may be as high as 41% after 5 years [6]. However, rapid assessment and organized treatment in a stroke unit, including a multi-disciplinary approach to rehabilitation, investigation of the underlying cause, attention to secondary prevention medications and avoidance of complications can improve outcome [7]. There are many causes of stroke or TIA, and identification of the aetiology in each patient will be guided by the patient’s demographics, the results of clinical examination, the pattern of infarction or ischaemia in the brain and the results of investigations such as ECG, cardiac echo, vascular studies and blood tests.

This thesis focuses on patients with ischaemic stroke. In broad categories, ischaemic stroke may be caused by embolism (from arterial atheroma, from the heart or paradoxical embolism from the venous system in patients with atrial septal defect), thrombosis of an intracranial artery, haemodynamic disturbance (particularly in the setting of carotid or vertebral artery occlusion), or cerebral venous thrombosis [8].

12.1.2 Stroke and large-vessel vascular disease

Increasing age is a major risk factor for stroke [9]. A major cause of ischaemic stroke in the elderly, along with atrial fibrillation, is atherosclerosis affecting the carotid arteries, the aorta or small penetrating vessels in the brain. The estimate of the proportion of stroke due to underlying large-vessel disease (largely atheromatous carotid stenosis) ranges from 13% to 68% in heterogeneous populations [10].

Atheroma is formed wherever there is turbulent blood flow – frequently at sites of arterial branching such as the carotid arteries, at the origins of the supra-aortic vessels, in the coronary arteries, the intracranial arteries and the arterial supply to the leg where there is injury to the vascular endothelium as a result of haemodynamic shear stress [11]. The response to chronic injury at these sites is infiltration of inflammatory cells laden with fat ("foam cells"), followed by proliferation of smooth muscle cells. Some lesions will form a fibrous cap over the top. Reduction in the calibre of the vessel, stenosis, occurs over time and may give rise to a clinically-audible bruit. Lesions that are large in volume are more likely to be "unstable" with a high degree of inflammatory infiltration and a large lipid core [12], leading to rupture of any fibrous cap, exposure of the circulating blood components to underlying tissue antigens, platelet aggregation and thrombus formation. Both the thickness of the plaque [13] and irregularity of the plaque surface [14] have been demonstrated to predict the risk of subsequent stroke in asymptomatic patients. Progressive occlusion of the artery itself will not usually cause stroke because of the collateral supply to the brain through the circle of Willis, but if the circle is incompetent or there is reduction in perfusion due to atherosclerosis of the other carotid or vertebral arteries then ischaemia may result. However, if thrombus on the atherosclerotic plaque dislodges following plaque rupture and embolizes distally to the intracranial arteries then an embolic stroke may result.

Carotid atherosclerosis is relatively common, and can be found in over 2% of European populations [15]. It is particularly prevalent in patient populations with vascular disease in the coronary or peripheral arteries, with as many as one in four having co-existent carotid disease [16] [17]. As expected, therefore, the risk factors for developing carotid atheroma are similar to those for atheroma in other vessels – older age, smoking, high blood pressure and high cholesterol [18].

The value of screening patients for carotid disease with a view to primary stroke prevention is brought into question when the risk of subsequent stroke may be less than 1% per year in patients using modern secondary prevention medications [19].

However, amongst patients who have already had TIA or stroke, those with carotid atherosclerosis are at highest risk of early recurrence [20]. Targeted secondary prevention therapy, therefore, consists of aspirin [21] and dipyridamole [22] or clopidogrel monotherapy [23], antihypertensive medication [24], a statin where appropriate [25] and control of diabetes. Patients are also encouraged to modify their lifestyle risk factors for stroke by eating healthily, taking part in moderate-intensity exercise, smoking cessation and reducing alcohol intake [26].

12.2 Investigating carotid artery disease

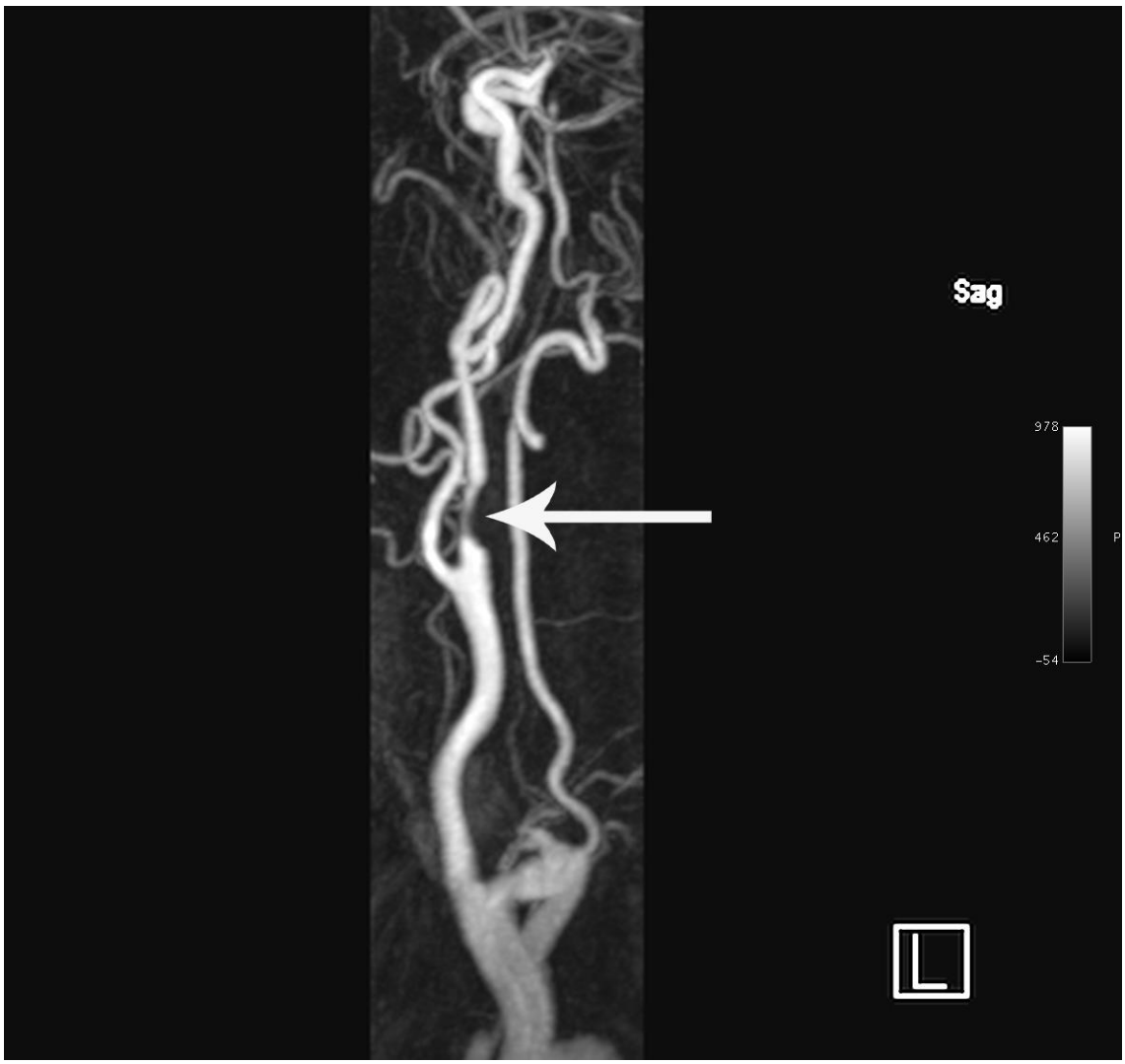
Carotid stenosis is difficult to detect clinically. Turbulent flow across a stenosis may produce a bruit clinically-detectable using a stethoscope, although high degrees of stenosis may reduce flow to a degree that no bruit is audible. Additionally, less-relevant external carotid artery (ECA) stenosis may also produce a bruit, as may transmitted sounds from an ejection systolic heart murmur. As such it is an unreliable sign and further radiological investigations are required to confidently make the diagnosis.

12.2.1 Catheter angiography

Digital subtraction catheter angiography (DSA or “XA”) is often regarded as the “gold standard” investigation for the diagnosis of carotid atheroma, and was the primary method of determining the degree of stenosis in most of the early clinical trials of carotid surgery versus medical therapy for symptomatic carotid stenosis. A catheter is advanced from a peripheral artery, usually the femoral, around the aortic arch. The common carotid is then cannulated and the carotid arteries imaged by means of radiopaque dye. A “mask” image obtained before the administration of intra-arterial contrast is then digitally subtracted from the contrast image to remove other radio-opaque structures such as bone from the final image. However, this invasive technique carries with it a risk of stroke or TIA of up to 4% in those with even lower-risk asymptomatic plaques [27] due to dislodgement of either atheroma in the vascular tree or thrombus on a complicated plaque. Figure 1 illustrates a stenosis of the left internal carotid artery just above the level of the carotid bifurcation (arrowed) as viewed on magnetic resonance angiography.

Figure 1. Magnetic resonance angiogram of internal carotid artery stenosis

An atheromatous plaque causing stenosis of the internal carotid artery just above the level of the carotid bifurcation is arrowed



12.2.2 Ultrasound

Because of their proximity to the surface of the neck, it is usually possible to examine the internal and external carotid arteries as they branch from the common carotid artery using ultrasound. Ultrasound may be used to visualize the internal carotid artery (ICA) itself, and although features such as plaque thickness can be measured, the degree of stenosis is usually is most closely correlated to the velocity of blood flowing through the artery. As the systolic blood pulse flows through a stenosis there is a corresponding increase in the velocity of the blood which is measured using Doppler-mode ultrasound. The degree of stenosis is derived from measurement of the peak systolic velocity (PSV) and end-diastolic velocity (EDV) of blood flow in the common carotid and internal carotid arteries and the ratio between the two measurements, although technical limitations to determining the degree of stenosis include acoustic shadowing from calcification in the plaque and difficulties interpreting velocity measurements in tortuous vessels or arteries without normal runoff [28].

12.2.3 CT and MR angiography

Computed tomography (CT) angiography is a less-invasive alternative to DSA. Risks associated with CT angiography include contrast nephropathy and allergic reaction to contrast media, and the ability to visualize the degree of stenosis may be limited in lesions with heavy calcification that can cause artefact on the scan image.

Magnetic resonance angiography (MRA) has a number of advantages over CT, including the avoidance of ionising radiation. However, patients do not tolerate the investigation as well, mostly because of the confined nature of the scanning tunnel. Contrast-enhanced MR has been reported to be more accurate investigation than CTA or DUS for the detection of high-grade (70-99%) stenosis than other non-invasive methods (>90% sensitivity and specificity) [29], although it is not clear whether combinations of non-invasive tests are as reliable for detecting carotid stenosis compared with catheter angiography as the results of different investigations do not always agree on the degree of stenosis. As MR angiography without contrast (“time of flight” sequences) can lead to over-estimation of the degree of stenosis [30] contrast-enhanced MRA is usually preferred. Because of the risk of complications associated with catheter angiography, non-invasive tests, sometimes in combination, are currently preferred for the initial investigation of carotid stenosis, with catheter angiogram being reserved for those cases where doubt over the diagnosis or degree of stenosis remains.

12.3 Carotid endarterectomy

That carotid artery stenosis could be a cause of focal neurological symptoms has long been recognized. Early forms of surgical intervention were focussed on attempts to improve blood flow through techniques such as cervical sympathectomy, based on the assumption that a lack of blood supply to the ipsilateral cerebral hemisphere produced symptoms ("brain claudication") similar to critical reduction of blood flow in the coronary arteries causing symptoms of angina through myocardial ischaemia. The first published descriptions of carotid endarterectomy – surgical removal of the atheromatous lesion – were from the surgeons DeBakey in the United States and Eastcott in the United Kingdom. In 1975 DeBakey reported having operating on a patient in 1953 with recurrent left hemisphere ischaemic symptoms due to carotid atheroma with good results [31]. Eastcott in 1954 reported endarterectomy and repair of the carotid artery on a 66-year-old housewife with similar ischaemic symptoms [32].

Endarterectomy for carotid stenosis was widely adopted before large-scale clinical trials could provide definitive evidence for its efficacy in the prevention of recurrent stroke, and by the early 1980s had become the third-most performed operation in the United States [33]. Surgery for carotid stenosis carries a risk of complications, including death, stroke, myocardial infarction, wound haematoma, cranial nerve palsy and pulmonary problems [34], and so to justify performing the procedure these short-term risks must be outweighed by the long-term benefit of the operation in terms of stroke prevention.

12.3.1 Trials of carotid endarterectomy versus medical therapy – symptomatic patients

In the 1980s and 1990s two large clinical trials were performed which provide the foundation for evidence-based intervention in recently-symptomatic patients since – the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [35] and the European Carotid Surgery Trial (ECST) [36].

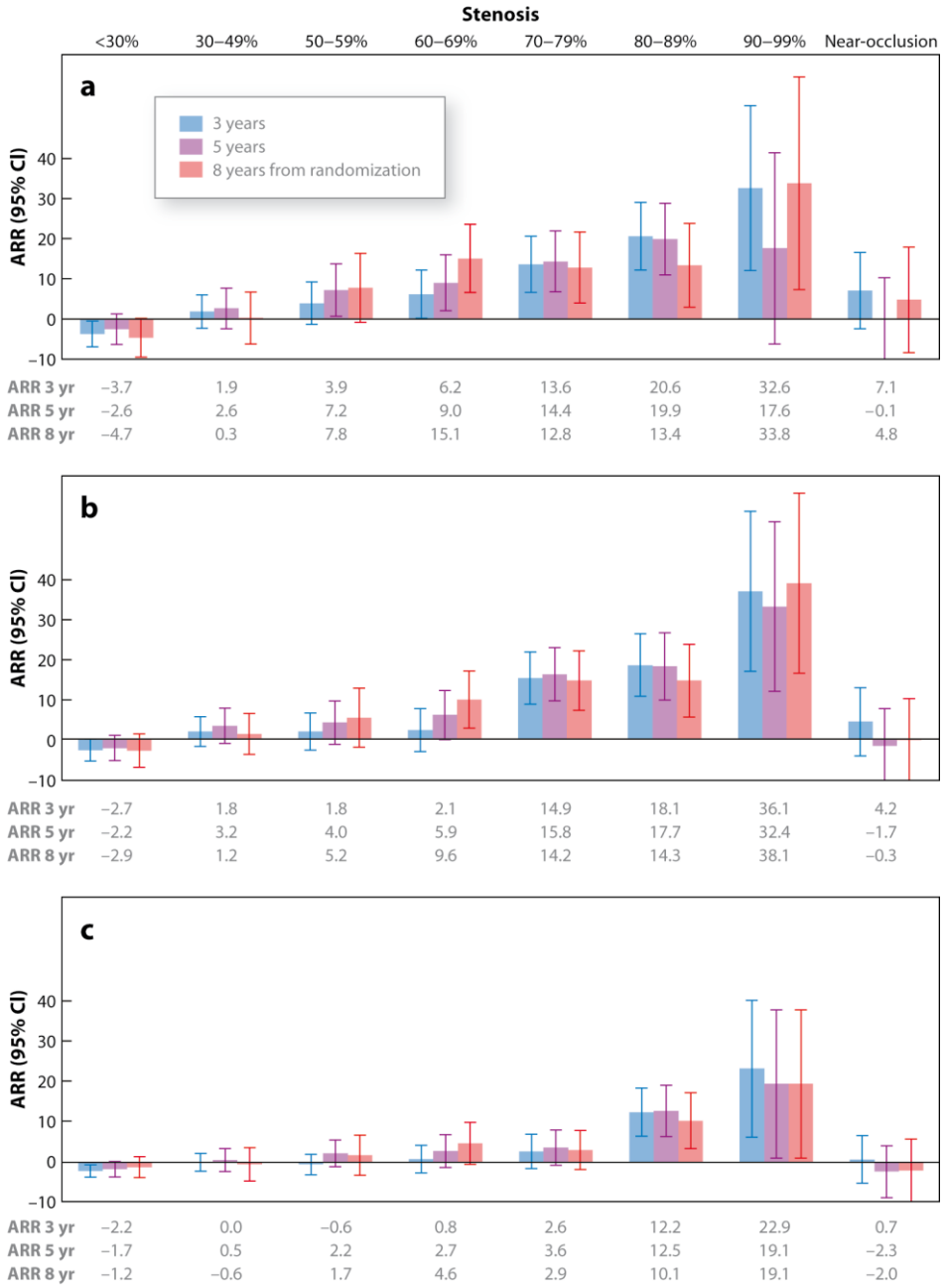
NASCET grouped patients into those with "low moderate" (<50%), "high moderate" (50-69%) and "severe" (70-99%) carotid stenosis. Patients were randomized to either CEA or medical treatment. Interim analysis of 659 patients with 70-99% stenosis revealed a statistically significant reduction in the risk of any stroke or death over 2 years in the surgery group (15.8%) as compared to the medical group (32.3%) [37]. The subsequent observation that the benefit of surgery in terms of stroke prevention was

reduced in groups with lower degrees of stenosis (and, indeed, absent in those with <50% stenosis) led the authors to conclude that “the degree of benefit individual patients received from carotid endarterectomy was directly proportional to the risk they faced without surgery” [35], with lesser degrees of stenosis conferring lower risk of recurrent stroke.

ECST, a trial that enrolled 3204 patients, reached a similar conclusion, but used a different method of measuring stenosis [36]. This trial showed a significant reduction in the risk of stroke or surgical death over 5 years in those undergoing CEA vs those on medical therapy of 21.2% (95% CI 12.9% to 29.4%) in patients with 70-99% stenosis and 5.7% (95% CI 0% to 11.6%) in those with 50-69% stenosis [38]. Like NASCET, there was no evidence of a benefit of surgery in patients with less than 50% carotid stenosis.

Meta-analysis of the results of NASCET, ECST and the smaller 189-patient trial from the Veterans Affairs Cooperative Studies Program 309 Trialist Group [39], using only the NASCET method of measuring stenosis [40], clarifies the extent of this risk reduction in patients with varying degrees of stenosis. Overall, the absolute risk of ipsilateral stroke was 16.0% lower ($p<0.01$) in those with more than 70% stenosis undergoing CEA as compared with those in the medical treatment group, and 4.6% lower ($p=0.04$) in patients with 50-69% stenosis undergoing surgery [38]. Patients with less than 50% stenosis did not benefit. A specific subgroup of patients with greater than 99% stenosis and vessel collapse due to poor runoff distal to the stenosis also did not benefit from surgery, perhaps because these lesions progressed to complete occlusion [41]. The relationship between the reduction in the main outcomes of these trials with CEA and the degree of stenosis is illustrated in Figure 2.

Figure 2. The effect of surgery on the absolute risk reduction in NASCET and ECST at 3, 5 and 8 years' follow-up stratified by the degree of carotid stenosis at baseline for a) any stroke or operative death, b) ipsilateral ischaemic or operative stroke and operative death and c) disabling or fatal ipsilateral or operative stroke and operative death



Patients								
Medical	995	767	438	370	262	225	31	148
Surgical	751	662	382	312	242	163	31	114
Total	1,746	1,429	820	682	504	388	62	262

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There is evidence that some subgroups of patients in whom surgery is recommended will benefit more than others. The risk/benefit ratio most favours surgery over medical treatment in men and the elderly. In addition, the overall benefit of surgery diminishes as the time between symptoms and surgery increases, strongly favouring intervention within 2 weeks of symptoms in stable patients [43].

The results of these trials, taken together, demonstrated a strong link between increasing degrees of carotid stenosis and increasing risk of recurrent stroke or TIA on medical treatment alone. This was matched by a corresponding decrease in risk for patients with high degrees of stenosis who undergo CEA. The most recent guidelines from the American Heart Association [44], the Society for Vascular Surgery [45] and the European Society for Vascular Surgery [46] continue to recommend carotid endarterectomy for the long-term prevention of stroke in patients with recently-symptomatic carotid artery stenosis >50% and in selected asymptomatic patients with 60-99% stenosis. However, stroke, myocardial infarction and death are not the only risks associated with CEA, and both cranial nerve palsy [47] [48] [49] [50] and neck haematoma [51] [52] are well-recognized “minor” complications which may have a major impact on the patient but have been less-extensively studied in clinical trials. These extra hazards of a neck incision have led to the consideration of carotid stenting as a less-invasive alternative to CEA, and as an alternative in patients with difficult surgical access owing to previous neck surgery or carotid stenosis secondary to radiotherapy [53].

12.3.2 Trials of carotid endarterectomy versus medical therapy – asymptomatic patients

The rate of ipsilateral stroke in patients with asymptomatic carotid disease is much lower than that of patients with symptomatic stenosis – possibly as low as 0.34% per year when optimal medical therapy is prescribed [19]. Two large randomized trials provide much of the data addressing the question of whether prophylactic CEA in asymptomatic patients prevents long-term stroke.

The North American Asymptomatic Carotid Atherosclerosis Study (ACAS) randomized 1662 patients with ≥60% stenosis to either daily aspirin treatment or daily aspirin plus carotid endarterectomy. In addition, patients in both groups received “medical risk factor management” targeting vascular risk factors. The primary comparison was between the rate of ipsilateral stroke or any perioperative stroke or death. CEA reduced

the risk of this outcome from 11.0% to 5.1% (relative risk reduction 53%, 95% CI 22% to 72%) [54].

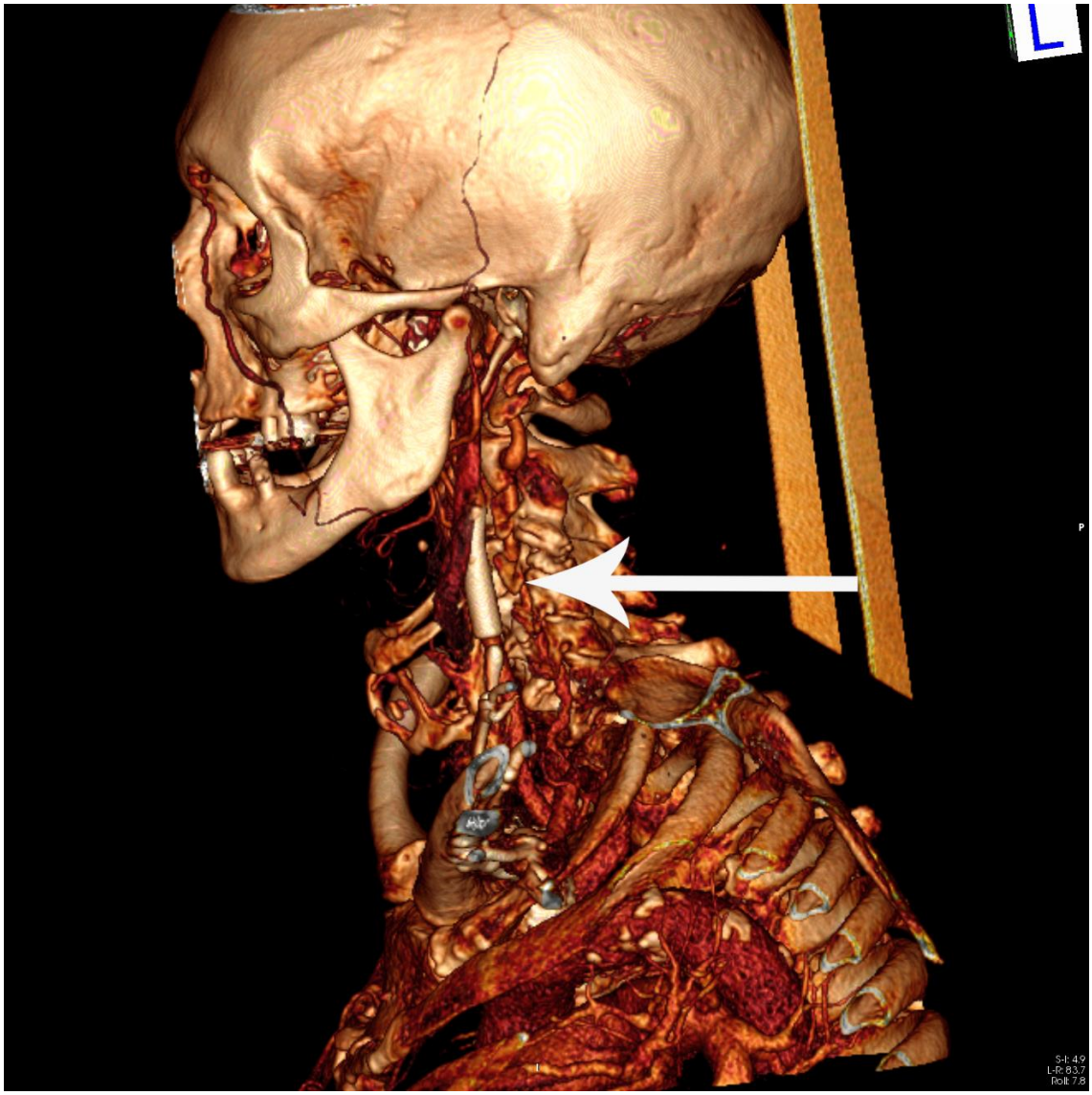
The Asymptomatic Carotid Surgery Trial (ACST) randomized 3120 patients with 60-99% carotid stenosis to either “immediate” endarterectomy or deferral of CEA until a clinician considered there to be a clear indication for proceeding with surgery. Half of the patients in the “immediate” CEA group were operated on within one month of randomization. The combined risk of perioperative and subsequent stroke over a five-year period was 11.8% in the deferred group and 6.4% in the immediate surgery group ($p<0.01$) [55]. Long-term results have since confirmed an extended benefit of CEA stroke prevention for patients under the age of 75 years [56] up to 10 years after surgery.

12.4 Carotid angioplasty and stenting

Carotid angioplasty and stenting evolved as a less-invasive alternative to CEA in part to avoid the hazards of a surgical incision. One of the first descriptions of the use of endovascular intervention for atheroma in a peripheral artery by balloon angioplasty was by Dotter in 1964, who recanalized the femoral artery of an elderly patient with peripheral vascular disease who had critically-reduced perfusion to the foot. The procedure was a clinical and radiological success [57]. (He would later develop the technique further by introducing the first stents (“coilspring grafts”) into the femoral or popliteal arteries of dogs, demonstrating that the stents remained patent after insertion [58]).

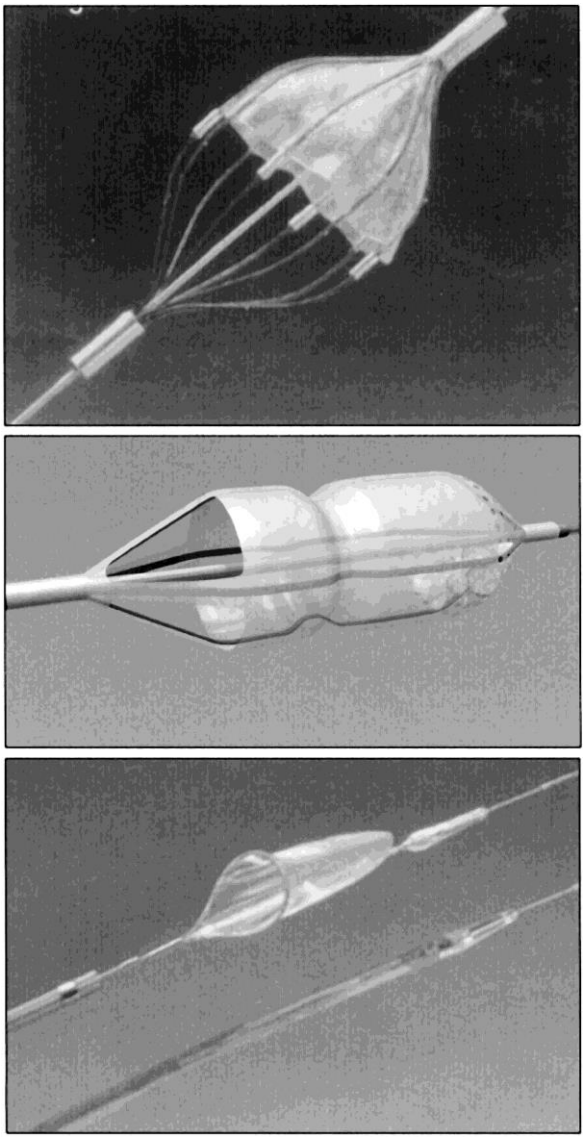
The first descriptions of using this technique to treat atheromatous disease of the carotid artery in humans emerged in the 1980s, although only small numbers of patients were included in published case series. Early results were promising, although the problem of transient neurological and cardiac symptoms due to balloon inflation and the hazards of carotid artery dissection were recognized [59] [60]. A significant restenosis rate was also reported [61], although early restenosis after angioplasty often represents smooth muscle growth rather than enlargement of the atheromatous plaque and therefore was thought to confer a lower risk of subsequent ischaemic stroke. However, much like endarterectomy, CAS was widely adopted before good-quality evidence from large randomized trials was available to support its routine use. By 2003 an estimated 10,000 patients worldwide had been recorded as having undergone CAS with a reported rate of recanalization over 99% [62]. Figure 3, below, shows a 3D reconstruction of a carotid stent in situ in the internal carotid artery (arrowed).

Figure 3. 3D reconstruction of CT angioram of head and neck of patient illustrating a carotid stent in situ in the left internal carotid artery (arrowed)



One of the major developments in CAS followed the observation that particulate debris generated during the procedure itself was a cause of periprocedural stroke. “Cerebral protection devices” (CPDs) were developed to catch this debris before entering the cerebral circulation, and employed either a mesh-type filter to trap particles or used proximal and/or distal balloons to obstruct flow. There is some conflicting evidence as to the efficacy of CPDs in preventing procedural cerebral ischaemia, and while one clinical trial found poor results in patients who did not receive a CPD [63], the International Carotid Stenting Study demonstrated a significantly higher rate of new ischaemic brain lesions after CAS versus CEA in patients recruited in centres with a policy of routine CPD use (OR 12.20, 95% CI 4.53 to 32.84) compared with CAS versus CEA in centres using unprotected stenting (OR 2.70, 95% CI 1.12 to 6.24, interaction p=0.02) [64]. Flow reversal systems, first described by Parodi [65], are a newer alternative to filter-type CPDs that use a system of inflatable balloons to create reversal of flow in the ICA into an arteriovenous shunt created by the operator. This technique has been less extensively studied, but is currently undergoing evaluation [66]. Figure 4, below, illustrates three cerebral protection devices used in ICSS.

Figure 4. Three cerebral protection devices used in the International Carotid Stenting Study – Anioguard (top), NeuroShield (middle) and FilterWire EX (bottom)



From [67] *with kind permission from Lippincott Williams & Wilkins / Wolters Kluwer Health*

Stenting carries hazards because of the endovascular nature of the procedure. Atheromatous lesions around the level of the carotid bifurcation are likely to contain friable material [68] which can be dislodged by catheterization or the passage of endovascular devices across the lesion causing TIA or stroke. Although avoiding an incision in the neck, there is still a risk of groin haematoma of around 2-3% which may necessitate repair of the femoral artery used for vascular access [69]. Patients who may have renal impairment should have their renal function checked prior to angiography and/or stenting as the procedure involves the administration of iodinated intravascular contrast.

12.4.1 Trials of CAS vs CEA – symptomatic stenosis

Early randomized trials comparing CAS and CEA yielded mixed results and generated some concern about the safety of CAS. In Leicester in the UK, Naylor and colleagues randomized 23 patients (of whom 17 received treatment) to CEA or angioplasty before the study was stopped owing to a periprocedural stroke risk of 71% (5/7 patients) in the stenting arm [70]. In contrast to this risk, Brooks and colleagues in Lexington, Kentucky, recorded only one death out of 51 patients randomized to CEA and one TIA in 53 patients randomized to CAS in their trial [71]. They noted the shorter length of hospital stay in CAS patients and concluded that CAS "challenged" CEA as the preferred treatment for patients with symptomatic carotid stenosis. The BACASS trial in Basel, Switzerland, reported similar results – none of the 10 patients randomized to CAS in this study suffered stroke, myocardial infarction or death before the trial was stopped when the centre decided to participate in the International Carotid Stenting Study [72]. The results of the WALLSTENT study [73] have only been published in abstract form, but it is known that after enrolling 219 patients the risk of any stroke or death within 30 days in the CAS arm was 12.1% vs 4.5% for CEA (p=0.05). The study was stopped on the grounds of futility.

Two larger multicentre trials more firmly established the basis for offering angioplasty as an alternative to CEA – the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial [74] and the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [75].

CAVATAS included patients with anterior circulation symptoms due to carotid stenosis as well as those with posterior circulation symptoms due to vertebral stenosis. Patients were randomized to either angioplasty or endarterectomy. The 30-day rate of stroke with symptoms persisting more than 7 days or death was almost identical between the

two groups [75], but during extended follow-up there was a non-significant increase in the 8-year incidence of ipsilateral non-perioperative stroke risk to 11.3% in the endovascular group versus 8.6% in the CEA group [76]. This study of 504 patients was therefore considered underpowered to detect a difference in treatment effect, and interpretation of the result was complicated by the introduction of stenting as a routine addition to angioplasty during the course of the trial.

SAPPHIRE enrolled symptomatic patients considered at “high risk” for CEA – those with cardiac or respiratory disease, contralateral carotid occlusion, recurrent stenosis, previous neck surgery or radiotherapy, age over 80 years or contralateral recurrent laryngeal nerve palsy – who had stenosis of at least 50%. Asymptomatic patients fitting the above criteria were enrolled if they presented with carotid stenosis greater than 80%. Patients were randomized between CAS and CEA, and CAS patients were treated using a CPD. At one year, the specified endpoint of death, stroke or MI was reached by 12.2% of CAS and 20.1% of CEA patients, but confidence intervals for this difference included equality of the two treatments [74]. At three years follow-up there was also no difference in the risk of the combined endpoint.

The results of the long-term follow-up in these and one other early trial of CAS vs CEA is presented in Table 1 below.

Table 1. Results of follow-up in the early randomized controlled trials of CA(S) vs CEA

Trial	**Region**	**N**	**Inclusion Criteria**	**Comparison**	**Primary Outcome**	**Follow-up**	**Risk of Primary Outcome**
Naylor et al. [70]	UK	23	>70% symptomatic ICA stenosis	Angioplasty vs CEA	Death or disabling or non-disabling stroke	30 days	71% vs 0% (p<0.01)
Brooks et al. [71]	USA	104	>70% symptomatic ICA stenosis	CAS vs CEA	Death or cerebral ischemia	2 years	1.9% vs 2.0%
Alberts et al. (WALLSTENT) [73]	USA	219	60 – 99% symptomatic ICA stenosis	CAS vs CEA	Ipsilateral stroke, procedure-related death, or vascular death within 1 year	1 year	12.1% vs 3.6% (p=0.02)

Table 1 continued

Trial	Region	N	Inclusion Criteria	Comparison	Primary Outcome	Follow-up	Risk of Primary Outcome
Hoffman et al. (BACASS) [72]	Switzerland	20	≥70% symptomatic ICA stenosis	CAS vs CEA	Periprocedural stroke, death or MI	4 years	0.0% vs 10.0%
Ederle et al. (CAVATAS) [75]	International	504	Carotid stenosis requiring treatment (90% symptomatic)	Angioplasty ± stenting vs CEA	Ipsilateral non-perioperative stroke	8 years	11.3% vs 8.6% (HR 1.22, 95% CI 0.59-2.54) by intention to treat
Yadav et al. (SAPPHIRE) [74]	North America	334	≥50% symptomatic stenosis / ≥80% asymptomatic ICA stenosis	CAS vs CEA	Death, stroke or MI within 30 days or death or ipsilateral stroke between 31 and 1080 days	3 years	24.6% vs 26.9% (absolute difference -2.3%, 95% CI –11.8% to 7.0%) by intention to treat

Four large randomized controlled open trials of CAS versus CEA that enrolled symptomatic patients have been carried out more recently, and all have formally reported results.

The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial was carried out in Central Europe. Of non-inferiority design, it enrolled 1200 patients with symptomatic “severe” stenosis (≥50% by NASCET method [40]) before analysis determined that it has failed to conclusively demonstrate non-inferiority. The trial was thus stopped early when its initial funding source expired and it was thought unlikely to reach a conclusive sample size. Analysis of 1183 patients showed a 30-day risk of death or ipsilateral stroke of 6.84% of the CAS group and 6.34% of the CEA group (absolute risk difference 0.51%, 90% CI -1.89% to 2.91%) [77]. At 2-year follow-up there was a similar rate of recurrent ipsilateral stroke in both groups, although it was noted that recurrent carotid stenosis was more common in the CAS group [78].

The French Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was also of non-inferiority design. After randomization of 527 patients recruitment was stopped on the advice of the safety committee – the primary combined endpoint of periprocedural stroke or death occurred in 9.6% of the CAS group (95% CI 6.4% to 14.0%) compared with 3.9% of the CEA group (95% CI 2.0% to 7.2%) [79]. Follow-up was continued out to four years, and showed that the subsequent long-term risk of recurrent ipsilateral stroke, excluding procedural risk, was low and “similar in both treatment groups” [80].

The International Carotid Stenting Study (ICSS) was funded mainly by the UK Medical Research Council, the Stroke Association and the European Union, and it recruited internationally. It randomized 1713 patients with greater-than 50% carotid stenosis using the NASCET method of measurement or non-invasive equivalent [81]. The trial protocol is described in brief in Chapter 13 and presented in full in Appendix IV. In an intention-to-treat analysis of results up to 120 days after randomization the risk of stroke, myocardial infarction or death in the CAS group was 8.5% versus 5.2% in the endarterectomy group (HR 1.92, 95% CI 1.27 to 2.89) [82]. Recruitment finished in 2008 and the results of long-term follow-up have been presented. The long-term risk of fatal or disabling stroke was no different between the two groups during a median follow-up duration of 4.2 years (HR 1.08, 95% CI 0.73 to 1.60, p=0.69), but the risk of any stroke was greater in the CAS group (HR 1.73, 95% CI 1.29 to 2.32, p<0.01) reflecting an excess of minor perioperative stroke in patients undergoing CAS [83].

Finally, the North American Carotid Revascularization: Endarterectomy versus Stent Trial (CREST) began recruiting symptomatic patients, but later amended its protocol to allow randomization of asymptomatic patients. CREST enrolled 2502 patients in total. Symptomatic patients were required to have ≥50% stenosis on angiography, ≥70% stenosis on Doppler ultrasound or ≥70% stenosis on MRA or CTA if ultrasound indicated 50-69% stenosis. Asymptomatic patients were required to have ≥60% stenosis on angiography, ≥70% on ultrasound, or ≥80% on MRA or CTA if ultrasound indicated 50-69% stenosis. CREST also differed from the European trials in mandating the use of a single manufacturer's devices for CAS – the Acculink stent and the Accunet CPD. No significant difference was found between CAS and CEA for the primary outcome measure of any periprocedural stroke, MI or death or postprocedural ipsilateral stroke at four years follow-up (7.2% vs 6.8%, HR 1.11, 95% CI 0.81 to 1.51), but there was a higher risk of periprocedural stroke in the CAS group (4.1% vs 2.3%, p=0.01) in keeping with the results of EVA-3S, SPACE and ICSS [84]. This analysis included both asymptomatic and symptomatic patients.

The short-term results of symptomatic patients only from these trials are summarized in Table 2.

Table 2. Results of the recent large randomized controlled trials of CAS vs CEA in symptomatic patients

Trial	**Region**	**Sample Size (n)**	**Comparison**	**Outcome**	**Risk of outcome at 30 days post-procedure**
EVA-3S [79]	France	527	CAS + CPD vs CEA	Any periprocedural stroke or death	9.6% vs 3.9% (p=0.01) by intention to treat
SPACE [77]	Germany, Austria, Switzerland	1183	CAS +/- CPD vs CEA	Any periprocedural ipsilateral ischemic stroke or death	6.8% vs 6.3% (p=0.09 for non-inferiority) by intention to treat
ICSS [82]	International	1713	CAS +/- CPD vs CEA	Any periprocedural stroke, MI or death	7.4% vs 4.0% (p<0.01) per protocol
CREST (symptomatic patients only) [85]	USA, Canada	1321	CAS + CPD vs CEA	Any periprocedural stroke, MI or death	6.7% vs 5.4% (p=0.30) by intention to treat

12.4.2 Trials of CAS vs CEA – asymptomatic stenosis

The safety and efficacy of CAS against CEA has also been tested in asymptomatic patients. Three large trials have reported results. The largest cohort of asymptomatic patients is found in the CREST study, which enrolled 1181 patients with carotid stenosis >50% but without symptoms. The combined risk of stroke, myocardial infarction (MI) or periprocedural death within 30 days of the procedure in these asymptomatic patients was 2.5% in the CAS group and 1.4% in the CEA group (HR 1.88, 95% CI 0.79 to 4.42, p=0.15) [85] suggesting that stenting was more risky than endarterectomy although the difference was not statistically significant. The results of long-term follow-up are awaited. In the older Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study, 7 out of 117 asymptomatic patients in the CAS group and 5 out of 120 asymptomatic patients in the CEA group suffered stroke or periprocedural death [86]. Brooks et al. also enrolled 85 asymptomatic patients with carotid stenosis >80% in their trial of CAS vs CEA, but none suffered stroke or death following the procedure [71].

Another study conducted in China, the Trial of Endarterectomy versus Stenting for the treatment of Carotid Atherosclerotic Stenosis (TESCAS-C) [87], enrolled a mixture of symptomatic and asymptomatic patients, but to date has not reported these results separately. And one further trial, the North American Asymptomatic Carotid Trial (ACT-1), was designed to compare CAS with CEA by randomizing patients in a 3:1 ratio to these treatments. Its protocol specified exclusive use of the Xact carotid stent and Emboshield protection device in the CAS arm, but has now stopped recruitment as a result of a decision by the sponsor to discontinue funding [88].

Meta-analysis of these trials suggests a trend towards worse outcome with CAS in asymptomatic patients in the short-term with a higher risk of periprocedural death or stroke, and in the long-term with a higher risk of periprocedural death or stroke or ipsilateral stroke thereafter. However, the total number of patients enrolled in asymptomatic trials is low, and this excess risk does not reach statistical significance [86].

12.4.3 Cost considerations

Limited research exists on the potential health economic benefits of carotid stenting versus endarterectomy. In theory, stenting may offer a reduced hospital stay, avoidance of a general anaesthetic and, at least in younger patients, a similar

complication rate to that of CEA while avoiding cranial nerve palsy or haematoma from a neck incision.

The data on the cost of the procedure itself is mixed – some studies find CAS to be more expensive [89], while other analyses attribute a higher cost to CEA [90]. Of interest, data from the USA showed that the net revenue for hospitals was 29% higher when patients were treated with CEA rather than CAS [91]. In order to be as cost-effective as surgery, CAS operators and device manufacturers will need to consistently demonstrate a similar complication rate to that of CEA in low-risk patients, reduce the cost of the procedure, or perhaps restrict the procedure to patients at higher surgical risk [92]. A cost-effectiveness analysis in the International Carotid Stenting Study is ongoing.

12.5 From trial data to individual patients: predicting procedural risk

Complications following any surgical procedure remain common, and occur in up to 7% of all patients even when specific interventions are applied to reduce their risk [93]. Examples of postoperative problems include cardiac arrest, myocardial infarction, pulmonary embolism, bleeding, pneumonia, wound problems including infection, sepsis and death. Data suggest that up to half of these events are potentially avoidable [94] [95]. Complication rates in carotid artery surgery and stenting remain significant [96] [97], and excluding those patients who would suffer stroke, myocardial infarction or other serious complications would prevent much perioperative morbidity and mortality.

Studies identifying subgroups of patients at risk of complications following CEA and CAS are reviewed in detail in Chapters 14, 15 and 17. However, an overview of important risk factors that appear to have a strong influence on outcome and that have been reported in multiple studies or meta-analysis is presented here.

12.5.1 Predicting the risk of CEA

Patient factors

Risk modelling drawing on patient data from ECST suggests that there are specific subgroups of patients at increased risk of stroke or death following CEA. These include female patients, those with peripheral vascular disease, and those with a high systolic blood pressure before surgery [98].

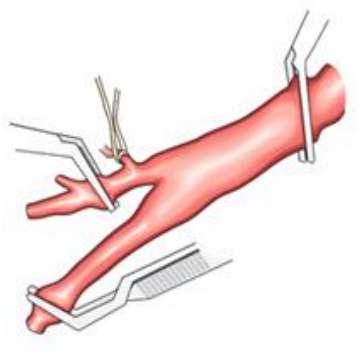
Some anatomical factors – previous surgery, radiotherapy, restenosis of a vessel, a high stenosis or inflexible neck – are thought to confer high risk for carotid endarterectomy because of limited surgical access to the carotid plaque or a technically difficult procedure, but there is some evidence from small case series to suggest that patients with some of these factors may not actually suffer more complications [99] [100]. In addition, the patient with heart or lung disease is often thought to be at increased risk from surgery [101], but again this is not always borne out in case series [100] [102].

Technical variables

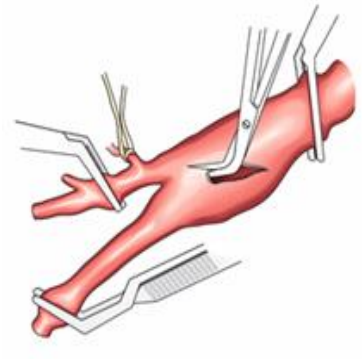
CEA can be performed under local or general anaesthesia with seemingly little difference in outcome [103] [104], but with the advantage of clinical monitoring of the patient for signs of focal neurological dysfunction during the procedure if local anaesthetic is used. Contralateral ICA stenosis appears to increase the perioperative risk of stroke [105], and the use of shunts during surgery to bypass arterial clamping on the ipsilateral side and maintain distal flow to the brain has become widespread despite limited evidence of efficacy [106]. After resection of the atherosclerotic plaque the vessel may be repaired by primary closure, by patch or by vein graft. The safety of differing surgical techniques appears similar, although there is some evidence that patch closure may reduce late restenosis [107]. Figure 5 illustrates the process of exposing the atheromatous plaque in eversion carotid endarterectomy – one surgical technique for performing arteriotomy and removal of the plaque.

Figure 5. Surgical technique for eversion carotid endarterectomy

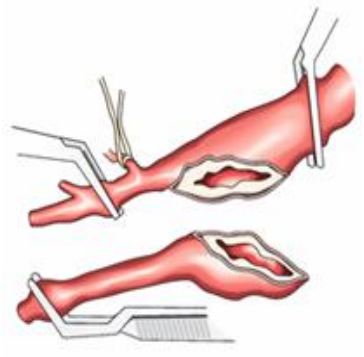
a. Haemostatic control is achieved by clamps on common, internal and external carotid arteries



b. Arteriotomy is made, extending toward the fork of the carotid bifurcation



c. Complete transection of the internal carotid artery is followed by resection of the plaque then surgical repair of the artery



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Centre and operator experience

Technical errors made during surgery may contribute to perioperative stroke [109]. Several studies address the influence of operator experience or volume in carotid endarterectomy. Surgeons performing a high volume of operations appear to have lower mortality and postoperative stroke rates [110] [111] [112]. There is also a relationship between the annual hospital volume of endarterectomies and adverse neurological outcome [113], and UK professional bodies are moving to support centralization of vascular surgical services in high-volume centres [114].

12.5.2 Predicting the risk of CAS

Patient factors

There appears to be a strong and consistent effect of the patient's age on the outcome of stenting, with a doubling of the risk of any stroke or death up to 120 days after CAS compared with CEA in patients over the age of 70 years (RR 2.04, 95% CI 1.48 to 2.82) in meta-analysis of the results of the European trials of CAS versus CEA [115]. CREST separately reported a strikingly similar finding – the efficacy of CAS and CEA was approximately equal at age 70, but the risk of CAS rose with increasing age while there was no corresponding increase in risk in the CEA group [84] [116]. There is also recent evidence that the patient with a higher burden of white matter brain disease at baseline has an increased risk of stroke following CAS [117], independent of the patient's age.

CREST reported a worse outcome after CAS in women – the 30-day risk of stroke, MI or death was 6.8% in women randomized to CAS versus 3.8% in women randomized to CEA (HR 1.84, 95% CI 1.01 to 3.37), whereas there was no significant difference between CAS and CEA complications in men. However, there was no difference in long-term outcome in CREST between the sexes and the Carotid Stenting Trialists' Collaboration did not report a difference in short-term outcomes between men and women in the European trials of CAS versus CEA [118] [84].

Technical variables

A variety of endovascular devices from different manufacturers are available to interventionists. While some clinical trials such as the International Carotid Stenting Study approved a wide range of devices [81], others including CREST mandated specific devices [84]. Thus evidence comparing devices to each other is sparse.

However, by grouping devices by their characteristics some distinction can be made between the performance of closed-cell and open-cell stents. Closed-cell stents offer enhanced coverage of the atheromatous lesion with a smaller area between metallic struts, and there is a suggestion that they offer better protection against stroke and TIA by containing debris at the site of the lesion [119].

Anatomical features

Several vascular anatomical features are thought to confer increased risk of stroke following CAS. Among those that have been shown to be associated with an increased risk are ICA angulation ≥60^{o} [120] [121], lesion length >15mm, type III or "bovine" aortic arch [122], aortic calcification [122], a calcified or ulcerated lesion [122] or an ostial lesion [122] [121]. In addition to these features, an angulated distal ICA and "pinhole" tight stenosis are described as technically challenging [123]. If some vascular anatomical variants are indeed more difficult to navigate and stent than others, it follows that more experienced operators could be able to avoid dislodging thrombus or fragmenting atheroma and therefore avoid perioperative stroke.

Centre and operator experience

While there appears to be remarkable consistency across the results of these randomized trials, the design of the European trials (ICSS, EVA-3S and SPACE) in particular have been criticized. As CAS is the newer procedure, the number of interventionists able to demonstrate substantial volumes of stenting procedures is smaller, and this was reflected in the criteria for centre enrolment in ICSS, for example. Surgeons performing endarterectomy in ICSS were required to have performed a minimum of 50 prior CEA procedures with a minimum volume of 10 cases per year and demonstrate acceptable patient outcome data. In contrast, interventionists could perform CAS procedures in the trial having placed only 10 carotid stents (albeit with a minimum of 50 stenting procedures in total including those in other vascular territories). Assessing the risk of complications with any individual operator is difficult, and larger numbers of patients are required to report a risk with narrow confidence intervals [124]. This has led to the suggestion that inexperience in these trials is responsible for the higher rate of stroke in CAS patients, and that perhaps "CAS performed by inexperienced interventionists has higher peri-procedural complication rates than CEA done by experienced surgeons" [125] is the most valid conclusion to be drawn from the data from these trials. Recent pooled analysis of the 1546 patients undergoing CAS in the three European trials suggests that the patients of interventionists who performed a

low number of procedures each year within the trials were at double the risk of stroke or death within 30 days of CAS compared with the patients of interventionists who performed more than 5 stenting procedures within the trial each year (RR 2.30, 95% CI 1.36 to 3.87) [126].

12.6 The current status of CAS & CEA for symptomatic patients

Carotid revascularization is recommended in UK, US and European guidelines for patients with symptomatic stenosis ≥50% where the operative morbidity is estimated to be low. 2014 AHA guidelines note the reduced benefit of CEA in patients with 50-69% stenosis, and suggest that the intervention in these patients should be "performed by a surgeon with excellent operative skills" [127]. In these guidelines, CAS is deemed to be indicated as an alternative to CEA in patients at average or low risk of complications, taking age into account, or in those with contraindications to CEA. In the UK the National Institute for Clinical Excellence (NICE) guidelines from 2008 do not specify a recommendation for the use of CAS other than in cases of symptomatic carotid stenosis ≥50% where endarterectomy might be high risk or contraindicated [128] [129]. Similarly, the European Vascular Society guidelines continue to recommend CEA over CAS for the majority of symptomatic patients [46] [130].

Are these guidelines reflected in clinical practice? Data from hospitals in England reveals that the overwhelming majority of revascularization procedures carried out on the carotid artery are endarterectomies, with only 5% of patients receiving stenting [131]. The results of the major randomized trials that overall favour CEA as the safer procedure – SPACE, EVA-3S, ICSS and CREST – appear not to have affected the number of CAS procedures being carried out between 2006 and 2012, but interestingly the patients undergoing CAS were younger in age, perhaps reflecting the recommendation that CAS be considered more carefully in older patients because of the higher risk of peri-procedural complications. In the United States, there has been a significant *increase* in the number of CAS procedures performed since the publication of the main results of these trials predominantly, again, in younger patients and those who were asymptomatic [132]. The debate as to which procedure is superior seems far from settled in clinicians' minds.

12.7 This thesis

This thesis will examine the risk of, and impact of, complications arising from carotid revascularization in symptomatic patients in the International Carotid Stenting Study –

stroke, myocardial infarction, death, cranial nerve palsy and neck haematoma. It will determine whether there are subgroups of patients at particular risk of these complications following CEA or CAS based on their demographic characteristics, the type of procedure they have undergone or their individual vascular anatomy. Finally it will examine the performance of existing risk-scoring systems for predicting complications of CEA and CAS when applied to the patients in ICSS who were randomized to those procedures. The thesis concludes with a summary and discussion of its main findings, and places the work in the context of recent and ongoing studies of CEA and CAS.

13. Methods – ICSS and the ICSS-MRI Substudy

13.1 The International Carotid Stenting Study

13.1.1 Introduction

The full protocol for ICSS is presented in Appendix IV, and is published elsewhere [81]. The ICSS-MRI Substudy protocol is presented in full in Appendix V. The International Carotid Stenting Study was conceived after the conclusion of CAVATAS [75], which found no statistically significant difference in outcome between CAS and CEA immediately following treatment or in the long term. However, carotid angioplasty continued to evolve during the trial, and the use of stents in the procedure developed while CAVATAS was still recruiting. CAS still promised the advantages of reduced hospital stay, potential avoidance of a general anaesthetic, and a reduced rate of surgery-specific complications such as neck haematoma and cranial nerve palsy. ICSS was therefore designed as an international, multicentre, randomized, controlled open clinical trial to test the difference between the long-term risk of fatal or disabling stroke in patients with symptomatic carotid artery stenosis greater than 50% after randomization to either CEA or CAS.

13.1.2 Selection and enrolment of trial centres & interventionists

50 academic centres in Europe, North America and Oceania enrolled patients in ICSS. Each was required to provide a principal investigator qualified in neurology or internal medicine to see patients prior to randomization and then again in follow-up. Surgeons performing trial procedures were required to have carried out 50 CEA operations with an annual rate of at least 10 cases per year, while CAS interventionists were required to have performed 50 stenting procedures, at least 10 in the carotid artery territory. All were expected to provide audit data to an ICSS accreditation committee showing a satisfactory complication rate similar to that of ECST (7.0% risk stroke or death within 30 days of the procedure, 95% CI 5.8% to 8.3%) [36].

Centres unable to fulfil the above requirements for CAS competency were allowed to join the trial and enrol patients as a “probationary centre”. CAS procedures carried out at these centres were supervised by an experienced interventionist until 10 more successful procedures were completed within the trial and the proctor was satisfied that the interventionist in question could carry out the procedure independently.

13.1.3 Selection of patients and randomization

Patients randomized in ICSS had symptomatic extracranial stenosis of the carotid artery attributable to atherosclerotic disease. Stenosis had to be greater than 50% as measured by the NASCET method [40] or an equivalent non-invasive method such as carotid ultrasound, and symptoms were required to have occurred within the last 12 months.

Patients were excluded if they were thought unsuitable for either treatment due to

- Tortuous carotid vascular anatomy
- Proximal common carotid artery disease or the presence of thrombus
- Pseudo-occlusion (>99% stenosis with normal distal runoff on angiography)
- Distal stenosis or rigid neck rendering surgery hazardous or impossible
- Previous CAS or CEA in the artery to be randomized
- Clinical instability or serious co-morbid illness (“not fit for surgery”)
- A life expectancy of less than 2 years due to a pre-existing condition
- Planned coronary artery bypass grafting within 1 month of CAS or CEA
- Refusal or inability to give written informed consent to trial participation or refusal to be randomized to either treatment
- Major stroke with no useful recovery of function within the territory of the artery to be randomized

Prior to randomization patients were given written information about the trial and informed consent to participate was given by the patient.

13.1.4 Baseline visit and investigations

At baseline visit, investigators recorded demographic information about the patient and details of past medical history including vascular risk factors. Brain imaging, in the form of CT or MRI, was required to identify previous areas of infarction or haemorrhage and to provide a comparison with any post-procedure scans.

To confirm the presence and extent of carotid stenosis, imaging from at least one of the following modalities was required

- Catheter angiogram showing the carotid bifurcation
- Bilateral MRI angiograms with a concordant Doppler ultrasound scan

- Bilateral CT angiograms with a concordant Doppler ultrasound scan
- Bilateral Doppler ultrasound scan only, if the centre was able to provide documented evidence of the reliability of their results through clinical audit and if it was standard practise to treat on the basis of ultrasound alone at that centre

Pre-randomization clinical and imaging data were returned to the trial office in London.

13.1.5 Randomization procedure

Randomization was carried out by the Oxford Clinical Trials Service Unit, stratified by centre with risk factors balanced between the two arms. Minimization was used to balance patient characteristics between the two arms. Patients with stenosis in both carotid arteries could only be randomized once, for the symptomatic artery to be treated first. The allocated procedure was then required to be carried out as soon as safely and practically possible after randomization. The possibility of a patient becoming ineligible for revascularization after randomization in the trial or crossing over to the other treatment was anticipated, and these patients were included in intention-to-treat analyses.

13.1.6 Carotid endarterectomy

Carotid endarterectomy was carried out according to the operating surgeon and the trial centre's usual protocol. The type of anaesthesia to be used was not specified nor was the choice of arterial reconstruction. The use of a patch to close the arteriotomy was optional. All patients undergoing surgery were required to receive "best medical care" including management of vascular risk factors and appropriate antiplatelet, antihypertensive or cholesterol-lowering drugs.

13.1.7 Carotid stenting

Devices used in the carotid stenting procedure were required to be CE-marked and were approved by the trial steering committee. The use of a cerebral protection device was optional, but recommended "whenever the operator [thought] one could be safely deployed". Aspirin and clopidogrel prescription prior to the procedure and for a minimum of 4 weeks after was recommended. The use of intra-procedural heparin to prevent acute thrombosis secondary to instrumentation of the carotid was mandatory, as was the administration of atropine or equivalent drugs to prevent haemodynamic disturbance secondary to manipulation of the carotid baroreceptors. Finally, it was anticipated that most patients would require balloon dilation ("pre-dilation") of the

stenotic lesion to facilitate the passage of equipment through the stenosis. Patients undergoing CAS otherwise received the same “best medical care” as the surgical group. Technical details of either CAS or CEA were returned to the trial office.

13.1.8 Post-procedure follow-up

Patients were monitored in hospital, and events occurring between the procedure and discharge were reported on the technical data form. Patients were then followed-up by a trial investigator at one month after the procedure.

13.1.9 Outcome events and adjudication

The main outcome events examined in the primary outcome of the trial and subsequently in this thesis are defined below

- Stroke – “an acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance”
- This diagnosis included retinal stroke causing loss of vision in one eye for more than 24 hours
- Myocardial infarction – recorded if the patient experienced two out of
    - Cardiac enzyme rise more than twice the upper limit of normal range
    - The development of specific ECG abnormalities
    - A history of chest discomfort for at least 30 minutes
- Cranial nerve palsy (within 30 days of the procedure) – reported by the investigator in individual patients who experienced motor or sensory disturbance, attributed to the procedure, in one of the cranial nerves.
- Haematoma – defined by the investigator in patients who experienced bleeding in the neck as a result of revascularization. “Severe haematoma” was defined as haematoma requiring blood transfusion, re-operation or one that prolonged hospital stay
- Death

A clinical diagnosis of stroke was confirmed by brain CT or MRI carried out as soon as possible after the clinical event. The cause of death was confirmed through clinical reports from the treating centre and death certificate or post-mortem results where available.

Potential stroke or MI outcome events were reported in detail to the trial office as above. An adjudication process was carried out to decide if the reported event met the criteria of one of the trial outcome events. Adjudication was carried out by two investigators at the trial office blinded to allocated treatment. A third, independent, adjudicator then reviewed the event. If a disagreement occurred between adjudicators the difference was resolved with the opinion of a second independent adjudicator and consensus. Additional information on the clinical consequences of cranial nerve palsy occurring within 30 days of CEA was sought by means of a questionnaire, detailed in Appendix II.

Stroke or cranial nerve palsy was flagged as “disabling” if the patient experienced an increase in their modified Rankin Scale (mRS) score to 3 or more where that increase was attributable to the event at a specified time-point during follow-up.

13.1.10 Sample size and statistical analysis

Sample size in ICSS was planned as 1500 patients in fully-enrolled centres, with a calculated 95% confidence interval for a difference in risk between CAS and CEA of ±3% for the composite outcome of stroke, myocardial infarction or death within 30 days of treatment. Additional patients were enrolled in probationary centres.

13.1.11 Ethical approval and safety monitoring

ICSS was approved by a Multicentre Research Ethics Committee (MREC) in the United Kingdom. In addition, individual centres obtained their own local ethics committee approval before starting randomization in the trial.

The safety of the patients enrolled in ICSS was overseen by a Data Monitoring Committee comprising a neurologist, medical statistician, surgeon and interventionist. Interim analyses were carried out during the trial to ensure that morbidity and mortality remained within acceptable limits. Individual centres’ results were monitored by the trial manager, with two consecutive deaths or three consecutive major events at an individual centre within 30 days of treatment in one arm of the study prompting a review of outcome events at this centre. Similarly, a cumulative stroke, MI or death risk of >10% over 20 cases would prompt a review.

During the course of the trial concern was raised, by the above mechanism, about the results of two investigators performing CAS procedures at two separate supervised centres. Both centres suspended recruitment while outcome events were reviewed,

although one centre subsequently re-started enrolment into ICSS with a different interventionist performing trial procedures [82]. The results presented in this thesis include patients treated by these investigators where the patients received their allocated treatment.

13.2 The ICSS-MRI Substudy

13.2.1 Introduction

Complementary to the International Carotid Stenting Study was the ICSS-MRI Substudy. The aim of this substudy was to compare the risk of ischaemic (and possibly sub-clinical) brain injury as assessed by MRI in patients undergoing stenting in ICSS compared to those undergoing surgery.

13.2.2 Substudy design

Patients enrolled in the ICSS-MRI Substudy received standard treatment as specified in the ICSS protocol above. They additionally underwent brain MRI 1-3 days before treatment, 1-3 days after treatment and approximately 30 days after revascularization. Patients with a contraindication to MRI (e.g. metallic implant or claustrophobia) were excluded from participation in the study. The following MRI sequences were specified in the trial protocol

- Diffusion-weighted imaging (DWI) to detect acute brain ischaemia or infarction
- Gradient echo T2*-weighted to detect brain haemorrhage
- T1-weighted and fluid-attenuated inversion recovery (FLAIR) to assess whether acute brain lesions on DWI persisted to become permanent FLAIR lesions at 30 days after the revascularization

13.2.3 Sample size, data and statistical analyses

A sample size of 200 patients was planned assuming a risk of new DWI lesions after endarterectomy of 25%, giving a 90% power to detect a doubling of the risk of a new DWI lesion in the stenting group.

The analysis of brain imaging in the ICSS-MRI Substudy is described in more detail in Chapter 18. Two investigators independently recorded the presence, volume and location of ischaemic and haemorrhagic lesions on each scan, and a third investigator

reviewed in cases of disagreement. Scans were reported blind to allocated treatment or the nature of the scan (e.g. pre- or post-procedural).

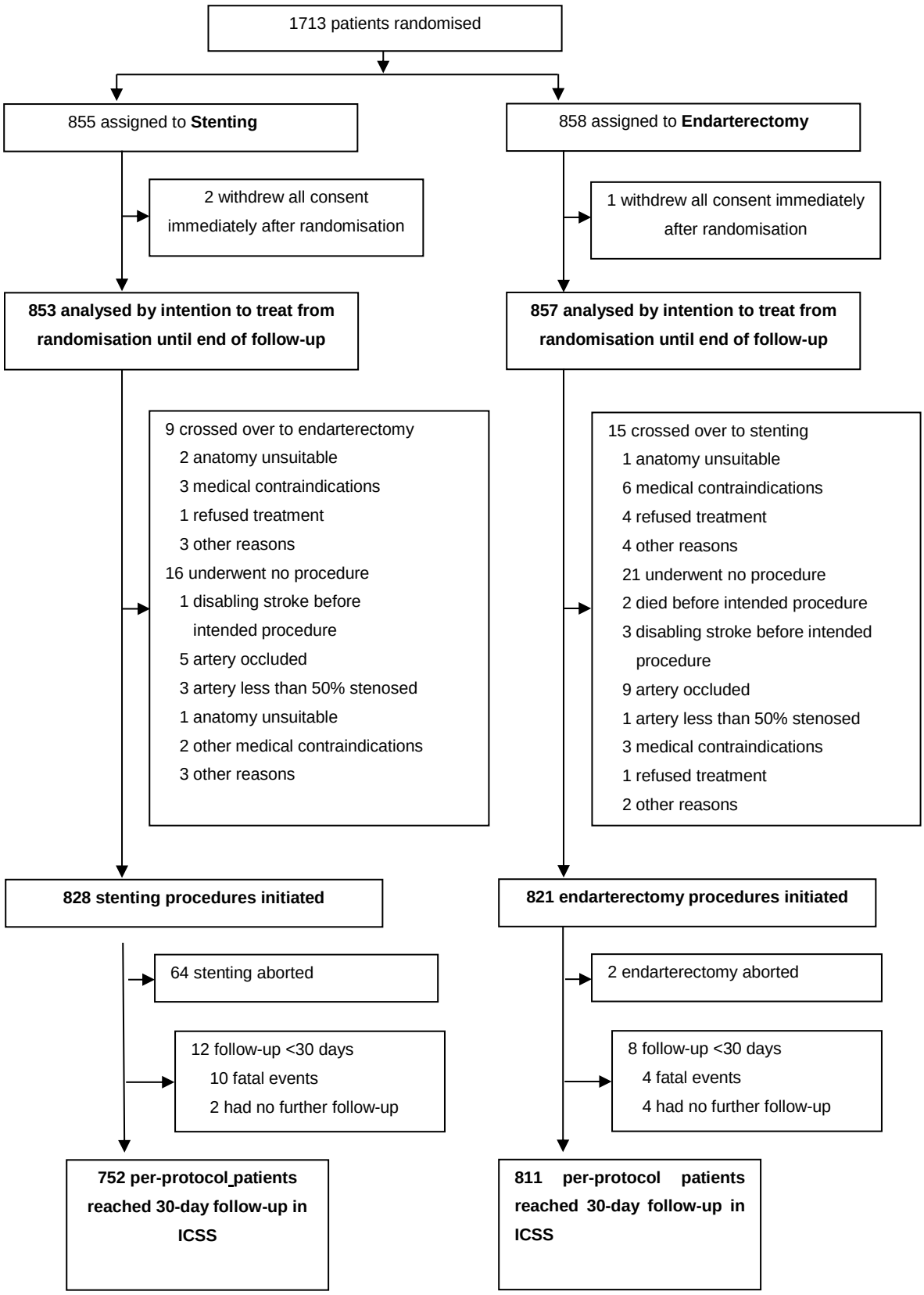
13.3 CONSORT flow diagram

The progress of patients through the International Carotid Stenting Study is outlined in the CONSORT flow diagram in Figure 6 below.

13.4 Trial funding

ICSS was funded by the UK Medical Research Council, the Stroke Association, Sanofi-Synthélabo, and the European Union. ICSS is a registered clinical trial: ISRCTN 25337470.

Figure 6. ICSS CONSORT trial diagram



14. Risk factors for stroke, myocardial infarction or death following carotid endarterectomy

14.1 Introduction

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [35], the European Carotid Surgery Trial (ECST) [36] and the smaller Veteran's Affairs Trial [39] demonstrated a reduction in the long-term rate of recurrent stroke in patients with >50% symptomatic carotid artery stenosis undergoing carotid endarterectomy compared with those on medical therapy. Meta-analysis of the results of these three trials, and two smaller studies, suggests that for every 11 symptomatic patients undergoing CEA one outcome event is prevented for the combined endpoint of any stroke or perioperative death [133].

However, CEA in these trials carried a risk of perioperative stroke or death of 7.0% (95% CI 6.2 to 8.0) [133] and subsequent studies, focussing on these short-term measures of safety, continue to demonstrate a significant risk of major complications following revascularization [134] [96]. Perioperative stroke and MI have been shown to have a significant adverse impact on long-term survival, and stroke in particular may halve survival in the first year after surgery [135]. The choice of anaesthesia and surgical technique during CEA varies [136] [137], and despite CEA being a long-established technique for revascularization there remains debate about the optimal processes of care for surgery including perioperative medical therapy, type of arterial reconstruction and mode of anaesthesia to prevent complications.

This analysis aimed to determine whether there were groups of patients at higher risk of stroke, MI or death within 30 days of CEA in the International Carotid Stenting Study and whether there are surgical practices associated with higher risk.

14.2 Methods

14.2.1 Study design & CEA procedure

This chapter presents a per-protocol analysis of patients enrolled in ICSS who were randomized to CEA and in whom the allocated procedure was initiated. The inclusion and exclusion criteria for ICSS are outlined in Chapter 13.1 and the trial protocol is detailed in full in Appendix IV. Patients over the age of 40 years old could be enrolled in ICSS if they presented with recently-symptomatic carotid artery stenosis >50% due to

atheroma. Patients were excluded from randomization in ICSS if they were unsuitable for surgery due to a surgically-inaccessibly high level of stenosis, if they had a rigid neck making positioning difficult for surgery, or if there was previous revascularization of the artery to be randomized.

CEA in ICSS was performed according to the surgeon's usual practice – the type of arterial reconstruction was not specified, nor was the mode of anaesthesia. Medical therapy for control of vascular risk factors was required in both groups in the trial, but the prescription of one or more antiplatelet agents prior to or after surgery was at the operator's discretion. Surgeons in ICSS were required to provide audited complication rates within acceptable limits and to have performed a minimum of 50 CEA procedures prior to joining the trial with a minimum volume of 10 procedures per year. In addition to this technical information, centres provided demographic information about patients and specified whether their general policy was to send patients to a specialized post-procedure ward such as a high-dependency or intensive care unit, or whether patients were admitted to a general surgical or medical ward post-operatively.

14.2.2 Outcome events

The combined endpoint of stroke, MI or death within 30 days of the procedure was analysed. Events were reported in detail to investigators at the central trial office. Confirmatory evidence was required where available: CT or MRI brain after stroke, cardiac enzymes and / or ECG after MI, death certificate and autopsy report if available following death. Stroke was defined as "an acute disturbance of focal neurological function lasting more than 24 hours resulting from intracranial vascular disturbance". A diagnosis of MI required two out of three features – a clinical history of chest discomfort lasting at least 30 minutes, cardiac enzyme rise more than twice the upper limit of normal or the development of specific ECG abnormalities. Outcome events were submitted to an external, independent, adjudicator who was masked to treatment allocation. If their assessment differed from the trial office's initial assessment a second external adjudicator reviewed the event. Differences in adjudication were resolved by consensus.

14.2.3 Statistical methods

Only patients in ICSS in whom the allocated procedure was initiated were included in this analysis. Trial patients who crossed-over to medical therapy or received CEA after a prior stenting procedure (attempted or completed) were excluded from this analysis.

CEA was considered “initiated” if the patient underwent either local or general anaesthesia prior to surgical incision. Risk factors for stroke, MI or death were examined sequentially in a univariable binomial regression analysis using maximum likelihood estimation. Second events within 30 days of the procedure were not counted. Patients with missing data were excluded from each relevant analysis. The risk ratio for each baseline or technical variable was estimated with a 95% confidence interval. Wald tests were used for continuous and binary predictors, with an overall likelihood test for categorical predictors of more than two levels. No correction was applied for multiple comparisons. $p<0.05$ was accepted as conferring statistical significance in all analyses. A multivariable model was developed using a forward stepwise approach. Analyses were performed with Stata (StataCorp, 2011. *Stata Statistical Software: Release 12.* College Station, TX: StataCorp LP).

14.3 Results

14.3.1 Outcome events

14.3.2 Patient and procedure characteristics

CEA was initiated in 821/855 patients allocated to the procedure in ICSS. Patient and procedural characteristics for this group are presented in detail in Figure 7 along with the results of univariable analysis. 70.4% of patients were male and 52% of patients were aged 70 years or more (the median age in the CEA arm of ICSS at the date of enrolment). Vascular risk factors were common. 21.2% of patients were diabetic, 66.2% were receiving treatment for hyperlipidaemia and 69.7% were receiving treatment for hypertension.

Arterial reconstruction was by patch closure in 55.9%, “standard” closure without patch in 22.1% and by eversion endarterectomy in 6.0%. Vein interposition was used in only 0.4%. General anaesthesia or combined local-general anaesthesia was administered to 79.2% of patients. A shunt was used during the procedure in 39.5%. An antiplatelet drug was prescribed to 88.4% of patients prior to the procedure, of whom 30.1% were taking two or more antiplatelet medications.

14.3.3 Characteristics and timing of outcome events

27/821 patients (3.3%) suffered a stroke of any severity within 30 days of the procedure, 5 suffered MI, and one patient died of another cause giving a combined risk of stroke, death or MI within 30 days of the procedure of 4.0%. 13/33 (39.4%) of these

events occurred on day 0 – the day of the procedure, the remainder occurring between days 1 and 30. 7/33 (21.2%) events occurred on or after the date of discharge. The median length of stay was 4 days before discharge.

14.3.4 Patient and procedural risk factors for stroke, MI or death within 30 days of the procedure

The results of univariable analyses of patient and procedural factors on the risk of stroke, MI or death within 30 days of CEA are presented in Figure 7. The risk of the combined outcome was significantly higher in female patients (RR 1.98, 95% CI 1.02 to 3.87, p=0.05) and with each increasing 10mmHg of baseline diastolic blood pressure (RR 1.31 for each +10mmHg, 95% CI 1.20 to 1.66, p=0.04). The time from the index event that prompted randomization in the trial (stroke or TIA) to the date of surgery was also a significant predictor, but this this result was influenced by one outlying patient. Removing this patient from the per-protocol population in a sensitivity analysis resulted in a non-significant p-value (RR 1.01 per 7 days, 95% CI 0.97 to 1.06, p=0.48). The age of the patient, the side of surgery, the level of disability and the degree of ipsilateral or contralateral carotid artery stenosis were not predictors of the risk of stroke, MI or death within 30 days of surgery.

Shunt use (RR 0.99, 95% CI 0.50 to 1.96, p=0.98), local anaesthesia only vs general or combined local-general anaesthesia (RR 0.48, 95% CI 0.15 to 1.57, p=0.23) and the type of surgical reconstruction (i.e. primary closure vs patch vs vein interposition) did not statistically significantly influence risk despite one out of three patients in whom vein interposition was used experiencing an event.

Centres with a policy of sending patients to a specialized ward (such as a high dependency or intensive care unit) following CEA reported a lower risk of stroke, MI or death within 30 days of surgery (RR 0.57, 95% CI 0.29 to 1.13, p=0.11), but this result was not statistically significant.

Figure 7. Univariable predictors of the risk of stroke, myocardial infarction or death in 821 patients undergoing CEA in whom the procedure was initiated

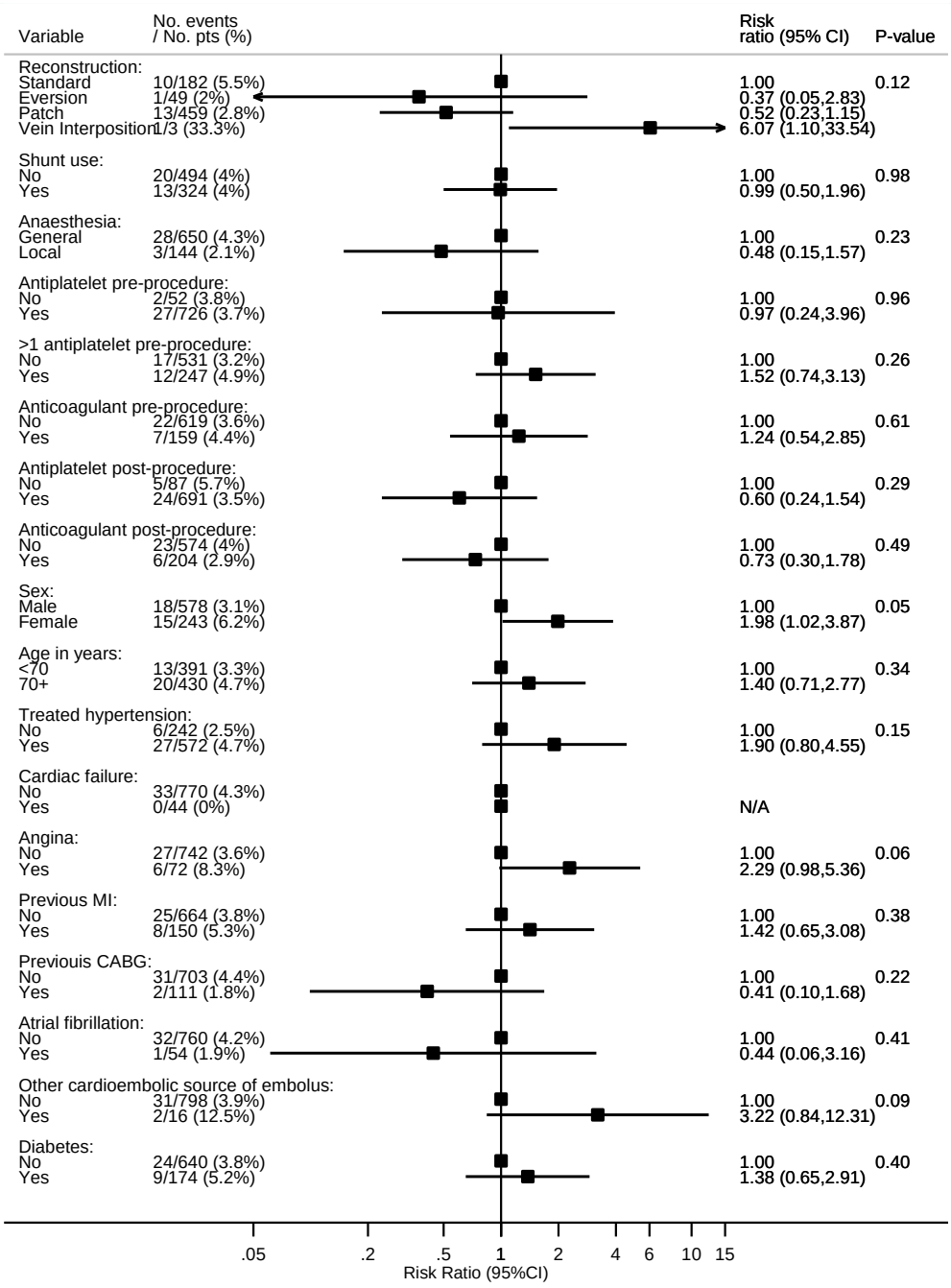
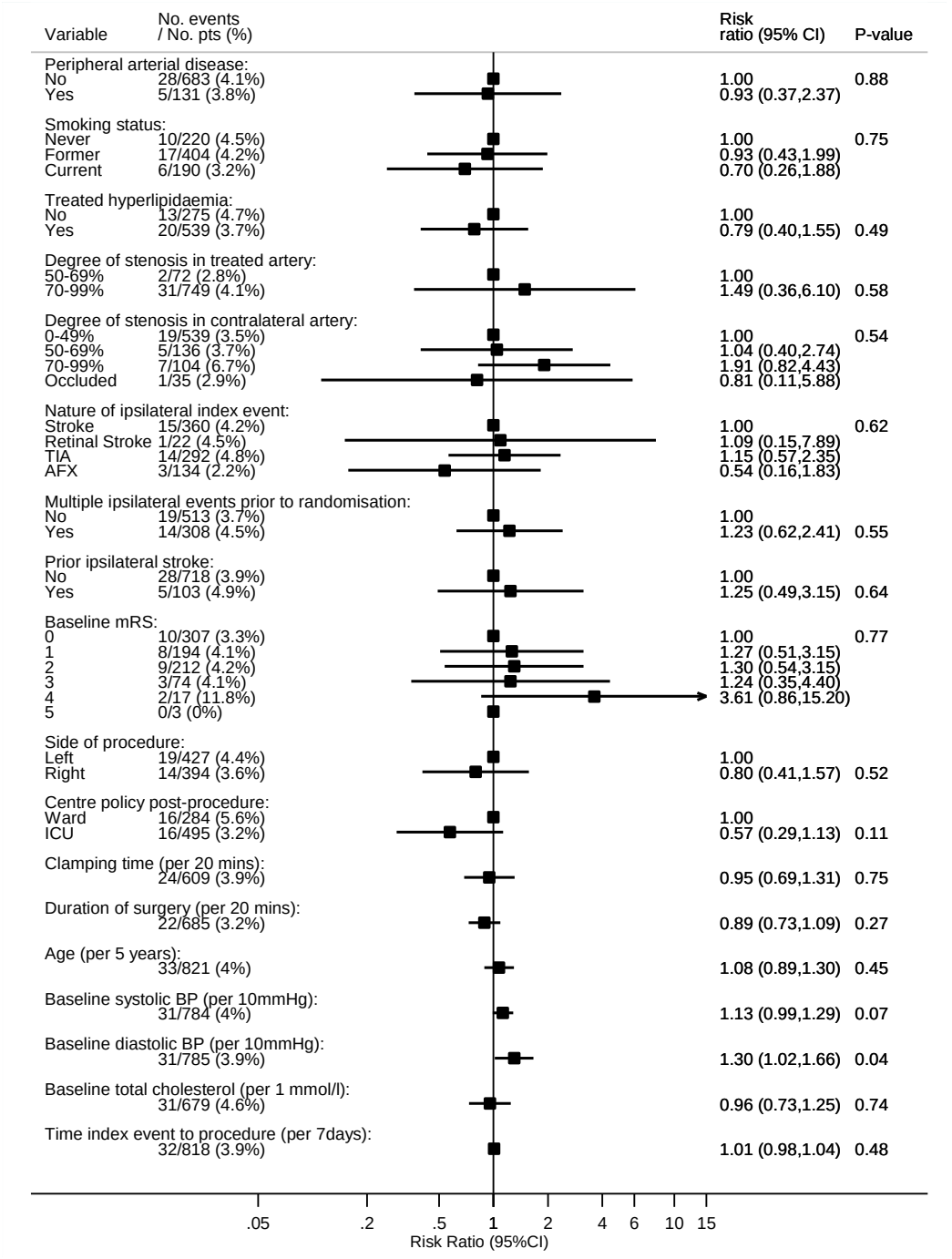


Figure 7 continued



In a multivariable model, only diastolic blood pressure remained a significant predictor of the risk of stroke, MI or death within 30 days of the procedure in the presence of any other included variables (RR 1.30 for each +10mmHg, 95% CI 1.02 to 1.66, p=0.04). This model included only 785 patients for whom complete predictor data were available.

14.4 Discussion and conclusion

14.4.1 Summary

The overall risk of stroke, MI or death within 30 days of CEA in ICSS was 4.0%. The majority of these events were strokes, and the majority of events occurred before discharge. Of the baseline demographic and vascular risk factors examined, only sex and increasing diastolic blood pressure at baseline significantly predicted the risk of stroke, MI or death. Female patients experienced roughly double the risk of male patients of reaching the composite endpoint. In a multivariable model, only baseline diastolic blood pressure remained a significant predictor of risk after adjustment for all other included variables.

None of the surgical technical variables examined – type of anaesthesia, type of arterial reconstruction, variation in medical therapy or shunt use – significantly predicted risk.

14.4.2 Discussion

The finding that women undergoing CEA in ICSS experienced a higher risk of stroke, MI or death than men is broadly consistent with findings from other randomized trials and audits of carotid endarterectomy outcomes [138] [133] [139] [140], although recent data from the Society for Vascular Surgery Vascular Registry suggest a similar complication rate (around 4% risk of stroke, MI or death within 30 days of CEA) for both men and women outside a clinical trial setting [141]. Although a statistically significant difference was observed in ICSS this result was not confirmed in multivariable analysis. This suggests that differences in baseline patient characteristics between male and female patients might explain this difference in risk [118], although this analysis had limited power to detect predictors because of the relative paucity of outcome events. An alternative explanation for a higher observed risk of complications in women may be that the smaller carotid artery diameter in women is associated with procedural stroke due to in-situ thrombosis following more technically-demanding surgery [142] [143] [139]. Or perhaps women, with an older age of onset of cerebrovascular disease than

men, might have more medical comorbidities that increase procedural risk [144]. In addition, many of the post-procedural strokes experienced by ICSS patients undergoing CEA occurred some days after the procedure, and it has been suggested that women are at a higher risk of post-procedural embolism [145] [146].

Notably, women with symptomatic carotid stenosis may also experience less benefit in terms of stroke prevention from CEA, particularly where the procedure is delayed [147]. Thus any risk-benefit discussion with female patients should highlight both a potential increased risk of minor complications as well as a reduced overall benefit as compared with men.

Time from the index event prompting randomization in ICSS to the date of surgery did not appear to influence risk, but the majority of patients in ICSS waited more than 14 days after randomization for surgery [82] which exceeds the maximum recommended delay in current guidelines [128]. In 2012, 33% of UK patients undergoing CEA were operated on within 14 days of their symptoms. However, there is some evidence that very early CEA, within 48 hours of symptoms, is associated with increased risk [148].

In ICSS surgical technique and mode of anaesthesia had less influence on short-term outcome than patient characteristics. The largest randomized trial of general vs local anaesthesia for CEA, the General Anaesthesia versus Local Anaesthesia for carotid surgery trial (GALA), found no difference in the risk of stroke, MI or death within 30 days of surgery between the two groups [104] [103]. There is currently insufficient evidence to suggest that routine shunt use reduces perioperative stroke or death [106], by maintaining cerebral perfusion pressure in the presence of a tight contralateral carotid stenosis, although there is some suggestion that patch closure of the artery, as opposed to primary closure, is associated with a lower risk of perioperative ipsilateral stroke [107].

The association between baseline blood pressure and outcome of surgery has also been demonstrated previously in a systematic review including patients from the European Carotid Surgery Trial [149]. Despite detailed baseline and follow-up measurements, ICSS investigators did not collect perioperative blood pressures and therefore it was not possible to assess the influence of perioperative haemodynamic control on outcome. Patients who are transferred to Intensive Care or a similar specialized unit after the procedure might be expected to have better optimization of their blood pressures and medications. In ICSS 8.3% of patients undergoing CEA experienced post-procedural hypertension which was associated with higher baseline

blood pressure [150] and in other studies has been shown to be associated with stroke or death [151] [152]. What is not known is whether closer control of blood pressure after stroke or TIA could reduce the risks of subsequent CEA. Although not statistically significant, ICSS patients treated in centres with a policy of sending the patient to intensive care afterwards experienced a much-reduced rate of complications, which could in turn be due to closer monitoring of haemodynamic parameters and treatment of excessively high or low blood pressures. Current guidelines for CEA have focussed on patient selection, procedural technique and medication use [153]. Therefore given our findings on diastolic blood pressure, and that more events occurred on the days following the procedure than the day of the procedure itself, future work on the safety of CEA should additionally address overall perioperative care and management of physiological parameters.

14.4.3 Limitations

The risk of stroke, MI or death associated with carotid endarterectomy was acceptably low in ICSS. However, a low number of outcome events limited the power to detect a significant difference between subgroups of patients and limited the number of factors supported in a multivariable model. Multiple statistical comparisons are made in this analysis without correction, raising the possibility of a Type 1 (false positive) error. Associations between baseline characteristics or processes of care and the outcome do not necessarily imply causation, and this was not a randomized comparison between surgical techniques.

Other factors or more generalized measures of health not recorded in ICSS, such as the patient's American Society of Anaesthesiology (ASA) grade, may be more useful predictors of adverse outcome [154].

14.4.4 Conclusions

The relative safety of CEA in ICSS limited power to detect predictors of risk. Nonetheless, diastolic blood pressure at baseline was a significant independent predictor of the risk of stroke, MI or death within 30 days of carotid endarterectomy. It is possible that careful attention to blood pressure control following stroke or TIA may reduce the risks associated with subsequent CEA in patients with underlying carotid stenosis, although concern exists about acute lowering of blood pressure following stroke or TIA in the presence of carotid stenosis. The finding that around 20% of events occurred on or after the day of discharge underlines the importance of post-discharge

follow-up to ensure that patients receive treatment for any late complications and to ensure that surgical audit data include all late events. Surgical results should also be carefully audited in female patients to ensure that the risk of complications remains acceptably low.

15. Validation of existing risk scores for carotid endarterectomy

15.1 Introduction

CEA remains the standard of care for patients with 50-99% symptomatic carotid stenosis, as measured by the NASCET method [40]. However, despite improvements in the care of surgical patients, and despite innovations in surgical and anaesthetic technique for carotid endarterectomy, data from a systematic review of studies published between 1994 and 2001 suggest that risk of stroke or death within 30 days of surgery remained clinically significant at 6.5% (95% CI 4.3% to 8.7%) in studies involving assessment of study endpoints by neurologists [96]. These studies are comparable with ICSS in which 4.7% of patients randomized to CEA suffered stroke or death [82] within 30 days of surgery.

Research since the landmark NASCET and ECST trials has attempted to define the patient at high risk of complications following surgery. Complications of specific concern in CEA include stroke, myocardial infarction, death, neck haematoma and cranial nerve palsy. However, few risk factors or scoring systems found to be significant predictors in one group of patients have been validated in other cohorts and the usefulness of their application in everyday clinical decision-making remains unclear. Risk scores may give patients and clinicians an individualized estimate of the risk of suffering stroke or death within 30 days of endarterectomy, and could allow calculation of the net benefit of surgery in long-term stroke prevention.

The performance of three risk scores in patients allocated to surgery the International Carotid Stenting Study is assessed in this chapter. The patient populations from which these scores derived most closely match the inclusion criteria for ICSS and comprise clinical characteristics that are apparent at baseline visit.

Rothwell et al. [98] developed a prognostic model using data from patients undergoing CEA in the European Carotid Surgery Trial (ECST) in the 1990s. ECST enrolled patients with symptomatic carotid stenosis and randomized them to either carotid endarterectomy or medical treatment [36]. A model to predict the risk of stroke or death within 30 days of the procedure was calculated in patients with 0-69% stenosis of the symptomatic artery and later validated in patients with 70-99% stenosis. Predictors of risk were female sex, peripheral vascular disease, and high systolic blood pressure.

Tu et al. [155] developed a score to predict the risk of stroke or death within 30 days of CEA in 6038 patients undergoing surgery in Ontario, Canada. 69% of those patients were symptomatic, and 95% had ICA stenosis between 50-100%. The average age was 68 years. Significant predictors of stroke were TIA or stroke in the 6 months prior to surgery, atrial fibrillation, heart failure, diabetes and contralateral carotid occlusion.

Finally, the prediction model developed by Kuhan et al. [156] examined the patient and procedural characteristics of 839 patients undergoing CEA in 2 vascular units in the United Kingdom between 1992 and 1999. 87% of these patients were symptomatic, 60% were male and the median age was 68. Significant risk factors for stroke or death within 30 days of CEA were “heart disease” (comprising angina, myocardial infarction, heart failure or arrhythmia), diabetes and stroke as the index event prompting intervention. None of the surgical variables included in the study (shunt use, patch use, operating surgeon, vascular unit or the side of operation) significantly predicted risk.

A number of other publications address risk factors for complications of CEA, but were not validated in this patient cohort as they included factors not measured at baseline in ICSS patients [157] [158] [159] [160], included a large proportion of asymptomatic patients [158] [161] [162] or focus on operator, hospital or process of care factors that are modifiable and therefore of limited use in predicting the risk in individual patients [163] [164] [165].

15.2 Methods

The performance of the three risk scores predicting the risk of stroke or death within 30 days of CEA was evaluated [98] [155] [156]. To test the performance of each risk score, patients were assigned “risk points” according to their baseline characteristics. The characteristics predicting risk in each risk score are outlined in Tables 3 to 5 below. Baseline patient characteristics were collected by investigators in ICSS at the time of the patient’s enrolment into the trial and sent to the central trial office in London.

The occurrence of stroke or death within 30 days of the procedure was examined in a per-protocol population of patients in ICSS in whom the allocated procedure was initiated. CEA was deemed to have been initiated if local or general anaesthesia was administered prior to the planned commencement of surgery. The adjudication of events is described in more detail in Chapters 13 and 14. In brief, stroke was defined as “an acute disturbance of focal neurological function lasting more than 24 hours resulting from intracranial vascular disturbance”, and confirmatory evidence was

required where available in the form of CT or MR brain imaging. Centres reporting death within 30 days of the procedure provided either a death certificate or autopsy report if available.

Table 3. Allocation of risk points in the Rothwell risk score

Study	**Risk factors**	**Risk points**
Rothwell et al. (1999) [98]	Female sex	1
	Peripheral vascular disease	1
	Systolic BP > 180mmHg	1

Table 4. Allocation of risk points in the Tu risk score

Study	Risk factors	Risk points
Tu et al. (2003) [155]	TIA or stroke in the 6 months prior to surgery	1
	Atrial fibrillation	1
	Heart failure	1
	Diabetes	1
	Contralateral carotid occlusion	1

Table 5. Allocation of risk points in the Kuhan risk score

Study	Risk factors	Risk points
Kuhan et al. (2001) [156]	Heart disease (any of angina, MI, heart failure, arrhythmia)	1
	Stroke as the index event prompting surgery	1
	Diabetes (any type)	1

A 95% confidence interval for the risk of stroke or death within 30 days of the procedure was generated, and the performance of the risk score across groups with increasing score was tested by means of a chi-squared ($\chi 2$) test for trend. The "predicted" risk of stroke or death within 30 days of surgery represents the result of applying the risk score to the population in which it was originally developed. Groups in which no events occurred were combined with lower-risk groups to enable the statistical comparison to be carried out. Receiver operator curves (ROC) were plotted to assess the performance of each risk score, and the area under the curve (AUC) was calculated with 95% confidence intervals and significance test. Statistical analyses were performed using GraphPad (GraphPad Software, 2013. *GraphPad Instat version 3.00 for Windows 95*. San Diego, California: www.graphpad.com).

15.3 Results

The baseline characteristics of patients included in this analysis, and how many patients possessed characteristics which feature in each of the three risk scores, are presented in detail in Chapter 14.3.2 and Figure 7. 70.4% of patients were male, and 52% were aged 70 years or more. 59/821 (7.2%) patients had systolic blood pressure >180mmHg, and 236 patients (28.7%) had "heart disease" as defined in the Kuhan risk score (any of angina, MI, heart failure or arrhythmia). 174 patients (21.2%) were diabetic, and 131 (16.0%) had a diagnosis of peripheral vascular disease.

28/821 (3.4%) patients allocated to CEA in ICSS, in whom the procedure was initiated, suffered stroke or death within 30 days of the procedure.

15.3.1 Rothwell (1999) risk score

The results of applying the Rothwell score to ICSS patients allocated to CEA are detailed in Table 6. The risk of stroke or death within 30 days of surgery was 2.5% (95% CI 1.3% to 4.4%) in those with a score of 0, 4.4% (95% CI 2.6% to 7.4%) in those with a score of 1 and 5.4% (95% CI 1.3% to 15.2%) in those with a score of 2. 2 patients had a score of 3 but neither suffered an event. There was an increase in the observed risk of an outcome event with increasing score that was not statistically significant (p=0.10). 25/28 (89.2%) events occurred in the lowest risk groups (score 0 to 1).

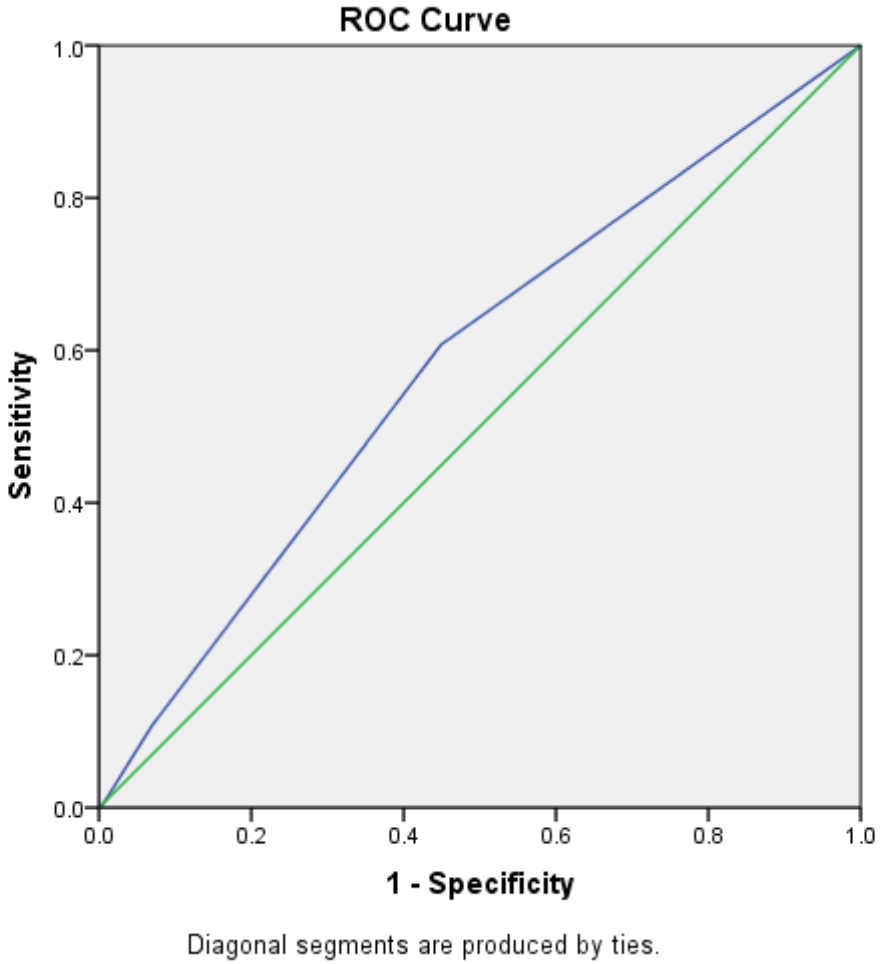
A receiver operator curve (ROC) was plotted for the results of applying the Rothwell score to the ICSS dataset and is presented in Figure 8. The area under the curve was 0.58 (95% CI 0.48 to 0.69, p=0.14), indicating poor performance.

Table 6. Results of application of the Rothwell (1999) risk score to 821 patients undergoing CEA in ICSS

Score	Number at risk	Number of events	Predicted event rate % (95% CI)	Observed event rate %	95% CI for observed event rate
0	448	11	4.7 (2.6 to 7.6)	2.5	(1.3 to 4.4)
1	315	14	7.3 (4.3 to 11.0)	4.4	(2.6 to 7.4)
2	56	3	12.1 (5.0 to 23.0)	5.4	(1.3 to 15.2)
3	2	0	16.7 (4.2 to 64.0)	0.0	
Totals	**821**	**28**			

χ2 test for trend p=0.10

Figure 8. Receiver operator curve for application of the Rothwell (1999) risk score to 821 patients undergoing CEA in ICSS



Darker line represents receiver operator curve

Straight line represents area under curve =0.5

15.3.2 Tu (2003) risk score

The results of applying the Tu score to the ICSS dataset are detailed in Table 7. The risk of stroke or death within 30 days of the procedure was 2.6% (95% CI 0.6% to 7.6%) in those with a score of 0, 3.4% (95% CI 2.0% to 5.4%) in those with a score of 1 and 4.7% (95% CI 2.4% to 8.9%) in those with a score of 2. Patients with higher scores did not experience an event. The increase in the risk of an event with increasing score did not reach statistical significance (p=0.49). All events occurred in lower risk groups (score 0 to 2).

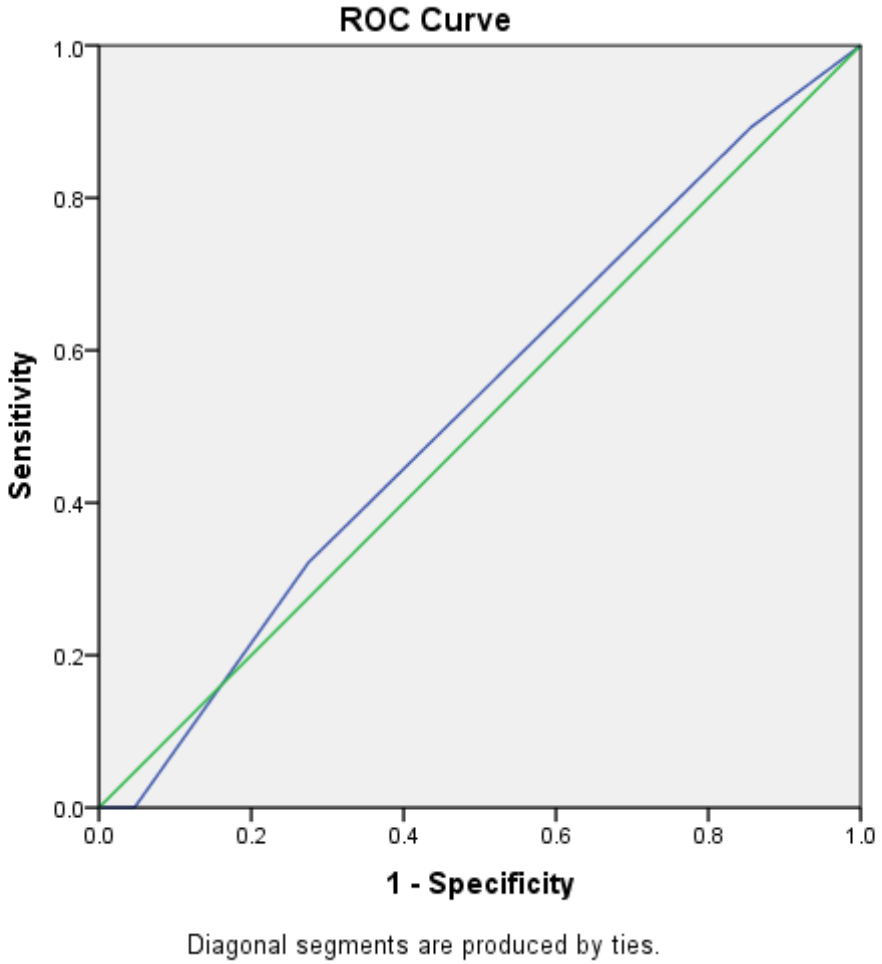
In a receiver operator curve plot of these results, presented in Figure 9, the AUC was 0.526 (95% CI 0.42 to 0.63, p=0.64) indicating poor performance.

Table 7. Results of application of the Tu (2003) risk score to 821 patients undergoing CEA in ICSS

Score	Number at risk	Number of events	Predicted event rate % (95% CI)	Observed event rate %	95% CI for observed event rate
0	117	3	3.3	2.6	(0.6 to 7.6)
1	477	16	6.1	3.4	(2.0 to 5.4)
2	190	9	9.5	4.7	(2.4 to 8.9)
3	33	0	9.8	0.0	N/A
4	4	0	15.8	0.0	N/A
5	0	0	N/A	N/A	N/A
Totals	**821**	**28**			

$\chi 2$ test for trend p=0.49

Figure 9. Receiver operator curve for application of the Tu (2003) risk score to 821 patients undergoing CEA in ICSS



Darker line represents receiver operator curve

Straight line represents area under curve =0.5

15.3.3 Kuhan (2001) risk score

The results of applying the Kuhan score to the ICSS dataset are outlined in Table 8 below. The risk of stroke or death within 30 days of CEA was 2.2% (95% CI 0.9% to 4.8%) in patients with a score of 0, 3.7% (95% CI 2.1% to 6.3%) in those with a score of 1, 4.2% (95% CI 1.9% to 8.6%) in those with a score of 2 and 5.9% (95% CI 0.7% to 20.0%) in those with a score of 3. 19/28 (67.9%) events occurred in lower risk groups (scores 0 to 1).

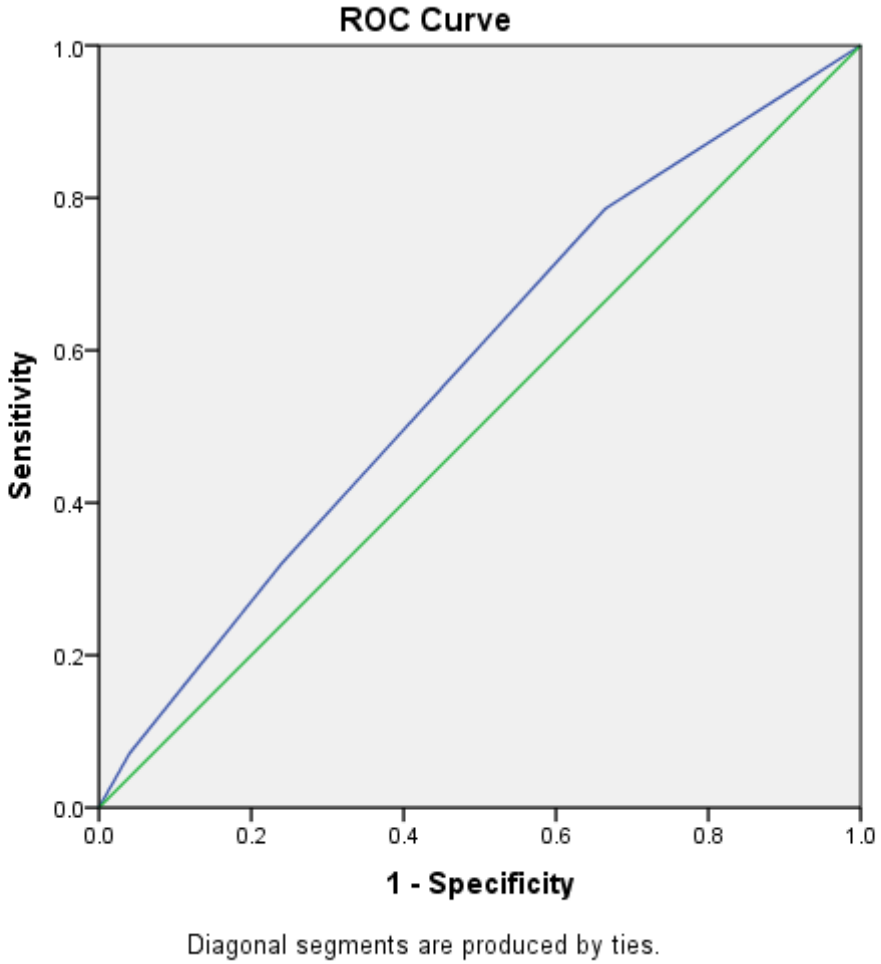
The area under the receiver operator curve, illustrated in Figure 10, was 0.58 (95% CI 0.47 to 0.68, p=0.18), indicating poor performance.

Table 8. Results of application of the Kuhan (2001) risk score to 821 patients undergoing CEA in ICSS

Score	Number at risk	Number of events	Predicted event rate % (95% CI)	Observed event rate %	95% CI for observed event rate
0	272	6	1.4 (0.9 to 2.1)	2.2	(0.9 to 4.8)
1	349	13	3.2 (2.1 to 4.8)	3.7	(2.1 to 6.3)
2	166	7	7.2 (2.5 to 19.0)	4.2	(1.9 to 8.6)
3	34	2	15.3 (2.8 to 53.1)	5.9	(0.7 to 20.0)
Totals	**821**	**28**			

$\chi 2$ test for trend p=0.15

Figure 10. Receiver operator curve for application of the Kuhan (2001) risk score to 821 patients undergoing CEA in ICSS



Darker line represents receiver operator curve

Straight line represents area under curve =0.5

15.4 Discussion and conclusion

15.4.1 Summary

Each of the three risk scores tested in this analysis demonstrated a similar pattern of results: a small increase in the risk of stroke or death within 30 days of the procedure as the score increased, a lower observed risk of an event in ICSS than predicted, and the majority of events occurring in those groups of patients predicted to be at lower risk. None of the scores tested were sufficiently discriminating to be able to demonstrate a statistically significant difference in risk between groups of patients with different scores and all showed poor sensitivity and specificity.

15.4.2 Limitations

The ability to accurately test many existing published risk scores was limited by the data collected at baseline in ICSS, and the type of patients enrolled in the study. The ability to detect significant differences in risk between groups predicted to be at low or high risk was limited by the relative safety of CEA in ICSS and therefore the low number of outcome events.

15.4.3 Discussion

“Complications” following any surgical procedure are common throughout the world, occurring in up to 7% of those undergoing surgery even after specific interventions designed to reduce the risk of adverse outcome [93]. CEA may be different to some other types of major surgery due to the higher risk of stroke. Therefore there is a need for unique risk scores to identify the patient at high risk during revascularization. To be useful to clinicians, clinical risk scores should be effective, accurate and generalizable to other patient populations [166] [167].

The risk models analysed in this chapter did not satisfactorily discriminate between high- and low-risk groups of patients, and indeed excluding patients in higher risk groups for undergoing surgery would not have prevented the majority of periprocedural events.

Other reasons that these models may not have performed so well include differences between the inclusion and exclusion criteria in the studies from which they are derived as compared to the criteria in ICSS, the influence of unmeasured factors such as operator experience or case volume [168], the type of hospital the surgery is carried

out in [165], and the influence of vascular features not routinely recorded at baseline in ICSS, such as ulcerated plaque or fresh thrombus in the carotid artery, which may double the risk of stroke after CEA [158]. There is also a need to update risk models as the higher risks observed in original trials as compared with new trials means that the models tested all over-estimate risk, a common finding in prediction models [169].

Other authors have examined the implications of applying the Rothwell score to a population of patients with symptomatic carotid stenosis in a single unit. Their results show a similar distribution of risk scores, with patients at lower predicted surgical risk (score 0 or 1) making up the majority of those undergoing surgery [170]. However, the rate of major stroke or death within 31 days of surgery in this study was only 0.75%, and the authors conclude that excluding high-risk patients from surgery in this series would have exposed the patients to a high risk of stroke on medical therapy alone with no reduction in the risk of a major event in the group undergoing surgery.

As demonstrated in the European Carotid Surgery Trial, the factors that determine of the risk of surgery may well be different from those that determine the risk of stroke without treatment [98], and therefore patients should not be excluded from surgery because of a high predicted risk of CEA without taking into consideration the risk of stroke on secondary prevention medications alone [169]. In addition, the decision to operate or not is made more complex by the availability of CAS, which may in turn have different risk factors for periprocedural stroke or death as discussed in Chapter 17. Authors drawing on data from the European trials of stenting vs surgery for symptomatic carotid stenosis have developed a clinical rule based on the patient's sex, age, contralateral carotid occlusion and the presence of restenosis (the "SCAR" rule [171]) to address this issue and enable practitioners to choose between the two revascularization procedures in patients where revascularization is the preferred treatment option.

15.4.4 Conclusions

The observed risk of CEA in ICSS was acceptably low, and only 3.4% of patients suffered stroke or death within 30 days of the procedure. In each of the three risk scores evaluated, increasing score was associated with an increasing observed risk of the outcome, although this association did not reach statistical significance in any of the scores tested. The ability of the scores to discriminate between patients at low and high risk was poor as demonstrated by the area under the receiver operator curve measurements. Most events in ICSS occurred in groups of patients predicted to be at

low risk, and thus the overall performance of these scores was unsatisfactory, and routine use of the scores to predict operative risk is not supported.

Patient risk factor profiles and the nature of surgical care for endarterectomy have changed since the landmark NASCET and ECST trials, and influence of risk factors for surgical complications from older studies may have diminished. The availability of non-invasive detailed plaque imaging raises the possibility of developing modern and better-performing risk scores for the procedural risk of CEA or the risk of stroke on medical therapy alone, drawing on data from large-scale studies or ongoing trials randomizing patients to CEA such as ECST-2 [172], SPACE-2 [173] and ACST-2 [174].

16. Risk factors for, and impact of, cranial nerve palsy and haematoma following carotid endarterectomy

16.1 Introduction

The results of landmark trials of carotid surgery versus medical therapy, NASCET [175], ECST [36] and the Veterans' Affairs Trial [39] provided evidence that carotid endarterectomy for symptomatic atherosclerotic carotid stenosis greater than 50% provided a better long-term reduction in the risk of recurrent ipsilateral stroke than medical therapy. Subsequent trials of CEA vs carotid stenting have suggested that, in the short-term at least, surgery remains the safest treatment for carotid stenosis, with CAS carrying a higher risk of any stroke, myocardial infarction or death within 30 days of the procedure in meta-analysis (OR 1.44, 95% CI 1.15 to 1.80) [176]. However, the primary endpoints of these trials and analyses do not contain outcomes that specifically relate to the additional hazards of a surgical incision in the neck – namely cranial nerve palsy (CNP) and haematoma.

Carotid stenting developed as an alternative to CEA in part to avoid these hazards of a surgical incision. The higher procedural risk associated with CAS in ICSS was mainly due to an excess of non-disabling stroke [82], and this disadvantage could be balanced by an increased incidence of cranial nerve palsy in the surgical group.

CNP and haematoma are less extensively studied, but have long been recognised as complications of surgery [47], and these "minor outcomes" have been associated with an increased risk of major outcomes following surgery such as stroke or death [177]. Haematoma has been associated with an increased time spent in critical care following surgery [178]. Published case series have highlighted frequently-affected cranial nerves which include facial, vagal, hypoglossal and accessory [47] [48] [49] [50], and there is a potential for these injuries to cause significant postoperative disability.

In this chapter the incidence and severity of CNP and haematoma in ICSS are examined to determine whether these complications merit consideration in the selection of revascularization procedure. Risk factors for their development are analysed.

16.2 Methods

The ICSS trial protocol is summarized in Chapter 13 and presented in full in Appendix IV. As reported in Chapter 14, the type of anaesthetic or surgical technique for CEA were not specified in the trial protocol, but all patients were required to receive medical therapy for secondary prevention of stroke as appropriate. A technical case report form was completed for each endarterectomy procedure in ICSS and the occurrence of CNP or haematoma was reported by investigators. CNP was defined as "weakness or sensory impairment in the distribution of one of the cranial nerves attributed to treatment". Each patient was re-assessed at their one-month follow-up appointment by a neurologist or investigator with an interest in stroke. CNPs were adjudicated at the trial office based on the best available clinical evidence, and deemed "disabling" if the patient's modified Rankin Score (mRS) increased to 3 or more at 30 days post-procedure where that increase was thought due to CNP. A questionnaire requesting additional information about the clinical impact of an event and whether or not symptoms eventually resolved (Appendix II) was sent to centres reporting CNP.

Haematoma was defined as "bleeding attributed to the treatment of carotid narrowing". Severe haematoma was defined as a haematoma "requiring new surgery, transfusion or prolonging hospital stay".

16.2.1 Statistical methods

The data were analysed per-protocol, including only those patients in ICSS in whom the allocated CEA procedure was initiated. A procedure was deemed to have been initiated if local or general anaesthesia was administered prior to commencement of surgery. Patients who crossed-over to CAS or medical treatment were excluded. Risk factors for CNP and haematoma were examined sequentially in a univariable binomial regression analysis using maximum likelihood estimation. The risk ratio for each factor is given with corresponding 95% confidence interval. Wald tests were used for continuous and binary predictors, with an overall likelihood ratio test for categorical predictors of more than two levels. A multivariable model was developed using a forward stepwise-based approach with a significance level of 0.1 for predictors in univariable analysis accepted for inclusion in the multivariable model. Patients with missing data were excluded from each relevant analysis. Analyses were performed using Stata (Stata Corp. 2011. *Stata Statistical Software: Release 12.* College Station, TX, USA: Stata Corp LP).

16.3 Results – cranial nerve palsy

858 patients in ICSS were randomized to CEA, of whom 821 had their allocated procedure initiated (95.7%). 4/821 patients (0.5%) died after initiation of the procedure but before 30-day follow-up. 45/821 (5.5%) patients were reported to have developed CNP between initiation of the procedure and 30-day follow-up. The results of an adjudication of which cranial nerves are affected are presented in Table 9. The facial nerve was involved in 23 patients, vagus nerve in 6, hypoglossal in 13, glossopharyngeal in 4, accessory in 1 and trigeminal in 1. The nerve affected was undetermined in two patients. In five patients more than one cranial nerve was affected. It was not possible to determine the nerve affected in two patients.

One patient was judged to have disabling CNP at 30-day follow-up due to glossopharyngeal nerve palsy. This caused impairment of swallowing with subsequent need for naso-gastric feeding.

In those patients in whom CNP resolution was confirmed (n=20), the median estimated duration of symptoms was 30 days (minimum 2 days, maximum 520 days). Permanent injury (i.e. without resolution of symptoms by the end of their follow-up in the trial) was reported in two patients who were followed-up over 6.4 and 3.1 years respectively.

Table 9. Summary of cranial nerve palsies following endarterectomy in ICSS

Cranial nerve	**Number of postoperative CNPs (n=50 in 45 patients)**	**Number of disabling CNPs (mRs≥3 at 1 month due to CNP)**	**Number of CNPs confirmed persisting after 30 days**
Facial	23	0	4
Hypoglossal	13	0	2
Vagus	6	0	4
Accessory	1	0	0
Glossopharyngeal	4	1	1
Trigeminal	1	0	0
Undetermined	2	0	0

The results of univariable regression analysis to determine risk factors for the development of CNP within 30 days of the procedure are presented in Figure 11 below. The risk of CNP was increased in female patients (RR 1.90, 95% CI 1.08 to 3.36, p=0.03) and decreased in those with a high degree of contralateral carotid artery stenosis. Other demographic factors did not predict the risk of CNP. Technical factors, including the type of arterial reconstruction (standard closure, patch closure, eversion endarterectomy or vein interposition), type of anaesthesia or shunt use, were not significant predictors of risk.

Figure 11. Univariable predictors of the risk of cranial nerve palsy within 30 days of endarterectomy in 821 ICSS per-protocol participants in whom the procedure was initiated

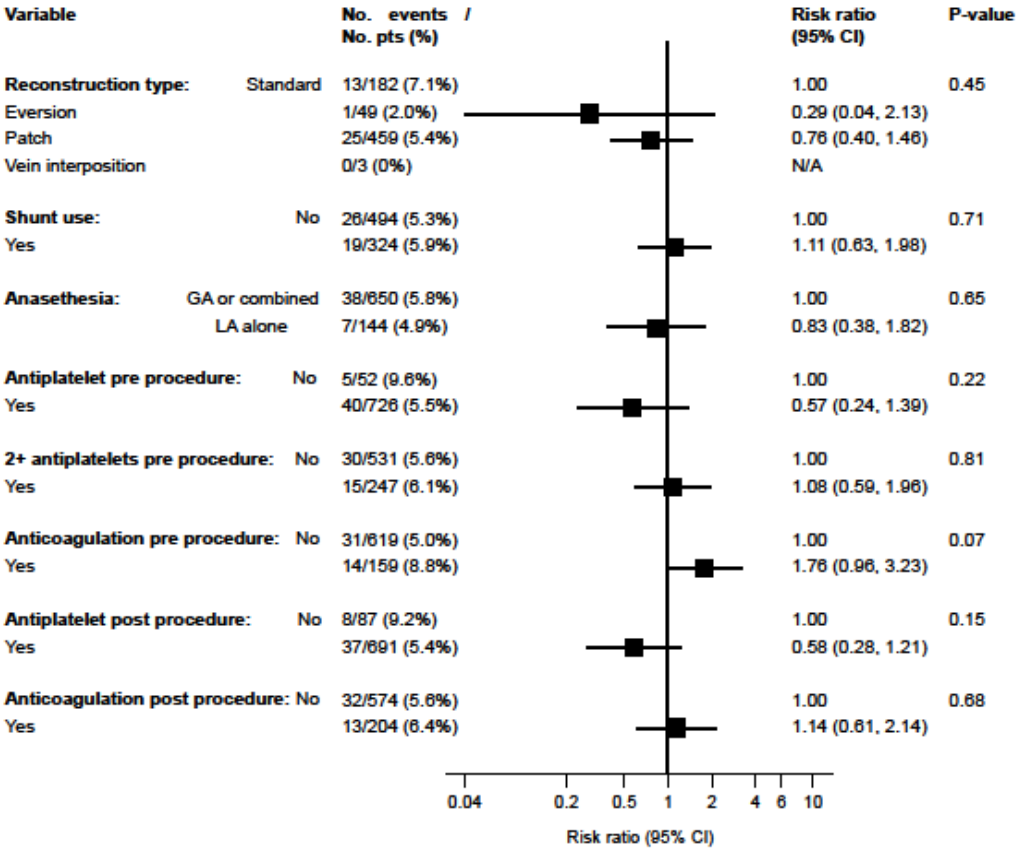


Figure 11 continued

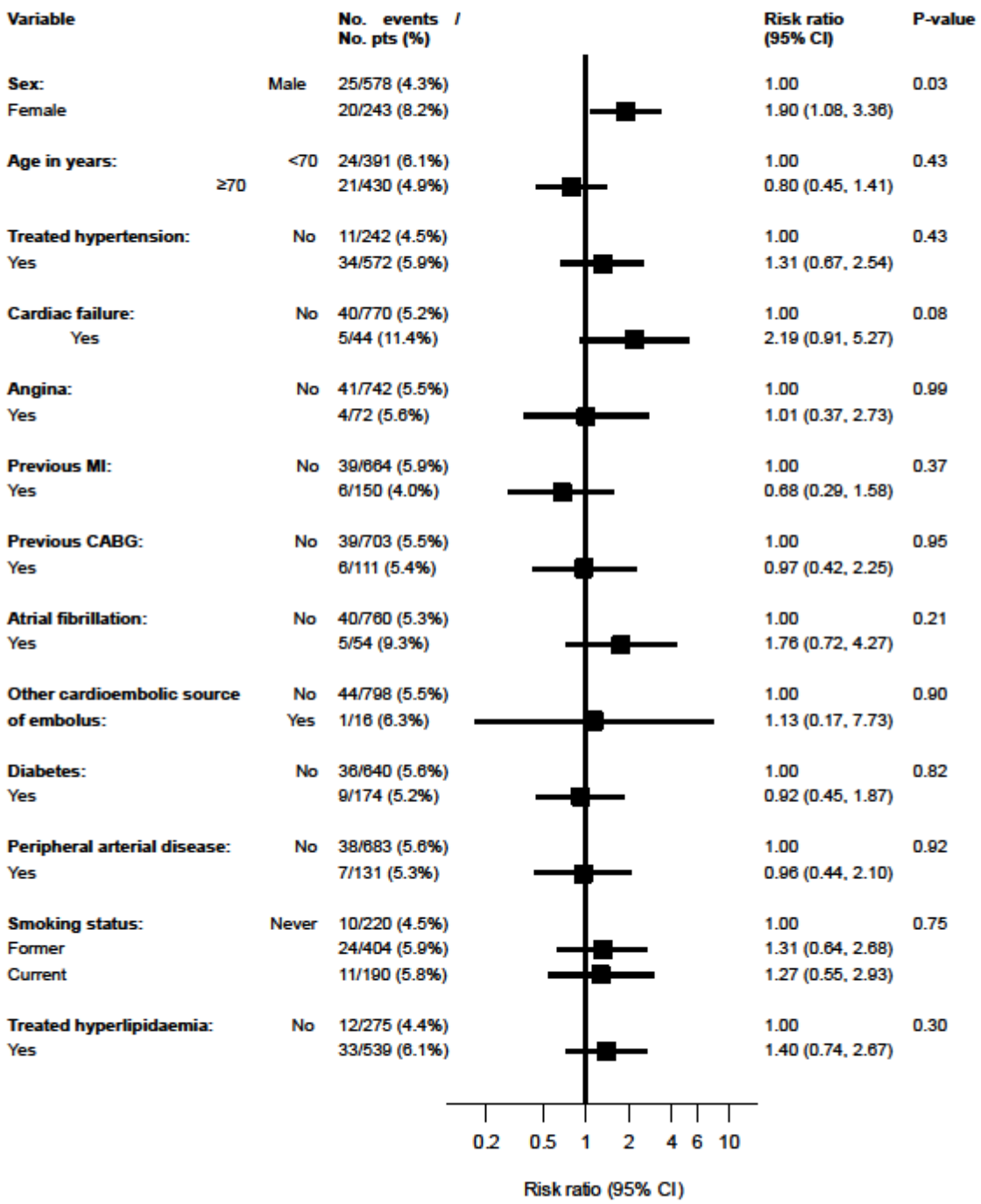
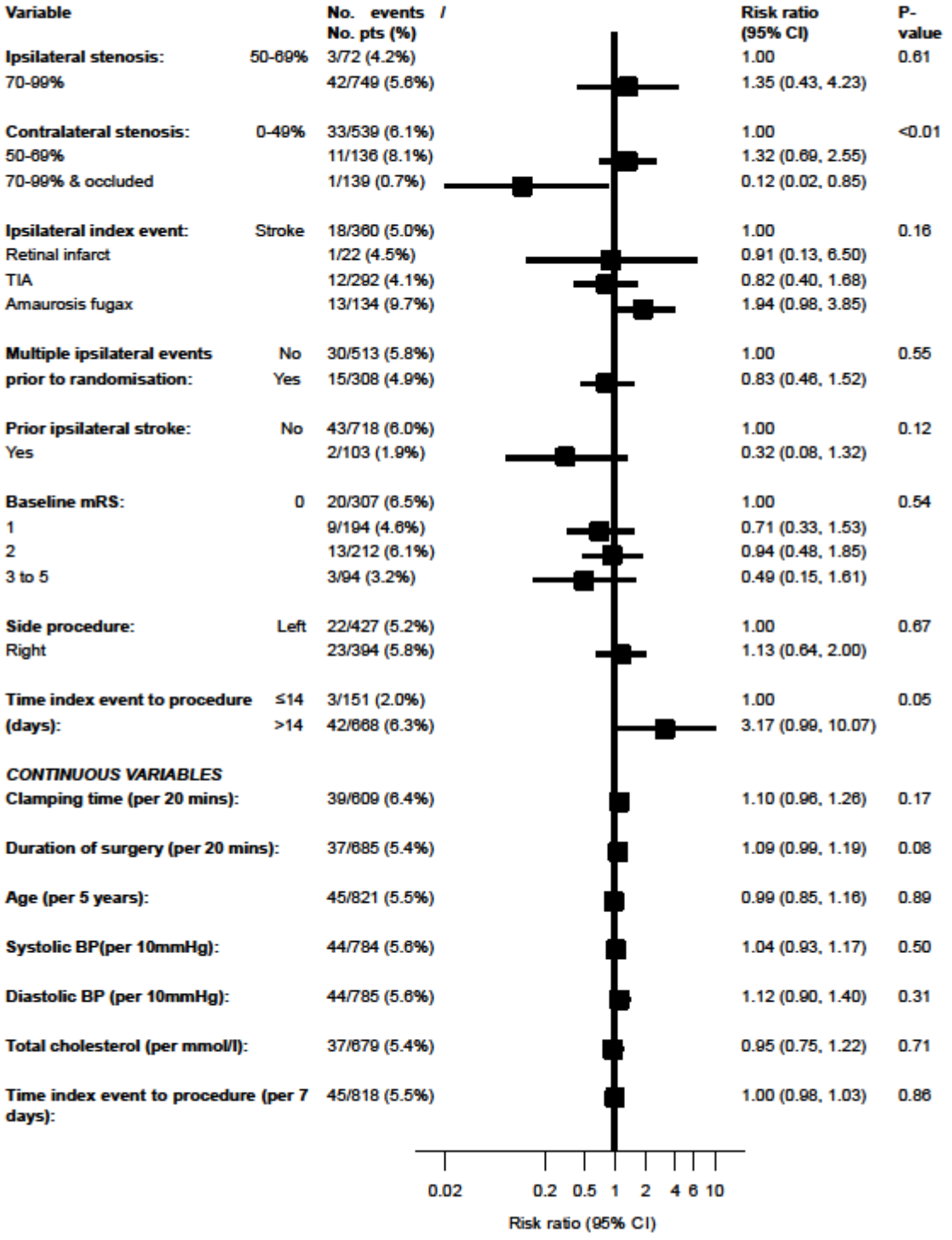


Figure 11 continued



The result of multivariable analysis of independent predictors of the risk of CNP is given in one possible model in Table 10 below. In this model, independent predictors of risk were cardiac failure (RR 2.66, 95% CI 1.11 to 6.40, p=0.03), female sex (RR 1.80, 95% CI 1.02 to 3.20, p=0.04), the degree of contralateral carotid artery stenosis and a time of greater than 14 days from randomization in the trial to surgery (RR 3.33, 95% CI 1.05 to 10.57, p=0.04).

The risk of cranial nerve palsy in the stenting group in ICSS was 1/828 (0.12%), and on adjudication this complication was attributed to a second procedure (CEA) carried out before 30-day follow-up.

Table 10. Independent predictors of risk of cranial nerve palsy within 30 days of endarterectomy in 805* ICSS per-protocol participants in whom the procedure was initiated

Variable	**Adjusted Risk Ratio (95% CI)**	**Adjusted p-value**
Cardiac failure	2.66 (1.11 to 6.40)	p=0.03
Female sex	1.80 (1.02 to 3.20)	p=0.04
Time from randomization to treatment >14 days	3.33 (1.05 to 10.57)	p=0.04
Degree of contralateral stenosis		Overall p<0.01
0-50%	1.00	
50-69%	1.18 (0.62 to 2.27)	p=0.62
>70%	0.13 (0.02 to 0.91)	p=0.04

** patients with missing data excluded from this analysis*

16.4 Results – haematoma

50/828 (6.1%) patients in the CEA arm of ICSS who had their procedure initiated developed haematoma. 28/828 (3.4%) patients had severe haematoma, requiring transfusion, re-operation or prolonging hospital stay. 12 of those 50 patients who suffered haematoma also developed CNP, and there was a significant association between these complications ($p<0.01$, Fisher's exact test).

The results of univariable analysis of factors predicting the risk of haematoma within 30 days of CEA are presented in Table 11 below. Those factors that increased the risk of haematoma were preoperative prescription of anticoagulant medication (RR 1.83, 95% CI 1.04 to 3.23, p=0.04), atrial fibrillation (RR 2.29, 95% CI 1.08 to 4.85, p=0.03), previous cardiac bypass graft surgery (RR 2.46, 95% CI 1.37 to 4.42, $p<0.01$) and the duration of arterial clamping (RR per each 20 minutes 1.13, 95% CI 1.04 to 1.24, $p<0.01$). Factors that decreased the risk of haematoma were shunt use (RR 0.54, 95% CI 0.29 to 0.99, p=0.05), the prescription of an antiplatelet agent pre-procedure (RR 0.44, 95% CI 0.21 to 0.93, p=0.03) and each increase in 1mmol/l of cholesterol at baseline (RR 0.69, 95% CI 0.55 to 0.88, $p<0.01$). Other demographic and technical factors were not statistically significant predictors of the risk of haematoma.

Table 11. Univariable predictors of risk of haematoma within 30 days of endarterectomy in 821 ICSS per-protocol participants in whom the procedure was initiated

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Type of reconstruction	Standard	9.3	1	0.26
	Eversion	8.2	0.87 (0.31 to 2.48)	
	Patch	5.2	0.56 (0.31 to 1.02)	
	Vein interposition	0	N/A	
Shunt use	No	7.5	1	0.05
	Yes	4.0	0.54 (0.29 to 0.99)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Type of anaesthesia	GA or LA/GA combined	6.5	1	0.69
	LA alone	5.6	0.86 (0.41 to 1.79)	
Antiplatelet agent pre-procedure	No	13.5	1	0.03
	Yes	5.9	0.44 (0.21 to 0.93)	
Two or more antiplatelet agents pre-procedure	No	6.0	1	0.50
	Yes	7.3	1.21 (0.69 to 2.11)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Anticoagulant pre-procedure	No	5.5	1	0.04
	Yes	10.1	1.83 (1.04 to 3.23)	
Antiplatelet agent post-procedure	No	9.2	1	0.26
	Yes	6.1	0.66 (0.32 to 1.36)	
Anticoagulant post-procedure	No	5.6	1	0.11
	Yes	8.8	1.58 (0.91 to 2.76)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Sex	Male	5.2	1	0.10
	Female	8.2	1.59 (0.92 to 2.74)	
Age	<70 years	6.1	1	0.96
	≥70 years	6.0	0.99 (0.58 to 1.69)	
Treated hypertension	No	5.0	1	0.36
	Yes	6.6	1.34 (0.71 to 2.52)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Cardiac failure	No	6.1	1	0.85
	Yes	6.8	1.12 (0.36 to 3.45)	
Angina	No	6.1	1	0.77
	Yes	6.9	1.15 (0.47 to 2.79)	
Previous MI	No	5.4	1	0.07
	Yes	9.3	1.72 (0.95 to 3.11)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Previous CABG	No	5.1	1	<0.01
	Yes	12.6	2.46 (1.37 to 4.42)	
Atrial fibrillation	No	5.7	1	0.03
	Yes	13.0	2.29 (1.08 to 4.85)	
Other cardioembolic source of embolus	No	6.1	1	0.99
	Yes	6.3	1.02 (0.15 to 6.92)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Diabetes	No	6.3	1	0.81
	Yes	5.7	0.92 (0.47 to 1.80)	
Peripheral arterial disease	No	6.3	1	0.68
	Yes	5.3	0.85 (0.39 to 1.85)	
Smoking status	Never smoked	4.1	1	0.23
	Former smoker	7.4	1.82 (0.88 to 3.75)	
	Current smoker	5.8	1.42 (0.60 to 3.34)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Treated hyperlipidaemia	No	6.5	1	0.73
	Yes	5.9	0.91 (0.52 to 1.59)	
Degree of stenosis in treated artery	50 – 69%	6.9	1	0.75
	70 – 99%	6.0	0.87 (0.36 to 2.11)	
Degree of stenosis in contralateral artery	0 to 49%	6.1	1	0.39
	50 to 69%	7.4	1.20 (0.61 to 2.38)	
	70 to 99%	2.9	0.47 (0.15 to 1.51)	
	Occluded	8.6	1.40 (0.45 to 4.34)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Nature of ipsilateral index event	Stroke	5	1	0.32
	Retinal stroke	4.5	0.91 (0.13 to 6.51)	
	TIA	6.2	1.23 (0.65 to 2.33)	
	Amaurosis fugax	9.7	1.94 (0.98 to 3.85)	
Multiple ipsilateral events prior to randomization	No	5.5	1	0.33
	Yes	7.1	1.31 (0.76 to 2.25)	
Prior ipsilateral stroke	No	5.8	1	0.45
	Yes	7.8	1.33 (0.64 to 2.75)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Baseline Rankin score	0	6.5	1	0.42
	1	6.2	0.95 (0.48 to 1.90)	
	2	7.1	1.09 (0.57 to 2.07)	
	3	1.4	0.21 (0.03 to 1.52)	
	4	5.9	0.90 (0.13 to 6.33)	
	5	0	N/A	
Side of procedure	Left	5.9	1	0.77
	Right	6.3	1.08 (0.63 to 1.86)	

Table 11 continued

Variable	Category	30-day risk of haematoma (%)	Risk Ratio (95% CI)	P-value
Time from randomization to treatment	≤14 days	4.6	1	0.41
	>14 days	6.4	1.39 (0.64 to 3.03)	
Clamping time	(Per 20 minutes of clamp applied)	6.9	1.13 (1.04 to 1.24)	<0.01
Duration of surgery	(Per 20 minutes of operation length)	6.4	0.97 (0.86 to 1.10)	0.66
Age	(Per 5 years of age)	6.1	1.02 (0.88 to 1.18)	0.84
Baseline systolic blood pressure	(Per 10mmHg of blood pressure)	6.3	1.08 (0.98 to 1.21)	0.13
Baseline diastolic blood pressure	(Per 10mmHg of blood pressure)	6.2	0.92 (0.74 to 1.14)	0.45
Baseline cholesterol	(Per each mmol/l total cholesterol)	6.3	0.69 (0.55 to 0.88)	<0.01

The results of multivariable analysis of predictors of the risk of haematoma are presented in Table 12 which illustrates one possible model. Independent predictors of increased risk were female sex (RR 2.03, 95% CI 1.13 to 3.62, p=0.02), atrial fibrillation (RR 2.38, 95% CI 1.07 to 5.27, p=0.03) and the prescription of an anticoagulant drug pre-procedure (RR 1.86, 95% CI 1.01 to 3.42, p=0.05). Independent factors that decreased the risk were shunt use (RR 0.40, 95% CI 0.21 to 0.80, p<0.01) and baseline cholesterol level (RR 0.68 per 1mmol/l increase, 95% CI 0.54 to 0.86, p<0.01).

Table 12. Independent predictors of the risk of haematoma within 30 days of endarterectomy in 639 ICSS per-protocol participants in whom the procedure was initiated

Variable	Risk Ratio (95% CI)	Adjusted p-value
Anticoagulant pre-procedure	1.86 (1.01 to 3.42)	0.05
Shunt use	0.40 (0.21 to 0.80)	<0.01
Cholesterol (per each mmol/l)	0.68 (0.54 to 0.86)	<0.01
Female	2.03 (1.13 to 3.62)	0.02
Atrial fibrillation	2.38 (1.07 to 5.27)	0.03

** patients with missing data excluded from this analysis*

16.5 Results – impact of adding CNP to ICSS trial primary outcomes

Table 13 below details the impact of adding cranial nerve palsy to the primary and secondary outcomes of ICSS in interim analysis [82]. For the combined outcome of stroke, MI, death or cranial nerve palsy within 30 days of CEA there was no significant difference in risk between CAS and CEA groups (RR 0.81, 95% CI 0.59 to 1.12, p=0.20). For the combined outcome of disabling stroke, disabling CNP or death only there was also no significant difference in risk (RR 1.41, 95% CI 0.79 to 2.51, p=0.24).

Table 13. Composite outcome events within 30 days of CEA versus CAS in ICSS

Endpoint **(within 30 days of the procedure)**	**CAS (n=828)** **Events (%)**	**CEA (n=821)** **Events (%)**	**Risk ratio** **(95% CI)**	**Risk difference** **(95% CI)**	**P-value** **(Chi-squared)**
Stroke, MI or death	61 (7.4%)	33 (4.0%)	1.83 (1.21, 2.77)	3.3% (1.1, 5.6)	<0.01
Stroke, MI, death or CNP	62 (7.5%)	76 (9.3%)	0.81 (0.59, 1.12)	-1.8% (-4.4, 0.9)	0.20
Disabling stroke or death	26 (3.1%)	18 (2.2%)	1.43 (0.79, 2.59)	0.9% (-0.6, 2.5)	0.23
Disabling stroke, disabling CNP or death	27 (3.3%)	19 (2.3%)	1.41 (0.79, 2.51)	0.9% (-0.6, 2.5)	0.24

16.6 Results – influence of sex on combined outcomes

Table 14 below summarises the findings of both Chapter 14 and this chapter regarding the influence of sex on the outcomes of CNP, haematoma, or stroke, MI or death. Women had a statistically significantly higher risk of each of these outcomes in the surgical arm of ICSS. When these outcomes were combined, the risk of any surgical complication (i.e. CNP, haematoma, stroke, MI or death) in the endarterectomy arm of ICSS was considerably higher in women (19.7%) compared with men (10.9%, $p<0.01$).

Table 14. Results of univariable binomial regression analyses of female vs male in 821 per-protocol CEA patients in whom the allocated procedure was initiated

30-day outcome	**Number events / Number patients (%)**		**Risk Ratio (95% CI), p-value**
	Females	**Males**	
CNP	20/243 (8.2%)	25/578 (4.3%)	1.90 (1.08, 3.36), p=0.03
Haematoma	20/243 (8.2%)	30/578 (5.2%)	1.59 (0.92, 2.74), p=0.10
Stroke, MI or death	15/243 (6.2%)	18/578 (3.1%)	1.98 (1.02, 3.87), p=0.05
CNP, haematoma, stroke, MI or death	48/243 (19.7%)	63/578 (10.9%)	1.81 (1.28, 2.56), p<0.01

16.7 Discussion and conclusion

16.7.1 Summary

5.5% of ICSS patients who were allocated to carotid endarterectomy, and in whom the procedure was initiated, developed CNP. 6.1% developed haematoma within 30 days. There was a statistically significant association between the two outcomes. The most commonly-affected nerves were facial and hypoglossal, although only one CNP was classified as disabling at 30 days. Independent predictors that increased of the risk of cranial nerve palsy were cardiac failure, female sex, the degree of contralateral carotid stenosis and a time between randomization and surgery of >14 days. The risk of haematoma was raised in female patients, those with atrial fibrillation and those taking anticoagulant medications pre-procedure.

16.7.2 Discussion - cranial nerve palsy

The European Carotid Surgery Trial found a motor CNP risk of 5.1% and a long-term CNP risk of 0.5% at 4 months [179]. Similarly, the North American Symptomatic Carotid Endarterectomy Trial found a postoperative risk of CNP of 8.6%, the majority of which were mild in severity [175]. The finding of a 5.5% risk of CNP in ICSS, the 5.6% risk of CNP in 6878 patients included in the Vascular Study Group of New England study [180] and recent results from CREST showing a CNP risk of 4.6%, four-fifths of which resolved within 1 year [181], suggests that the risk of CNP following CEA has remained relatively constant over time. However, reassuringly, the risk of disabling CNP is small – around 1 in 1000 operations. The symptoms of CNP may persist for several weeks, but half of patients in whom the lesion resolves will experience an improvement within 30 days.

The higher risk in female patients has not previously been described, and this finding is worth confirming in other patient groups. It may be that surgical anatomy is more challenging in female patients, who have a smaller diameter of carotid artery on average [142], leading to inadvertent trauma to the cranial nerves running adjacent. Female patients were also at risk of haematoma, perhaps for the same reason.

16.7.3 Discussion - haematoma

Female sex, anticoagulants and atrial fibrillation were independent risk factors for the development of neck haematoma in this patient population. Although less well-studied than cranial nerve palsy and major outcomes, previously-identified causes of

haematoma following CEA have included postoperative hypertension, anticoagulants and antiplatelet agents [182] [183] (which might cause increased bleeding), as well as inadequate surgical drainage [184]. Independent risk factors in another study were found to be non-reversal of heparin, intraoperative hypotension and carotid shunt placement [178].

A risk of haematoma in ICSS of 6.1% is similar to the risk of "wound complications" (haematoma and infection) of 6.0% seen in a large multicentre case series of 1998 patients undergoing CEA [51], and a severe haematoma risk of 3.4% is similar to the reported risk of requiring re-exploration in patients undergoing CEA while taking antiplatelet medication of 3.6% [52].

Antiplatelet agents prevent recurrent stroke in patients with symptomatic carotid stenosis [21] [185] [186] [187]. However, there is concern that clopidogrel, or clopidogrel in combination with aspirin increases the risk of haematoma following surgery [52]. Importantly, in ICSS there was no evidence that dual antiplatelet therapy increased the risk of haematoma. Indeed, the clinical practise of most UK surgeons is to continue single or dual antiplatelet therapy in the perioperative period where patients are already taking these medications [188].

The association between neck haematoma and preoperative anticoagulation is not unexpected, but our results reinforce the importance of careful attention to haemostasis before closure of the wound.

16.7.4 Discussion – adding CNP to composite trial outcomes

Some systematic reviews have included CNP in a composite outcome of death or neurological complications up to 30 days after treatment [176]. In ICSS, the total number of events in the composite outcome of any stroke, myocardial infarction or death was greater after CEA compared with CAS, the numbers in the composite outcome of disabling stroke, disabling CNP or death were greater after CAS compared with CEA, but neither difference was statistically significant. Thus it is unlikely to be useful to include CNP in the composite endpoints of future trials, and it would not be appropriate exclude patients from CEA because of an increased risk of CNP as compared with CAS.

16.7.5 Discussion – the influence of sex on composite trial outcomes

Women were at higher risk of any surgical complication within 30 days of CEA in ICSS. Indeed, the combined risk of CNP, haematoma, stroke, MI or death reached nearly 20%. While this finding may inform discussions with patients about procedural risk, it should be remembered that female sex was not an independent predictor of the risk of a major complication (stroke, MI or death) and that the impact of CNP appears to be limited in duration and severity. Nonetheless, outcome data captured in clinical trials may underestimate the quality of life impact of, for example, permanent facial nerve palsy.

16.7.6 Limitations

Baseline and technical information regarding the procedure was missing for some patients, limiting the ability to include them in multivariable modelling. Information about the clinical effects and duration of CNP was limited in some patients. Multiple comparisons in the univariable analysis raise the possibility of type 1 (false positive) error, and no statistical correction was made for the number of tests carried out. Patients were not randomized to particular techniques or medication regimens, and it is likely that unmeasured confounders such as surgical expertise also influence the risk of CNP or haematoma.

16.7.7 Conclusion

Long-term disability due to cranial nerve palsy following carotid endarterectomy appears to be rare. As a result of this finding, CNP is unlikely to be included in composite endpoints of future trials involving carotid surgery. However, CNP remains common following CEA and is associated with haematoma. The results presented here should give surgeons confidence to reassure patients that long-term disability due to cranial nerve palsy following carotid endarterectomy is rare, to continue antiplatelet therapy around the time of surgery, and to carefully consider the risk-benefit ratio for revascularization in female patients.

Measurement of quality of life after CNP or haematoma might reveal that apparently “minor” clinical outcomes have disproportionate effects on the patient’s well-being, and future studies should focus on the quality of life impact of these complications.

17. Risk factors for stroke, myocardial infarction or death following carotid stenting

17.1 Introduction

Carotid artery stenting was developed as a less-invasive alternative to carotid endarterectomy for the prevention of TIA or stroke in patients with atheromatous carotid stenosis. However, in interim analysis of the International Carotid Stenting Study the risk of stroke, myocardial infarction or death within 30 days of revascularization was higher in those patients who received their allocated CAS procedure than in those who received their allocated CEA procedure (7.4% vs 4.0%, $p<0.01$) [82].

Endovascular revascularization is a complex procedure requiring attention to pre-procedure medication, haemodynamic control, stent design and optimal adjuvant medical therapy [153]. Optimal stenting technique, patient selection and processes of care for CAS have yet to be determined. For example, the use of cerebral protection devices has become more common in recent years in the UK [97], but there is conflicting evidence of their efficacy.

This analysis examines patients allocated to CAS in ICSS to determine whether there are specific techniques, processes of care or baseline patient characteristics that are associated with stroke, MI or death within 30 days of the procedure.

17.2 Methods

17.2.1 The stenting procedure

The trial protocol and inclusion/exclusion criteria for ICSS are summarised in Chapter 13 and presented in full in Appendix IV. Patients with more than 50% recently-symptomatic carotid stenosis were eligible for randomization in the study if they were felt suitable to undergo either CEA or CAS. Patients were excluded from enrolment in the trial if the stenosis was due to non-atheromatous disease, if cardiac bypass was planned within 1 month of the carotid procedure, or if there was previous stenting or surgery on the symptomatic artery. Additionally, patients were specifically excluded from CAS if their vascular anatomy was “unfavourable” – if there was vessel tortuosity proximal or distal to the stenosis, visible thrombus, proximal CCA disease or “pseudo-occlusion” (99% or more stenosis but with normal distal runoff on angiography).

Centres enrolling patients into ICSS were required to provide evidence that CAS interventionists were sufficiently experienced in the procedure, having performed a minimum of 50 stenting procedures and at least 10 of those in the carotid territory with an acceptable complication rate. More inexperienced interventionists joined the trial in probationary centres where procedures were supervised by a proctor until such time as the required level of competency was achieved.

CAS in ICSS was performed in accordance with trial protocol: aspirin and clopidogrel prior to the procedure was recommended, as was the use of a CPD whenever the interventionist thought one could be safely deployed. CPDs and stents used at each centre were approved by the ICSS steering committee and were CE-marked. The administration of heparin during the procedure was mandatory. A CAS technical data form was returned to the trial office by interventionists giving details of the equipment and medications used in the procedure.

17.2.2 Outcome events

The combined endpoint of stroke, MI or death within 30 days of CAS is examined in this analysis, and was reported to the trial office by investigators at each centre. For each of these outcomes, confirmatory evidence was required (brain scan in the case of stroke, ECG and / or cardiac enzyme levels for MI, death certificate and autopsy report if available for death). Stroke was defined as “an acute disturbance of focal neurological function with symptoms lasting more than 24 hours resulting from intracranial vascular disturbance”. Two out of the three following criteria were required for a diagnosis of MI – a clinical history of chest discomfort lasting more than 30 minutes, the development of specific ECG abnormalities consistent with MI or cardiac enzyme levels more than twice the upper limit of the reference range. Two investigators from the trial office adjudicated each event and then it was sent to a third, independent, clinician for adjudication. Disagreements between investigators were resolved by consensus after a second independent review.

17.2.3 Statistical analysis

A per-protocol analysis, including only those patients randomized to CAS in ICSS in whom the stenting procedure was initiated, is presented in this chapter. Stenting was deemed initiated if the patient received local or general anaesthesia prior to the procedure. Patients crossing over to surgery or best medical therapy were therefore excluded. Risk factors for stroke, MI or death within 30 days of the CAS procedure

were investigated sequentially in a binomial regression model. Patients with missing data were excluded from each relevant analysis. The effect of cerebral protection type and stent type could only be investigated in patients in whom these devices were deployed, and the effect of post-stent dilation was examined only in those patients in whom a stent was deployed. A multivariable model was developed using a forward stepwise approach including variables potentially available for all CAS patients, therefore excluding CPD type, stent type and post-dilation. A p-value of <0.05 was considered "significant" in all analyses. Analyses were performed with Stata (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP).

17.3 Results

17.3.1 Patient and procedure characteristics

1713 patients were randomized in ICSS, of whom 853 were allocated to CAS. In this group, 828 procedures were initiated. Baseline characteristics of included patients are presented in Figure 12 below. In summary, 70.4% of patients were male, and 53.5% of patients were over the median age of 70 years. A stent was deployed in 752/816 (92.2%) procedures for which data were available. 367/816 (48.8%) of these procedures used an open-cell design of stent, 371/816 (49.3%) used a closed-cell stent. A CPD was deployed in 585/828 (70.6%) procedures, of which the majority (n=464) were distal filter-type devices. 71.7% of patients were taking the combination of aspirin and clopidogrel prior to the procedure.

17.3.2 Timing and cause of events

61/828 (7.4%) patients undergoing CAS suffered stroke, MI or death within 30 days of the procedure. The events reported in these patients were 58 strokes, three myocardial infarctions and one death unrelated to stroke or MI. One patient with stroke suffered a subsequent (fatal) MI. 44/61 (72.1%) events occurred on the day of the procedure itself (day 0), of which 21 were adjudicated to have occurred during the procedure. 21 occurred between the end of the procedure and day 1. In one patient a retinal infarct was noted during follow-up and attributed to the procedure on day 0, but the timing in relation to CAS was uncertain. In one further patient there was insufficient information to determine the timing of the event.

Table 15 below summarizes the immediate cause or timing of the event, as reported by the interventionist, in the 21 patients whose event was adjudicated to have occurred

during the procedure itself. The majority of these events (12/21) were precipitated by the insertion, retrieval or use of endovascular equipment around the site of the lesion itself.

Table 15. Reported immediate cause or timing of event in patients undergoing CAS in ICSS

Precipitant	**Number of events (n=21)**
Uncertain / undetermined	6
Post-dilation	5
Stent deployment	4
CPD manipulation	3
Intra-operative hypotension	2
Catheter angiography	1

17.3.3 Demographic and technical risk factors for stroke, MI or death within 30 days of the procedure

The results of univariable analysis of the influence of baseline demographic and technical risk factors on the risk of stroke, MI or death within 30 days of CAS are presented in Figure 12. The risk of the combined outcome increased 1.24 times for each 5 years increase in age (95% CI 1.07 to 1.42, p<0.01). The risk was also increased in patients with an open-cell carotid stent (RR 1.86, 95% CI 1.09 to 3.19, p=0.02) and in patients with atrial fibrillation (RR 2.31, 95% CI 1.16 to 4.61, p=0.02). The risk was lower in those who were current or former smokers at baseline as compared to those who had never smoked (RR 0.25, 95% CI 0.10 to 0.63 and RR 0.77, 95% CI 0.46 to 1.29 respectively, global p<0.01) and those with amaurosis fugax as the initial event prompting randomization in the trial as compared with those who suffered stroke as the index event (RR 0.25, 95% CI 0.08 to 0.80 respectively, global p<0.01). The risk was also lower in patients undergoing a right-sided procedure (RR 0.54, 95% CI 0.32 to 0.91, p=0.02). Patients in whom a CPD was used had a higher risk of stroke, MI or death with nearly double the number of events, but this increase was not statistically significant (RR 1.86, 95% CI 0.98 to 3.52, p=0.06).

Patients treated in centres who enrolled more than 50 patients in ICSS experienced a lower risk of stroke, death or MI within 30 days of CAS (RR 0.60, 95% CI 0.37 to 0.96, p=0.04), although the results in provisional centres where procedures were supervised were not statistically different from those at more experienced centres.

Figure 12. Univariable predictors of the risk of stroke, myocardial infarction or death in 828 patients undergoing CAS in whom the procedure was initiated

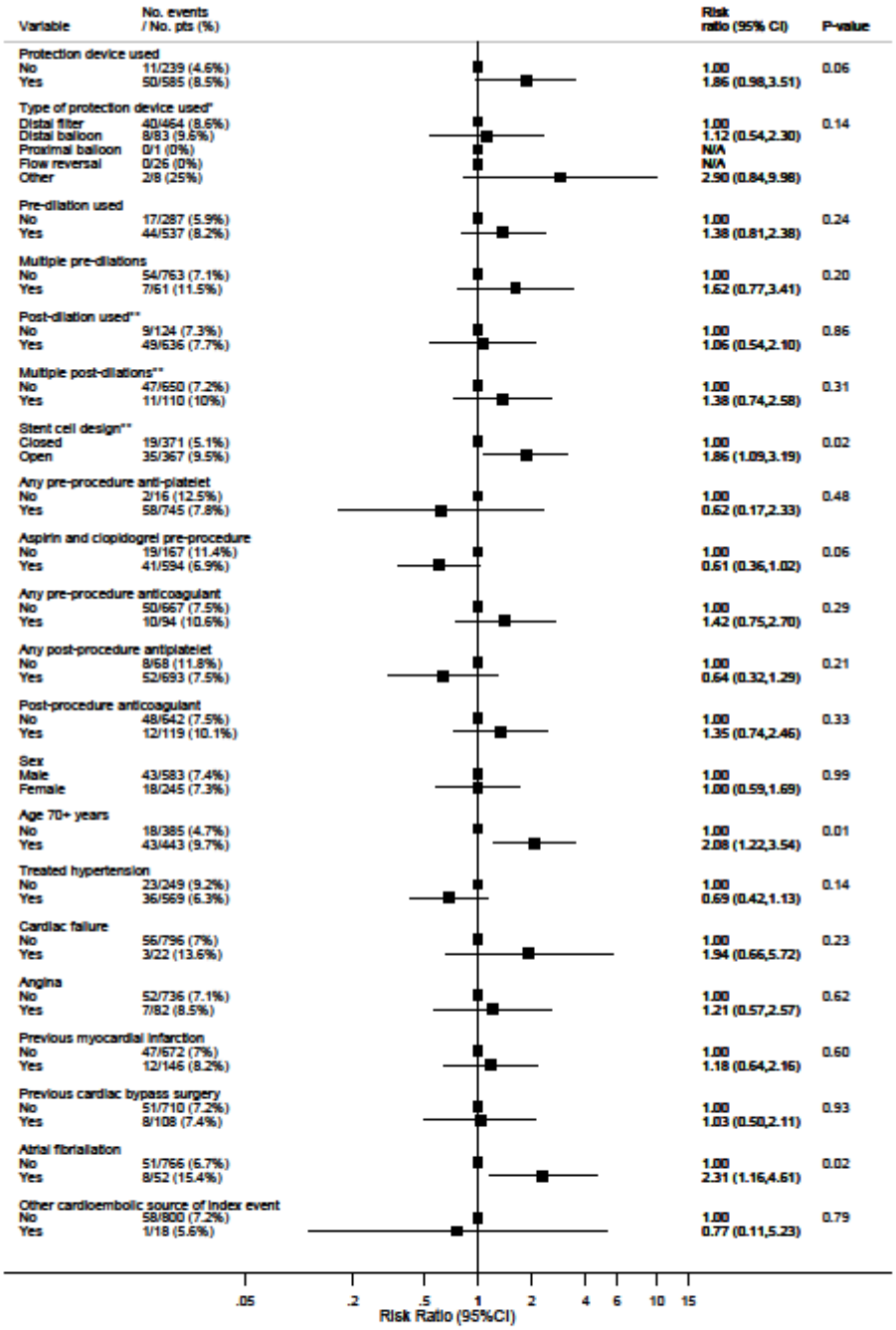
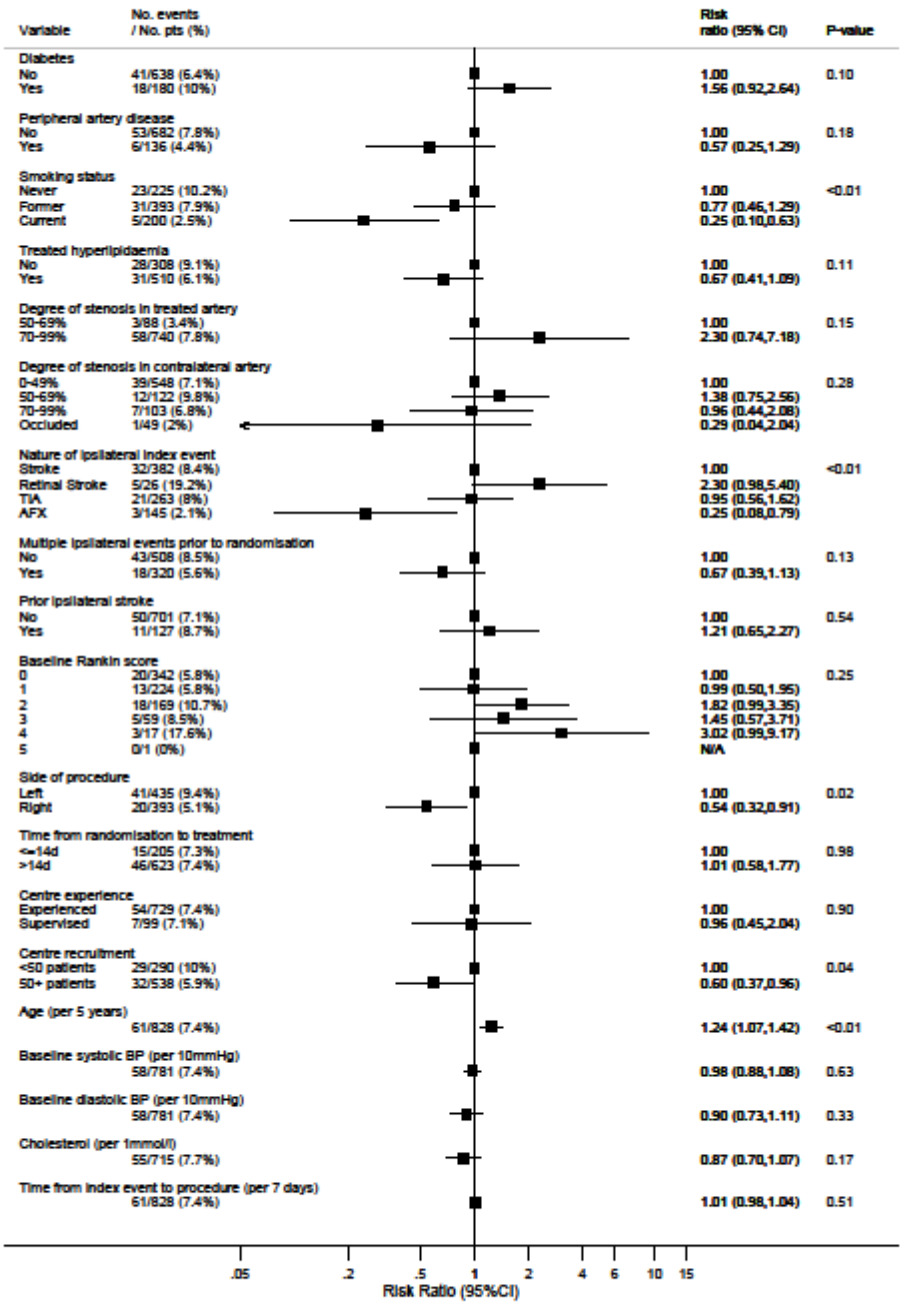


Figure 12 continued



One possible multivariable model investigating the effect of all variables potentially available for all CAS patients (i.e. excluding those in whom a stent or CPD was not deployed) is presented in Table 16. Independent predictors of the risk of stroke, MI or death within 30 days of CAS were increasing age (RR 1.17 per 5 years increase, 95% CI 1.01 to 1.37, p=0.04) and a right-sided procedure (RR 0.54, 95% CI 0.32 to 0.91, p=0.02). The risk was significantly lower in patients taking the combination of aspirin and clopidogrel prior to the procedure, as compared with any other antiplatelet regimen (RR 0.59, 95% CI 0.36 to 0.98, p=0.04), and higher in those with retinal stroke as the index event prompting randomization in the trial.

The model was reconstructed in a sensitivity analysis to exclude those patients in whom a stent was not deployed. In this model, the use of an open-cell stent conferred higher risk (RR 1.92, 95% CI 1.11 to 3.33, p=0.02).

Table 16. Independent predictors of risk of stroke, MI or death within 30 days of CAS in 748 ICSS per-protocol participants in whom the procedure was initiated and for whom complete predictor data are available. Results obtained from multivariable binomial regression.

Variable	**Adjusted Risk Ratio (95% CI)**	**P-value**
Age (per 5 years increase)	1.17 (1.01 to 1.37)	0.04
Smoking status		
Never smoked	1.00	N/A
Ex- smoker	0.86 (0.52 to 1.43)	0.55
Current smoker	0.33 (0.13 to 0.85)	0.02
Right-sided procedure	0.54 (0.32 to 0.91)	0.02

Table 16 continued

Variable	**Adjusted Risk Ratio (95% CI)**	**P-value**
Type of index event pre randomization in ICSS		
Stroke	1.00	N/A
Retinal Stroke	2.47 (1.11 to 5.52)	0.03
TIA	0.99 (0.58 to 1.68)	0.96
Amaurosis Fugax	0.32 (0.10 to 1.02)	0.06
Type of antiplatelet regimen		
Any other antiplatelet	1	N/A
Aspirin and clopidogrel in combination	0.59 (0.36 to 0.98)	0.04

17.4 Discussion and conclusion

17.4.1 Summary

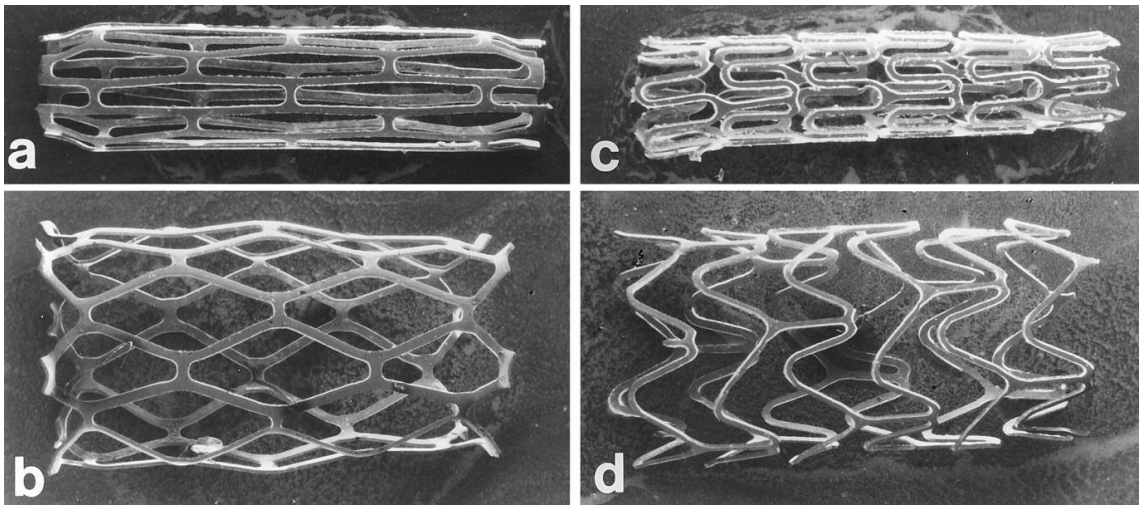
The risk of stroke, myocardial infarction or death within 30 days of carotid stenting in ICSS was significantly higher in older patients, those undergoing a left-sided procedure, in non-smokers, in patients who were not taking the recommended combination of aspirin and clopidogrel and in those with retinal stroke as the index event prompting randomization on the trial. Restricting the analysis to only those patients in whom a stent was deployed revealed the use of an open-cell stent design to be an independent predictor of increased risk compared with a closed-cell design.

17.4.2 Discussion

Evidence is building that CAS is less safe in older patients. Individual patient data meta-analysis from the three European trials of CAS vs CEA found that although the risks of stroke or death within 120 days of revascularization was similar between patients allocated to CAS or CEA under the age of 70 years (5.8% vs 5.7%, RR 1.00, 95% CI 0.68 to 1.47), the risk of these complications with CAS were much higher in patients 70 years or older (12.0% vs 5.9%, RR 2.04, 95% CI 1.48 to 2.82, interaction $p<0.01$) [189]. There was no reduction in the severity of events in older patients. The CREST study also showed a similar effect of age [84]. Age should therefore be taken into account when selecting patients for the procedure, and the use of CAS in patients over 70 years old should be largely reserved for those with a clear indication (e.g. “hostile” surgical anatomy or post-radiotherapy).

Patients in ICSS in whom an open-cell stent was deployed were at higher risk of complications, a finding echoed in other studies. A higher rate of ipsilateral stroke or ipsilateral stroke death was found in patients treated with an open-cell stent in the SPACE study (OR 2.13, 95% CI 1.07 to 3.76) [190], and similar trends have been found by other groups [191] [192]. The effect of stent design may be more pronounced in symptomatic patients because plaque is unstable, ulcerated or recently-complicated with fresh thrombus which is stabilized by the greater coverage of closed-cell stents with a smaller open area between cell struts, containing debris generated during deployment of the stent to the site of the lesion. The structural difference between open- and closed-cell stents is illustrated in Figure 13 below.

Figure 13. A scanning electron micrograph of closed-cell stent design before (a) and after (b) expansion, and an open-cell stent before (c) and after (d) expansion.



From [193] *with kind permission from Lippincott Williams and Wilkins / Wolters Kluwer Health*

CPDs were developed for use in CAS in the assumption that they would reduce embolism during stent deployment or lesion dilation. However, it is conceivable that the passage of the device itself may produce particulate debris, and the deployment of a filter could damage the distal vessel endothelium such that post-procedure thrombus may form. The combination of findings in this chapter that many procedural minor strokes were caused by manipulation of equipment around the site of the lesion itself, and that certain types of patients were at higher risk of stroke, suggests that perhaps both the generation of a shower of emboli during stenting and the brain's ability to tolerate these may be the clinical mechanism of causation in procedural stroke [194].

A systematic review comparing older case series with results after the introduction of CPDs appeared to confirm the case for their use [195], but these results could be improved by changes in patient selection and other developments in CAS technique over time. The EVA-3S trial issued a clinical alert after randomizing 80 patients when their finding that the 30-day risk of stroke in patients undergoing unprotected CAS was four times that of those undergoing protected CAS [63], but the excess strokes in this group may not have been down to CPD use alone, since only two strokes in those treated without a CPD occurred on the day of the procedure itself. This analysis found that CPD use in ICSS did not protect against stroke, MI or death within 30 days of the procedure. Indeed ICSS patients enrolled in the ICSS-MRI Substudy in centres with a general policy of CPD use experienced a 2.7-fold higher risk of new ischaemic brain lesions seen on diffusion-weighted MRI following the procedure than those enrolled in other centres where CPDs were not routinely used [64].

Two small randomized trials of CAS with and without filter-type CPDs have reported results. One carried out in the United States showed no reduction in new DWI lesions post-procedure in the CPD group [196], while the other which enrolled patients in the UK demonstrated an increase in new ischaemic brain lesions post-procedure and procedural micro-emboli as detected by transcranial Doppler in the CPD group [197]. The predominant design of CPD used in ICSS was a distal filter type, and newer systems such as flow reversal devices may be more effective [65]. In the meantime, the routine use of CPDs for the prevention of procedural stroke cannot be supported by the results of ICSS and further research on newer devices is required to ensure their safety and efficacy.

The reduction in 30-day neurological complications in patients taking combination antiplatelet therapy to cover their CAS procedure has been described before [198], and reinforces the recommendation that all CAS patients receive aspirin and clopidogrel

where appropriate to prevent thrombus forming on the metallic stent struts. The finding that smoking was associated with a lower risk of complications is more difficult to explain, and has not previously been described. It is therefore possibly a chance finding, or one due to residual confounding.

It is interesting to contrast findings regarding the possible procedural precipitants of stroke with findings from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study [199]. This trial involved potentially more hazardous intracranial artery stenting, but included those with carotid and vertebral disease. Of 19 periprocedural ischaemic strokes, 12 were thought to have been caused by perforator artery occlusion and 2 by delayed stent occlusion. Embolism was only thought to be a contributing event in 5 patients. These different mechanisms of stroke aetiology perhaps reflect the unique hazards of intracranial artery stenting as compared with carotid stenting, but the contribution of embolism to the mechanism of stroke in several patients highlights the extra danger of stenting in symptomatic patients who may have fresh thrombus at the site of the stenosis.

17.4.3 Limitations

The technology of carotid stenting is developing rapidly and findings related to the specific stent types and device types used in ICSS may be superseded as newer equipment enters common use. In some patients, information regarding baseline risk factors was unavailable, and these patients were excluded from each relevant analysis. Some procedures were abandoned before the deployment of a CPD or stent, and these patients were not included in multivariable modelling which included as many patients as possible with baseline predictor data. Multiple comparisons have been made without statistical correction, raising the possibility of a Type I (false positive) error. This is not a randomized comparison of stenting technique or processes or care, and it is possible that unmeasured confounders are associated with the risk of stroke, MI or death within 30 days of CAS. The limited number of outcome events in ICSS limited the number of variables supported in a multivariable model.

17.4.4 Conclusion

Interventionists selecting patients suitable for CAS should take into account risk factors for periprocedural stroke, MI or death that include the patient's age, the side of the procedure, and the nature of the event prompting intervention. Until such time as

consistently safe results can be demonstrated in older patients, stenting for those over the age of 70 should have a clear indication (surgically-inaccessible stenosis, post-radiotherapy or the patient's wish to avoid surgery, for example). Those who require revascularization of the left carotid artery should be aware of a potentially higher procedural risk – although this of course should be balanced against the risk of stroke without treatment. The results presented in this chapter favour the use of a closed-cell stent without routine deployment of a cerebral protection device. They also reinforce the need for dual antiplatelet cover with aspirin and clopidogrel in all patients.

18. Vascular anatomical factors influencing the risk of new ischaemic brain lesions following carotid artery stenting

18.1 Introduction

Patients in the CAS arm of ICSS experienced a higher rate of stroke, MI or death within 30 days of the procedure than patients in the CEA arm, mostly attributable to an excess of minor stroke [82]. Patients enrolled in the ICSS-MRI Substudy were examined further with pre- and post-procedure brain scans to determine the number and volume of new diffusion-weighted imaging (DWI) lesions – indicative of ischaemia or infarction. 50% of patients allocated to CAS in the substudy were discovered to have developed at least one new ischaemic brain lesion due to the procedure, compared with just 17% of those allocated to CEA (OR 5.21, 95% CI 2.78 to 9.79, $p<0.01$) [64]. Lesions were more numerous in patients undergoing CAS, and were also more likely to occur in cortical and adjacent white matter areas than those in CEA patients [200].

CAS is a technically demanding procedure that requires the passage of equipment through the vascular tree up to and beyond the atherosclerotic lesion. There is emerging evidence from the randomized clinical trials of CAS versus CEA that patients undergoing CAS procedures performed by operators with low annual volumes of cases may be at higher risk of stroke or death within 30 days of the procedure [126].

A number of vascular anatomical characteristics have been proposed by expert opinion as contributing to a technically challenging procedure [123] [201]. This analysis investigates the influence of baseline patient characteristics, procedural technique and variation in vascular anatomy seen on pre-stenting catheter angiography on the risk of new DWI brain lesions following CAS in patients enrolled into the ICSS-MRI Substudy.

18.2 Methods

18.2.1 The ICSS-MRI Substudy

The ICSS-MRI Substudy is discussed in Chapter 13 and the full protocol is supplied in Appendix V. To be eligible for randomization in ICSS patients over 40 years old with recently-symptomatic carotid stenosis were required to be suitable for revascularization by either CAS or CEA. Importantly, they were excluded from randomization if they presented with a stenosis that was known to be unsuitable for stenting due to pseudo-occlusion (distal collapse of the artery with “string sign” indicating poor runoff from the

lesion), tortuous vascular anatomy, proximal common carotid artery stenosis or visible thrombus on vascular imaging. CAS was carried out by accredited interventionists according to trial protocol described in Appendix IV. CPD use was recommended whenever the interventionist could “safely deploy” one, but was not mandatory. Operators were required to use devices approved by the trial steering committee.

Patients who additionally enrolled in the ICSS-MRI Substudy underwent pre-procedure brain MRI at either 1.5T or 3.0T field strength carried out up to a week before revascularization. MRI was then repeated post-procedure at one to three days after CAS and then at one month after CAS. Scan protocols contained diffusion-weighted imaging (DWI) sequences to identify recent ischaemic brain lesions.

Patients underwent carotid stenting as per the ICSS protocol. This analysis includes patients allocated to CAS in whom the stenting procedure was initiated and for whom a baseline or pre-stenting catheter angiogram was available and of sufficient quality to be analysed.

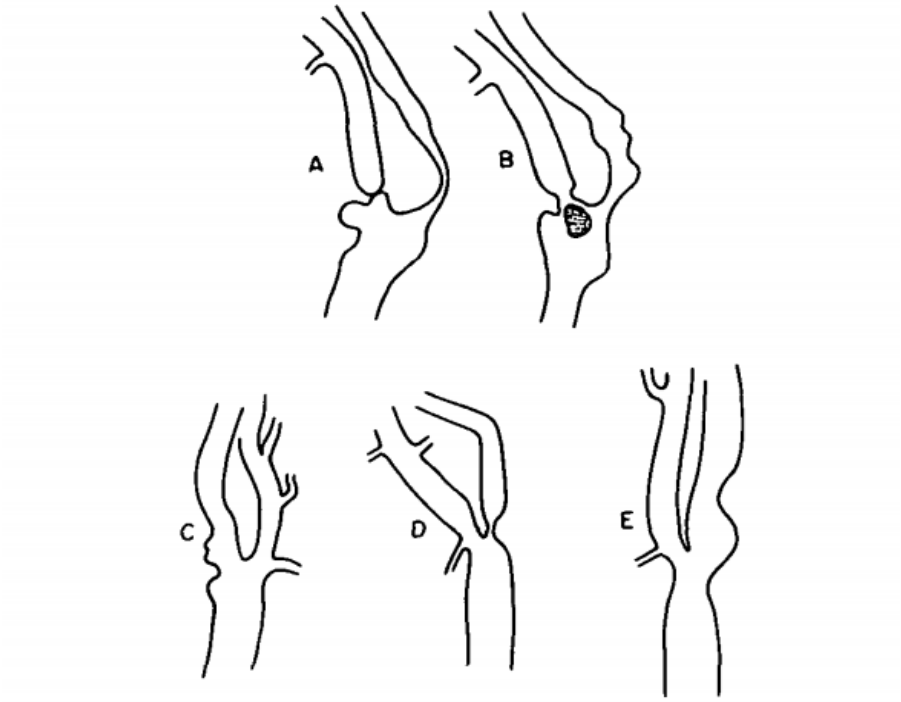
18.2.2 Analysis of brain and vascular imaging

A “lesion count” for each DWI sequence was obtained by the consensus reading of a neurologist and neuroradiologist blind to the patient’s identity, the date and the nature of the scan (e.g. pre- or post-procedural). The location (ipsilateral or contralateral) and the total volume of lesions were also recorded.

Catheter angiograms showing vascular anatomy before stent insertion were evaluated initially by one trained reader and then read again by the author to enable inter-rater reliability to be calculated. Both readers were blind to the patient’s identity and the selected outcome variable (number of new ischaemic brain lesions on post-procedure DWI MRI). Standard definitions were agreed between the ICSS-MRI Substudy investigators prior to the first scans being read. The degree of carotid artery stenosis was calculated using the formula developed in NASCET [40], being the ratio of the smallest diameter of the ICA at the level of the lesion divided by the distal ICA diameter expressed as a percentage. ECA stenosis was measured in the same way, using the distal ECA diameter. “Ulceration” and “irregularity” of the atherosclerotic plaque was also defined according to the NASCET investigators’ methods [202], as illustrated in Figure 14. “Pinhole” stenosis was defined as a luminal diameter too small to accurately measure but with normal distal run-off in the vessel and no distal collapse. Many digital copies of catheter angiography in the ICSS-MRI Substudy did not contain calibration

information, so “lesion length” was defined as the distance between proximal and distal shoulders of the atherosclerotic lesion where the luminal diameter decreased to 20% of its maximum expressed as a fraction of the common carotid artery on angiographic views that most elongated that stenosis [203], as illustrated in Figure 15. A “diseased CCA” was one that had the appearance of luminal stenosis or irregularity consistent with atherosclerosis. The contralateral carotid artery was not always imaged in the sequences available to the readers, so the measurement of contralateral carotid stenosis provided by trial investigators at the time of the patient’s enrolment in ICSS was used in the analysis. Images were prepared and analysed using Osirix MD, (Pixmeo SARL, 2012).

Figure 14. Determination of smooth (D, E), irregular (C) or ulcerated (A, B) atheromatous plaque at the carotid bifurcation



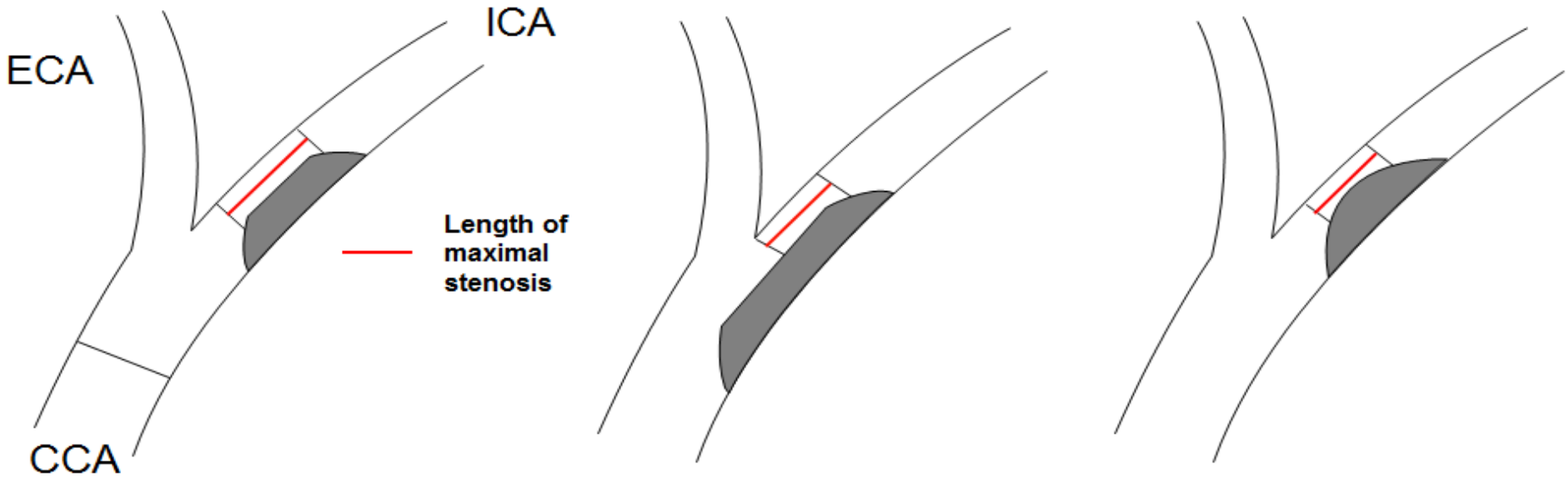
Schematic representation of possible appearances of carotid plaque on angiography. A, Definite ulcer niche at the bifurcation; B, definite double density on ''en face'' view (same patient as in panel A); C, irregular plaque; D, smooth plaque; and E, smooth outpouching between two smooth plaques.

From [202] *with kind permission from Lippincott Williams & Wilkins / Wolters Kluwer Health*

Figure 15. Measuring the length of maximal stenosis in three vascular anatomical profiles

CCA = common carotid artery, ICA = internal carotid artery, ECA = external carotid artery

Adapted from [203] *under the terms of the Creative Common Attribution License. Original figure ©The Authors.*



18.2.3 Statistical Methods

Each demographic, vascular or anatomical risk factor was investigated sequentially in a negative binomial regression model, with the number of new DWI brain lesions on post-procedure scan set as the dependent (outcome) variable. Comparisons between groups are expressed as an odds ratio with 95% confidence interval, demonstrating how many times more or less lesions occurred. Factors with statistical significance, $p<0.05$, were considered for entry into a multivariable model constructed using a forward stepwise approach. Patient with missing data were excluded from each relevant analysis. Post-hoc sensitivity analyses for lesions ipsilateral to the treated artery only as the outcome variable and for lesion volume as the outcome variable were carried out in the same manner. Inter-rater reliability was calculated to produce a kappa (κ) statistic and p-value, interpreted as proposed by Landis and Koch [204]. All analyses were performed using SPSS version 22.0.0.0 (IBM Corp, 2013).

18.3 Results

18.3.1 Baseline patient characteristics

A total of 127/231 patients randomized in the ICSS-MRI Substudy were allocated to CAS. Baseline (n=7) or pre-procedural (n=110) catheter angiograms with views sufficient for analysis were available for 115 patients. The baseline demographic characteristics and vascular risk factors of the patients included in this analysis are shown in Table 17. Measured vascular anatomical features are shown in Table 18 below.

The median age of patients in this analysis was 71 years. 70% of patients were male. A protection device (CPD) was used in 46/115 (40%) procedures, of which 91% were distal filters and 9% were flow reversal systems. 53% procedures were on the right carotid artery, 47% on the left.

Table 17. Demographic and procedural characteristics of 115 patients allocated to CAS in the ICSS-MRI Substudy for whom adequate pre-procedure catheter angiography was available

Parameter	**Number of patients (%) n=115**
Right-sided procedure	61 (53%)
Cerebral protection device used	46 (40%)
Age (mean)	70.4 years
Female	34 (30%)
Treated hypertension	77 (67%)
Diabetes (any type)	22 (19%)
Treated hyperlipidaemia	71 (62%)
Current or former smoker	87 (76%)
Coronary heart disease	26 (23%)
Other cardioembolic source of thrombus	7 (6%)
Cardiac failure	3 (3%)
Peripheral arterial disease	21 (18%)
Contralateral carotid occlusion	7 (6%)
Contralateral carotid stenosis 70-99%	23 (20%)

Table 17 continued

Parameter	**Number of patients (%) n=115**
Contralateral carotid stenosis 50-69%	12 (10%)
Contralateral carotid stenosis <50% (reference group)	73 (64%)
Baseline mRS=4	2 (2%)
Baseline mRS=3	6 (5%)
Baseline mRS=2	28 (24%)
Baseline mRS=1	29 (25%)
Baseline mRS=0 (reference group)	50 (44%)
Cholesterol (mean)	4.9 mmol/l
Diastolic blood pressure (mean)	83.0 mmHg
Systolic blood pressure (mean)	157.3 mmHg
ARWMC (median)	4
Qualifying event was stroke	49 (43%)
Qualifying event was TIA	41 (36%)
Qualifying event was retinal TIA or retinal stroke	25 (22%)

Table 18. Vascular anatomical characteristics of 115 patients allocated to CAS in the ICSS-MRI Substudy for whom adequate pre-procedure catheter angiography was available

Parameter	**Value**
Carotid artery NASCET degree of stenosis (median)	62.7%
Ratio of maximal stenosis length to CCA diameter (mean)	0.41 times
Angle between common and internal carotid arteries (median)	23.6 degrees
External carotid artery stenosis >50%	6 (5%)
Plaque ulceration	40 (35%)
Pinhole stenosis	2 (2%)
Common carotid artery atheroma	13 (11%)

18.3.2 Patient, procedural and vascular anatomical risk factors for new ischaemic brain lesions on the post-procedural scan following CAS

62/115 (50.4%) of patients had at least one new DWI-MRI-positive lesion on their post-procedure scan. The results of negative binomial regression analysis of the influence of baseline demographic variables, vascular risk factors and vascular anatomical characteristics on the number of new DWI-positive lesions on the post-procedure MRI are summarized in Tables 19 and 20 below.

Factors that increased the risk of new DWI lesions on the post-procedure scan were increasing age (OR 2.26 for each 10 years increase in age, 95% CI 1.74 to 2.89, p<0.01), treated hypertension (OR 2.61, 95% CI 1.68 to 4.05, p<0.01), increasing ARWMC (age-related white matter change score seen on baseline brain imaging) (OR 1.13 for each point increase, 95% CI 1.06 to 1.20, p<0.01) and stroke or TIA as the qualifying event for enrolment into ICSS as compared with those who experienced a retinal event (OR 4.30, 95% CI 2.46 to 7.53, p<0.01 for stroke and OR 1.91, 95% CI 1.06 to 3.43, p=0.03 for TIA).

Factors associated with a lower number of new DWI lesions on the post-procedure scan were being female (OR 0.49, 95% CI 0.31 to 0.76, p<0.01), being a current or former smoker (OR 0.48, 95% CI 0.31 to 0.76, p<0.01), cardiac failure (OR 0.17, 95% CI 0.03 to 0.85, p=0.03) and 50-69% contralateral carotid artery stenosis as compared with <50% contralateral carotid artery stenosis (OR 0.18, 95% CI 0.08 to 0.40, p<0.01). Patients with a mRS score of 3 at baseline had a lower number of new lesions compared with patients with no disability scoring 0 (OR 0.20, 95% CI 0.06 to 0.62, p<0.01). The number of new DWI lesions was lower in patients undergoing right-sided procedure (OR 0.57, 95% CI 0.38 to 0.85, p<0.01).

The vascular anatomical variables measured for this analysis – the degree of ipsilateral carotid stenosis, the length of maximum stenosis, the CCA/ICA angle, plaque ulceration, the presence of CCA atheroma or the presence of “pinhole” stenosis did not significantly influence the number of new lesions.

Table 19. Univariable demographic and procedural predictors of new DWI-MRI lesions following CAS in 115 patients in the ICSS-MRI Substudy for whom adequate pre-procedure catheter angiography was available

Parameter	**p-value**	**Odds Ratio (OR)**	**95% confidence interval for OR**	
			Lower	**Upper**
Right-sided stenosis	<0.01	0.57	0.38	0.85
Cerebral protection device used	0.22	1.30	0.83	1.88
Age (per 10-year increase)	<0.01	2.26	1.74	2.89
Female	<0.01	0.49	0.31	0.76
Treated hypertension	<0.01	2.61	1.68	4.05
Diabetes (any type)	0.07	1.59	0.97	2.61
Treated hyperlipidaemia	0.69	0.92	0.61	1.38
Current or former smoker	<0.01	0.48	0.31	0.76
Coronary heart disease	0.43	1.21	0.76	1.94
Other cardioembolic source of thrombus	0.28	1.56	0.69	3.49
Cardiac failure	0.03	0.17	0.03	0.85
Peripheral arterial disease	0.29	0.75	0.45	1.27
Contralateral carotid occlusion	0.21	1.69	0.75	3.80

Table 19 continued

Parameter	**p-value**	**Odds Ratio (OR)**	**95% confidence interval for OR**	
			Lower	**Upper**
Contralateral carotid stenosis 70-99%	0.12	0.66	0.39	1.11
Contralateral carotid stenosis 50-69%	<0.01	0.18	0.08	0.40
Contralateral carotid stenosis <50% (reference group)	N/A	1	N/A	N/A
Baseline mRS=4	0.14	0.26	0.04	1.57
Baseline mRS=3	<0.01	0.20	0.06	0.62
Baseline mRS=2	0.20	1.38	0.84	2.26
Baseline mRS=1	0.40	0.81	0.49	1.33
Baseline mRS=0 (reference group)	N/A	1	N/A	N/A
Cholesterol (1 mmol increase in serum total cholesterol)	0.30	0.89	0.71	1.11
Diastolic blood pressure (per 10mmHg increase)	0.13	0.90	0.98	1.00
Systolic blood pressure (per 10mmHg increase)	0.98	1.00	0.91	1.09

Table 19 continued

Parameter	**p-value**	**Odds Ratio (OR)**	**95% confidence interval for OR**	
			Lower	**Upper**
ARWMC (per unit increase)	<0.01	1.13	1.06	1.20
Qualifying event was stroke	<0.01	4.30	2.46	7.53
Qualifying event was TIA	0.03	1.91	1.06	3.43
Qualifying event retinal TIA or retinal stroke (ref. group)	N/A	1	N/A	N/A

Table 20. Univariable vascular anatomical predictors of new DWI-MRI lesions following CAS in 115 patients in the ICSS-MRI Substudy for whom adequate pre-procedure catheter angiography was available

Parameter	**p-value**	**Odds Ratio (OR)**	**95% confidence interval for OR**	
			Lower	**Upper**
Carotid artery NASCET degree of stenosis (per 10% increase)	0.69	0.97	0.83	1.13
Ratio of maximal stenosis length to CCA diameter (per unit increase)	0.46	1.28	0.67	2.45
Angle between common and internal carotid arteries	0.12	0.99	0.98	1.00
External carotid artery stenosis >50%	0.08	0.42	0.16	1.10
Plaque ulceration	0.66	1.10	0.73	1.66
Pinhole stenosis	0.88	1.13	0.25	5.05
Common carotid artery atheroma	0.69	0.88	0.47	1.65

Factors in the univariable analysis with significance <0.05 were considered for entry into a multivariable model. One possible model is illustrated below in Table 21. Factors independently increasing the number of new DWI brain lesions on the post-procedure scan in this model are a left-sided procedure (OR 1.59, 95% CI 1.04 to 2.44, p=0.03), increasing age (OR 2.10 per 10 years increase, 95% CI 1.61 to 2.74, p<0.01), being male (OR 2.83, 95% CI 1.72 to 4.67, p<0.01), treated hypertension (OR 2.04, 95% CI 1.25 to 3.33, p<0.01) and absence of a diagnosis of cardiac failure (OR 6.58, 95% CI 1.23 to 35.07, p=0.03).

Inter-rater agreement, calculated for binary anatomical characteristics, was moderate for CCA atheroma (κ=0.50, p<0.01), substantial for the type of stenosis (smooth, irregular or ulcerated, κ=0.76, p<0.01) and slight for pinhole stenosis (κ=0.13, p=0.06).

Table 21. Independent predictors of new DWI-MRI lesions following CAS in 115 patients in the ICSS-MRI Substudy for whom adequate pre-procedure catheter angiography was available

Parameter	**p-value**	**Odds ratio (OR)**	**95% confidence interval for OR**	
			Lower	**Upper**
Left-sided stenosis	0.03	1.59	1.04	2.44
Age (per 10-year increase)	<0.01	2.10	1.61	2.74
Male	<0.01	2.83	1.72	4.67
Treated hypertension	<0.01	2.04	1.25	3.33
Absence of cardiac failure	0.03	6.58	1.23	35.07

18.4 Discussion and conclusions

18.4.1 Summary

Of the vascular anatomical characteristics measured specifically for this analysis, none significantly influence the risk of new DWI-positive lesions on the post-procedure scan. Independent factors increasing the number of new lesions were age, approximately doubling risk for each advancing decade of life, and treated hypertension. A diagnosis of cardiac failure, being female and undergoing a right-sided procedure all independently decreased the number of new lesions.

18.4.2 Discussion

The assumption that a difficult procedure – technically challenging for an inexperienced investigator – will be associated with an increased procedural risk has led to attempts to define which vascular anatomical variants require extra skill to navigate during CAS. A Delphi panel of CAS experts proposed a scoring system for rating difficulty based on vessel angulation, tortuosity of the arteries, the presence of external or common carotid artery disease or aortic arch variants [123]. Studies focussing on clinical endpoints, usually stroke or death, have found a number of vascular anatomical factors that increase the risk of an adverse outcome – lesion length [203] [122] [120], plaque ulceration or plaque calcification [122], aortic arch variants [122] [205], angulation of the ICA-CCA bifurcation [120] and the side of the procedure [120]. Atypical aortic arch configuration may also be linked to longer catheter manipulation times, which itself may be linked to adverse outcome [206]. However, other authors have failed to find a link between lesion or vascular characteristics and outcome [207].

Factors specifically associated with an increased risk of new DWI-MRI lesions following CAS in other studies include age [208], the presence of an ulcerated stenosis [208], aortic atherosclerotic lesions [209] and increasing lesion length [208].

New ischaemic brain lesions following CAS are of concern. Subclinical injury to the brain from microemboli generated during the procedure, i.e. insufficient to cause clinically-apparent focal neurological symptoms, is thought to be a risk factor for cognitive dysfunction perhaps too subtle to be detected without neuropsychological testing [210]. CAS was associated with a larger decrease in cognitive ability than CEA in selected patients enrolled at two ICSS centres, although the difference was not statistically significant and the sample size was relatively small compared to the overall

trial size [211]. A decrease in cognitive performance in both groups occurred regardless of the baseline white matter lesion burden of the patients studied [212].

This analysis demonstrated a higher number of new DWI-MRI lesions following CAS in patients undergoing left-sided procedures, but was not able to replicate the findings of others of an increased procedural risk with pinhole stenosis, length of stenosis or ICA-CCA angulation. In ICSS the anatomical suitability of the stenosis for CAS or CEA (the patient was required to be suitable for either to be included in the trial) was determined prior to randomization using non-invasive imaging including duplex ultrasound or CT or MR angiography. Pre-stenting catheter angiograms were primarily obtained to plan procedures, and thus the films or DICOM images available for this analysis did not routinely include the contralateral carotid artery or the aortic arch and CCA origin. It is possible that patients thought to be “high risk” for stenting because of their vascular anatomy were excluded from enrolment in ICSS. The trial protocol specified tortuous anatomy proximal or distal to the stenosis, the presence of visible thrombus, proximal CCA stenotic disease or pseudo-occlusion as examples of high risk anatomies. The relatively low percentage of patients with pinhole stenosis and the low average CCA-ICA angle in our study may reflect this. Inter-rater agreement for some of the measured features, such as plaque ulceration, has also been shown to be poor [202].

Given the lack of inter-rater agreement for binary features, and the lack of a strong association between vascular characteristics and the outcome, this data does not support selecting patients for CAS based on “safe” vascular anatomy. In future, newer imaging techniques such as 3T MRI looking at the composition of carotid plaque may prove more useful in risk stratification if they are able to accurately identify fragile plaques vulnerable to fragmentation and dislodgement by a vascular catheter [213].

Older patients in the ICSS-MRI Substudy were found to have a higher number of new ischaemic brain lesions after stenting, and the trial also demonstrated as association between the total volume of DWI lesions and hemispheric stroke in this patient group [64] [200]. This finding agrees with clinical data from the Carotid Stenting Trialists’ Collaboration (CTSC) which conducted a meta-analysis of individual patient data from ICSS [82], EVA-3S [79] and SPACE [77]. This revealed a doubling of risk of stroke, myocardial infarction or death within 30 days of CAS compared with CEA in patients over the age of 70 years with no significant difference in the risk in younger patients. The mechanism by which age increases risk is not apparent from this analysis, but could be related to an increase in the overall burden of atheroma in the vasculature over time, a greater baseline ARWMC score and therefore decreased “cerebral

reserve" when ischaemia occurs, or age may be a marker of decreased physiological reserve to tolerate the procedure and hospitalization. An increase in atheroma in the aorta with age may also go some way to explaining concerns about the occurrence of new DWI lesions on MRI brain following catheterization of the coronary arteries where the carotid artery is not manipulated [214].

That cerebral protection devices did not protect against the occurrence of new DWI brain lesions in our analysis agrees with the findings of two small randomized studies of protected vs unprotected CAS [196] [197], but disagrees with one other study and one systematic review which found a reduction in embolic load with CPD use [215] [192]. However, even these two analyses demonstrate that new DWI lesions still frequently occur following protected CAS. Most CPDs in ICSS and the ICSS-MRI Substudy were of the distal filter type, and newer flow-reversal devices may offer better protection against distal embolism [66].

18.4.3 Limitations

Views on catheter angiography were often limited, and thus it was not possible to evaluate the anatomy of the intracranial portion of the ICA, the proximal CCA or the anatomy of the aortic arch. All of these may be important areas of technical difficulty, and could be further studied on CT or MR angiogram in the ICSS-MRI Substudy or other patient cohorts. There is no correction in this analysis for multiple statistical comparisons, and there is therefore a possibility of type I (false positive) error in interpreting a positive result.

18.4.4 Conclusions

It is unlikely that the excess of new DWI brain lesions seen in CAS patients in the ICSS-MRI Substudy was due to vascular anatomical variation alone. Patients who match the inclusion criteria for ICSS and in whom stenting is thought viable need not be excluded from the procedure on the basis of individual vascular anatomical characteristics as assessed on catheter angiogram. In agreement with other studies, age remains a risk factor for CAS and should be taken into account when deciding between CAS and CEA. Caution should be exercised in offering CAS to patients over the age of 70, as discussed in Chapter 17. There is mounting evidence that filter-type CPDs do not offer protection against brain ischaemia during CAS, and our findings therefore do not support their routine use.

19. Validation of an existing risk score for carotid stenting

19.1 Introduction

Patients allocated to stenting in the International Carotid Stenting Study experienced a higher risk of stroke than patients allocated to endarterectomy in an analysis limited to those whose procedures were initiated (7.0% vs 3.3%, $p<0.01$). This was mostly attributable to an excess of minor (non-disabling) stroke [82]. Matching this finding, three times the number of patients allocated to CAS in the ICSS-MRI Substudy were found to have new ischaemic brain lesions on post-treatment MRI scans compared with those undergoing endarterectomy [64]. CAS patients not only had higher numbers of ischaemic lesions after revascularization, but these were more likely to occur in cortical tissue and sub-adjacent white matter areas [200]. Patients who developed clinical signs of hemispheric stroke had a higher overall lesion volume than those who did not [64]. “Silent” brain infarction has been associated with dementia and cognitive decline in other patient cohorts [216], and new lesions are thus of concern in the context of carotid revascularization.

A risk score for the development of new ischaemic brain lesions following CAS, constructed by Gröschel et al, was developed from a dataset of 176 patients undergoing CAS at one centre from 2000-2006 who underwent diffusion-weighted brain MRI sequences before and up to 48 hours after the procedure. Just over 51% of their patients were symptomatic, and all had ≥70% carotid stenosis. Age over 70 years, the presence of an ulcerated stenosis and lesion length over 1cm were identified as risk factors for any new ipsilateral lesion on diffusion-weighted MRI following CAS [208]. An analysis of the performance of this risk score is presented in this chapter.

Other risk prediction scores for CAS complications have been developed, but are not studied here as they focus on clinical endpoints [122], address the choice between CAS and CEA [217] [171], use MR plaque imaging techniques not in routine use in ICSS [217] or focus on “high risk” patients not suitable for surgery [218] that would not meet the inclusion criteria for the ICSS-MRI Substudy.

19.2 Methods

19.2.1 The ICSS-MRI Substudy and anatomical feature rating

The ICSS-MRI Substudy protocol is summarized in Chapter 13 and described in greater detail in Appendix V. In summary, patients over the age of 40 with greater than 50% symptomatic carotid stenosis and capable of giving informed consent to trial participation were randomized in ICSS to either CAS or CEA. CAS was carried out according to ICSS trial protocol [81], including the use of a cerebral protection device when the operator thought it safe to deploy one. It was recommended that patients be prescribed aspirin and clopidogrel to cover the procedure.

Patients who additionally enrolled in the ICSS-MRI Substudy underwent pre-procedural MRI at 1.5T or 3.0T field strength up to 7 days before CAS with repeat sequences one to three days after the procedure. Scan protocols included diffusion-weighted sequences to demonstrate areas of acute of subacute brain ischaemia or infarction. The presence or absence of at least one new ipsilateral DWI-positive lesion was decided by the consensus reading of a neurologist and neuroradiologist. Vascular anatomical features – lesion length and the presence or absence of ulceration – were recorded by a trained reader in a separate analysis blind to the selected outcome of any new ipsilateral ischaemic brain lesion on the post-procedure scan as detailed in Chapter 18.

Patients in the ICSS-MRI Substudy allocated to CAS in whom the procedure was initiated, and for whom sufficient baseline or procedural catheter angiography was available, were studied in this analysis. A score was allocated to each patient in the analysis according to the characteristics in Table 22 below. The patient's age in years on the day of enrolment in ICSS is used in this analysis. Many digital angiograms did not contain calibration information to directly measure the length of stenosis. Therefore the "total stenosis length" was defined as the distance between the most proximal and distal shoulders of the lesion, expressed as a fraction of the common carotid artery diameter as illustrated in Figure 16. This was then multiplied by an assumed "average" common carotid diameter of 0.65cm [142] to give a total length of stenosis in centimetres. "Ulceration" was defined, as proposed by the NASCET investigators, as "a crater penetrating into a stenotic plaque and double density on 'en face' view" [202], illustrated in Figure 14 (Chapter 18). DICOM images were evaluated using Osirix MD, (Pixmeo SARL 2012).

Figure 16. Measuring the total length of stenosis in three vascular anatomical profiles

CCA = common carotid artery, ICA = internal carotid artery, ECA = external carotid artery

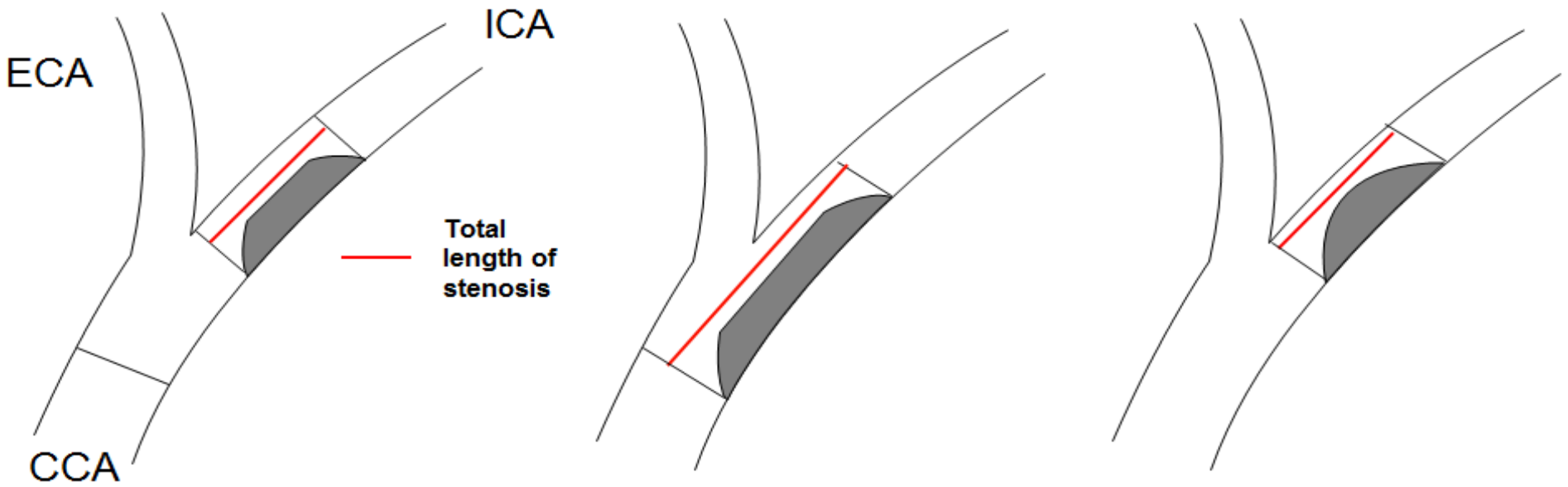


Table 22. Allocation of risk points in the Gröschel (2008) risk score

Study	Risk factors	Risk points
Gröschel et al. (2008) [208]	Age ≥ 70 years	1
	Age ≥ 80 years	1
	Lesion length > 1cm	1
	Ulcerated stenosis	1

19.2.2 Statistical Methods

The proportion of patients with at least one new ipsilateral DWI-positive lesion on post-procedure imaging was calculated for patients in each score bracket, expressed as a percentage. A 95% confidence interval is given for each proportion. Differences between the proportions of patients with a new DWI lesion in each group was assessed by means of a chi-squared (χ^2) test for trend. A receiver operator curve was constructed to assess the performance of the score in our dataset, and the area under the curve calculated with 95% confidence interval. In all analyses $p<0.05$ was assumed to confer statistical significance. Analyses were performed using GraphPad (GraphPad Software, 2013. *GraphPad Instat version 3.00 for Windows 95*. San Diego, California: www.graphpad.com).

19.3 Results

Baseline characteristics of patients included in this analysis are presented in Tables 17 and 18 (Chapter 18). In summary, the mean age was 70.4 years, and 70.4% of patients were male. 52/115 (45.2%) patients had at least one new DWI-positive lesion ipsilateral to the treated artery of post-procedure MRI.

Using an assumed diameter of 0.65cm, the mean length of stenosis was 1.35cm. 18/115 (15.7%) patients had an ulcerated lesion.

33.3% of patients with a Gröschel score of 0 had at least one new ipsilateral ischaemic brain lesion on the post-procedure MRI scan, 36.6% of those with a score of 1, 51.6% of those with a score of 2, 61.1% of those with a score of 3 and 75.% of those with a score of 4. The numbers of patients in each group and 95% confidence interval for the proportion with a new ischaemic lesion is presented in Table 23. The observed increase in patients with an increasing Gröschel score was statistically significant ($p=0.02$, χ^2 test for trend).

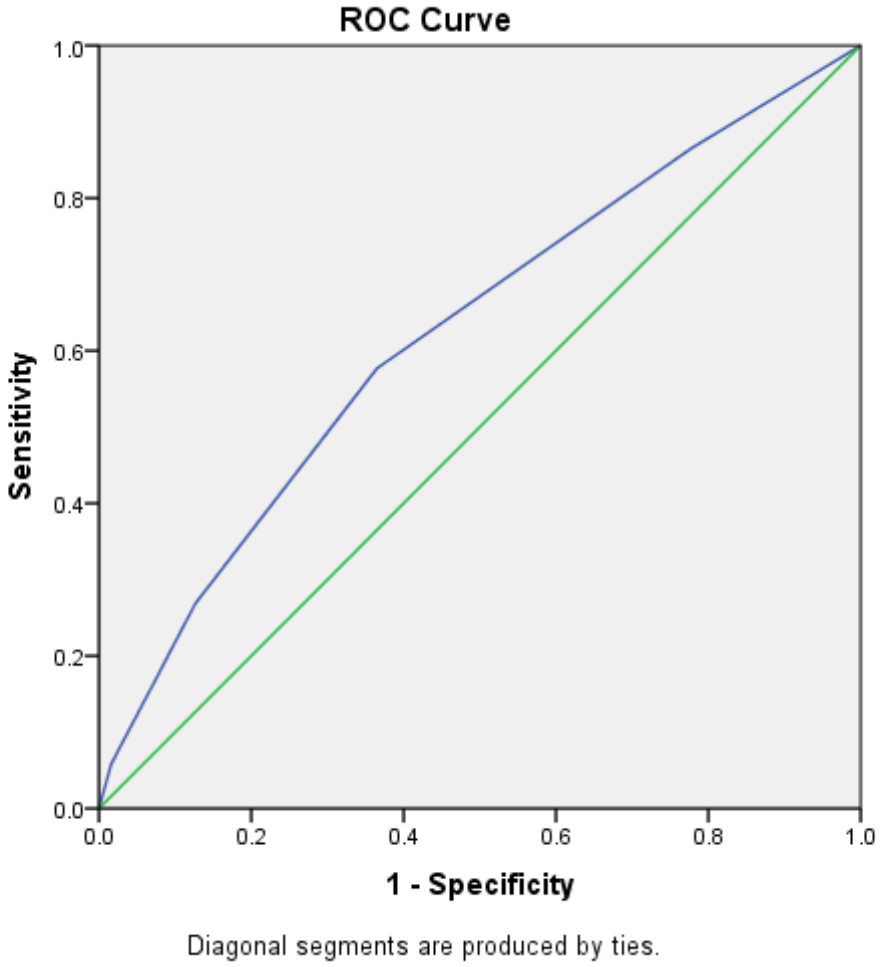
The receiver operator curve for the performance of the Gröschel risk score is presented in Figure 17 below. The area under the curve is 0.62 (95% CI 0.52 to 0.73, p=0.02).

Table 23. Results of application of the Gröschel (2008) risk score to 115 patients undergoing CAS in the ICSS-MRI Substudy

Gröschel Score	Number of patients with no new ipsilateral DWI-positive lesions following after CAS (n)	Number of patients with new ipsilateral DWI-positive lesions following CAS (n)	Proportion of patients with new ipsilateral DWI-positive lesions following CAS (%)	95% CI for proportion of patients with new ipsilateral DWI-positive lesions following CAS
0	14	7	33.3%	17.1% to 51.4%
1	26	15	36.6%	23.6% to 51.9%
2	15	16	51.6%	34.8% to 68.0%
3	7	11	61.1%	38.5% to 79.8%
4	1	3	75.0%	28.9% to 96.6%

χ^2 test for trend p=0.02

Figure 17. Receiver-operator curve for the application of the Gröschel (2008) risk score in 115 patients undergoing CAS in the ICSS-MRI Substudy



Darker line represents receiver operator curve

Straight line represents area under curve =0.5

19.4 Discussion and conclusions

19.4.1 Summary

45.2% of patients in the ICSS-MRI Substudy who were allocated to CAS, and in whom adequate baseline or pre-procedure catheter angiography was available, suffered at least one new ipsilateral ischaemic brain lesion on the post-procedure DWI-MRI scan. While the Gröschel score distinguished between lower-risk and higher-risk groups (χ^2 test for trend p=0.02), the sensitivity and specificity of the score in a receiver operator curve was limited (AUC 0.62, 95% CI 0.52 to 0.73, p=0.02).

19.4.2 Limitations

The length of stenosis as measured in our study is an approximation – calibration information was not contained in many digital angiograms, so to maintain consistency we use the diameter of the CCA to derive a calculated length. However, the diameter of the CCA has previously been found to vary by the side of the artery, sex, age, body surface area, blood pressure and neck length [142] and in fact may vary as much as 14% within individuals depending on the phase of the cardiac cycle during which it is imaged [219]. Patients randomized in the ICSS-MRI Substudy were required to be equally suitable for both CAS and CEA, and it is possible that patients with very long or ulcerated stenosis were excluded from randomization if interventionists thought them unsuitable for CAS because of a high anticipated procedural risk.

19.4.3 Discussion

The area under the receiver operator curve (AUC) in this analysis (0.62) compares unfavourably with the original performance of this score in the patient population from which it was derived, which was 0.71 (0.76 for patients treated after the year 2004 only, n=75) [208]. It should be noted that as the AUC corresponds to sensitivity and specificity cut-offs for discriminating between those with or without new ischaemic brain lesions, it does not necessarily indicate the level of clinical relevance [220]. The high proportion of patients suffering new lesions in the lowest risk group in the ICSS-MRI Substudy suggests that the Gröschel score is not sufficiently sensitive to be clinically useful in classifying patients at risk of MRI-detected ischaemic brain lesions after following CAS.

Chapter 18 illustrates that while age was a significant risk factor for the occurrence of new ischaemic lesions in the ICSS-MRI Substudy, ulceration and the length of the

target lesion appeared to have little influence. This finding suggests that the performance of the score in this patient cohort was mainly driven by the effect of age on the outcome. Therefore it is more likely that the key factor in the formation of new ischaemic brain lesions during the procedure is the ability of the brain to tolerate microemboli, rather than an increased risk of generation of debris during the procedure. Indeed, the clinical outcome of CAS also appears to be strongly influenced by the age of the patient, with a higher rate of stroke in this patient population [221] [222] [189] [116] [223]. Reduced physiological reserve to tolerate the procedure, medications and hospitalization, a higher burden of white matter disease with decreased cerebral reserve to tolerate emboli, or an association between ageing and anatomical features increasing the complexity of intervention [224] are all possible explanations for this effect.

As detailed in Chapter 18, inter-rater agreement for the detection of carotid plaque ulceration was limited in the ICSS-MRI Substudy, and other authors have reported little agreement between angiographic appearances and subsequent histology [202] [225]. However, it should also be noted that while lesion ulceration was not a strong predictor of subsequent brain ischaemia in the ICSS-MRI Substudy the risk of stroke without any revascularization procedure may be higher than in patients with smooth lesions. Patients enrolled in NASCET with a high degree of stenosis and an ulcerated lesion experienced an up to 73% risk of subsequent ipsilateral stroke within 24 months compared to a 21% risk in those patients without ulceration of the plaque [226]. Likewise, increasing age is a risk factor for stroke on medical therapy alone for symptomatic carotid stenosis [43]. Thus the Gröschel score tested in this chapter may give an indication of the risk of intervention, but it does not give an indication of the likely risks of stroke on medical treatment alone or the likely risk of CEA, and therefore is of limited use in selecting an overall treatment strategy in patients with greater than 50% symptomatic carotid stenosis.

19.4.4 Conclusions

Although there was an increase in the number of new ischaemic brain lesion on post-procedure MRI after CAS with increasing Gröschel score, this risk score did not exhibit adequate discrimination between low- and high-risk groups for routine clinical use, in part because 33.3% of the lowest-risk group still suffered at least one new ipsilateral ischaemic brain lesion on the post-procedure scan. Its routine use for selection of patients for CAS cannot be recommended without validation in further patient groups.

Age is a strong predictor of both clinical outcome and “silent” brain embolism, and should continue to be taken into account when selecting patients for carotid stenting.

20. Discussion, conclusions and future directions

20.1 Discussion of key findings

20.1.1 Carotid endarterectomy

This thesis presents several key findings regarding the safety of carotid endarterectomy. Most notably, women had around double the risk of the combined endpoint of stroke, myocardial infarction or death and nearly double the risk of the combined risk of any major complication (stroke, MI, CNP, haematoma or death) following CEA compared with men. That women might experience a greater operative risk has been described before [98], and this is of particular concern because of their lower risk of stroke on medical therapy alone – hence the observation in ECST that the number of patients needed to undergo surgery to prevent one ipsilateral stroke over 5 years was just nine in men against 36 for women [105]. Surgeons should carefully consider the risk-benefit calculation for revascularization in this patient group.

Although women experienced a higher risk of cranial nerve palsy in ICSS, the risk of persisting disabling CNP was around 1 in 1000, with most CNPs resolving within 30 days. The association between haematoma and CNP suggests that careful attention to haemostasis may reduce the latter's incidence. Although patients should be warned about possible symptoms of CNP, they can also be reassured of a generally good eventual outcome even when CNP does occur, and this complication should not dissuade surgeons from offering revascularization.

There is evidence that in the last few years the short-term risks associated with CEA may have fallen slightly [227]. The risk of surgery was acceptably low in ICSS – only 3.3% of patients in whom the allocated CEA procedure was initiated suffered a stroke within 30 days of the procedure – and the only independent predictor of the risk of complications was baseline diastolic blood pressure. Attention to blood pressure in symptomatic patients undergoing revascularization might reduce subsequent complications, but this should be managed in the clinical context with particular care in patients who have contralateral carotid stenosis or vertebral artery stenosis.

It is not surprising that risk scores derived from other patient populations did not adequately discriminate between low- and high-risk groups of ICSS patients given the lack of strong predictors of risk. Nonetheless, most published surgical risk scores have

not previously been validated, so to be of use in clinical decision-making they should be tested in other patient cohorts or updated.

20.1.2 Carotid stenting

This thesis identifies advancing age as a risk factor for complications following CAS, but not for CEA, in agreement with individual patient meta-analysis across the European trials of CAS vs CEA which suggested that CAS was as safe as CEA in younger patients [115].

The finding that cerebral protection devices – mostly distal filters – offered no statistically significant protection from stroke, myocardial infarction or death or the occurrence of new ischaemic brain lesions following CAS in ICSS is disappointing, but concurs with the results of other randomized comparisons [196] [197]. At best the benefit of their deployment in CAS is unproven, and cannot be recommended as routine. Similarly, results were disappointing in those patients treated using an open-cell stent and the findings in this thesis favour the use of a closed-cell stent.

Inexperienced CAS interventionists are sometimes advised to avoid undertaking stenting in patients with “challenging” vascular anatomy [123] thought to make the procedure more technically difficult. In Chapter 18, this thesis argues that the influence of patient characteristics, such as age, male sex and hypertension, exert a greater influence on the number of new post-procedure ischaemic lesions as measured on MRI brain, although patients with a left-sided stenosis experience approximately double the number of new lesions. While an important observation, it must be kept in mind that patients with lesions thought “unsuitable” for stenting were excluded from randomization in ICSS, and that more inexperienced operators who performed trial procedures were supervised. Indeed, patients treated in supervised centres in ICSS experienced a lower risk of stroke, MI or death following CAS [82].

20.2 Conclusions

The case for offering carotid revascularization in suitable patients with ≥50% symptomatic carotid stenosis due to atherosclerosis, who would otherwise experience a high risk of recurrent stroke on medical therapy alone, is clear. Some groups of patients, however, at are increased risk from intervention. In isolation, the subgroup analyses presented in this thesis should be interpreted with caution. Yet combined with data from individual patient meta-analysis of the European trials of CAS vs CEA, and risk modelling data from the original NASCET and ECST trials of carotid surgery versus

medical therapy, there is evidence from the work presented in this thesis that in the short term stenting is more hazardous in the elderly, that the routine use of filter-type cerebral protection devices in CAS is not supported by high-quality evidence, that closed-cell stents are safer than open and that women should be informed of a potentially small increased risk of stroke, MI, cranial nerve palsy, haematoma or death following endarterectomy.

What is not addressed in these analyses is whether the overall benefits of intervention extend to lower-risk patients, and it is this question that is the subject of ongoing research.

20.3 Future directions – who should have what treatment?

20.3.1 Revisiting the case for intervention

The standard of care for clinically stable patients with greater than 50% symptomatic carotid stenosis has been to perform carotid endarterectomy (in preference to carotid stenting in low-risk patients) to remove the symptomatic plaque and thus reduce the long-term risk of recurrent stroke or TIA [128] [153] [130]. However, since the landmark large randomized trials of CEA vs medical therapy, NASCET and ECST, there have been a number of developments in care that call into question the benefit of intervention in all patients with this degree of stenosis. This thesis has explored the subject of which patients are at risk of complications from CEA or CAS, but in order to select patients who will benefit in the long-term from revascularization it is necessary to consider their risk of stroke without intervention as well.

Medical therapy for secondary prevention of stroke has changed. Previous trials of CAS or CEA for carotid stenosis did not specify targets for control of vascular risk factors, but numerous guidelines now exist for primary and secondary prevention therapy [228] [229] [230] [231]. Cholesterol-lowering statins were not available during recruitment into NASCET, but their use in secondary prevention for stroke is now widespread in the knowledge that they reduce the risk of stroke in patients with carotid disease [232] [233].

The pathology of symptomatic carotid plaque is well-described. An inflamed plaque with macrophage infiltration, fresh thrombus, a large lipid core and rupture of the fibrous plaque are all histological features associated with stroke (as opposed to TIA or amaurosis fugax) [234]. Catheter angiography, the method used to determine the degree of stenosis for entry to the NASCET and ECST trials, has fallen out of common

use as newer less invasive imaging techniques have been developed – ultrasound, CT and MR angiography and advanced plaque imaging with MRI or 3D ultrasound. The degree of stenosis on its own is currently used in the selection of patients to undergo revascularization and is one potential marker of plaque instability – larger plaques causing higher degrees of stenosis are more likely to cause symptoms due to a more unstable plaque composition with less fibrous tissue. The ability to directly image plaque components associated with high stroke risk such as a lipid-rich core [235] [236], ulceration, thin or ruptured fibrous cap [235] [236] or intra-plaque haemorrhage [235] [237] [236] with MRI is beginning to change the way patients are risk stratified and may blur the line between asymptomatic and symptomatic patients when selecting patients for revascularization based on their risk of stroke. Work is underway, for example, in the Plaque At Risk (PARISK) study to enrol 300 patients with <70% recently-symptomatic carotid stenosis, who are not scheduled to undergo carotid endarterectomy. These patients will undergo detailed MR, CT and US of the carotid arteries to determine which plaque characteristics confer a high risk of recurrent stroke [238].

20.3.2 The risks of intervention

Detailed plaque imaging may similarly give clues as to the risk of the revascularization procedure itself. Echolucent plaques on ultrasound – unstable, lipid-rich or haemorrhagic plaques more likely to cause neurological symptoms untreated have been shown to increase the risk of carotid stenting, perhaps through the dislodgement of adherent thrombus during the passage of endovascular equipment across the lesion [239]. Ongoing randomized trials with a carotid intervention arm such as ECST-2, described below, are incorporating detailed modern carotid imaging into their baseline assessment of patients and will use detailed post-procedure MRI to examine the occurrence of procedural brain ischaemia, opening up the possibility of further characterising the risk of intervention based on radiological plaque appearance.

Collaborative work continues to establish the determinants of the risks of intervention, pooling individual patient data from the European trials of carotid stenting and surgery through the Carotid Stenting Trialists' Collaboration [240]. This larger dataset, which includes data from patients enrolled in ICSS, has examined the effect of baseline patient characteristics on procedural risk as described in Chapters 14 and 17, and has recently published an analysis of the effect of operator experience on the outcome of carotid stenting, demonstrating a more favourable outcome in those interventionists that performed more than five procedures per year within the trials [126].

20.3.3 Ongoing clinical trials

The second European Carotid Surgery Trial (ECST-2) [172], designed by many of the trialists involved in ICSS, intends to answer some of these questions about how best to treat patients with carotid stenosis. It is a prospective randomized trial of patients with low-to-intermediate risk carotid stenosis ≥50%, enrolling those with asymptomatic plaques and recently-symptomatic patients whose calculated risk of ipsilateral stroke is less than 15% over 5 years. The Carotid Artery Risk Score used to calculate risk is adapted from an algorithm designed at Oxford University taking into account age, sex, the degree of stenosis, the nature of any symptomatic event and how recently it occurred, vascular risk factors and plaque morphology [241]. Patients in a medical therapy group will receive "optimized medical therapy" (OMT) – antiplatelet therapy, target-led control of cholesterol level and blood pressure – while an intervention group will receive OMT plus revascularization. The trial tests the hypothesis that patients with a low predicted stroke risk on OMT alone will not benefit from revascularization due to periprocedural complications.

SPACE-2 (Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis versus Endarterectomy Trial-2) [173] was originally designed as a randomized trial for patients with asymptomatic carotid stenosis ≥70% as measured by ultrasound. Its protocol called for a recruitment target of 3640 patients in three arms: best medical treatment, CEA in addition to best medical treatment, and CAS in addition to best medical treatment. The trial investigators recently redesigned the SPACE-2 protocol such that now patients are enrolled into SPACE-2a comparing best medical treatment with CAS in addition to best medical treatment, and SPACE-2b comparing best medical treatment with CEA in addition to best medical treatment [242]. Interestingly, CREST-2 (the second Carotid Revascularization Endarterectomy versus Stenting Trial) has a similar design and inclusion criteria to the new SPACE-2 protocol, in that neither trial directly compares CAS with CEA. This role is taken by the second Asymptomatic Carotid Surgery Trial (ACST-2) [174], which aims to compare the safety and efficacy of CAS with CEA in 5000 patients with asymptomatic carotid stenosis who are "though to need some procedural intervention" to prevent future stroke [243]. Recently-published interim results from this study indicate that the risk of stroke, myocardial infarction or death within 30 days of either procedure was low at 1.0% in 691 patients [174].

When clinicians are uncertain about which treatment will provide the greatest benefit to the patient in return for an acceptably low risk of harm, it is appropriate to discuss with them enrolment in a clinical trial. Patients can benefit from inclusion in randomized

clinical trials, even when allocated to the control therapy – close attention to control of vascular risk factors and frequent follow-up may improve management of the patient's condition over and above routine clinical care. Almost all patients with low-risk carotid stenosis can therefore be enrolled in one of the above trials, provided they can be treated at a participating centre. Patients with low-risk symptomatic carotid stenosis could be suitable for enrolment in ECST-2. When the medical team are uncertain as to whether intervention is warranted in an asymptomatic patient they may enrol in ECST-2, SPACE-2 or CREST-2. And when intervention is thought necessary in asymptomatic patients, ACST-2 compares CAS with CEA for the long-term primary prevention of stroke.

When the pace of change in stroke prevention is fast, there is a need for good-quality evidence from randomized clinical trials to inform decision making from the individual patient level up to the design of healthcare systems. If these four trials can recruit their target numbers and report definitive results, then we may be some way further to answering the question of "who should receive what treatment" for carotid stenosis.

21. Bibliography

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22. Appendix I – ICSS post-treatment care questionnaire

ICSS Questionnaire: Post-treatment care

Please complete the following questionnaire about the type of care a non-disabled patient enrolled in ICSS would receive after uncomplicated treatment. Please tick the type of ward patients are referred to immediately after treatment and fill in the average length of time that the patient will normally stay there. There are 2 columns for each treatment to describe the ward the patient goes to on the day of treatment (e.g. intensive care) and the ward they go to when they leave the first ward (e.g. when they leave intensive care).

Please fill in your name and ICSS centre: Name: _____

Centre : _____ ICSS centre Nr.: _____

Patient care after uncomplicated carotid stenting:					
Ward care immediately after treatment			*The next ward after the ward on the left is:*		
Type of ward (please tick)	Usual duration		Type of ward (please tick)	Usual duration	
	days	hours		days	hours
☐ **Intensive Care or specialised post-interventional care unit**			☐ **Any other type of hospital ward* State what type:**		
☐ **Any other type of hospital ward* State what type:**			☐ **Discharged home from first ward**		
☐ **Directly discharged home**					

Patient care after uncomplicated carotid endarterectomy:					
Ward care immediately after treatment			*The next ward after the ward on the left is:*		
Type of ward (please tick)	Usual duration		Type of ward (please tick)	Usual duration	
	days	hours		days	hours
☐ **Intensive Care or specialised post-interventional care unit**			☐ **Any other type of hospital ward* State what type:**		
☐ **Any other type of hospital ward* State what type:**			☐ **Discharged home from first ward**		
☐ **Directly discharged home**					

***NB Please state what type of hospital ward e.g. neurology or vascular surgery, where relevant**

Comments:

PLEASE POST OR FAX THIS FORM TO THE ICSS OFFICE.
Fax 020 7837 9632 (+44 20 7837 9632 outside UK)
ICSS Office, Stroke Research Group, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK

23. Appendix II – ICSS cranial nerve palsy questionnaire

ICSS Cranial Nerve Palsy Questionnaire

Centre ID:															
ICSS trial number:															
Patient date of birth (dd/mm/yyyy):															
Date of carotid endarterectomy (dd/mm/yyyy):															
Date of cranial nerve palsy (dd/mm/yyyy):															
Date of completion of this questionnaire (dd/mm/yyyy):															
Name of person completing this questionnaire:															
Which cranial nerves were affected? (*delete as appropriate*)	Vagal	Yes / No													
	Hypoglossal	Yes / No													
	Glossopharyngeal	Yes / No													
	Accessory	Yes / No													
	Facial	Yes / No													
Are details of the cranial nerve palsy documented in the clinical notes? (*delete as appropriate*) *	Yes / No														
What symptoms were recorded as a result of cranial nerve palsy? (*see aide memoire for suggestions*)															
What neurological signs were recorded as a result of cranial nerve palsy? (*see aide memoire for suggestions*)															
What functional consequences occurred as a result of the cranial nerve palsy (*e.g. patient had to have a nasogastric tube*)															
How long did the cranial nerve palsy last? *			days			weeks			months						
Was hospital discharge delayed by cranial nerve palsy? (*delete as appropriate*)	Yes / No														
If so, please estimate by how long:			days			weeks			months						
Did the patient receive investigation for cranial nerve palsy? (*delete as appropriate*)	Yes / No														
If yes, what investigation?															
What date was this carried out? (dd/mm/yyyy):															
Did the patient receive treatment for cranial nerve palsy?	Yes / No														
If yes, what treatment?															
What date was this carried out? (dd/mm/yyyy):															

*** If CNP not documented or date of resolution is unknown please contact the patient, if alive, to see if they can answer the questions that follow**

ICSS Cranial Nerve Palsy - *Aide Memoire*

Clinical symptoms of cranial nerve palsy

Vagal	Change in voice / hoarseness of voice
	Difficulty swallowing
	Choking / cough
Hypoglossal	Problems with tongue / clumsiness
	Difficulty swallowing
Glossopharyngeal	Difficulty swallowing
Accessory	Shoulder droop
	Winged scapula
Facial	Uplifting of the mouth on one side
	Facial droop

Any other comments regarding this patient's cranial nerve palsy?

24. Appendix III – List of ICSS centres and investigators

Location of ICSS recruiting centres, number of patients recruited at each centre in square brackets, and collaborators at each centre (PI) = local principal investigator [82].

24.1.1 Australia

Austin Health, Heidelberg [46]: M Brooks, B Chambers (PI), A Chan, P Chu, D Clark, H Dewey, G Donnan, G Fell, M Hoare, M Molan, A Roberts, N Roberts

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Monash Medical Centre, Clayton [26]: R Bell, S Bower, W Chong, M Holt, A Saunder, PG Than (PI)

Princess Alexandra Hospital, Brisbane [48]: S Gett, D Leggett, T McGahan (PI), J Quinn, M Ray, A Wong, P Woodruff

Repatriation General Hospital, Daw Park, Adelaide [6]: R Foreman, D Schultz (PI), R Scroop, B Stanley

Royal Melbourne Hospital, Melbourne [57]: B Allard, N Atkinson, W Cambell, S Davies (PI), P Field, P Milne, P Mitchell, B Tress, B Yan

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AZ St Blasius, Dendermonde [5]: M Bosiers (PI), K Deloose, E van Buggenhout

AZ Sint Jan Brugge-Oostende, Campus Brugge, Brugges [18]: J De Letter, V Devos, J Ghekiere, G Vanhooren (PI).

Cliniques Universitaires St Luc, Bruxelles [1]: P Astarci, F Hammer, V Lacroix, A Peeters (PI), R Verhelst

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Liverpool Royal Infirmary [21] **and The Walton Centre**, Liverpool [7]: JA Brennan, TP Enevoldson, G Gilling-Smith (PI), DA Gould, PL Harris, RG McWilliams, H-C Nasser, R White

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25. Appendix IV – ICSS trial protocol

25.1 Protocol summary

25.1.1 Background

Clinical trials have shown that carotid surgery prevents stroke but also has significant morbidity. Stenting has become an established alternative treatment for coronary and peripheral vascular disease and has the advantage of avoiding general anaesthesia and neck incision. In July 1997, randomization was completed in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). The results did not show a difference in the major risks or benefits of carotid angioplasty and surgery, but the trial did show that both methods still carry a significant risk of causing a stroke. Techniques of carotid angioplasty have improved and stenting is increasingly used. The International Carotid Stenting Study (ICSS or CAVATAS 2) is a follow-on study to CAVATAS designed as an international, multicentre, randomized trial, which will evaluate stenting of carotid artery stenosis in patients with cerebrovascular disease.

25.1.2 Centre requirements

A neurologist or physician with an interest in stoke, a surgeon with expertise in carotid endarterectomy and an interventionalist with expertise in carotid angiography and the techniques of angioplasty and stenting.

25.1.3 Inclusion criteria

Symptomatic atheromatous carotid stenosis, >50% by NASCET criteria, suitable for stenting and surgical endarterectomy.

25.1.4 Treatments

Patients will be randomised in equal proportions to be treated by carotid endarterectomy or stenting. New designs of stents, filters and protection devices will be incorporated into the study to allow tracking of new technology if approved by the Steering Committee. Surgery can be performed with local or general anaesthesia.

25.1.5 Sample size

N=1500 patients from fully enrolled centres. Sample size calculations show that the 95% confidence intervals will be ±3.0 percentage points for the outcome measure of 30 day stroke, myocardial infarction and death rate and ±3.3 percentage points for the outcome measure of death or disabling stroke during follow-up.

25.1.6 Primary outcome measure

- Long term survival free of disabling stroke

25.1.7 Secondary outcome measures

- Any stroke, myocardial infarction or death within 30 days of treatment, treatment-related cranial nerve palsy or haematoma
- Stenosis (>70%) and occlusion on ultrasound follow-up
- Transient ischaemic attack
- Stroke during follow-up
- Further treatment procedure
- Quality of life and economic measures

25.2 Background

Stroke is the major cause of acquired adult physical disability and is responsible for 12% of all deaths in the UK. Reducing the burden of stroke is one of the priorities of the recent government white paper*, Saving Lives: Our Healthier Nation*. In Europe alone, there are approximately one million new cases of stroke a year. Atherosclerotic stenosis of the carotid artery is an important cause of stroke, which may be heralded by a transient ischaemic attack (TIA) or minor stroke, which recovers without serious disability. The risk of recurrent stroke in recently symptomatic patients with severe carotid stenosis is as high as 28% over two years. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) have demonstrated convincingly that this risk is reduced significantly by carotid endarterectomy [36] [35]. Carotid surgery has therefore become a standard treatment for these patients. However, the trials showed a significant risk of stroke or death resulting from surgery of between 6 and 8%. Surgery also caused significant morbidity from myocardial infarction during the general anaesthetic used in most centres, and minor morbidity, including cranial nerve palsy and wound haematoma, from the

incision. An increasing number of surgeons are performing carotid endarterectomy under local anaesthesia in the belief that it reduces the risks, although there is currently little evidence to support this practice, until the data from the General Anaesthesia versus Local Anaesthesia for Carotid Endarterectomy (GALA) trial are reported.

Stenting is a new method of treating carotid stenosis which has evolved from the technique of percutaneous transluminal angioplasty (PTA). Stenting avoids some of the hazards of surgery and has become an established treatment for peripheral and coronary artery stenosis. Stenting is less invasive than carotid endarterectomy and has advantages in terms of patient comfort, because the procedure avoids an incision in the neck, and is usually conducted under local anaesthesia. Hospital stay need only be for 24 hours after treatment if uncomplicated. When given the choice, stenting is preferred by many patients. On the other hand, stenting does not remove atheromatous plaque, has not been shown to prevent stroke and may have an unacceptable incidence of restenosis. We therefore propose a multicentre randomised trial to compare carotid stenting with carotid surgery.

25.2.1 Previous work in the field

Percutaneous transluminal angioplasty

A number of groups have published series of patients with carotid stenosis treated by PTA. The cumulative total of patients in these series is over 1000, with a reported major complication rate of less than 5% at the time of the procedure [244]. These data suggested that carotid PTA has a similar risk to carotid surgery, but the results could not be taken as definitive because none of the data were from randomised trials. We therefore started a randomised trial, known as the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) in l992. We completed randomisation in July 1997.

Results of CAVATAS

560 patients were entered, from 24 centres in the UK, Australia, Canada, Finland, Germany, Italy, Spain, Switzerland, and the USA. Patients with carotid stenosis suitable for surgery were randomised between PTA (n=251) and carotid surgery (n=253). Patients with carotid stenosis unsuitable for surgery (n=40) and patients with vertebral artery stenosis (n=16) were separately randomised between PTA and medical care alone. The number of patients in these last 2 groups was too small to form any firm conclusions. The analysis has therefore been restricted to the 504

patients with carotid stenosis randomised between PTA and surgery [75]. Baseline variables were well matched. Almost all patients had severe stenosis (mean 86%). The 30-day outcome events were almost identical in the two groups with a rate of death or any stroke lasting more than 7 days of 10.0% after angioplasty and 9.9% after surgery, giving a hazard ratio of 1.01 (95% CI 0.56 to 1.81, p=NS). Analysis of the other risks of treatment has confirmed that PTA was safer than surgery in terms of minor morbidity. Cranial or peripheral nerve palsy was reported in 9% of surgical patients, but not in any PTA patients (p<0.01). Haematoma requiring operation or prolonging hospital stay was reported in 7% of surgical patients compared with 1% of PTA patients (p<0.01). PTA also appeared safer than surgery with regard to perioperative myocardial infarction, which occurred in 0.8% of surgical patients, but not in any PTA patients. Survival analysis from randomisation showed no difference in outcome events of ipsilateral stroke and any disabling stroke or death during follow up for up to 3 years with very few events in either arm after the treatment period, suggesting that both treatments were equally effective at preventing stroke. However, 19% of PTA patients had stenosis of >70% or occlusion by ultrasound criteria at 12 months after randomisation compared with 5% of surgical patients (p<0.01). Restenosis was not associated with new symptoms, but long-term follow up is limited.

Causes and timing of stroke in CAVATAS

The cause of stroke within 30 days of first treatment in CAVATAS was cerebral infarction in 22 patients in the PTA group and 20 patients in the surgery group. Primary cerebral haemorrhage caused the other three strokes in the PTA group and two strokes in the surgery group. All but one stroke was ipsilateral to the randomised artery. Surprisingly, a significant proportion of these treatment-related strokes were delayed after the day of treatment. Eight (36%) of the strokes in PTA patients occurred between the second and 21st day after treatment. Delayed stroke was also found in six (27%) of the surgical group between the third and 10th day after operation. Delayed stroke may account for the relatively high rate of 30-day morbidity in CAVATAS at 10% compared to 7.5% in ECST and 5.8% in NASCET.

Carotid stenting

Stents suitable for carotid use have only become available recently. The CAVATAS Steering Committee decided to allow the use of stents at the discretion of the interventionist. Stents were used in 55 patients randomised to PTA, usually as a secondary procedure i.e. after initial balloon dilation. The indication for using a stent in

these cases was usually an inadequate angiographic result and in some cases stents were deployed because of stroke at the time of full balloon inflation, as a 'bail-out' procedure. Only one stroke occurred at the time of stent deployment (1.8%), although there were a small number of delayed strokes after stenting.

The need for a trial of carotid stenting

It would be inappropriate to use the results of CAVATAS to propose the widespread introduction of PTA for the treatment of carotid stenosis as an alternative to surgery, because the 95% confidence interval surrounding the 10% risk of any stroke within 30 days of treatment in the surgical and angioplasty groups is ±5%. Nevertheless, the results support the need for further randomised studies. The interventional technique used to treat carotid stenosis has evolved over the 7 years since we started CAVATAS, from the use of simple inflatable balloon catheters at the beginning of the trial to the increasing use of stenting towards the end of the trial. Initially stents were used only as a secondary procedure after full balloon inflation for inadequate results or complications of treatment. The desire to prevent these complications and superior early results in stented patients has led to the increasing use of the technique of primary stenting in which the intention is to deploy a stent in every patient before dilation (but after pre-dilatation to allow the atraumatic passage of the stent) of the artery [245]. Primary stenting is now accepted as best practice and has become the radiological technique of choice for carotid stenosis, replacing balloon angioplasty.

Advantages of carotid stenting

The majority of major strokes after carotid PTA are the result of dissection of the carotid artery at the time of balloon inflation with subsequent thrombosis. It is believed that stenting is safer than simple balloon angioplasty because embolisation, dissection and closure of the carotid artery are less likely to occur [246] [247]. The subgroup analysis of stented patients in CAVATAS is consistent with this suggestion. The adverse consequences of dissection are minimised, because the stent maintains laminar flow across the stenosis and seals the site of dissection, preventing a free intimal flap. In addition, the stent mesh limits the size of any thrombus or atheromatous debris that may be dislodged from the plaque at the time of dilation of the artery. Superior dilation achieved by stenting compared with balloon angioplasty may also reduce the rate of stroke in the early post-treatment period. In the coronary circulation, stenting has been shown to produce superior outcomes compared with balloon angioplasty [248] [249]. Individual case series suggest that carotid stenting has a

similar rate of procedural stroke to that of carotid surgery [246] [247], while a recent registry reported a total of 2048 patients from 24 centres undergoing carotid stenting with a complication rate of stroke and death within 30 days of treatment of 5.8% [250].

Disadvantages of carotid stenting

Although acceptable safety at the time of stenting has been suggested by the case series and registry data, stenting has not been subjected to a randomised trial in comparison to conventional surgical treatment and has not been demonstrated to prevent stroke, which is the aim of treatment. Stenting does not remove atheromatous plaque and stents may stimulate neo-intimal hyperplasia. In the long term it is likely that the rate of restenosis will be greater after stenting than after carotid surgery, which could well result in an unacceptable rate of long-term stroke recurrence. There is an important need to establish the efficacy of carotid stenting in comparison to surgery before the technique is widely introduced without adequate trial based evidence.

Antiplatelet therapy

In cardiological practice, ischaemic complications during coronary stenting have been shown to be significantly reduced by using a combination of two antiplatelet agents, ticlopidine and aspirin. In one coronary trial, stent thrombosis was reduced from 3.6% in patients assigned aspirin alone down to 0.5% in patients assigned aspirin and ticlopidine [251]. A recently completed trial has shown that similar results with less risk of side effects can be achieved during coronary stenting by using the combination of clopidogrel with aspirin [252]. It is likely that this combination would also reduce the risks of stroke during carotid stenting. A pilot study is currently being carried out at one of the centres to establish the safety of the combination of clopidogrel and aspirin given before and for 30 days after carotid stenting. It is likely that this will become standard therapy. Most surgeons currently believe that combination antiplatelet therapy during surgery is hazardous because of excess bleeding.

Economic and quality of life considerations

Quality of life and general health status were assessed in CAVATAS using the SF36 and EuroQol EQ-5D questionnaires. These showed a similar quality of life for patients randomised to either treatment. Operating and radiology suite costs were similar in a sample of patients at two UK centres, but surgery was associated with a longer hospital stay and greater use of ITU beds. Surgery was therefore considerably more expensive than angioplasty (mean difference £946). However, the mean cost of an angioplasty

increased from £1086 to £1864 if a stent was used. The use of stents in every case is therefore likely to increase the costs of stenting close to that of surgery, but this might be counterbalanced by performing carotid stenting as a day case procedure. Surgical length of stay is also declining. Follow up costs might be very different if restenosis is more frequent in one arm. Economic analysis will therefore be an important component of ICSS.

25.2.2 Aims of ICSS

To compare the risks, benefits and cost effectiveness of a treatment policy of referral for carotid stenting compared with referral for carotid surgery.

25.3 Trial design

ICSS is an international, multicentre, randomised, controlled, open, prospective clinical trial comparing carotid surgery with carotid stenting.

25.3.1 Participating centre requirements

Each centre must have a neurologist or physician with an interest in stroke who will see patients prior to randomisation and for follow up. Carotid endarterectomy must be carried out by designated surgeons with expertise in the operation. Carotid stenting will be carried out by designated consultant interventionists with expertise in carotid angiography and the techniques of angioplasty and stenting. Good collaboration between the neurologists, surgeons and interventionists is essential and centres should have regular neurovascular meetings. Attendance at training sessions in carotid stenting provided by credentialing centres will be required for all interventionists prior to participation. Participating centres will be required to submit *curriculum vitae* for all participating clinicians and an audit of recent carotid surgery and PTA / stenting results. An accreditation committee will decide if they have appropriate experience and expertise to join the study. As a guide, surgeons and interventionists will be expected to show a stroke and death rate within 30 days of treatment, consistent with the centres in ECST who had an average rate of 7.0% with a 95% confidence interval of 5.8 to 8.3% [36]. Surgeons will be expected to have performed a minimum of 50 carotid operations with a minimum annual rate of at least 10 cases per year. Interventionists will similarly be expected to have performed a minimum of 50 stenting procedures, of which at least 10 should be in the carotid territory. Centres where there is little or no experience of carotid stenting may join ICSS for a probationary period in order to gain the minimum experience of ten carotid stenting procedures required to join the trial

fully. The results in patients randomised during the probationary period will be analysed separately.

All centres will have to provide proof of ethical committee approval for the study before commencing randomisation.

25.3.2 Probationary centres

Probationary centres will be required to fulfil all the other requirements for entry, but will not have to provide audited data on ten carotid stenting procedures initially. Probationary centres will randomise patients within the ICSS protocol between surgery and stenting. Individual interventionists who are not able to satisfy the credentialing requirements will be identified as probationary investigators. Stenting procedures carried out during the probationary period must be proctored by an experienced carotid interventionist, until the proctor is satisfied that the interventionist(s) at the centre can satisfactorily carry out procedures unproctored. Probationary interventionists will become fully enrolled in ICSS when both the proctor is satisfied that the interventionist can perform procedures unsupervised and the interventionist has 10 or more successfully completed cases in the trial, with an acceptable complication rate. When an investigator has done sufficient successful procedures, the trial office will get comments from the relevant proctor, and then have any decision to promote the investigator or centre signed off by the chair of steering committee.

25.3.3 Proctoring

Proctors for probationary centres will be approved by the accreditation committee in consultation with the probationary centre via the central ICSS office. Probationary centres may suggest an appropriate proctor, but he or she will require prior approval from the accreditation committee, based on review of the proctor's experience of carotid stenting. It is the responsibility of the probationary interventionist to make contact with an approved ICSS proctor and to ensure a convenient date is organised for the stenting procedure at which the proctor can be present. Copies of the relevant radiology should be available for the proctor for review prior to starting the stenting procedure. This should be done prior to randomisation if there was any doubt about the suitability of the patient for stenting. In the event of a centre requiring proctoring for surgery the same procedure will apply.

It is the responsibility of the probationary interventionist and the proctor in discussion to ensure the lesion is appropriate for treatment (e.g. sufficiently severe), that the patient

has received appropriate premedication (e.g. a combination of clopidogrel and aspirin) and that the lesion is suitable for stenting. They should agree the type, range and sizes of equipment required and the probationary interventionist should ensure that this equipment is available to complete the procedure. If any of these conditions are not met, the procedure should be abandoned and if appropriate rescheduled for another occasion.

Catheter or arch angiography is not required in ICSS prior to randomisation if the centre does not routinely perform angiography prior to treatment. However, the centre interventionist, the proctor and the patient should be aware that if preliminary angiography at the time of planned stenting shows a lesion which is not suitable for stenting, the procedure should be abandoned and the patient referred for surgery, or continued medical management. This type of cross over is envisaged in the trial design.

Where a centre has an adequately qualified surgeon and interventionist they may supervise surgeons and interventionists at the same centre whose experience would not initially qualify them for the trial until they have gained sufficient experience. These new investigators must enrol with the central ICSS office (see participating centre requirements).

25.3.4 Inclusion criteria

- Symptomatic extracranial, internal or bifurcation atheromatous carotid artery stenosis that is suitable for both stenting and surgery and is deemed by the randomising clinician to require treatment
- The severity of the stenosis of the randomised artery should be at least 50% (as measured by NASCET method or non-invasive equivalent)
- Symptoms must have occurred in the 12 months before randomisation. It is recommended that the time between symptoms and randomisation should be less than 6 months, but patients with symptoms occurring between 6 and 12 months may be included if the randomising physician considers treatment indicated
- The patient must be clinically stable following their most recent symptoms attributable to the stenotic vessel
- Patients must be willing to have either treatment, be able to provide informed consent, and be willing to participate in follow up

- Patients must be able to undergo their allocated treatment as soon as possible after randomisation
- Any age greater than 40 may be included. There is no upper age limit
- Patients should only be randomised if the investigator is uncertain which of the two treatments is best for that patient at that time

25.3.5 Exclusion criteria

- Patients refusing either treatment
- Patients unable or unwilling to give informed consent
- Patients unwilling or unable to participate in follow up for whatever reason
- Patients who have had a major stroke with no useful recovery of function within the territory of the treatable artery
- Patients with a stenosis that is known to be unsuitable for stenting prior to randomisation because of one or more of:
    - Tortuous anatomy proximal or distal to the stenosis
    - Presence of visible thrombus
    - Proximal common carotid artery stenotic disease
    - Pseudoocclusion (‘string sign’)
    - Patients not suitable for surgery due to anatomical factors e.g. high stenosis, rigid neck
- Patients in whom it is planned to carry out coronary artery bypass grafting or other major surgery within 1 month of carotid stenting or endarterectomy
- Carotid stenosis caused by non-atherosclerotic disease e.g. dissection, fibromuscular disease or neck radiotherapy.
- Previous carotid endarterectomy or stenting in the randomised artery
- Patients in whom common carotid artery surgery is planned
- Patients medically not fit for surgery
- Patients who have a life expectancy of less than two years due to a pre-existing condition, e.g. cancer

25.3.6 Non-randomised patients

An anonymised log will be kept of patients undergoing treatment for carotid stenosis by the trial investigators but not randomised at the participating centres. Patients undergoing stenting but not randomised should also be included on a suitable registry, such as EUROCAST.

25.3.7 Consent

Written witnessed, informed consent will be obtained from all patients and a copy must be retained by the randomising centre. All patients will be provided with a written explanation of the study.

25.3.8 Randomisation

Randomisation will be by a telephone call or fax to a computerised service provided by the Oxford Clinical Trials Service Unit. Randomisation will be stratified by centre with minimisation of the main risk factors and balanced between the arms. Patients who need treatment of both carotid arteries will only be randomised for the carotid artery to be treated first. Patients can only be randomised once.

25.3.9 Investigations before randomisation

The following investigations are required: Routine haematology (FBC, platelets), blood biochemistry (renal function, blood sugar, cholesterol), chest x-ray, ECG, brain CT or MRI scans. The brain scan is required to exclude other pathology, to identify existing infarcts and to provide a baseline reference against which any subsequent infarction or haemorrhage can be assessed. Copies of the CT or MRI scans should be sent to the ICSS office.

25.3.10 Carotid imaging

Mandatory investigation is required for entry into the study to confirm the presence and severity of the ipsilateral stenosis and to assess contralateral carotid disease. The following are acceptable:

- Arch arteriogram showing both carotid bifurcations
- Selective catheter carotid angiography showing the randomised carotid artery with non-invasive investigation of the contralateral carotid bifurcation
- Bilateral magnetic resonance carotid angiograms together with a concordant ultrasound scan
- Bilateral spiral CT angiograms together with a concordant ultrasound scan
- Bilateral duplex and Doppler ultrasound scan, only if this is standard practice to treat on the basis of ultrasound alone in individual centres and the centre has

been able to provide proof of the reliability of their ultrasonographic imaging through clinical audit

The following data from the pre-randomisation imaging will be sent to the Central Office for review:

- A copy of the written reports of the studies
- A film copy of the view of the vessel to be treated showing the stenosis at its most severe
- A film copy of the view of the contralateral vessel showing any stenosis at its most severe
- Velocity data from the ultrasound examination

Patients who are randomised to stenting after ultrasound or other non-invasive investigation, in which subsequent angiography, prior to stenting, reveals one or more exclusion criteria should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be analysed on an intention to treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation.

25.3.11 Ultrasound

Ultrasound study of the carotid artery to be treated will be performed at or before randomisation, at one month after treatment and then annually after randomisation in all patients. The following information is required for each study: Peak systolic velocity of internal carotid artery (PSV ICA), end diastolic velocity of internal carotid artery (EDV ICA), peak systolic velocity of common carotid artery (PSV CCA). The accuracy of individual ultrasound laboratories will be audited by comparing the pretreatment ultrasound examination against catheter angiography films, which will be available in patients randomised after angiography and in all the patients treated by stenting.

25.3.12 Baseline data

Baseline data collected at randomisation will include demographic data; existing medical risk factors; neurological symptoms including an assessment of disability using

the Modified Rankin Scale; current antiplatelet therapy and blood pressure. Films and/or reports of pre-randomisation imaging as detailed above and in all cases the results of Doppler ultrasound as detailed below are required to allow assessment of any subsequent stenosis.

25.3.13 Baseline assessment

Patients will be seen by the study neurologist or physician interested in stroke prior to randomisation to confirm suitability for the study.

25.3.14 Stenting protocol

Stenting will be carried out as soon as possible after randomisation using percutaneous transluminal interventional techniques from the femoral, brachial or common carotid artery by a designated interventional consultant using an appropriate stent. A cerebral protection system should be used whenever the operator thinks one can be safely deployed. Stents and other devices used in the trial must be CE marked and approved by the Steering Committee. Pre-medication will be discretionary. The combination of aspirin and clopidogrel is recommended as the antiplatelet regime of choice to cover the period of stenting and for a minimum of 4 weeks afterwards. Intra-procedural heparin is mandatory at a dose determined by the operator, post-procedural heparin may be given according to clinical requirements. Patients should be monitored for changes in their neurological status and heart rate throughout the procedure. If femoral or brachial access is being used a long sheath introducer or a guiding catheter is placed in the common carotid artery allowing pre-dilation and stent placement under direct arteriographic imaging. Atropine, or a similar agent, must be administered prior to stent deployment to counteract any effects on the carotid artery baroreceptors, which could lead to severe bradycardia and/or asystole. Virtually all patients will require pre-dilatation of the stenosis by balloon angioplasty prior to stent deployment. This will minimise the embolic load caused by passage of the endoluminal stent through the stenosis. The size of the pre-dilatation balloon will be determined by the size of the delivery system being used. Further balloon dilation of the stent will usually be required to ensure apposition of the stent against the arterial wall. Angiographic images showing the stenosis at its most severe prior to stenting and the same view and any other view that demonstrates the maximum residual stenosis after stenting must be sent to the Central Office. Details of the procedure, including all peri-procedural complications, drug therapy and devices used in the procedure, must be reported and

the stenting and cerebral protection technical data sheet returned to the trial Central Office.

25.3.15 Endarterectomy protocol

Endarterectomy is to be done as soon as possible after randomisation by a designated consultant surgeon who has been approved by the Credentials Committee. It is to be carried out using whichever procedures are standard at the individual centre, including the use of local or general anaesthesia, shunts or patches as required by the operating surgeon. Standard or eversion endarterectomy may be performed.

25.3.16 Reporting of suspected problems with surgical or stenting techniques at individual centres

If the local investigator or other member of the team at a trial centre has concern about the outcome of their trial procedures they should inform the ICSS trial office which will organise a blinded assessment of the relevant outcome events. This will be submitted by the central office to the chairman of the data monitoring committee who may recommend further action, such as suspending randomisation at the centre. Similarly, the database manager at the trial office will monitor outcome events and if there are two consecutive deaths or three consecutive major events at a single centre within 30 days of treatment in the same arm of the study, then assessment of the events will be triggered. A cumulative major event or death rate of more than 10% over 20 cases would also trigger careful assessment of the relevant outcome events.

25.3.17 Medical treatment

All patients will receive best medical care including antiplatelet therapy or anticoagulation (when appropriate) and control of medical risk factors such as hypertension, smoking and hyperlipidaemia before treatment and throughout the period of follow up.

25.3.18 Prevention of thrombosis

Therapy to prevent thrombosis during or soon after surgery or stenting will be prescribed according to standard practice in each centre. This may include heparin, dextran, aspirin, dipyridamole, ticlopidine, clopidogrel, or a combination of aspirin and another antiplatelet agent. Glycoprotein IIb/IIIa antiplatelet receptor antagonists will not be used routinely.

25.3.19 Follow-up

Patients will be followed up by a neurologist or a physician interested in stroke at the participating centres at 30 days after treatment, 6 months after randomisation and then annually after randomisation. All post-procedural complications occurring within thirty days after the procedure will be reported to the central office at the 30 day follow up. At each visit, levels of stroke-related disability will be assessed using the modified Rankin Scale and any relevant outcome events will be notified to the Central Office. A Doppler ultrasound will be used to measure carotid arterial diameter to assess patency at one month after treatment and then annually after randomisation. In addition, ultrasound re-examination and CT or MRI scan should be performed in patients who have any transient ischaemic events and/or stroke during follow up. The duration of follow up will be a minimum of 5 years (or until termination of the trial if earlier). At the 5 year follow up, patients will be asked if they are willing to continue follow up, in which case annual follow up will continue up to a maximum of 10 years from randomisation.

25.3.20 Sample size calculations and recruitment

The planned sample size is 1500. We do not anticipate any large difference in the principal outcome between surgery and stenting. We propose to estimate this difference and present a confidence interval for difference in 30-day death, stroke or myocardial infarction and for three-year survival free of disabling stroke or death. For 1500 patients, the 95% confidence interval will be the observed difference ±3.0% for the outcome measure of 30 day stroke, myocardial infarction and death rate and ±3.3% for the outcome measure of death or disabling stroke over three years follow up. However, the trial will have the power to detect major differences in the risks of the two procedures, for example if stenting proves to be much riskier than surgery or associated with more symptomatic restenosis. The differences detectable with power 80% are 4.7% for 30 day outcome and 5.1% for survival free of disabling stroke. Similar differences are detectable for secondary outcomes. We expect to achieve this recruitment within 6 years.

25.4 Principal research questions to be addressed

25.4.1 Primary analysis

- What is the difference in the long-term rate of fatal or disabling stroke in any territory of patients with severe symptomatic stenosis after randomisation to a policy of carotid stenting compared to surgery?

25.4.2 Secondary analysis

- What are the differences in mortality and morbidity within 30 days of carotid stenting compared to surgery?
- What is the rate of symptomatic and asymptomatic restenosis after carotid stenting compared to surgery?
- What are the differences in the rate of ipsilateral stroke during follow-up after carotid stenting compared to surgery?
- What is the cost-effectiveness of carotid stenting compared to surgery?
- What are the risk factors for stroke within 30 days and during long term follow up (including those related to age, gender, symptoms, imaging, centre and technique)?

25.4.3 Outcome events

- Any stroke or death
- Transient ischaemic attack
- Myocardial infarction within 30 days of treatment
- Cranial nerve palsy within 30 days of treatment
- Haematoma caused by treatment requiring surgery or transfusion or prolonging hospital stay
- Stenosis greater than 70% or occlusion during follow-up
- Further treatment of the randomised artery by interventional radiology techniques or surgery after the initial attempt
- Quality of life, health status and health service costs (see paragraph below)

25.4.4 Outcome event reporting

Outcome events will be documented in detail by the investigating centre, censored after receipt at the central office to remove clues as to the treatment received, and then

adjudicated by an independent neurologist. Patients suffering stroke should have a CT or MRI brain scan as soon as possible after the event. A film copy of this, together with a film copy of the pre-randomisation scan (if done) should be submitted together with a report of the event. The event report should include copies of discharge summaries, death certificates and post mortem results if relevant. Deaths of UK patients will be tracked by flagging patients against the UK Registry of Births and Deaths. Disability after stroke and cranial nerve palsy will be assessed 30 days and six months after treatment or onset, using the modified Rankin Scale. Duration of symptoms will be recorded and outcome events will be classified as disabling if the Rankin score is 3 or more at six months.

25.5 Learning curve

Carotid stenting is a new procedure, while the techniques of carotid surgery are well established. It is likely that there will be a learning curve for carotid stenting and the results may improve with experience during the trial. However, we believe it is better that carotid stenting should be performed as part of a randomised clinical trial at this stage of its development, because this will ensure careful assessment and follow up of all patients treated in the trial and supervision from the Data Monitoring and Ethics Committee ensures that continuing treatment with the new technique remains ethical. The influence of the early part of the learning curve for carotid stenting will be limited by careful training of individual interventionists. The total experience of carotid PTA and stenting of individual interventionists will be recorded prior to entry into the trial. This will allow the average duration of the learning curve to be analysed, taking into account the current experience of the individual interventionists. This information may have implications for interpretation of the results of the trial and for the future training and supervision of the procedure. Similarly, there may be improvements in individual surgical or anaesthetic techniques during the trial.

25.6 Effect of changes in technology during the course of the study

The field of carotid stenting is an area of fast changing technology. The protocol does not at present specify the type or manufacturer of the stents or protection devices to be used, but devices to be used in the trial will be CE marked and approved by the Steering Committee who will expect a peer reviewed report of device safety. More than one device may be recommended to allow the interventionist to tailor the choice of stent to the individual stenosis and to use new designs of stent or protection devices if appropriate. The protocol will not specify the technique to be used during carotid

surgery. Decisions about the use of shunts or specific suture materials will be left to the individual surgeon. Local or general anaesthesia will be allowed in both arms. Technical details of surgical and stenting technique, including the manufacturer and type of stent used, the use of local or general anaesthesia, and the use of antithrombotic agents, will be recorded. The analysis will include a subgroup comparison of different techniques in both arms and the data will be presented to the DMC meetings to ensure that no one technique is significantly inferior to another. Randomisation will use a computer program to minimise variation between centres and over time, so that equal numbers of patients will be entered into the stenting and surgery arms before and after any change in practice.

25.7 Health service research issues

If the trial confirms the hypothesis that carotid stenting and surgery are equivalent in terms of the major risks of stroke and death, then the choice between the two procedures will be determined primarily by differences between the two procedures in other outcomes e.g. the disadvantage of a scar or cranial nerve palsy, or the effects of surgery on health related quality of life. If these differences are minor, the choice between the procedures will be made primarily on economic grounds. The effects of cranial nerve palsy may be detected by a minor increase in the disability score, but it is not easy to assess the effect of these outcomes during follow-up on clinical examination alone. Quality of life and health status will therefore be assessed using the EuroQol (EQ5D) questionnaire to compare patients' feeling of well-being, health and quality of life before and after stenting or surgery at one month, six months and annual follow-up. The results will be analysed blind to treatment arm. The first questionnaire will be completed at the time of randomisation and subsequent questionnaires at each follow-up visit. The investigator performing randomisation or follow-up should ensure the patient completes the EQ5D at the same time. The English language version of the EQ5D has been modified to record the date on which it is completed and the patient's trial number. Those centres using versions in other languages should also record the date and trial number on each completed form. If patients are too disabled to complete the questionnaires themselves, the patient's carer may complete them. The EQ5D should be returned to the central office with the other trial forms.

Information on hospital resource use during the treatment and follow up, including the type and manufacturer of the devices employed in carotid stenting procedures, will be collected to measure treatment costs and estimate the costs of stroke and any consequences of restenosis (e.g. re-treatment) during follow up. Unit costs will be

obtained from a sample of representative centres. The costs of stroke caused by treatment are a major component of the total cost of treatment, and therefore have a major influence on cost effectiveness. As the additional length of stay in hospital resulting from stroke largely drives these costs, the prospective collection of length of stay data will be designed to capture the stroke-related data in addition to direct operative stay. The economic evaluation will address cost-effectiveness and cost-utility (cost per QALY). The latter will be estimated from patients' responses to the EuroQol (EQ-5D) questionnaires using the York MVH tariff. Uncertainty regarding specific parameters within the analysis will be subjected to a sensitivity analysis, and uncertainty around the point estimate of the cost utility ratio will be represented using cost-effectiveness acceptability curves. To inform the economic analyses, the preferences of potential patients and clinicians between carotid endarterectomy and carotid stenting given various differences in outcomes will be explored using the technique of conjoint analysis (discrete choice experiments). A sample of members of the general population (matched to the ICSS patients) and clinicians will be asked to complete a questionnaire after completion of randomisation, informed by the preliminary safety results. Preliminary work, structuring and piloting the conjoint analyses, will be undertaken earlier.

25.8 Stenosis after treatment

Patency of the carotid artery will be monitored by Doppler ultrasound at a minimum of 30 days after treatment and then annually after randomisation. Restenosis should only be treated by further angioplasty or surgery if the patient has relevant new symptoms. Restenosis is usually the result of smooth muscle hypertrophy or neo-intimal hyperplasia, rather than recurrence of atherosclerosis and hence may not cause embolic stroke. Asymptomatic restenosis will not be an indication to retreat the lesion because the risk of disabling symptoms after restenosis is not known.

25.9 Crossovers

Crossovers before any attempt to treat the randomised artery by the allocated treatment will be avoided unless clinically essential, because the trial data will be analysed by intention to treat. Patients who are randomised to stenting after ultrasound or other non-invasive investigation, in whom subsequent angiography prior to stenting reveals one or more exclusion criteria, should be treated by surgery, if appropriate, or medical care only if surgery is not appropriate (e.g. because the stenosis is less than 50%). These patients will continue follow up in the trial and will be analysed on an

intention-to-treat basis. A similar approach should be taken to patients randomised to surgery in whom contraindications to surgery emerge after randomisation. Patient refusal of the treatment to which they are randomised can be minimised by careful consent. Patients requiring re-treatment because of further symptoms should be re-treated with whichever treatment is most appropriate. This is also the case if the non-randomised carotid artery requires treatment. Patients in whom an attempt at stenting fails may proceed to early surgery if appropriate and vice versa.

25.10 Data analysis

The data will be analysed by intention to treat using standard statistical tests by the trial statistician. The analyses will compare the treatment groups with respect to the length of time before treatment failure (i.e. occurrence of an outcome event) by means of the Mantel-Haenszel chi-squared test and Kaplan-Meier survival curves. Secondary analysis will compare the proportions of outcome events within 30 days of treatment. All analyses will be adjusted for centre and predetermined risk factors. Subgroup analyses will examine risk factors for outcome events and will examine the influence of different devices, surgical techniques and experience within the trial. Results at probationary centres will be analysed separately. The results of any interim data analysis will remain confidential to the trial statistician and Data Monitoring Committee until after completion or early discontinuation of the trial. Investigators and the Steering Committee will remain blind until such point.

25.11 Publication

Publication of the results of ICSS will be prepared by the Central Office and circulated to participating centres for comment prior to submission of the manuscript for publication on behalf of all the ICSS collaborators.

25.12 Ethical Committee approval

Multicentre Research Ethics Committee approval will be sought in the UK. In addition, individual centres are expected to obtain local ethical committee approval for the study.

25.13 Data Monitoring Committee

The safety aspects of the trial will be overseen by a Data Monitoring Committee consisting of an independent neurologist, medical statistician, surgeon and interventionist. The progress of the study will be assessed at regular intervals

determined by the Data Monitoring Committee. During the period of intake to the study, interim analyses of mortality and of any other information that is available on major endpoints (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the Data Monitoring Committee, along with any other analyses that the Committee may request. In the light of these analyses, the Data Monitoring Committee will advise the chairman of the Steering Committee if, in their view, the randomised comparisons in ICSS have provided both (i) "proof beyond reasonable doubt" that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in outcome, and (ii) evidence that might reasonably be expected to influence materially patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the number of interim analyses is of little importance.

25.14 Steering Committee

A Steering Committee, consisting of individuals participating in and independent of the trial with experience in stroke medicine, neurology, vascular surgery, vascular radiology, interventional neuroradiology, health economics, clinical trials and statistics will oversee the management of the trial.

25.15 Trial organisation

The study will be organised on behalf of the collaborators by the central office, located at the UCL Institute of Neurology in London. The office will be responsible for protocol design, data collection and management, and analysis of the results in consultation with the Steering and Data Monitoring Committees, but will consult with the collaborators at an annual meeting and at other times as necessary. Communication with investigators will also take place via a regular newsletter and the trial website.

25.15.1 Payments to centres

While funding is available, the Lead Institution (UCL Institute of Neurology, London) will pay the participating centres a one-off payment of £100 for each patient randomised patient for whom correctly filled-out randomisation, technical data and one month follow-up forms have been received. Participating centres must invoice to the Lead Institution within 6 months of receipt of this revised protocol and thereafter 6-monthly in

arrears. The Lead Centre may vary or terminate such payments in the future in accordance with budgetary needs and will inform the participating centre of such changes as they occur.

25.15.2 Indemnity

ICSS is an academic trial performed as a collaborative effort for the benefit of patients, and is not performed for, or on behalf of, an industry sponsor. The trial compares two existing forms of treatment currently used in many hospitals. The various devices approved for use in the trial are not investigational devices and are required by the protocol to be marketed and already in use in the carotid artery as recognised by the CE mark. Hence, the trial is not an industry sponsored test of a new treatment with unknown hazards. The trial protocol anticipates that some patients may be harmed inadvertently as a result of treatment in the trial. Indeed, the determination of the rate of these adverse outcome events is a major aim of the trial. However, we believe that the risks of these adverse events will be outweighed by the benefits of treatment in either arm of the trial. The trial protocol does not subject patients to hazards that the patient would not have encountered if they had received the trial treatments outside the context of the trial in routine practice. Hence, the organisers of the trial cannot take responsibility for any harm occurring to patients as a result of partaking in the trial. Individual investigators and hospitals are required to take responsibility for the occurrence of any adverse events in the same way as they would do if the treatments were performed outside the trial.

25.15.3 Website

The trial website contains updated information about the trial together with downloadable copies of the protocol, trial data collection forms, newsletters and contact information. The names of the collaborating centres will be included on the website. The website address is http://www.cavatas.com and all the pages are accessible to the public, patients and collaborators alike without a password. At present, the data collection forms cannot be completed on line.

26. Appendix V – ICSS-MRI Substudy protocol

Symptomatic and asymptomatic ischaemic and haemorrhagic brain injury following protected and unprotected stenting versus endarterectomy in the International Carotid Stenting Study – the ICSS-MRI Substudy.

26.1 Summary

26.1.1 Background and aim

Diffusion weighted imaging (DWI) – a modern magnetic resonance imaging (MRI) technique – may detect ischaemic brain lesions after carotid interventions in patients who do not experience symptoms. Previous studies showed that DWI lesions are found more frequently after endarterectomy than after stenting of carotid stenosis, and more frequently after stenting without the use of cerebral protection devices than after protected stenting. However, methodological shortcomings of those non-randomised studies may account for the observed differences. Moreover, it is not clear how ischaemic lesions on DWI relate to the risk of clinically apparent cerebrovascular events (stroke or TIA) associated with the intervention. About one in ten strokes occurring as a complication of carotid interventions is caused by intracerebral haemorrhage (ICH), but asymptomatic ICH after carotid interventions has never been assessed. We therefore aim to study the frequency and significance of symptomatic and asymptomatic ischaemic and haemorrhagic brain injury in protected and unprotected stenting and endarterectomy in a randomised trial.

26.1.2 Primary objective

- To compare the rate of ischaemic brain injury detectable on MRI after treatment of symptomatic carotid stenosis by stenting or endarterectomy

26.1.3 Secondary objectives

- To test for an interaction between the use of cerebral protection devices and ischaemic brain injury associated with stenting
- To compare the rate of haemorrhagic brain injury detectable on MRI after treatment of symptomatic carotid stenosis by stenting or endarterectomy
- To evaluate the usefulness of ischaemic and haemorrhagic brain lesions visible on MRI as surrogate markers of the procedural risk of carotid interventions

26.2 Methods

Multicentre prospective MRI substudy of the International Carotid Stenting Study (ICSS). Multimodal MRI to detect ischaemic and haemorrhagic brain injury will be performed at 3 time points in patients with symptomatic carotid stenosis randomised to stenting or endarterectomy in ICSS: 1-3 days before, 1-3 days after and again 30±3 days after intervention.

26.3 Background and aim

Carotid stenting has emerged as a treatment alternative to endarterectomy in patients with symptomatic carotid stenosis. Cerebral protection devices are used in stenting with the aim of reducing the risk of plaque embolisation during the procedure. Recently completed randomised trials comparing the safety of stenting and endarterectomy yielded conflicting results [79] [77]. Concern that stenting without cerebral protection may be associated with an increased risk of stroke led to the abandonment of unprotected procedures in one trial [63] but in another trial, there was no difference in the risk of stenting with and without protection [77]. Although clear evidence that cerebral protection enhances treatment safety is lacking [253], protection devices are widely used today, significantly contributing to the cost of carotid stenting.

Until clinical trials investigating the benefit of cerebral protection devices can be realised, surrogate markers of brain injury may provide further insights into the risk of protected and unprotected stenting in comparison to endarterectomy. Diffusion weighted imaging (DWI), a modern magnetic resonance imaging (MRI) technique, may show ischaemic lesions after carotid interventions even in patients who do not experience symptoms [214]. In previous studies new ischaemic lesions on DWI were detected more frequently after stenting than after endarterectomy [254] [255] [256] [257] [258] [259] [260]. DWI lesions were also more frequent after unprotected stenting than after protected stenting [215] [261]. However, selection bias and the use of historical controls may be accountable for the observed differences in these non-randomised comparisons. Moreover, it is not clear how ischaemic lesions on DWI relate to the risk of clinically apparent cerebrovascular events (stroke or TIA) associated with the intervention. Larger studies with randomised treatment allocation are needed to gain further insight into the significance of asymptomatic DWI lesions and their potential role as surrogate markers of treatment risk.

About one in ten strokes occurring as a complication of carotid interventions is caused by intracerebral haemorrhage (ICH). A special MRI technique (so-called gradient echo imaging) allows the detection of small intracerebral bleedings, but has never been applied to detect ICH after carotid interventions. Asymptomatic ICH may be an expression of subclinical reperfusion damage following carotid revascularisation.

Thus, there is a clear need to study symptomatic and asymptomatic ischaemic and haemorrhagic brain injury in protected and unprotected stenting and endarterectomy in a randomised trial.

26.4 Objectives

The primary objective of this substudy is to compare the risk of ischaemic brain injury assessed on MRI in patients with symptomatic carotid artery stenosis undergoing stenting in comparison to those undergoing endarterectomy.

Secondary objectives are: to assess the effect of protection devices on the risk of ischaemic brain injury associated with stenting, to compare the risk of haemorrhagic brain injury assessed on MRI in stenting compared to endarterectomy, and to gain further insight into the usefulness of ischaemic and haemorrhagic brain lesions on MRI as surrogate markers of the risk of carotid interventions.

26.5 Study design

This project is an MRI-based substudy of a multicentre randomised trial known as the International Carotid Stenting Study [81], which is comparing the risks and benefits of stenting and endarterectomy of symptomatic carotid stenosis using clinical endpoints, e.g. stroke and death.

The ICSS-MRI Substudy allows a randomised comparison of the procedural risk of symptomatic and asymptomatic ischaemic and haemorrhagic brain injury visible on MRI between stenting and endarterectomy. The use of cerebral protection devices in patients undergoing stenting is not subject to randomisation in ICSS. However, the participating centres systematically use either protected or unprotected stenting. The risk of brain injury associated with either stenting technique can therefore be compared to a randomised control group of patients undergoing endarterectomy.

Outcome measures and analyses are defined as follows:

26.5.1 Primary outcome measure

- Rate of symptomatic and asymptomatic ischaemic brain injury detectable on MRI after endarterectomy and stenting

26.5.2 Secondary analyses

- Interaction between the use of protection devices and ischaemic brain injury in patients undergoing stenting
- Rate of symptomatic and asymptomatic haemorrhagic brain injury detectable on MRI after endarterectomy and stenting
- Relation of brain injury on MRI to risk of stroke during procedure and follow-up

26.5.3 Subject selection

Inclusion criteria

Patients are eligible to participate in the ICSS-MRI Substudy if they are enrolled in the ICSS trial and separately provide written informed consent to undergo three MRI exams. Detailed inclusion and exclusion criteria for ICSS are provided elsewhere [81]. In short, patients with recently symptomatic ≥50% carotid stenosis who are equally suitable for endarterectomy and stenting are eligible for enrolment in ICSS.

Exclusion criteria

Patients with contraindications to MRI, e.g. pacemakers, metallic implants, and claustrophobia, are excluded from the ICSS-MRI Substudy.

26.5.4 MRI protocol

Patients enrolled in the ICSS-MRI Substudy will undergo three MRI investigations, 1-3 days before, 1-3 days after and 30±3 days after the intervention. The following sequences will be performed in all three investigations:

- Diffusion weighted imaging (DWI) to detect acute ischaemic brain injury associated with the procedure
- Gradient echo T2*-weighted sequences to detect haemorrhagic brain injury associated with the procedure

- T1-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences will be used to assess whether acute brain lesions detected on DWI after the procedure lead to permanent scarring at 1 month

26.5.5 Data acquisition

Baseline data (such as age, gender, medical risk factors, degree of carotid stenosis, etc.) will be collected as part of ICSS.

Two researchers will independently score the presence, size and location (vascular territory) of ischaemic and haemorrhagic lesions on the MRI scans. A third researcher will review the scans in case of disagreement. The scans will be reported and scored blind to patient identifiers, treatment, date and time of the scans.

Patients will be clinically examined by a neurologist at the time of MRI examination and will be followed up after treatment as part of ICSS to determine outcome events including transient ischaemic attack, stroke, myocardial infarction and death.

26.5.6 Statistical considerations

Statistical analysis

The rates of ischaemic and haemorrhagic brain lesions will be compared between patients undergoing endarterectomy and stenting using chi-squared and Fisher's exact tests. Significance will be declared at $p<0.05$.

Sample size calculation

Power calculations are based on the primary outcome measure. The two largest series reported new ischaemic lesions on DWI after carotid endarterectomy in 17% and 34% of patients respectively [262]. If a rate of new DWI lesions after endarterectomy of 25% is assumed, a total sample size of 200 patients would have a 90% power to detect a twofold increase in the DWI lesion rate associated with carotid stenting. Testing the interaction between the use of cerebral protection devices and the rate of DWI lesions after stenting would have less power. 126 patients have been enrolled in the ICSS-MRI Substudy from its initiation in 2004 until July 2007 in two participating centres (Utrecht and Basel). The projected number of enrolled patients at the end of the ICSS randomisation period in those centres is 170. The target population of 200 could be reached with a contribution of 30 patients enrolled in ICSS centres in the UK.

26.5.7 Withdrawal of consent

Subjects enrolled in the ICSS-MRI Substudy can withdraw their consent at any time during the substudy. This will not affect their enrolment in ICSS or the standard of care they receive.