Personalising Treatment in Patients with Carotid Disease

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Content

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2. Overview and Summary

Approximately 10-15% of all ischaemic strokes are caused by atherosclerotic stenosis of the carotid artery. Conventionally, carotid stenosis was treated by surgical removal of the atherosclerotic plaque (carotid endarterectomy). Since the introduction of carotid artery stenting as a less invasive treatment alternative almost 20 years ago, the choice of the optimal treatment for the individual patient with carotid stenosis has remained controversial. This PhD thesis consisted of three individual projects and aimed to enable personalised treatment decisions for individual patients with carotid disease and explore parameters specifically linked to the mechanisms of stroke occurring as a complication of both revascularisation procedures.

The first project consisted of a systematic review and meta-analysis with the aim to compare short-term risks and long-term effects on stroke prevention between carotid stenting and endarterectomy in patients with symptomatic or asymptomatic carotid stenosis. To this end, we performed a systematic Cochrane Review of all published randomised trials comparing carotid stenting versus endarterectomy to obtain precise overall estimates of procedural risks and long-term stroke recurrence rates. We found that in patients with symptomatic carotid stenosis, stenting and endarterectomy are equally effective in preventing recurrent stroke in the long-term, while stenting is associated with a higher risk of procedure related stroke or death. In patients with asymptomatic carotid stenosis, there may be a small increase in the risk of procedure related stroke or death associated with stenting. However, more data from randomised trials are needed. Concerning the durability of carotid stenting in the long-term, only limited data are currently available for asymptomatic patients and the existing evidence does not yet allow any firm conclusions.

The second project comprised the systematic assessment of the anatomy of all supra-aortic arteries and pre-defined stenosis characteristics in order to investigate the association between vascular anatomy and the occurrence of procedure-related cerebral ischaemia after carotid artery stenting or carotid endarterectomy in patients with symptomatic carotid stenosis. We identified complex vascular

anatomy as an important predictor for cerebral ischaemia during stenting, but not during endarterectomy.

The third and fourth projects consisted of an individual patient data meta-analysis of four randomised clinical trials comparing carotid artery stenting versus endarterectomy for treatment of symptomatic carotid stenosis. This work resulted in two separate manuscripts. Within the first, we investigated whether the temporal distribution of stroke or death occurring within 30 days of treatment differed between the two procedures. In the second, we investigated if the procedural risks associated with carotid stenting and carotid endarterectomy within the examined trials had decreased over time. Our analysis revealed that the excess occurrence of stroke or death associated with stenting is limited to the day of treatment. In our analysis of temporal trends in procedure related risks, we were able to show that carotid revascularisation procedures became safer over time within the examined trials. This decline in risk was particularly apparent for endarterectomy.

3. List of Abbreviations

ACST-2	2nd Asymptomatic Carotid Surgery Trial
ACT-1	Randomised Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis
ACTRIS	Endarterectomy Combined with Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke
CAS	Carotid Artery Stening
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CE-MRA	Contrast Enhanced Magnetic Resonance Angiography
CI	Confidence Interval
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CSTC	Carotid Stenosis Trialists' Collaboration
CT	Computed Tomography
CTA	Computed Tomography Angiography
DSA	Digital Subtraction Angiography
DWI	Diffusion Weighted Imaging
ECA	External Carotid Artery
ECST	European Carotid Surgery Trial
ECST-2	2nd European Carotid Surgery Trial
EVA-3S	Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis
GLMM	Generalised Linear Mixed-Effects Model
ICA	Internal Carotid Artery
ICC	Intraclass Correlation Coefficient
ICSS	International Carotid Stenting Study
IPH	Intra-Plaque Haemorrhage
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OR	Odds Ratio
QE	Qualifying Event
RCT	Randomised Clinical Trial
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
SPACE-2	Stent-Protected Angioplasty versus Carotid Endarterectomy 2
TIA	Transient Ischaemic Attack
TOF MRA	Time of Flight Magnetic Resonance Angiography

4. Introduction

4.1 Stroke and carotid disease

Stroke is the leading cause of acquired disability in adult life and the second most common cause of death worldwide.[1] Stroke is commonly defined as a rapidly evolving clinical syndrome consisting of signs and symptoms of focal neurological disturbance due to ischaemia or haemorrhage, lasting more than 24 hours.[2] A transient ischaemic attack (TIA) on the other hand, has been recently defined as "a brief episode of neurologic dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction" on imaging.[3]

Diagnosis and early treatment of both stroke and TIA are of great importance to prevent disability, death and recurrent stroke. Atherosclerotic stenosis of the carotid artery is responsible for about 10 to 15% of all ischaemic strokes.[4] Carotid disease becomes more prevalent with increasing age, affecting approximately 7.5% of all men and 5.0% of all women over 80 years of age.[5] The primary mechanism underlying cerebral ischaemia caused by carotid disease is plaque rupture and subsequent embolism to the brain. This has fostered the concept of the vulnerable or high-risk plaque, which is prone to rupture and cause ischaemic stroke.[6, 7] In contrast to the high-risk plaque, the stable or low-risk plaque may remain inert over many years.

4.2. Diagnostic work-up of carotid disease

4.2.1. Digital subtraction angiography

Initially, digital subtraction angiography (DSA) was routinely performed for diagnosis and grading of carotid stenosis. It was the primary method for determining the degree of stenosis in early randomised clinical trials (RCTs) establishing the benefit of carotid endarterectomy compared to medical therapy alone for treatment of symptomatic carotid stenosis.[8] During DSA, a catheter is inserted in the femoral artery (or in some cases in the brachial artery) and advanced along the vascular tree to the carotid

arteries. A contrast medium is then injected which enables imaging of the lumen of all supra-aortic arteries including the cerebral arteries. However, due to its invasive nature, DSA carries a 4% risk of neurological complication (TIA or stroke), a 1% risk of disabling stroke, and a mortality rate of <0.1%.[9] Because of the risk of complications, other non-invasive imaging techniques to depict carotid stenosis have been developed (CT- and MR-angiography, ultrasound) and are now widely available. Nowadays, DSA is reserved for the rare instances in which non-invasive imaging provides inconclusive or inconsistent information.

4.2.2. CT- and MR-angiography

Carotid stenosis can also be imaged by computed tomography (CT) or magnetic resonance (MR) based angiography. Important advantages of these imaging modalities include their non-invasive nature, their wide availability and the possibility to depict carotid plaque composition.

CT-angiography (CTA) requires injection of a contrast medium to visualise the supra-aortic vessels and quantify carotid stenosis. Determining the degree of stenosis may be limited if heavy calcifications at the carotid bifurcation are present. Moreover, CTA has limited sensitivity in the distinction of moderate from severe carotid stenosis and the degree of stenosis might be underestimated using this non-invasive imaging technique.[10, 11]

MR based angiography is most commonly performed as contrast enhanced MRA (CE-MRA) although MR angiography without the application of a gadolinium-based contrast medium is also possible (time of flight MRA). CE-MRA has a higher sensitivity and specificity to accurately diagnose and grade carotid stenosis than time of flight (TOF) MRA.[12] However, sensitivity for detection of moderate stenosis is limited with both TOF MRA and CE-MRA.[13] An important advantage of MRA compared to CTA is the fact that it can be performed without the use of ionising radiation.

Sensitivity and specificity of these non-invasive imaging techniques can be increased by combining different modalities, e.g. CE-MRA and duplex ultrasound.[14]

4.2.3. Duplex ultrasound

Today, most neurovascular clinics rely strongly on Doppler and Duplex ultrasound for diagnostic work-up of carotid stenosis. Ultrasound of the supra-aortic arteries carries no risk for the patient, as it is non-invasive and does not rely on ionising radiation. Additional benefits include low cost and wide availability. However, carotid ultrasound is dependent on the examiner's experience and on the technical equipment used. Nevertheless, previous research demonstrated that contemporary ultrasound techniques using flow velocity measurements is highly accurate in detecting and quantifying carotid stenosis.[15, 16] In addition, duplex ultrasound provides information on the haemodynamic relevance of carotid atherosclerosis and stenosis.

4.2.4. Brain MRI as a surrogate outcome measure in carotid trials

MRI is much more sensitive than clinical assessment in detecting ischaemic brain lesions. In a subset of 810 middle-aged persons without clinical or MRI evidence of stroke at baseline enrolled in the Atherosclerosis Risk in Communities Brain Magnetic Resonance Imaging Study, 20.2% of participants developed cerebral infarcts visible on MRI over a median of 10.5 years follow up.[17] Silent ischaemic lesions on MRI are also found with increased frequency after minor stroke and TIA; in one study there was a 10% risk of new lesions on MRI, half of which were asymptomatic.[18] Silent infarcts detected on MRI are also seen after carotid revascularisation procedures and have been proposed as a surrogate outcome measure in carotid trials.[19-21] Thus, MRI detects cerebral infarcts in the absence of clinical signs and symptoms, both occurring as a complication of carotid revascularisation procedures and accumulating in patients treated medically for cerebrovascular atherosclerosis. These lesions appear to occur in at least twice the frequency as clinically manifest strokes. A main advantage of using MRI as an outcome measure is therefore that the power of the analysis is increased allowing to test a hypothesis in pilot studies with smaller sample sizes than in trials using clinical endpoints. In addition, MRI can be analysed blinded to the treatment modality, which is of relevance in randomised trials comparing carotid stenting versus carotid endarterectomy.

4.3. Treatment of carotid stenosis

4.3.1. Medical therapy

Medical therapy including the management of modifiable risk factors for cardiovascular disease plays an essential role in the care of patients with carotid disease. The main modifiable risk factors in cardiovascular disease include hypertension, diabetes mellitus, hyperlipidaemia, obesity, lack of sufficient exercise, and smoking.[22] In addition, antiplatelet therapy is an important component of medical management in patients with carotid disease as it reduces the risk of embolization from the plaque.[23] Recent studies have highlighted the importance of supporting the patient in achieving individually tailored lifestyle changes and adjusting medication to achieve personalised target values for blood pressure control and other vascular risk factors.[24]

Lowering lipid levels has become an essential part of medical therapy in patients with carotid disease, especially after publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial results. This randomised placebo controlled trial which compared high dose atorvastatin therapy versus placebo in patients with recent stroke or TIA, showed a 33% reduction in the risk of future stroke in patients with carotid atherosclerosis taking atorvastatin.[25]

4.3.2. Carotid endarterectomy (CEA)

For more than half a decade the standard treatment for carotid stenosis has been surgical removal of the atherosclerotic plaque (carotid endarterectomy). The first record of successful carotid endarterectomy was published in 1954 in the Lancet.[26] In the years following this early description, the number of carotid operations performed increased tremendously and carotid endarterectomy (CEA) was widely adopted before reliable evidence on its benefit was available.[27] Notably, CEA is not without risk and can cause death, stroke, myocardial infarction, and local complications such as haematoma and cranial nerve palsy.[8] There are various surgical techniques in use. However, only limited evidence on their influence on the outcome of CEA is available. Conventionally, CEA is performed by longitudinal

arteriotomy. Alternatively, a transverse arteriotomy and re-implantation of the internal carotid artery (eversion endarterectomy) is also possible. However, high-quality evidence on the superiority of one surgical technique over the other is sparse and has been conflicting.[28, 29] There is some evidence that the insertion of a synthetic or vein patch may reduce the risk of perioperative occlusion of the carotid artery and the occurrence of restenosis.[30, 31] Patch angioplasty may also reduce the risk of peri-operative stroke and mortality.[31] However, the available evidence is poor and does not allow for a general recommendation of patch angioplasty.[31] With regard to the use of shunts, which are applied as a temporary bypass to reduce the time during which blood flow is interrupted during CEA, only insufficient evidence is available to either support or refute its use.[32] CEA can be performed under local or general anaesthesia, both of which show similar outcomes.[33]

In order to justify performing CEA, the procedural risks must be outweighed by a long-term benefit in preventing stroke. In patients with recently symptomatic carotid stenosis, the benefit of CEA to prevent recurrent stroke was established in RCTs almost 30 years ago. In the 1980s and early 1990s, two large multicentre randomised controlled trials investigating the benefit of CEA versus medical therapy alone to prevent ipsilateral stroke in patients with symptomatic carotid stenosis were conducted: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).[34, 35]

CEA was shown to be greatly beneficial in patients with severe carotid stenosis (≥ 70%) with an absolute reduction in ipsilateral stroke risk of 16% after 5 years.[8, 36] However, in patients with moderate (50-69%) carotid stenosis the benefit of CEA was smaller and it remained unclear whether all patients in this group benefit from CEA.[36, 37]

4.3.3. Carotid artery stenting (CAS)

Towards the end of the 20th century, carotid artery stenting (CAS) was introduced as a less invasive alternative to CEA. This procedure consists of the insertion of an endovascular catheter, most commonly in the femoral artery, followed by dilation of the carotid stenosis with inflatable balloons

and self-expanding stent devices.[38] Initially, percutaneous transluminal balloon angioplasty without the insertion of stent devices was performed. Later, stent devices specifically developed for the carotid arteries were introduced and primary stenting has since replaced balloon angioplasty alone as the endovascular treatment of choice.[39] Today, various stent devices with different designs and configurations are in use. Previous studies demonstrated a higher risk of peri-procedural stroke in patients treated with open-cell stents, which is thought to be caused by incomplete coverage of the atherosclerotic lesion due to larger open areas between struts compared with closed-cell stents. [40-42] Closed-cell devices on the other hand are more rigid and therefore less flexible.[43] Consequently mesh covered stents have been developed to combine the lower risk of peri-procedural stroke associated with closed-cell stents and the flexibility of open-cell stents.[44]

Potential advantages of CAS compared to CEA include the avoidance of a surgical incision in the neck with the risk of cranial and cutaneous nerve injury and reduction in the rate of general surgical complications such as myocardial infarction.[45] However, CAS does not remove the atherosclerotic lesion at the carotid bifurcation and manipulation with the endovascular catheter in the vascular tree may dislodge emboli, which may cause distal embolization and stroke. Whether complex vascular anatomy increases the risk of dislodging emboli during catheter navigation, is currently unknown. In order to prevent procedure related stroke caused by dislodged emboli, cerebral protection systems have been introduced. The earliest of these devices were distal filters, which have to be advanced across the carotid stenosis first and deployed distally to capture any debris dislodged during the stenting procedure. However, whether these devices truly increase the safety of CAS remains controversial as they have to cross the lesion first, before they can be deployed and fulfil their intended purpose.[46, 47] Moreover, distal filter devices cannot prevent emboli originating from the aortic arch occurring during catheter navigation in transfemoral CAS. Due to these issues, alternative protection systems, so called proximal protection devices or flow reversal protection, have been developed. These devices introduce flow reversal across the carotid bifurcation in order to prevent any emboli dislodged during the procedure to cause ischaemic stroke. In addition, alternative access routes to avoid

navigation of the aortic arch have been proposed. In recent years, direct catheterization of the common carotid artery (T-CAR) has been increasingly implemented with promising results, especially in conjunction with flow-reversal protection systems.[48] However, high-quality evidence on the benefit of these novel protection systems is sparse and it remains to be shown whether these contemporary technologies improve procedural safety of CAS.

Following the introduction of CAS as an alternative to CEA, several large RCTs comparing both treatment options in patients with symptomatic or asymptomatic carotid stenosis were conducted.[49, 50, 51, 52, 53] The identification and evaluation of these RCTs was part of the first project of this PhD thesis, in which we performed an update of a systematic Cochrane Review with the aim to identify all available randomised evidence comparing CAS versus CEA in patients with carotid stenosis.

5. Gaps in research and aims of this PhD thesis

Atherosclerotic stenosis of the carotid artery is an important cause of ischaemic stroke. Following the introduction of CAS as a less invasive alternative to CEA, which allows revascularisation of the carotid stenosis by the insertion of self-expanding stents without the necessity of a surgical incision in the neck, the choice of the optimal treatment for the individual patient with carotid stenosis has remained controversial.

1. In order to compare short-term risks and long-term effects on stroke prevention between CAS and CEA, we updated a systematic Cochrane Review last published in 2012 and included all randomised trials comparing CAS versus CEA to obtain precise overall estimates of procedural hazards and long-term stroke recurrence rates in patients with symptomatic or asymptomatic carotid stenosis (Project 1, section 6.1.). The previous update of this Review had shown that in patients with symptomatic carotid stenosis, CEA was associated with a lower risk of death or any stroke than CAS occurring between randomisation and 30 days after treatment.[45] However, only limited evidence had been available at the time on the comparative effectiveness of CAS and CEA in long-term prevention of stroke, and on their effect in patients with asymptomatic carotid stenosis. To investigate whether age or sex should inform the choice between CAS and CEA we additionally compared outcomes for men and women, and for younger and older patients, separately.
2. Observational data suggests that anatomic features of the aortic arch and supra-aortic arteries may also increase the risk for procedure related cerebral ischaemia in CAS.[54-57] However, randomised evidence on the impact of complex vascular anatomy on the risk of procedural cerebral ischaemia in CAS and CEA, and whether vascular anatomy might help inform the choice between CAS and CEA is sparse. In Project 2 (section 6.2.), we therefore aimed to systematically assess vascular anatomy and stenosis characteristics in patients with recently symptomatic carotid stenosis who were randomly assigned to CAS or CEA within an MRI-based

substudy of the International Carotid Stenting Study (ICSS). We sought to investigate the association between vascular anatomy as well as pre-defined stenosis characteristics and the risk of procedure-related cerebral ischaemia assessed on MRI after treatment. We hypothesized that difficult vascular anatomy would pose patients at greater risk of cerebral ischaemia during CAS, but not during CEA.

3. To date, it has been unclear whether the excess risk of procedure related stroke associated with CAS is present throughout the 30-day peri-procedural period or whether it is limited to the day of treatment. Previous RCTs had been underpowered to investigate this question. In Project 3 (section 6.3.), we pooled data at individual patient level from four RCTs to investigate whether the risk of stroke or death occurring on the day of treatment versus between 1-30 days thereafter differed between CAS and CEA. We additionally investigated, whether clinical risk factors for stroke or death differed between these two time periods. We hypothesized that the majority of strokes in both treatment groups would occur on the day of treatment, and that the increased risk of stroke or death associated with CAS would originate on the day of treatment.
4. Since the introduction of CAS, technical advances and increasing operator experience might have led to a decrease in procedure related strokes. In Project 4 (section 6.4.), we aimed to analyse temporal changes in procedural stroke or death risks associated with CAS and CEA in the same pooled data set as in Project 3 (section 6.3.) of this thesis. We hypothesized that procedural risks associated with carotid revascularisation would have declined over time, and that procedural risks of CAS may have decreased more strongly than CEA risks due to technical development and increasing experience with this comparatively new procedure.

6. Projects

6.1. Project 1 - Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis: Results from the updated systematic Cochrane Review

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Abstract

Background **-** The previous update of this Review showed that in patients with symptomatic carotid stenosis, CEA was associated with a lower risk of death or any stroke occurring between randomisation and 30 days after treatment. However, only limited evidence was available on the long-term efficacy of CAS and on CAS in patients with asymptomatic carotid stenosis. Since the last update in 2012, several RCTs published results of extended follow-up periods and multiple trials comparing CAS versus CEA in patients with asymptomatic carotid stenosis were completed. We therefore aimed to update the previous version of this Review.

Methods **-** We searched the Cochrane Stroke Group Trials Register (last searched August 2018) and the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 4), MEDLINE (1950 to August 2018), EMBASE (1980 to August 2018) and Science Citation Index (1945 to August 2018). We also searched ongoing trials registers (August 2018), reference lists, and contacted researchers in the field. We included all randomised trials comparing carotid stenting (including balloon angioplasty or stenting) with endarterectomy or medical therapy for symptomatic or asymptomatic atherosclerotic carotid stenosis and calculated treatment effects as odds ratios (OR) and 95% confidence intervals (CI), with endarterectomy as the reference group. We quantified heterogeneity using the I^2 statistic.

Main Results **-** We included 22 trials involving 9,753 patients. Eight trials (5,184 patients) compared CAS with CEA in patients with symptomatic carotid stenosis at standard surgical risk. In these patients, CAS was associated with a higher risk of death or any stroke (primary safety outcome) occurring between randomisation and 30 days after treatment than CEA (crude risks 7.2% vs. 4.4%; OR 1.70, 95% CI 1.31 to 2.19, P < 0.0001, I^2=5%). The OR for the primary safety outcome was 1.11 (95% CI 0.74 to 1.64) in patients < 70 years old and 2.23 (95% CI 1.61 to 3.08) in patients ≥ 70 years old (interaction P = 0.007). There was no significant difference in the risk of death or major or disabling stroke between CAS and CEA (crude risks 3.2% vs. 2.4%; OR 1.36, 95% CI 0.97, 1.91, P = 0.08; I^2 = 0%). CAS was associated with lower risks of myocardial infarction (OR 0.47, 95% CI 0.24 to 0.94, P = 0.03; I^2 = 0%),

cranial nerve palsy (OR 0.09, 95% CI 0.06 to 0.16, P < 0.00001; I^2 = 0%) and access site haematoma (OR 0.32, 95% CI 0.15 to 0.68, P = 0.003; I^2 = 27%). The combination of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up (the primary combined safety and efficacy outcome) favoured endarterectomy (OR 1.51, 95% CI 1.24 to 1.85, P < 0.0001; I^2 = 0%). However, the rate of ipsilateral stroke after the peri-procedural period did not differ between treatments (OR 1.05, 95% CI 0.75 to 1.47, P = 0.77, I^2 =0%).

Seven trials (3,378 patients) compared CAS with CEA in patients with asymptomatic carotid stenosis. In these patients, there was a statistically non-significant trend of a higher risk of the primary safety outcome (death or any stroke between randomisation and 30 days after treatment; crude risks 2.6% vs. 1.4%; OR 1.72, 95% CI 1.00 to 2.97, P = 0.05; I^2 = 0%) with CAS compared with CEA. The risk of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up did not differ significantly between treatments (OR 1.27, 95% CI 0.87 to 1.84, P = 0.22; I^2 = 0%).

Two trials (397 patients) compared CAS with CEA in patients with symptomatic or asymptomatic carotid stenosis considered to be at elevated surgical risk. In these patients, treatment effects on the primary safety outcome (death or any stroke between randomisation and 30 days after treatment; OR 0.95, 95% CI 0.39 to 2.28, P = 0.90, I^2 = 0%) as well as the primary combined safety and efficacy outcome (death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up; OR 1.09, 95% CI 0.58 to 2.06, P = 0.79, I^2 = 0%) did not differ significantly between treatments.

There was no significant difference in risk of severe restenosis (≥70%) or occlusion after CAS compared with CEA (OR 1.26, 95% CI 0.79 to 2.00, P=0.33, I^2 =58%). Moderate or higher restenosis (≥50%) or occlusion during follow-up was more common after CAS (OR 2.00, 95% CI 1.12 to 3.60, P=0.02, I^2 =44%).

Conclusions - CAS in patients with symptomatic carotid stenosis is associated with an increased risk of stroke or death occurring within 30 days of treatment compared with CEA. The extra risk associated with CAS is mostly attributed to an increase in minor, non-disabling strokes occurring in patients older than 70 years. Beyond 30 days after treatment, CAS is as effective in preventing recurrent stroke as

CEA. However, combining procedural safety and long-term efficacy in preventing recurrent stroke still favours CEA over CAS.

In patients with asymptomatic carotid stenosis, there may be a small increase in the risk of stroke or death occurring within 30 days of treatment associated with CAS. However, confidence intervals of treatment effects were wide and further data from randomised trials are needed.

Introduction

Only randomised trials can answer the question whether CAS is equivalent to CEA in terms of treatment safety and long-term prevention of stroke in patients with carotid stenosis. We therefore aimed to systematically review all randomised controlled trials comparing CAS with CEA or medical care. The present review updates a previous version first published in 1997 and subsequently updated in 2004, 2007, and 2012.

In the 2012 update, sufficient evidence was available to compare treatment risks and short-term efficacy between CAS and CEA for symptomatic carotid stenosis. Data on long-term efficacy and for treatment of patients with asymptomatic carotid stenosis, however, were sparse. Since the last update, four previously identified trials published results of extended follow-up periods and six new randomised trials were identified which had completed recruitment and published their results. The number of asymptomatic patients available for comparison more than doubled.

Methods

We attempted to identify all unconfounded, truly randomised trials comparing CAS with CEA, and trials comparing CAS with medical therapy alone. We included trials in which the exact method of randomisation was still uncertain after communication with the authors. We excluded studies of carotid revascularisation procedures without control groups and studies without random allocation of treatment. We considered trials including patients of any age or either sex with symptomatic or asymptomatic carotid stenosis eligible for inclusion in the review. We reviewed trials that allowed any acceptable technique for CEA (for example, use of a shunt or not, patching or not, local or general anaesthesia) and which allowed any acceptable endovascular technique for treatment of carotid stenosis (for example, simple balloon angioplasty, use of a stent or not, any type of cerebral protection device).

We searched the Cochrane Stroke Group Trials Register (last searched in August 2018), and the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1950 to August 2018), EMBASE (1980 to August 2018) and Science Citation Index (1945 to August 2018). We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Search Coordinator and adapted it for the other databases. We also searched the following ongoing trials registers (August 2018): Stroke Trials Registry (www.strokecenter.org/trials/); ClinicalTrials.gov (http://www.clinicaltrials.gov/); Current Controlled Trials (www.controlled-trials.com). We additionally searched reference lists of relevant articles and contacted individual researchers active in the field.

Outcomes

The primary outcome measure for evaluation of treatment safety was the combined outcome of death or any stroke occurring between randomisation and 30 days after treatment. For patients who did not undergo carotid revascularisation, the corresponding period was defined as the first 30 days after randomisation, or according to the definition used in the source trial, in order to allow for intention-to-treat analysis of all randomised patients. Stroke was defined as an acute deficit of focal neurological function with symptoms lasting for longer than 24 hours, resulting from intracranial vascular disturbance (ischaemia or haemorrhage). Visual loss, resulting from retinal ischaemia that lasted for longer than 24 hours, was included within the category of stroke. Stroke was classified as disabling if leading to a loss of functional independence, characterised by a score of three or more on the modified Rankin scale[58] or the Oxfordshire Handicap Stroke scale[59]. The primary outcome measure for evaluation of combined safety and long-term efficacy was death or any stroke occurring between randomisation and 30 days after treatment, or ipsilateral stroke occurring thereafter until the end of follow-up. Secondary safety outcomes included the following events occurring between randomisation and 30 days after treatment: death or major or disabling stroke, death of any cause, any stroke, myocardial infarction, cranial nerve palsy, and access site haematoma. Secondary efficacy outcomes included the following events occurring between randomisation and end of follow-up: death or any

stroke, the combination of death or any stroke or myocardial infarction, ipsilateral stroke, severe or moderate restenosis, and cognitive performance.

Data collection and analysis

MDM screened the titles and abstracts of records identified from the searches of the electronic bibliographic databases and excluded obviously irrelevant studies. We obtained the full text of the remaining studies and two review authors (MDM, LHB) independently selected relevant trials based on the review inclusion criteria, and assessed trial quality. We resolved disagreements by discussion and consultation with the other authors if necessary.

Two review authors (MDM, PL) extracted trial data. We resolved disagreements by consensus. We had access to individual patient data from six trials and used reported outcomes of individual patients from two other trials, to perform subgroup analyses. For trials where access to individual patient data was available, we extracted short-term outcome events used for comparison of treatment safety according to the definition of the peri-procedural period used in this review (i.e. events occurring between randomisation and 30 days after treatment).

We quantified heterogeneity among trial results using the I^2 statistic and considered a value >50% as representing substantial heterogeneity.[60]

We analysed outcomes following the intention-to-treat principle, i.e. we compared all patients who were randomised and in whom any information on outcome was reported according to their randomly assigned treatment, irrespective of whether they received this treatment or not.

For trials comparing CAS with CEA, we analysed the data from patients with symptomatic and asymptomatic carotid stenosis and data from trials enrolling patients considered at increased surgical risk separately, whenever possible. For the outcome measures moderate or severe restenosis, cranial nerve palsy and access site haematoma, we provided pooled treatment effects including all trials with

available data because we did not expect any difference in treatment effects according to symptom status or general surgical risk.

We analysed summary data of all patients randomised and analysed in the included studies with Mantel-Haenszel random-effect models. We reported the treatment effects as odds ratios (OR), that is, the odds of an unfavourable outcome in patients treated by CAS compared with the corresponding odds in patients treated surgically, with a 95% confidence interval (CI). We chose $P < 0.05$ as the level of significance.

Among the eight trials with available individual patient data, we calculated the OR for the primary safety outcome measure separately for patients 70 years or older (which was at or near the mean age of the patient populations of most included trials) and younger patients. We also performed subgroup analysis by sex. In addition, we investigated for heterogeneity according to the required number of carotid endovascular procedures interventionists needed to have performed before joining the trials, separating the trials at an arbitrary cut-off of up to 10 procedures, or more. We formally tested interactions between treatment effect and subgroup variables using a standard test for heterogeneity across subgroup results.[60]

Results

To date, we identified 22 randomised controlled trials involving 9,753 patients with available outcome data that fulfilled the inclusion criteria (Figure 1).

Symptomatic carotid stenosis

Eight trials including 5,184 participants compared CAS with CEA in patients with symptomatic carotid stenosis at standard surgical risk. The largest among those trials were EVA-3S, SPACE, ICSS, and CREST, and are briefly described below. Individual patient-level data from these trials were used for further analyses in Project 3 and 4 (sections 6.3. and 6.4.).[61]

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) was a French multicentre trial, which started in November 2000 and randomised patients with ≥60% symptomatic carotid stenosis between CAS and CEA. The trial was stopped early by the safety committee because of safety and futility concerns in September 2005, after 527 patients had been enrolled (CAS: 265 patients, CEA: 262 patients). Two hundred and sixty patients and 257 patients received the randomly allocated treatment in the two arms respectively. Results up to six months after randomisation were published in 2006,[52] and up to four years after randomisation in 2008.[62] Results of long-term follow-up of a median of 7.1 years were published in 2014.[63]

The Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial (SPACE) trial randomised 1214 patients with symptomatic carotid stenosis of ≥50% or ≥70% (depending on the method of measurement) between CAS (613 patients) or CEA (601 patients) in Germany, Austria and Switzerland, from March 2001 until February 2006. Following an interim analysis, the trial was stopped by the steering committee for reasons of futility and lack of funding. The randomly allocated treatment was initiated in 591 and 567 patients in the two arms respectively. Short-term outcomes were published in 2006,[51] and results up to two years after randomisation in 2008.[64]

The International Carotid Stenting Study (ICSS) randomised 1713 patients with symptomatic carotid stenosis of ≥ 50% to CAS (855 patients) or CEA (858 patients) between May 2001 and October 2008 in Europe, Australia, New Zealand and Canada. Short-term results up to 120 days after randomisation were published in 2010.[65] The randomised procedure was initiated in 828 and 821 patients in the two arms respectively. Long-term follow-up in this trial ended in 2011 and the results were published in 2014.[66]

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was a multicentre randomised trial conducted in the USA and Canada (CREST 2010). Between December 2000 and July 2008, 2522 patients with carotid stenosis were randomly assigned to CAS (1271 patients) or CEA (1251 patients). The trial initially enrolled only patients with symptomatic carotid stenosis, but the eligibility criteria were changed in 2005 to include asymptomatic patients in addition to symptomatic patients. The final population consisted of 1321 patients with symptomatic and 1181 patients with asymptomatic stenosis. Results up to four years after randomisation were published in 2010.[50] The randomly assigned treatment was initiated in 1152 and 1194 patients in the two arms respectively. Results over 10 years of follow-up were published in 2016.[67]

An additional two small trials included both patients with symptomatic and asymptomatic carotid stenosis, but did not report outcomes separately.[68, 69] These data were nonetheless included in the comparisons for symptomatic carotid stenosis.

In all 10 trials combined, CAS was associated with a higher risk of death or any stroke between randomisation and 30 days after treatment than CEA (primary safety outcome; crude risks 7.2% vs. 4.4%; OR 1.70, 95% CI 1.31 to 2.19, P < 0.0001, I^2=5%; Figure 2). CAS was furthermore associated with a higher risk of the following outcome measures occurring between randomisation and 30 days after treatment than CEA: death or any stroke or myocardial infarction (crude risks 7.8% vs. 5.6%; OR 1.43, 95% CI 1.14 to 1.80, P = 0.002, I^2 = 0%), and any stroke (crude risks 6.9% vs. 4.0%; OR 1.78, 95% CI 1.38 to 2.29, P < 0.00001, I^2 = 0%). Our subgroup analysis revealed that the OR for the primary safety outcome was 1.11 (95% CI 0.74 to 1.64) in patients < 70 years old and 2.23 (95% CI 1.61 to 3.08) in patients ≥ 70 years old, resulting in a significant interaction between patient age and treatment modality (interaction P = 0.007; Figure 3). In contrast, treatment effects in men (OR 1.82, 95% CI 1.10 to 3.02, I^2 = 54%) and women (OR 1.52, 95% CI 0.96 to 2.41, I^2 = 6%) did not differ significantly (interaction P = 0.61; Figure 4).

There was a statistically non-significant trend suggesting a higher rate of death or major or disabling stroke with CAS (crude risks 3.2% vs. 2.4%; OR 1.36, 95% CI 0.97 to 1.91, P = 0.08, I^2 = 0%) than with CEA. CAS was associated with lower risks of myocardial infarction (crude risks 0.4% vs. 1.0%; OR 0.47, 95% CI 0.24 to 0.94, P = 0.03; I^2 = 0%), cranial nerve palsy (crude risks 0.3% vs. 4.8%; OR 0.09, 95% CI 0.06 to 0.16, P < 0.00001; I^2 = 0%), and access site haematomata (crude risks 0.5% vs. 1.8%; OR 0.32, 95% CI 0.15 to 0.68, P = 0.003; I^2 = 27%). The combination of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up (the primary combined safety and efficacy outcome) favoured endarterectomy (OR 1.51, 95% CI 1.24 to 1.85, P < 0.0001 ; I^2 = 0%; Figure 5). However, the rate of ipsilateral stroke after the peri-procedural period did not differ between treatments (OR 1.05, 95% CI 0.75 to 1.47, P = 0.77, I^2 =0%).

Asymptomatic carotid stenosis

Our literature search identified seven trials including 3,378 participants, which compared CAS with CEA in patients with asymptomatic carotid stenosis. The two largest trials, which had enrolled patients with asymptomatic carotid stenosis were CREST, which also included patients with symptomatic carotid stenosis, and the Randomised Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis (ACT-1). The Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial 2 (SPACE 2) was stopped early due to slow recruitment.[70]

ACT-1 was a multicentre randomised controlled trial conducted in the USA. Between April 2005 and March 2013, 1,453 patients with asymptomatic carotid stenosis of >70% were randomly assigned in a 3:1 ratio to CAS (1089 patients) or CEA (364 patients). The initially planned sample size was 1,658 patients, but the study was stopped prematurely due to slow enrolment. Results over five years of follow-up were published in 2016.[71]

In 2009, SPACE 2 began recruiting patients. Initially the trial was planned as a three-armed, randomised controlled trial comparing best medical treatment alone (BMT) to endarterectomy plus BMT or endovascular therapy plus BMT.[72] Due to slow enrolment the study design was amended in 2013 to become two parallel randomised trials, one comparing BMT alone to endarterectomy and the second comparing BMT to endovascular therapy. This change in study design did not lead to an increase in patient recruitment and the trial was stopped early after inclusion of 513 patients over a 5 year period. Outcomes within the procedural time period of the recruited patients were reported in 2016.[70]

In patients with asymptomatic carotid stenosis, we found a statistically non-significant trend towards a higher risk of death or any stroke between randomisation and 30 days after treatment (primary safety outcome; crude risks 2.6% vs. 1.4%; OR 1.72, 95% CI 1.00 to 2.97, P=0.05; I^2=0%; Figure 6) with CAS compared with CEA. The risk of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up did not differ significantly between treatments (OR 1.27, 95% CI 0.87 to 1.84, P = 0.22; I^2 = 0%; Figure 7).

Restenosis

There was statistically no significant difference in risk of severe restenosis (≥70%) or occlusion after CAS compared with CEA (OR 1.26, 95% CI 0.79 to 2.00, P=0.33, I^2 =58%). Moderate or higher restenosis (≥50%) or occlusion during follow-up was more common after CAS (OR 2.00, 95% CI 1.12 to 3.60, P=0.02, I^2 =44%). However, we found substantial heterogeneity in both of these comparisons and the results must be interpreted with caution.

Discussion and Conclusions

In patients with symptomatic carotid stenosis, CAS and CEA are equally effective in preventing stroke in the long-term. However, CAS was associated with a higher risk of stroke or death occurring within

30 days of treatment. This excess risk occurred mostly in the form of minor, non-disabling stroke and was limited to patients over the age of 70 years. The choice between the two procedures should therefore be based on minimising short-term risks. For this reason, symptomatic carotid stenosis should not be routinely treated with CAS in patients above the age of 70, provided the patients are fit and willing to undergo surgery, and CEA can be performed at standard risk. CAS can be offered as an alternative to CEA in patients with symptomatic stenosis who are younger than 70 years at centres achieving short-term stroke or death rates in this age group comparable to those with CEA. Factors such as patients' preference, cardiovascular risk and vascular anatomy should also be taken into consideration in the choice between the two procedures.

In patients with asymptomatic carotid stenosis, there may be a small increase in the risk of procedure related stroke or death occurring within 30 days of treatment associated with CAS. However, the quality of the evidence was merely moderate and confidence intervals of treatment effects were wide reflecting the need for more data from randomised trials. Concerning the durability of CAS in patients with asymptomatic carotid stenosis, only limited data are currently available and the existing evidence does not yet allow any firm conclusions. The data urge caution and the results of the ongoing 2nd Asymptomatic Carotid Surgery Trial (ACST-2), as well as extended follow-up data from ACT-1 and the SPACE-2 are needed. ACST-2 is a multicentre, randomised controlled trial in which patients with asymptomatic carotid stenosis considered to require revascularisation are randomised in a 1:1 ratio between CAS and CEA. This trial with a planned sample size of 3,600 patients is scheduled to complete recruitment by the end of 2019.[73]

If uncertainty remains whether revascularisation provides benefit over modern medical treatment alone, patients should be randomised in CREST-2 (including patients with asymptomatic carotid stenosis) or in ECST-2 (including patients with asymptomatic or low-to-intermediate risk symptomatic stenosis).

Figures

Figure 1 – Study flow chart

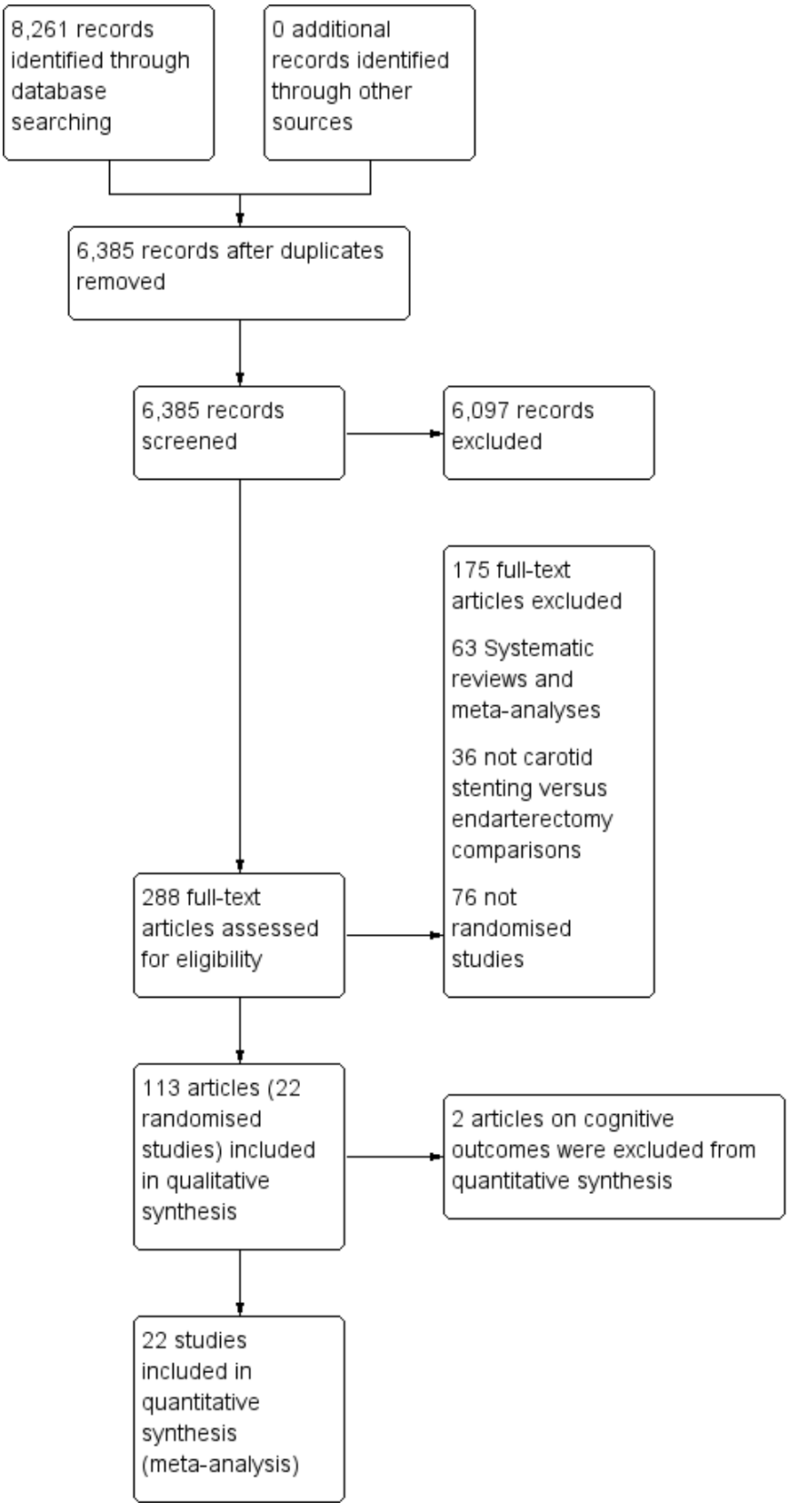
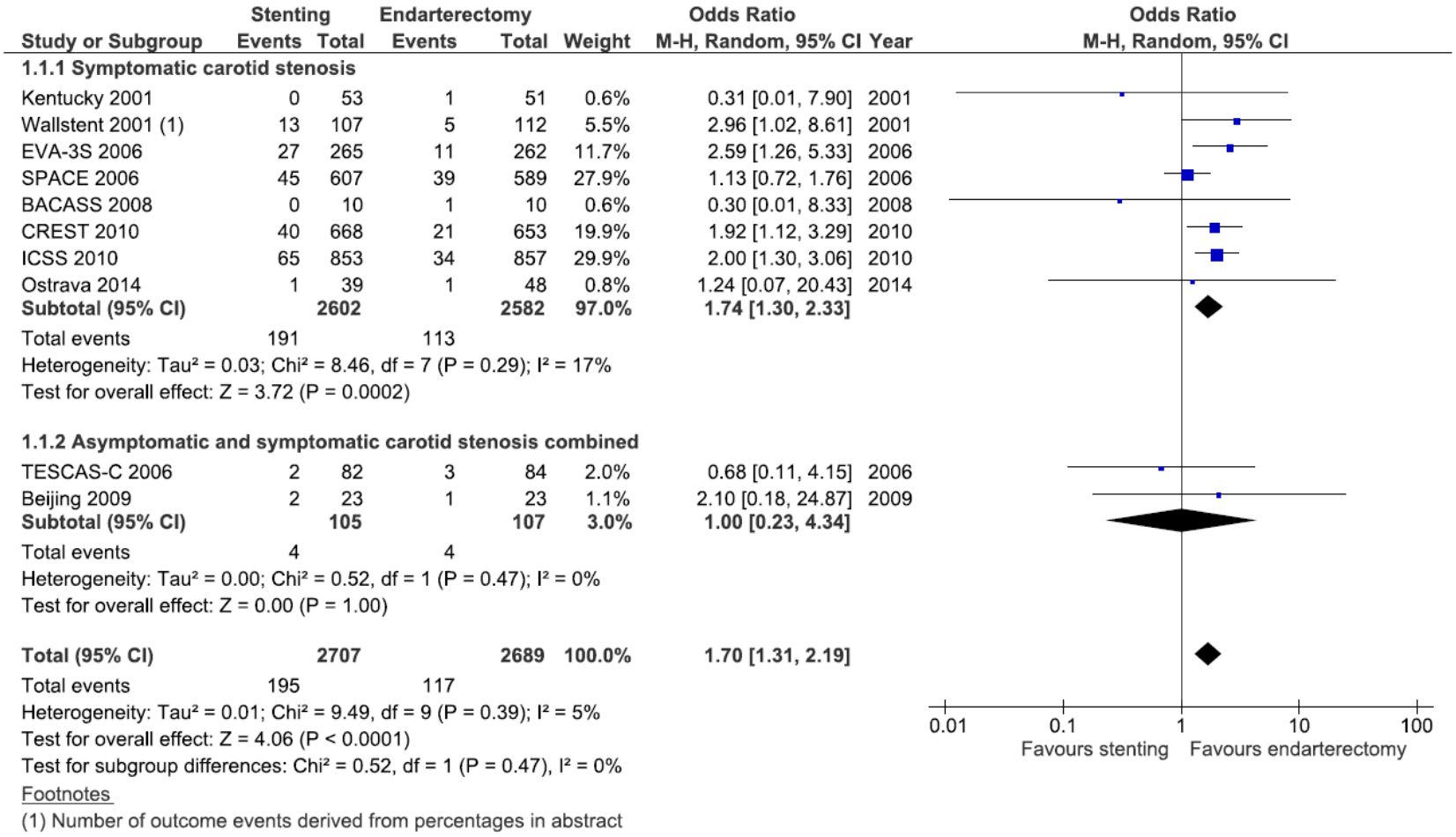


Figure 2 – Death or any stroke between randomisation and 30 days after treatment in patients with <u>symptomatic</u> carotid stenosis



<u>Footnotes</u>

(1) Number of outcome events derived from percentages in abstract

Figure 3 - Death or any stroke between randomisation and 30 days after treatment according to age(<70 years vs. ≥70 years) in patients with <u>symptomatic</u> carotid stenosis

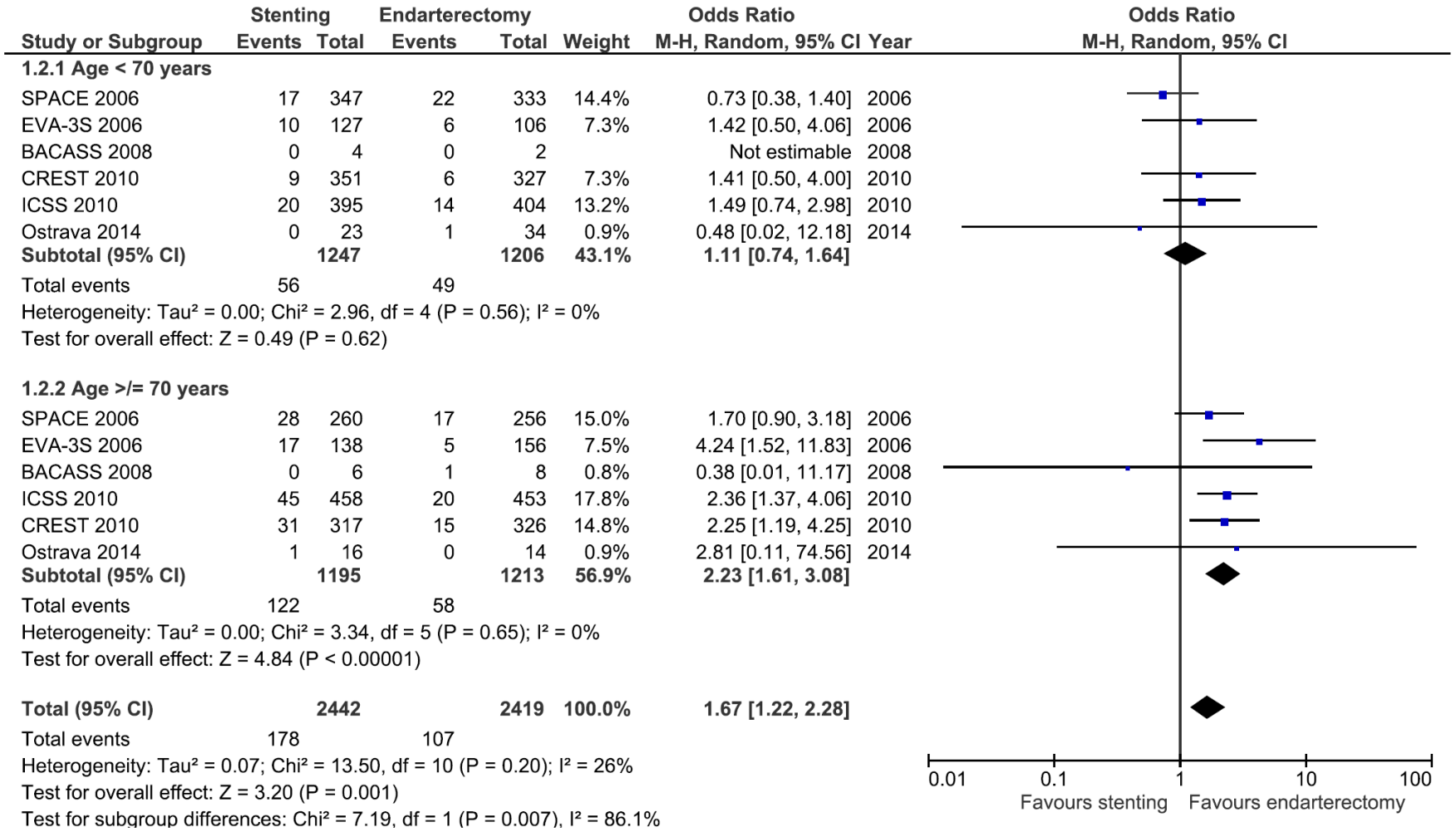


Figure 4 - Death or any stroke between randomisation and 30 days after treatment according to sex (men vs. women) in patients with symptomatic carotid stenosis

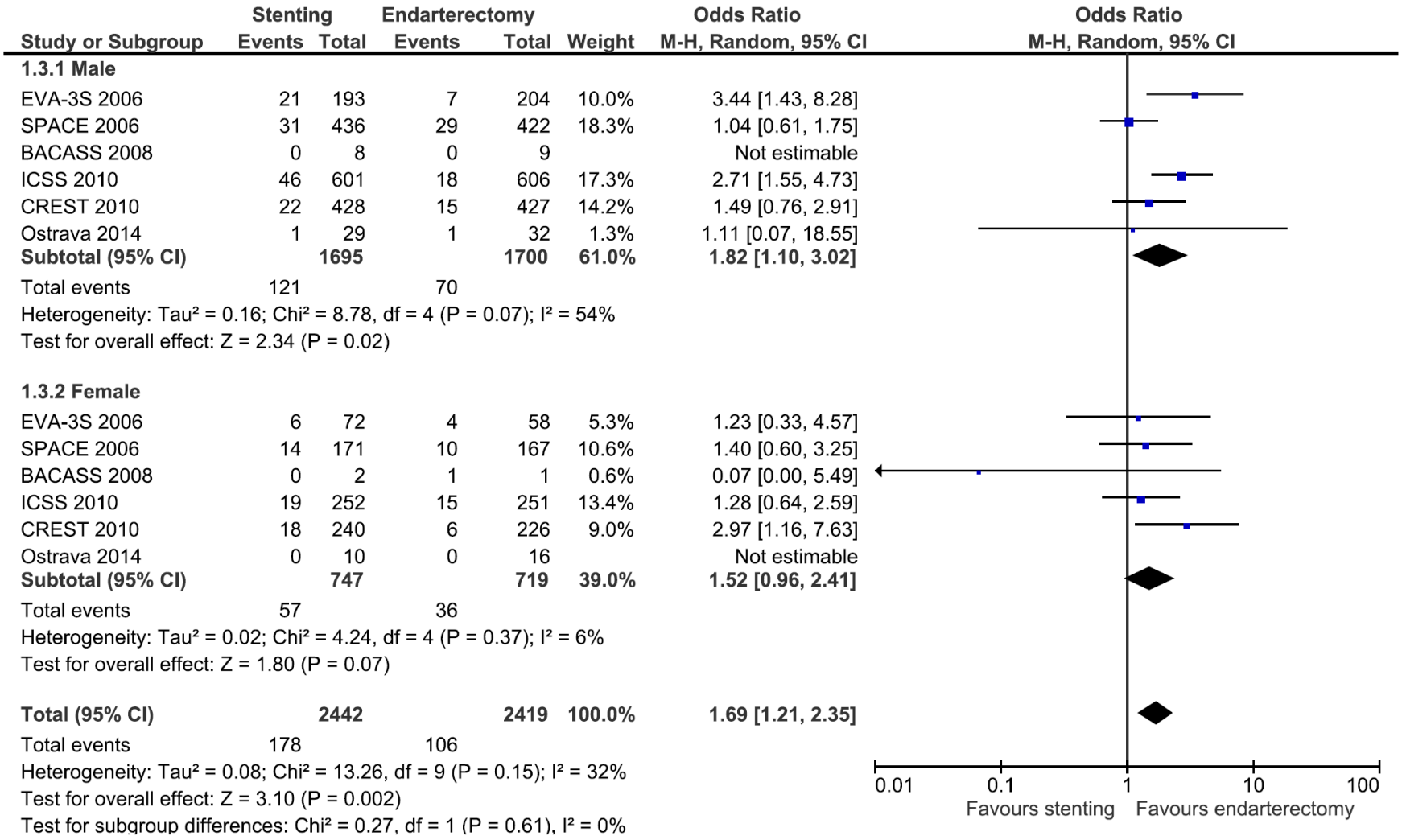
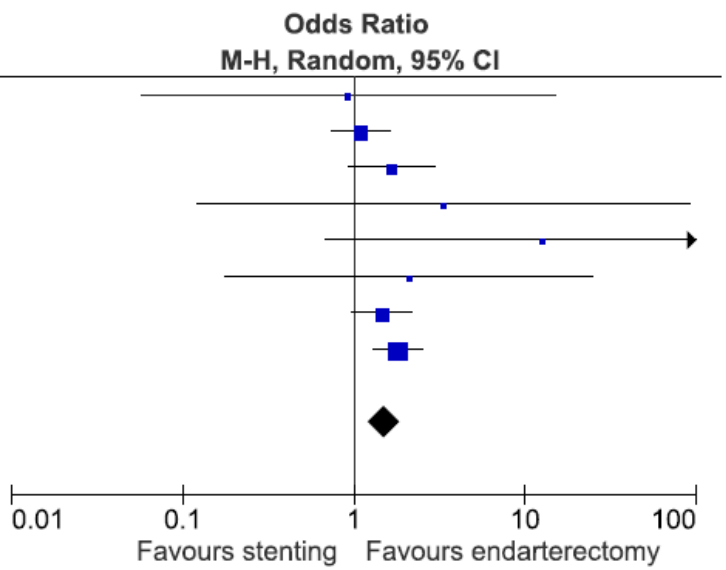


Figure 5 – Death or any stroke between randomisation and 30 days after treatment or ipsilateral stroke until the end of follow-up in patients with <u>symptomatic</u> carotid stenosis

	Stenting		Endarterectomy			Odds Ratio	
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**
Kentucky 2001	1	90	1	83	0.5%	0.92 [0.06, 14.97]	2001
SPACE 2006	56	607	50	589	25.2%	1.10 [0.73, 1.63]	2006
EVA-3S 2006	32	265	20	262	11.7%	1.66 [0.92, 2.99]	2006
BACASS 2008	1	10	0	10	0.4%	3.32 [0.12, 91.60]	2008
Regensburg 2008	5	43	0	44	0.5%	12.71 [0.68, 237.40]	2008
Beijing 2009 (1)	2	23	1	23	0.7%	2.10 [0.18, 24.87]	2009
CREST 2010	61	668	42	653	24.1%	1.46 [0.97, 2.20]	2010
ICSS 2010	105	853	62	857	37.1%	1.80 [1.29, 2.50]	2010
Total (95% CI)		**2559**		**2521**	**100.0%**	**1.51 [1.24, 1.85]**	
Total events	263		176				

Heterogeneity: Tau² = 0.00; Chi² = 6.15, df = 7 (P = 0.52); I² = 0%

Test for overall effect: Z = 4.03 (P < 0.0001)



<u>Footnotes</u>

(1) Includes data from patients with symptomatic and asymptomatic carotid stenosis

Figure 6 - Death or any stroke between randomisation and 30 days after treatment in patients with <u>asymptomatic</u> carotid stenosis

Study or Subgroup	Stenting Events	Stenting Total	Endarterectomy Events	Endarterectomy Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Kentucky 2004	0	43	0	42		Not estimable	2004
CREST 2010	15	594	8	587	39.8%	1.88 [0.79, 4.46]	2010
Ostrava 2014	0	38	0	25		Not estimable	2014
Houston 2014	0	29	0	31		Not estimable	2014
ACT-1 2016	31	1089	6	364	38.3%	1.75 [0.72, 4.22]	2016
SPACE-2 2016	5	197	4	203	16.9%	1.30 [0.34, 4.90]	2016
Carmel Medical Center 2017	2	68	1	68	5.1%	2.03 [0.18, 22.93]	2017
Total (95% CI)		**2058**		**1320**	**100.0%**	**1.72 [1.00, 2.97]**	
Total events	53		19				

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 3 (P = 0.97); I² = 0%

Test for overall effect: Z = 1.95 (P = 0.05)

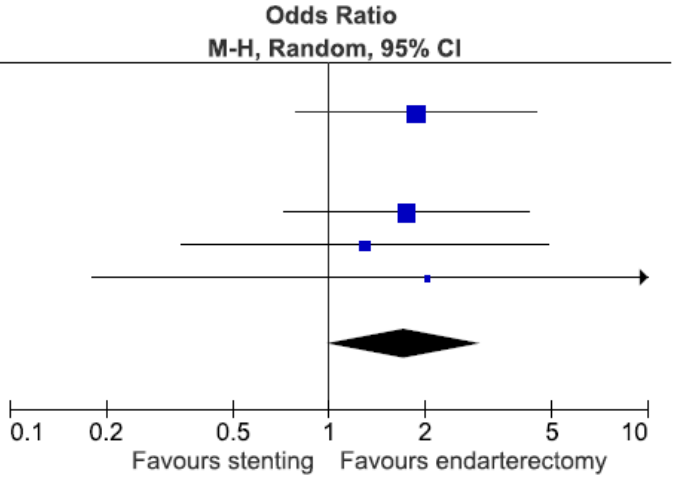
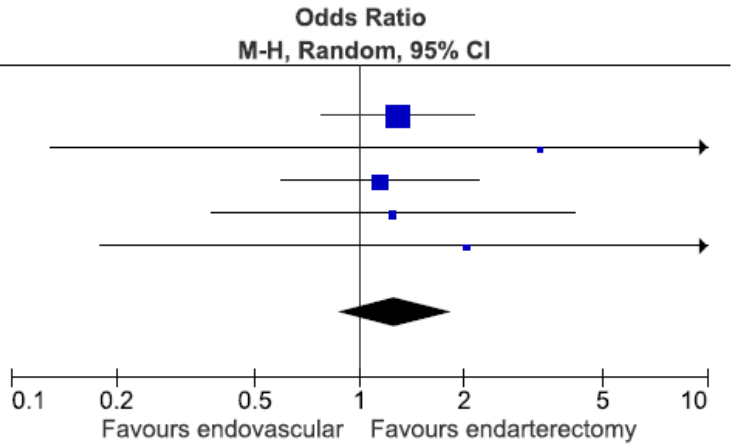


Figure 7 – Death or any stroke between randomisation and 30 days after treatment or ipsilateral stroke until the end of follow-up in patients with <u>asymptomatic</u> carotid stenosis

Study or Subgroup	Endovascular Events	Endovascular Total	Endarterectomy Events	Endarterectomy Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Kentucky 2004	0	43	0	42		Not estimable	2004
CREST 2010	36	594	28	587	54.1%	1.29 [0.78, 2.14]	2010
Houston 2014	1	29	0	31	1.3%	3.32 [0.13, 84.70]	2014
ACT-1 2016	41	1089	12	364	32.6%	1.15 [0.60, 2.21]	2016
SPACE-2 2016	6	197	5	203	9.6%	1.24 [0.37, 4.14]	2016
Carmel Medical Center 2017	2	68	1	68	2.4%	2.03 [0.18, 22.93]	2017
Total (95% CI)		**2020**		**1295**	**100.0%**	**1.27 [0.87, 1.84]**	
Total events	86		46				

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 4 (P = 0.97); I² = 0%

Test for overall effect: Z = 1.24 (P = 0.22)



6.2. Project 2 - Vascular Anatomy Predicts the Risk of Cerebral Ischaemia in Patients Randomised to Carotid Stenting versus Endarterectomy

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Abstract

Background and Purpose **-** Complex vascular anatomy might increase the risk of procedural stroke during CAS. Randomised controlled trial evidence that vascular anatomy should inform the choice between CAS and CEA has been lacking.

Methods **-** We included 184 patients with symptomatic internal carotid artery stenosis who were randomly assigned to CAS or CEA in the ICSS (International Carotid Stenting Study) and underwent magnetic resonance (n=126) or computed tomographic angiography (n=58) at baseline and brain MRI before and after treatment. We investigated the association between aortic arch configuration, angles of supra-aortic arteries, degree, length of stenosis, and plaque ulceration with the presence of at least one new ischaemic brain lesion on diffusion-weighted magnetic resonance imaging (DWI) after treatment.

Results **-** In the CAS group, 49 of 97 patients (51%) and 14 of 87 in the CEA group (16%) were had at least one new DWI lesion after treatment (OR 6.0; 95% CI 2.9–12.4; *P*<0.001). In the CAS group, aortic arch configuration type 2 or 3 (OR 2.8; 95% CI 1.1–7.1; *P*=0.027) and the degree of the largest internal carotid artery angle (≥60° versus <60°; OR 4.1; 95% CI 1.7–10.1; *P*=0.002) were both associated with new DWI lesions, also after correction for age. No predictors for the occurrence of new DWI lesions were identified in the CEA group. The risk for new DWI lesions in CAS increased further over CEA if the largest internal carotid artery angle was ≥60° (OR 11.8; 95% CI 4.1–34.1) than if it was <60° (OR 3.4; 95% CI 1.2–9.8; interaction *P*=0.035).

Conclusions **-** Complex configuration of the aortic arch and internal carotid artery tortuosity increase the risk of cerebral ischaemia during CAS, but not during CEA. Vascular anatomy should be taken into account when selecting patients for stenting.

Introduction

The selection of patients to whom CAS can be offered as an alternative to CEA is controversial. In ICSS, CAS carried a higher risk of non-disabling, procedure-related stroke than CEA, but was as effective at preventing recurrent stroke in the long term.[66] Thus, the choice of the optimal treatment for individual patients should be based on minimising procedural risks. In patients with symptomatic carotid stenosis, the extra risk of procedural stroke associated with CAS seems to be limited to patients older than 70 years,[74] the reasons of which remain unclear. Anatomic features of the aortic arch and supra-aortic arteries may increase procedural risk in CAS,[54-56, 75, 76] but also in CEA.[77] Randomised trial evidence whether vascular anatomy constitutes a risk for procedural stroke independently of age, and whether it should inform the choice between CAS and CEA, has been lacking.

In the magnetic resonance imaging (MRI) substudy of ICSS, three times more patients had new ischaemic brain lesions after CAS than after CEA.[19] In the present analysis of the ICSS-MRI substudy, we investigated the association between vascular anatomies observed on baseline contrast-enhanced magnetic resonance angiography (CE-MRA) or computed tomographic angiography (CTA) and the risk of subsequent procedure-related cerebral ischaemia. We hypothesized that increased difficulty of vascular anatomy would pose patients at greater risk of ischaemia during CAS, but not during CEA.

Methods

In the ICSS-MRI substudy 231 patients with symptomatic carotid stenosis were examined with brain MRI 1-7 days before intervention (pre-treatment scan) and 1-3 days thereafter (post-treatment scan), including diffusion-weighted sequences (DWI) to detect ischaemic brain lesions. The primary outcome was procedural cerebral ischaemia, defined as the presence of ≥1 new DWI lesion on the post-treatment scan.[19] The study was approved by local ethics committees for non-UK centres and by the Northwest Multicentre Research Ethics Committee in the United Kingdom. Patients provided written informed consent to undergo MRI when the scans were not part of clinical routine.

The following anatomic parameters were defined before assessment and then evaluated on baseline CE-MRA or CTA in each patient by a single trained neurologist (MDM) blinded to the findings on brain MRI. To test inter-rater reliability, the scans of the first 40 patients were additionally assessed by a neuroradiologist (FJA). *Degree of stenosis* in the ICA (internal carotid artery) considered for treatment and in the ipsilateral external carotid artery (ECA) was calculated according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria.[78, 79] Patients with ICA near occlusion were not eligible to participate in ICSS. *Length of stenosis* was defined as the distance between the proximal and the distal shoulder of the plaque, or if not clearly visible, between the proximal and distal point where the vessel reached 80% of its original diameter.[77] *Ulcerated stenosis* was defined if fulfilling the criteria of an ulcer niche, "seen in profile as a crater penetrating into a stenotic plaque".[80] In addition, the side of carotid stenosis (left versus right) was recorded.

The current *configuration of the aortic arch,* which represents a combination of variations of the original anatomy and acquired changes, was classified using a modification of the original definition[81], in line with previous studies:[57] type 1, if all supra-aortic arteries originated at the level of the outer curvature of the aortic arch; type 2, if at least one supra-aortic artery originated between the outer and inner curvature; and type 3, if at least one supra-aortic artery originated below the level of the inner curvature (Figure 8). Aortic arch variants such as the left common carotid artery (CCA) originating from the brachiocephalic artery were recorded.[57, 82]

The *angle* between the aortic arch and CCA (or brachiocephalic artery) was measured on the plane defined by the aortic arch by drawing a tangential line along the outer curvature of the aortic arch connecting the origin of the left subclavian artery and the brachiocephalic artery. Then the angle apex was positioned at the origin of the CCA or brachiocephalic artery, one angle leg was drawn parallel to the tangential line and the second one was placed in the centre of the CCA or brachiocephalic artery (Figure 9A). Subsequently, choosing the projection on which the angle was most pronounced, each angle along the course of the brachiocephalic artery, between the brachiocephalic artery and the CCA (in case of carotid stenosis on the right or stenosis on the left and CCA originating the brachiocephalic

artery), and along the CCA and extracranial ICA was recorded if greater than 30° by positioning the angle apex at the turning point of the artery, and the angle legs in the centre of the proximal and distal segment (Figure 9B). The angle between the CCA and ICA was always recorded. Each angle was measured as the change in direction from the caudal to the cranial segment by subtracting the angle between the two legs from 180°, as shown by an asterisk (*) in Figure 9.

In addition, we applied a previously published score of anatomic features considered to increase procedural risk in CAS.[76] The score includes type of aortic arch configuration, arch atheroma, presence of "bovine arch", i.e. origin of the left CCA from the brachiocephalic artery, CCA disease, pinhole stenosis (>90%), ECA stenosis >50%, CCA tortuosity defined as any vessel angulation >90° and ICA tortuosity defined as any vessel angulation >60°.

Statistical Analysis

Inter-observer agreement of anatomical parameters between the two raters was tested with intra-class correlation coefficients (ICC) for continuous variables, with values >0.75 indicating excellent, 0.40-0.75 fair to good, and <0.40 poor reliability,[83] and Cohen's kappa for categorical variables, with values >0.81 indicating excellent, 0.61-0.80 substantial, and 0.41-0.60 moderate agreement.[84]

Associations between side, degree and length of stenosis, plaque ulceration, angle between aortic arch and brachiocephalic artery or CCA, angle between the brachiocephalic artery and CCA (if applicable), largest angle in the CCA, CCA/ICA angle, largest angle in the ICA and type of aortic arch configuration and the primary outcome measure were investigated with binary logistic regression in each treatment group separately. Continuous variables were dichotomized at the population median. All analyses were adjusted for the time interval between treatment and the post treatment MRI, which was longer in the CEA group than in the CAS group.[19] Analyses were additionally adjusted for age, which is the strongest clinical predictor for procedural stroke or death associated with CAS and may itself be

associated with complex vascular anatomy. In addition, we tested whether anatomic parameters which were significantly associated with the primary outcome measure in one treatment group also modified the odds ratio (OR) of the primary outcome measure between CAS and CEA, by testing of statistical interaction. SPSS version 22.0, IBM Corp (Chicago, IL, USA) was used.

Results

Baseline CE-MRA (n= 126) or CTA (n=58) was available in 184 of 231 patients (80%) included in the ICSS-MRI substudy; 97 were assigned to CAS and 87 to CEA (Figure 10). Clinical, anatomic and interventional characteristics were well balanced between groups (Table 1), and broadly comparable between patients with and without available baseline vascular imaging, with the exception of a longer delay to treatment in the latter group.

Inter-rater agreement was excellent for degree of stenosis (ICC=0.951), length of stenosis (ICC=0.886), AO/CCA angle (ICC=0.948), largest CCA angle (ICC=0.968), CCA/ICA angle (ICC=0.887) and largest ICA angle (ICC=0.944; p<0.001), and substantial for aortic arch configuration (0.724; 95% CI 0.535 -0.912; p<0.001).

Procedural cerebral ischaemia was found in 49 patients in the CAS group (51%) and 14 patients in the CEA group (16%; OR 6.0, 95% CI 2.9-12.4, p<0.001). In 6 of the 49 patients in the CAS group and in 2 of the 14 patients in the CEA group, the new DWI lesions on the post-treatment scan were associated with symptoms of ischaemic hemispheric stroke occurring between initiation of treatment and the post-treatment scan. DWI lesions in the remaining patients were silent.[19] Among both treatment groups combined, stroke symptoms occurred in 5 patients with DWI lesions located in the territory supplied by the right carotid artery and in 3 patients with DWI lesions located in the territory supplied by the left carotid artery (with or without involvement of other territories).

In the CAS group, aortic arch configuration type 2 or 3 as opposed to type 1 (OR 2.8, 95% CI 1.1-7.1, p=0.027), as well as the largest angle along the course of the ICA separated at the population median (≥60° versus <60°; OR 4.1, 95% CI 1.7-10.1, p=0.002) were associated with cerebral ischaemia (Figure 11). Both associations remained significant after correction for age (OR 2.9, 95% CI 1.1-7.7, p=0.032; and OR 3.4, 95% CI 1.4-8.9, p=0.01; respectively). To account for potential confounding, we additionally corrected these associations for the duration of the stenting procedure (OR 2.9, 95% CI 1.1-8.1, p=0.038 for ICA angle and OR 2.6, 95% CI 0.9-7.5, p=0.079 for aortic arch configuration, respectively). None of the other parameters predicted the occurrence of cerebral ischaemia (Figure 11). In addition, patients with a higher score of anatomic difficulty[76] were also at increased risk for cerebral ischaemia (OR 3.2, 95% CI 1.3-7.9, p=0.014, values separated at the population median 4.3), but not after correction for age (OR 2.2, 95% CI 0.8-5.7, p=0.123).

In the surgery group, none of the assessed parameters for vascular anatomy or stenosis characteristics (or the expert score for anatomic suitability) were significantly associated with procedural cerebral ischaemia. However, we observed a non-significant trend that patients with aortic arch configuration type 2 or 3 had a higher risk of cerebral ischaemia (OR 3.5, 95% CI 0.7-17.1; Figure 11).

We performed a sensitivity analysis excluding patients without available arch angiography from all analyses: Among 89 remaining patients in the CAS group, the association between cerebral ischaemia and largest ICA angle ≥60° remained statistically significant (OR 3.2, 95% CI 1.2-8.5, p=0.023). In the remaining 76 patients in the CEA group, we again found no significant associations.

The interaction between the largest ICA angle and the effect of treatment (CAS versus CEA) on cerebral ischaemia was statistically significant: the extra risk of DWI lesions in CAS increased further over CEA if the largest ICA angle was ≥60° (OR 11.8, 95% CI 4.1-34.1) than if it was <60° (OR 3.4, 95% CI 1.2-9.8,

interaction p=0.035). The interactions between treatment effect and aortic arch configuration or anatomic suitability score were not significant (Figure 12).

Discussion

In this substudy of a randomised trial comparing CAS versus CEA for symptomatic carotid stenosis, difficult configuration of the aortic arch as well as the largest angle along the course of the ICA were found to increase the risk of procedural cerebral ischaemia in patients treated with stenting, but not in patients undergoing endarterectomy. ICA angulation differentially increased the extra risk of cerebral ischaemia associated with CAS versus CEA.

In most previous studies investigating procedural stroke risk in CAS, vascular anatomy was assessed on digital subtraction angiography (DSA) performed as part of the procedure. To date, no study has compared the impact of vascular anatomy on procedural risks between CAS and CEA. We assessed baseline non-invasive carotid imaging (CE-MRA and CTA) obtained at the time of random assignment to CAS or CEA, before treatment was initiated. These tests are commonly available and used in routine diagnostic work-up for carotid disease. Hence, our findings seem more relevant to inform the choice between CAS and CEA among patients with symptomatic carotid stenosis in routine practice than the results of studies based on pre-procedural DSA.

A complex configuration of the aortic arch and the supra-aortic arteries increases the technical difficulty of the stent procedure. Repeated attempts to advance the catheter and guide wire may cause endothelial micro-trauma or dislodge atherosclerotic plaque and ultimately cause cerebral emboli. The protocol of ICSS did not contain detailed precautions against these complications, such as advice on catheter and guidewire handling, limiting guidewire manoeuver time between flushing, syringe aspiration and cleansing, concentration of heparin in saline flush, use of constant infusion via infusion ports to stopcocks, etc. We are therefore unable to verify that all possible precautions against

thromboembolism were taken. This limitation must be borne in mind when interpreting the results of our study.

Despite this important limitation, key findings of our study were supported by previous research. Faggioli et al. reported a statistically significant association between aortic arch configuration and variants such as origin of the left CCA from the brachiocephalic artery (termed “bovine arch”) and the incidence of neurological complications in patients undergoing CAS.[82] In our study, we were able to confirm an increased incidence of cerebral ischaemia in patients with type 2 or 3 aortic arch configuration. The aortic arch variant mentioned above was present in 11% of our study population, which is within the frequency range reported in the literature, and showed no association with the occurrence of new lesions on MRI after treatment, possibly because of a lack of power.

With regard to tortuosity of the supra-aortic arteries, a higher risk of stroke or death within 30 days of CAS has been reported in patients with ICA/CCA angulation ≥60° on pre-procedural DSA.[56] Other authors described a significant association between tortuosity of the CCA and proximal ICA and the occurrence of complications in CAS, but found no increase in adverse events in patients with tortuous ICA distal to the stenosis.[55] We were able to confirm that greater tortuosity along the course of the ICA increases the incidence of cerebral ischaemia in CAS.

A scoring system derived from expert opinion has been developed to grade the difficulty of vascular anatomy (and hence to judge the suitability of the patient) for CAS.[76] Our results suggest that this system might indeed be able to predict the occurrence of ischaemic brain lesions in patients with symptomatic carotid stenosis undergoing CAS, although perhaps not independently of age.

We found no significant association between supra-aortic vascular anatomy or stenosis characteristics and procedural cerebral ischaemia in the surgery group. Problems with CAS related to navigating

difficult vascular anatomy do not apply to endarterectomy where the atherosclerotic lesion can be directly accessed. However, there was a strong non-significant trend that patients with aortic arch configuration type 2 or 3 had a higher risk of cerebral ischaemia, possibly because these configurations are associated with increased atherosclerotic burden or represent markers of vascular risk in general.

By including two broadly comparable treatment groups in this observational substudy of a randomised trial, we were able to investigate whether a given anatomic risk predictor would modify the relative risk of cerebral ischaemia between CAS and CEA, by formal testing for statistical interaction. The extra risk of DWI lesions associated with CAS increased further over CEA if the largest measured ICA angle was ≥60° (the population median) than if it was <60°. ICA tortuosity therefore seems to be a feature which should specifically be taken into account when deciding between CAS and CEA.

Characteristics of the carotid plaque (degree and length of ipsilateral stenosis and plaque ulceration) studied on CE-MRA and CTA did not predict the occurrence of new DWI lesions after CAS, in line with a previous DSA-based substudy of ICSS.[85] In contrast, several studies showed that the presence of an ulcerated plaque on pre-procedural DSA increases the risk for the occurrence of DWI lesions after stenting.[86-88] In addition, lesion length has been found to constitute a risk factor for adverse events in CAS,[77, 86-88] but also in CEA.[77] CE-MRA and CTA are inferior to DSA in accurately depicting plaque ulceration and lesion length which might explain the discrepant findings between these studies and ours.

Older age has consistently been shown a risk factor for procedural stroke in CAS, but not in CEA.[74] It has been speculated whether the association might be mediated by vascular anatomy. Elongation of the aortic arch and supra-aortic arteries was found to be more prevalent in elderly patients,[54, 57] possibly leading to more difficulties during the CAS procedure. Notably in our analysis, the associations between ICA angulation and aortic arch configuration with cerebral ischaemia in the stenting group

remained significant after correction for age. Hence, vascular anatomy should be taken into account when selecting the appropriate treatment option for an individual patient, independent of the patient's age.

This analysis has further limitations. The fact that the ICSS protocol excluded patients with a stenosis that was thought to be unsuitable for stenting because of proximal tortuous anatomy is likely to have limited the number of patients with very unfavourable anatomy. The full impact of vascular anatomy on CAS risk may therefore have been underestimated in this study. Secondly, although allocation of treatment was randomised, only seven out of 50 study sites participated in the ICSS-MRI substudy, and not all patients enrolled in ICSS at these sites completed the substudy for various reasons, as previously reported.[19] Analysing a subset of a clinical trial implies many of potential risks: the population of the substudy may differ from the original trial population and treatment groups in the substudy may differ in characteristics not measured in the trial because of selection bias. Thirdly, the classification of aortic arch configuration used in this study did not capture the full spectrum of anatomic variation seen in practice; in particular, we did not assess varying degrees of separation between origins of left CCA and brachiocephalic arteries. Fourth, the limited power of our study has several implications: the observed associations in the CAS group must be interpreted with caution. The lack of adjustment for other clinical predictors of CAS risk because of limited power, such as previous stroke and atrial fibrillation,[88, 89] represents an important drawback; and a true impact of vascular anatomy on CEA risk may have been missed. Nonetheless, we think that the observed associations between vascular anatomy and cerebral ischaemia in the stenting group are valid, because they confirm the findings of previous, non-randomised studies. Finally, a key limitation for the generalizability of our findings to modern practice is that technical advances in access routes (cervical versus femoral), stent design (e.g. multi-layered stents) and cerebral protection devices (e.g. flow-reversal) have likely lowered the risk of thromboembolic complications in CAS since the time of recruitment in ICSS. Patients with complex vascular anatomy may derive the greatest benefit from these advances. Protection devices were only

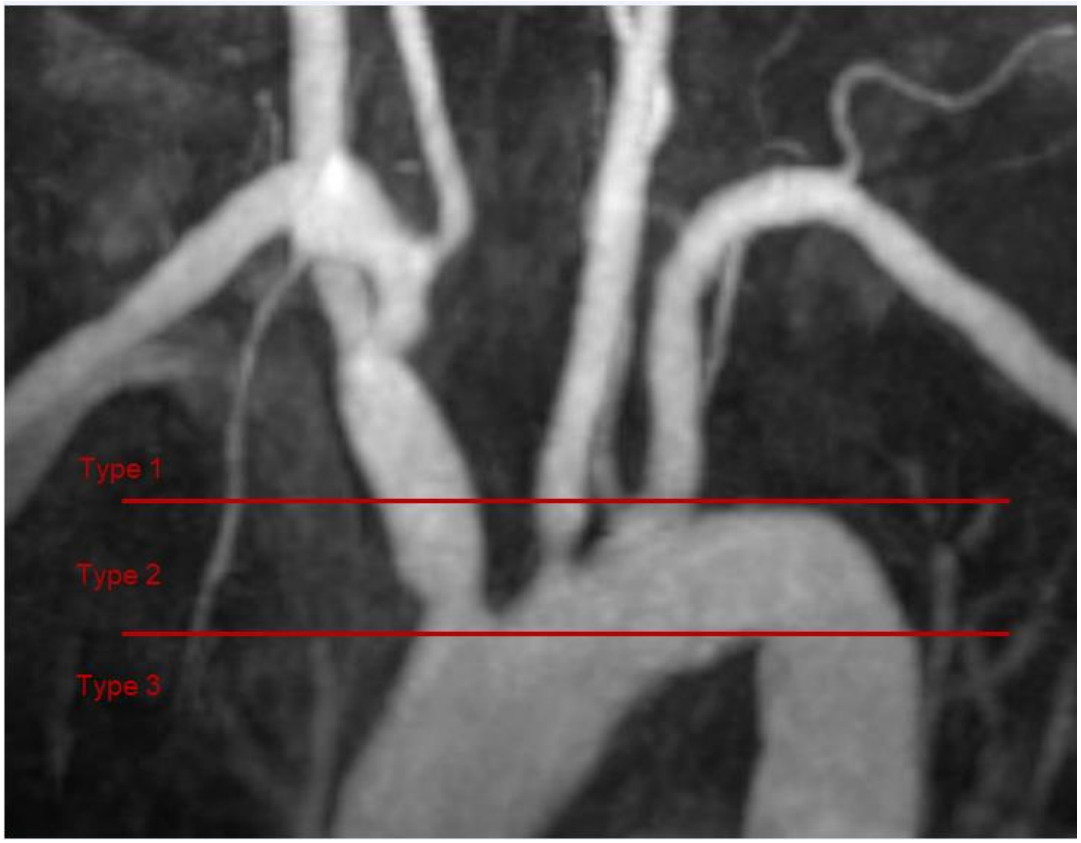
used in a minority of patients and they were mostly of the distal filter type. A previous analysis of the ICSS-MRI data showed that - contrary to their intended purpose and the results of previous MRI-based studies[20] - the use of distal protection devices was associated with an increased risk of DWI lesions.[19]

Conclusions

In this MRI substudy of a randomised trial, we have shown that ICA angulation and difficult configuration of the aortic arch both represent possible risk factors of cerebral ischaemia during stenting for symptomatic carotid stenosis, independent of patient age. No anatomic parameters significantly increasing the risk of endarterectomy were identified. ICA angulation was the sole parameter differentially increasing the risk of cerebral ischaemia with stenting versus endarterectomy. The risk of cerebral ischaemia might be lower and the observed associations with aortic arch configuration and carotid anatomy weaker, or no longer present at all, if technical precautions against thromboembolism were maximized, including the use of modern cerebral protection systems. Nonetheless, vascular anatomy should be taken into account before selecting patients for stenting, irrespective of their age.

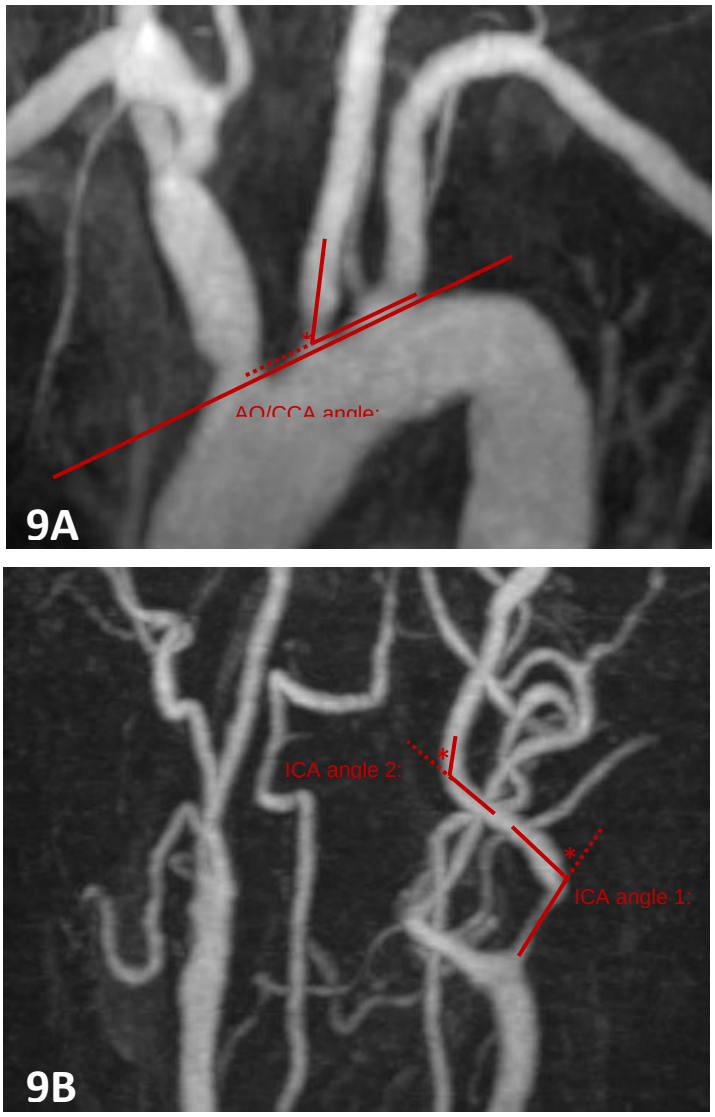
Figures

Figure 8 - Classification of aortic arch configuration according to the origin of the supra-aortic arteries on contrast-enhanced magnetic resonance angiography.



The two horizontal lines mark the outer and inner curvature of the aortic arch. The figure illustrates a type 2 aortic arch configuration.

Figure 9 – Measurement of vessel angles on contrast-enhanced magnetic resonance angiography.



9A - Assessment of the angle between aortic arch and left CCA: first, a parallel line to the upper curvature of the aortic arch is drawn by connecting the origin of the brachiocephalic artery and the left subclavian artery. Then, one angle leg is positioned parallel to the tangent and the other in the centre of the left CCA respecting its distal course. (Of note, the left vertebral artery in this patient, instead of originating from the subclavian artery, has a combined origin with the latter). 9B - Assessment of angles in the course of the ICA: the angle apex is positioned at the turning point of the vessel and the legs at the centre of the ICA respecting its distal and proximal course. Angles were measured as the change in direction from the caudal to the cranial segment by subtracting the angle between the two legs from 180°, as shown by an asterisk (*) in figure 9.

Figure 10 - Study flow diagram.

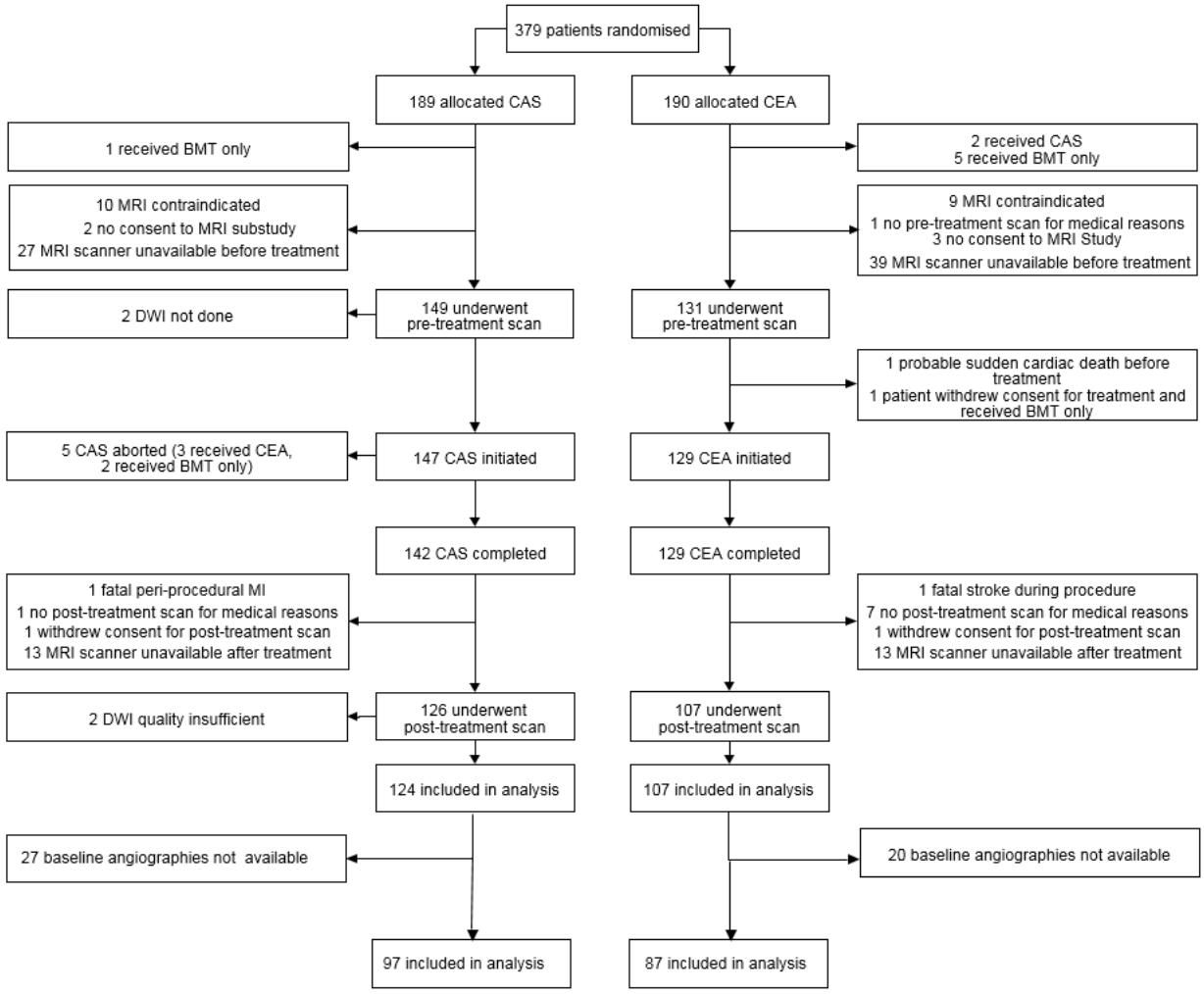
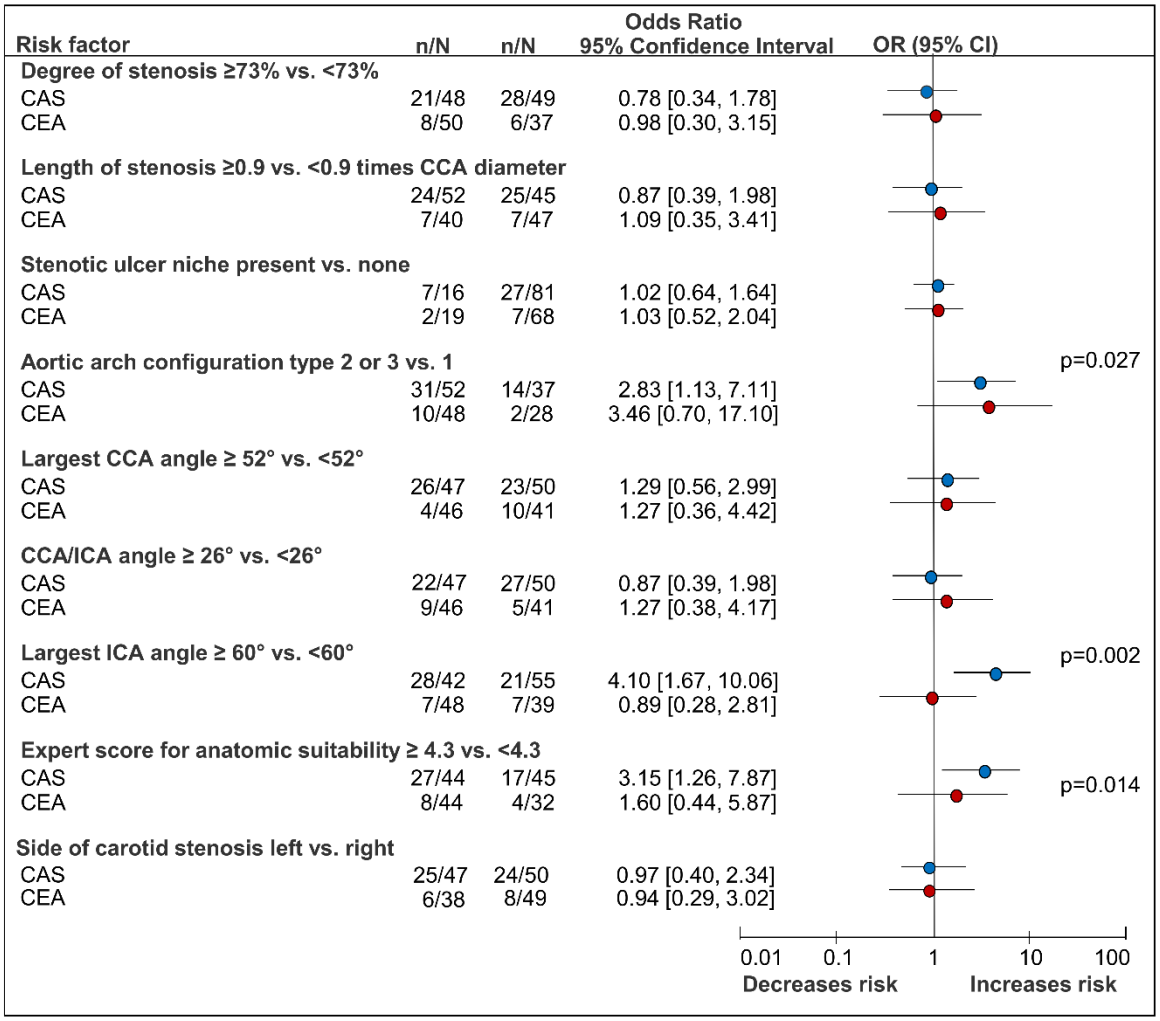


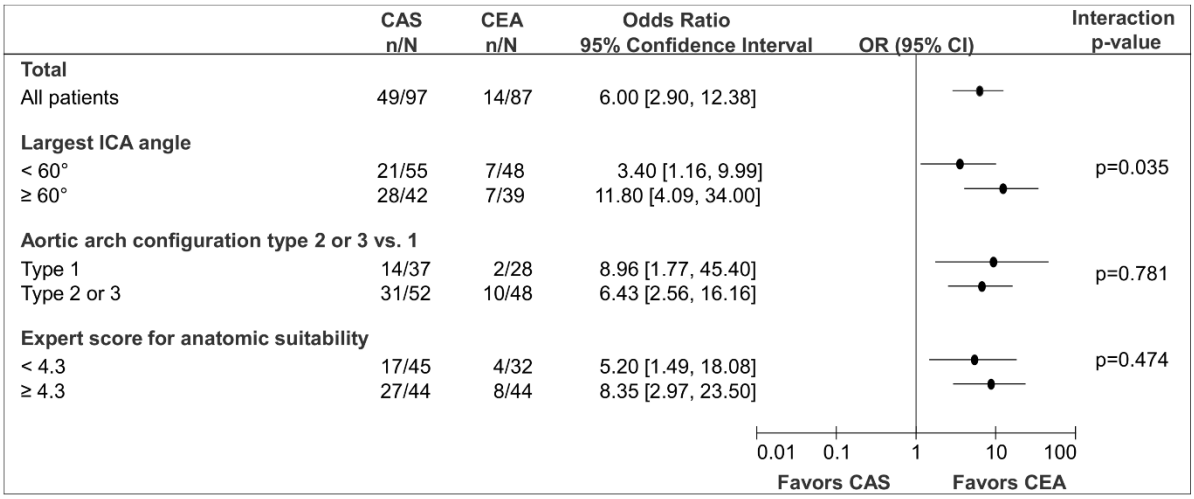
Diagram depicting the two treatment arms of the study, including events that precluded patients from analysis. Scans are magnetic resonance imaging (MRI). BMT = best medical treatment; CAS = carotid artery stenting; CEA = carotid endarterectomy; DWI = diffusion weighted imaging; MI = myocardial infarction

Figure 11 – Risk factor analysis.



Impact of vascular anatomy on the risk of new DWI lesions after carotid artery stenting (CAS) and carotid endarterectomy (CEA). Data are numbers of patients with new DWI lesions on post-treatment MRI scans (n) and total numbers of patients (N) per group. Circles and horizontal lines are odds ratios (OR) and 95% confidence intervals (CI) for presence of new DWI lesions in patients with versus without each risk factor, adjusted for interval between treatment and post-treatment scan and age. Continuous variables (degree and length of stenosis, angles and expert score for anatomic suitability) were separated at the median values of the study population. Missing data: In the CAS group the aortic arch was not visible in 8 patients; in the CEA group the aortic arch was not visible in 11 patients. CCA = common carotid artery; ICA = internal carotid artery.

Figure 12 – Subgroup analysis.



Data are numbers of patients with new DWI lesions on post-treatment scans (n) and total numbers of patients (N) per treatment group. Circles and horizontal lines are odds ratios (OR) and 95% confidence intervals (CI) for presence of new DWI lesions in patients treated with carotid artery stenting (CAS) versus carotid endarterectomy (CEA), adjusted for interval between treatment and post-treatment scan. Continuous variables were separated at the median values of the study population. Interaction p-values are shown. Missing data: In the CAS group the aortic arch was not visible in 8 patients; in the CEA group the aortic arch was not visible in 11 patients. ICA = internal carotid artery.

Tables

Table 1- Patient and intervention characteristics

	CAS (n=97)	CEA (n=87)
Age (years) *median (IQR)*	70.45 (14.4)	71.65 (13.8)
Male *n (%)*	65 (67%)	65 (74.7%)
Vascular risk factors *n (%)*		
Hypertension	67 (69.1%)	63 (72.4%)
Diabetes	18 (18.6%)	19 (21.8%)
Hyperlipidaemia	56 (57.7%)	55 (63.2%)
Smoking	73 (75.3%)	65 (74.7%)
Peripheral artery disease	17 (17.5%)	12 (13.8%)
Coronary heart disease	24 (24.7%)	20 (23.0%)
Qualifying event type *n (%)*		
Retinal or TIA	56 (57.7%)	52 (59.7%)
Hemispheric stroke	41 (42.3%)	35 (40.2%)
Contralateral severe stenosis or occlusion *n (%)*	20 (20.6%)	16 (18.4%)
Delay to treatment (days) *median (IQR)*	30 (63)	40 (52)
Anatomical risk factors		
Left sided stenosis *n (%)*	47 (48.5%)	38 (43.7%)
Type of aortic arch configuration		
Aortic arch type 1 *n (%)*	37 (38.1%)	28 (32.2%)
Aortic arch type 2 or 3 *n (%)*	52 (53.6%)	48 (55.2%)
Left CCA originating from the brachiocephalic artery *n (%)*	11 (11.3%)	10 (11.5%)
Aortic arch not visible *n (%)*	8 (8.2%)	11 (12.6%)
Largest CCA angle *median (IQR)*	48 (45)	52.5 (35)
Angle CCA-ICA *median (IQR*)	24 (22)	27 (21)
Largest ICA angle *median (IQR)*	57 (32)	66 (47)
Degree of stenosis *median (IQR)*	72.13 (20)	75.0 (23)
Length of stenosis *median (IQR)*	6.3 (6)	6.0 (4)
Plaque ulceration *n (%)*	16 (16.5%)	19 (21.8%)
Expert score of anatomic suitability *median (IQR)*	4.0 (2.2)	4.3 (2.2)
Cerebral protection device		
Cerebral protection device used *n (%)*	31 (36%)	-
No cerebral protection device used *n (%)*	55 (64%)	-
Stent design		
Open cell *n (%)*	53 (61.6%)	-
Closed cell *n (%)*	33 (38.4%)	-
Type of anaesthesia		
General anaesthesia *n (%)*	-	71 (81.6%)
Local anaesthesia *n (%)*	-	10 (11.5%)
Patch		

Patch used *n (%)*	-	49 (56.3%)
No patch used *n (%)*	-	19 (21.8%)
Shunt		
Shunt used *n (%)*	-	11 (12.6%)
No Shunt used *n (%)*	-	76 (87.4%)

Baseline data of patients in the stenting and endarterectomy group as well as details of stenting and endarterectomy procedure. Percentages exclude missing data; missing data were: Carotid artery stenting (CAS) group: n=11 patients no interventional details known; carotid endarterectomy (CEA) group: n= 6 patients no information on type of anaesthesia available, n=19 patients no information on patch use available. IQR = interquartile range; TIA = transient ischaemic attack; CCA = common carotid artery; ICA = internal carotid artery.

6.3. Project 3 - Immediate and Delayed Stroke or Death in Stenting versus Endarterectomy for Symptomatic Carotid Stenosis

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Abstract

Background and Purpose - Stenting for symptomatic carotid stenosis (CAS) carries a higher risk of procedural stroke or death than endarterectomy (CEA). It is unclear whether this extra risk is present both on the day of procedure and within 1-30 days thereafter and whether clinical risk factors differ between these periods.

Methods - We analysed the risk of stroke or death occurring on the day of procedure (immediate procedural events) and within 1-30 days thereafter (delayed procedural events) in 4597 individual patients with symptomatic carotid stenosis who underwent CAS (n=2326) or CEA (n=2271) in four randomised trials.

Results - Compared with CEA, patients treated with CAS were at greater risk for immediate procedural events (110 versus 42, 4.7% versus 1.9%; OR 2.6, 95% CI 1.8-3.8), but not for delayed procedural events (59 versus 46, 2.5% versus 2.0%, OR 1.3, 0.9-1.9; interaction p=0.005). In patients treated with CAS, age increased the risk for both immediate and delayed events, while qualifying event severity only increased the risk of delayed events. In patients treated with CEA, we found no risk factors for immediate events, while a higher level of disability at baseline and known history of hypertension were associated with delayed procedural events.

Conclusions - The increased procedural stroke or death risk associated with CAS compared with CEA was caused by an excess of events occurring on the day of procedure. This finding demonstrates the need to enhance the procedural safety of CAS by technical improvements of the procedure and increased operator skill. Higher age increased the risk for both immediate and delayed procedural events in CAS, mechanisms of which remain to be elucidated.

Introduction

In patients with recently symptomatic carotid stenosis, CAS is associated with a higher risk of stroke or death in the peri-procedural period than CEA.[61] Within this 30-day period, it has been unclear whether the extra risk associated with CAS is present both on the day of procedure and within 30 days thereafter.

The Carotid Stenosis Trialists' Collaboration (CSTC) pooled data of individual patients with symptomatic carotid stenosis enrolled in the Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S), the Stent-Protected Angioplasty versus Carotid Endarterectomy trial (SPACE), the International Carotid Stenting Study (ICSS) and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). All trials have completed their long-term follow-up and the results have been published.[63, 64, 66, 67]

In the present analysis, we compared the risk of stroke or death occurring on the day of procedure and within 1-30 days following both treatments. In addition, we investigated if clinical risk factors for stroke or death differed between these periods.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. This meta-analysis includes individual patient data from EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), CREST (NCT00004732) and ICSS (ISRCTN 25337470). Patients were recruited from 2000-2005 in EVA-3S, from 2001-2006 in SPACE, from 2001-2008 in ICSS, and from 2000-2008 in CREST. Ethics approval for the contributing trials was obtained at the competent institutional review boards and all patients provided written informed consent. The pooled analysis of individual patient data was agreed upon at the design stage of these trials.[90] All four trials were

randomised clinical trials with blinded outcome adjudication. Detailed inclusion and exclusion criteria of all trials have been reported previously.[49, 91-93] In summary, all trials included patients with symptomatic moderate to severe carotid stenosis (≥50% reduction of lumen diameter measured according to the method used in the NASCET), who were equally suitable for either procedure. CREST additionally included patients with asymptomatic carotid stenosis, but only data from symptomatic patients were included in the present analysis. Patients were randomly allocated in equal proportions to CAS or CEA.

In EVA-3S, SPACE and ICSS all stents had to be CE (Communauté Européenne) marked. In CREST, the protocol specified the use of the *RX Acculink* stent. In EVA-3S, the use of distal filter protection devices became mandatory early in the trial, after the risk of stroke within the procedural period was found to be unacceptably high in patients treated with unprotected CAS. In CREST, the use of the *RX Accunet* embolic protection device was recommended whenever feasible. In ICSS and SPACE, the use of protection devices remained optional throughout the trials. Surgeons could perform standard or eversion endarterectomy under local or general anaesthesia, with or without the use of shunts or patches. CAS or CEA were deemed initiated if the patient had been given general or local anaesthetic in preparation for the intervention.

The primary outcome event for this analysis was stroke or death occurring either on the day of treatment (immediate procedural event) or within 1-30 days thereafter (delayed procedural event). Stroke was defined as an acute deficit of focal neurological function which led to symptoms lasting longer than 24 hours, resulting from intracranial vascular disturbance (ischaemia or haemorrhage). For the present analysis, only the first event was considered, because we assumed that second events (e.g. death or another stroke occurring after a first stroke) would rarely be independent of the first event. In addition, second events of the same type occurring in the peri-procedural may not have been reported separately in the source trials.

Statistical analysis

The primary analysis population included all patients in whom the randomly allocated treatment was initiated (per-protocol analysis).[61] Patients crossing over to the other treatment, those who did not receive either treatment, and those who died before treatment were excluded. A per-protocol analysis rather than intention-to-treat analysis was chosen because the main difference between the two analysis populations consisted of patients who did not receive either treatment (Figure 13). In addition, the primary aim of our research question was to investigate whether the risk of stroke or death differed between CAS and CEA in two distinct time periods (day of treatment and 1-30 days after treatment).

Data were analysed with generalized linear mixed-effects models (GLMM) with binomial error and logit link function, with a random intercept for each source trial. The CAS versus CEA treatment effect was expressed as an odds ratio (OR) with 95% confidence interval (CI), both for immediate procedural events and for delayed procedural events, with CEA as the reference treatment. To investigate whether the CAS versus CEA treatment effect differed between the immediate and delayed procedural period, we reshaped the analysis set to include two observations (rows) per patient, one for immediate procedural events and one for delayed procedural events, and included a random intercept for each source trial and patient. We chose this approach to be able to investigate whether the odds ratio for the primary outcome differed between the immediate and the delayed procedural period by formal testing of statistical interaction. We did this by including treatment (CAS versus CEA), time of event (immediate versus delayed) and an interaction term between treatment and time in the model. We performed a sensitivity analysis excluding patients who had the primary outcome event in the immediate procedural period from the population at risk in the delayed procedural period.

We investigated if the following baseline patient characteristics were associated with stroke or death in the immediate (day 0), the delayed (day 1-30) and the full procedural period (day 0-30) by a forward variable selection approach based on the Akaike information criterion (AIC), in each treatment group separately: patient age and sex, systolic blood pressure at baseline, previous diagnosis of hypertension,

diabetes mellitus, hyperlipidaemia and coronary heart disease, any history of smoking (current or past), modified Rankin Scale at baseline, degree of ipsilateral stenosis measured according to NASCET criteria[78] dichotomized into moderate (50-69%) or severe (70-99%), presence of contralateral stenosis (≥70%) according to NASCET criteria[78] or occlusion, and severity of the qualifying event (analysed by trend: hemispheric ischaemic stroke > TIA > ocular ischaemia [including amaurosis fugax or retinal infarction]). Qualifying event severity was analysed by trend because patients with previous ocular events have a lower risk of future ischaemic stroke compared to patients who had a TIA, and patients with a TIA have a lower risk than patients who had a hemispheric stroke.[36]

To investigate if associations between patient characteristics and procedural events differed between the immediate and the delayed procedural period, we again used the data structure with two observations per patient (using the subset with CAS or CEA) and included baseline patient characteristics which were associated with immediate or delayed procedural events and their interactions with time.

In addition, we fitted a GLMM for the immediate, the delayed and the full procedural period each, adjusted for any variables identified as significant predictors of the primary outcome event in any of these periods by the forward selection approach described above. We used these models to display the risk factor associations for the different periods in a forest plot.

A p-value of <0.10 for interaction terms was considered statistically significant. For all other statistical analyses, a p-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed as complete case analyses (no imputation of missing values), using the statistical software environment R (Version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 5956 patients were enrolled in the four contributing trials. The pooled per-protocol analysis set included 4,597 patients, 2,271 of whom received CEA and 2,326 CAS. Reasons for exclusion of patients from the per-protocol analysis are provided in Figure 13. Baseline characteristics were well balanced between the stenting and the endarterectomy group (Table 2). In ICSS, SPACE and EVA-3S closed-cell stents were used in 61.8%, while in CREST the use of the open-cell *RX Acculink* stent device was mandatory. In CREST 96.1% of patients were treated with the *RX Accunet* embolic protection device, while in ICSS, SPACE and EVA-3S 61% of patients were treated with various embolic protection devices.[94]

A total of 257 patients had a stroke or died during the full 30-day procedural period, 169 in the CAS group (7.3% risk) and 88 in the CEA group (3.9% risk; OR 1.94, 95% CI 1.50-2.53). Compared with CEA, patients treated with CAS more often had a stroke or died on the day of procedure (110 versus 42 patients, 4.7% versus 1.9% risk; OR 2.64, 95% CI 1.84-3.78), but not between 1 and 30 days thereafter (59 versus 46 patients, 2.5% versus 2.0% risk, OR 1.26, 0.84-1.87; Figure 14). The treatment effect ORs differed significantly between the time periods (interaction p=0.006). We performed a post-hoc sensitivity analysis excluding all patients who experienced the outcome measure on the day of procedure (n=152) from the population at risk for an event between day 1-30. This yielded very similar results compared to our original model and we again found no significant difference in the occurrence of the outcome measure between CAS and CEA between day 1-30 (OR 1.30, 95% CI 0.87-1.91). Only two patients who had a stroke on day 0, had another stroke between day 1-30.

Details of outcome events are provided in Table 3. In both treatment groups, the large majority of strokes, both occurring on the day of procedure and between day 1 and 30 after procedure, were located in the territory supplied by the treated carotid artery. In both treatment groups combined, 2 of 151 strokes (1%) occurring on the day of procedure and 15 of 95 strokes (16%) occurring between day 1 and 30 after the procedure were of haemorrhagic type.

In the stenting group, the forward selection model identified age and smoking as independent predictors of immediate procedural events: age was positively (OR 1.54 per decade, 95% CI 1.21-1.95) and smoking was negatively (OR 0.61, 95% CI 0.40-0.91) associated with stroke or death occurring on the day of treatment. For the delayed procedural period (day 1-30 after treatment) age (OR 1.63 per decade, 95% CI 1.21-2.21) and qualifying event (QE) severity (stroke > TIA > ocular ischaemia, analyzed by trend; OR 1.54, 95% CI 1.03-2.31) were found to be significant predictors for stroke or death. There were no significant differences in the strength of the associations between these risk factors and events between the immediate and delayed procedural period with the exception of smoking (interaction p=0.061; Figure 15). For the entire procedural period both age (OR 1.63 per decade, 95% CI 1.37-1.95) and QE severity (analysed by trend; OR 1.31, 95% CI 1.04-1.64) remained significant predictors for stroke or death occurring between day 0-30 after treatment.

In the endarterectomy group, we found no significant predictors for immediate stroke or death. However, a higher level of disability at baseline, assessed with the modified Rankin Scale, was a significant predictor for delayed stroke or death (OR 1.42, 95% CI 1.10-1.84). The association between this risk factor and procedural stroke or death did not differ significantly between the immediate and delayed procedural period (Figure 16). Higher level of disability at baseline and history of hypertension were found to be significant predictors for stroke or death in the full procedural period (OR 1.24, 95% CI 1.01-1.51, and OR 1.84, 95% CI 1.04-3.33, respectively).

Discussion

In this pooled analysis of individual patient data from four randomised clinical trials, we found that the excess occurrence of procedural stroke or death associated with CAS compared with CEA was limited to the day of treatment. For the remainder of the procedural period, there was no difference in the risk of stroke or death between the two treatments. Age was a risk factor for stroke or death in the

CAS group, notably both in the immediate (day of procedure) and the delayed procedural period (day 1-30).

Procedure-related stroke or death in carotid revascularization is commonly defined as all events occurring within 30 days after the procedure. However, from experience, most such events occur on the day of treatment. In our analysis, we were able to confirm this assumption. We found that about two thirds (110 out of 169) of all procedural stroke or death outcomes in patients receiving CAS and about half (42 out of 88) of the events in patients treated with CEA occurred on the day of procedure. On the day of procedure, the risk of procedural stroke or death was significantly higher in CAS than in CEA, but between 1 and 30 days thereafter the risk was similar in both treatment groups.

Stroke or death events occurring on the day of procedure might differ in pathogenesis and associated risk factors from events occurring later in the 30-day period. However, as far as clinical risk factors are concerned, we found no significant differences in the observed associations between the immediate and delayed procedural period. Most importantly, increasing age among patients treated with CAS was significantly associated with procedural stroke or death in both the immediate (day of procedure) and delayed procedural (day 1-30) period. It has been hypothesized that higher age is associated with vessel elongation and therefore more pronounced angulation of the vasculature, and that the resulting, more complex anatomy of the supra-aortic arteries could lead to increased technical difficulty of the procedure and hence to the higher risk associated with CAS in older patients.[54, 57] Our finding that age is associated with an increase in both immediate and delayed procedural events argues against vascular anatomy as the sole mediating factor. Older patients might have more unstable atheromatous lesions than younger patients, which may cause thromboembolic strokes not only on the day of procedure, but also during the following days.[95, 96] However, the mechanisms mediating the association between age and procedural risk of CAS remains poorly understood; our finding that older patients are also at risk for delayed procedural events adds to the complexity of this matter.

Interestingly, we found that history of smoking decreased the risk of stroke or death on the day of procedure in the CAS group. A similar association with stroke or death in the full procedural period was already described in ICSS.[40] One possible explanation for this rather surprising relationship might have been that smokers were younger than non-smokers and hence at lower risk. Indeed, the mean age of smokers in our study population was 67.5 years, while the mean age of non-smokers was 72.5 years. However, the effect of smoking was adjusted for age in our analysis indicating that the inverse association with stroke or death is not confounded by age. Nevertheless, we cannot rule out that this unexpected finding was due to residual confounding by patient characteristics not measured in the trials.

The fact that the excess of procedural stroke or death occurring in the stenting group is limited to the day of procedure suggests that these events might potentially be avoided by improving operator skill or technical aspects of the procedure itself. Whether the use of intraluminal protection devices reduces the risk of embolic stroke is a matter of ongoing controversy. In EVA-3S the use of distal filter protection devices became mandatory early in the trial, after the risk of stroke within the procedural period was found to be about three times higher in patients treated with unprotected CAS. In CREST the use of cerebral protection devices was recommended whenever feasible. In ICSS and SPACE the use of protection devices remained optional throughout the trials. The ICSS-MRI substudy showed that the use of distal filter devices, which was the type of protection device predominately used in all four contributing trials, was associated with an increased risk of new ischaemic brain lesions after the procedure.[19] Two small randomised studies comparing stenting with embolic filter protection to unprotected stenting confirmed these results.[46, 47] In light of these findings, considerable uncertainty remains, whether distal filter devices truly increase the safety of CAS.

Irrespective of this question, one must acknowledge the fact that the trials contributing to the present analysis largely enrolled their patients in the 2000s and that considerable technical advance of CAS has

occurred since. For example, alternative methods of cerebral protection such as systems exerting a reversal of blood flow before the lesion is crossed with the catheter have been introduced and appear to lower the risk of thromboembolism.[97] However, not all patients tolerate flow reversal in the carotid artery and to date insufficient data exist to justify a general recommendation for the use of such devices, although the available data seem promising.[98, 99] The ARMOUR (Proximal Protection with the Mo.MA Device During Carotid Stenting) study investigated the safety and effectiveness of proximal embolic protection with the Mo.MA device and showed a very low 30-day stroke rate of 0.9%.[99] Another possible source of thromboembolism to the brain during stenting is the aortic arch and the access vasculature. To avoid the necessity of navigating the aortic arch with potentially difficult anatomy, alternative access routes such as direct carotid access have been proposed.[100] The ROADSTER (Reverse Flow Used During Carotid Artery Stenting Procedure) study investigating CAS with direct transcarotid access and proximal embolic protection showed a very low 30-day stroke rate of 1.4%.[101] Although the ARMOUR and the ROADSTER studies enrolled patients with both symptomatic and asymptomatic carotid stenosis, which renders a direct comparison with our results difficult, these low stroke rates are remarkable.

In the endarterectomy group, the only clinical risk factors found to influence the risk of stroke or death were a higher level of disability at baseline and known history of hypertension. Hypertension increased the risk for stroke or death over the entire procedural period of 30 days, a finding which is consistent with previous reports.[36]

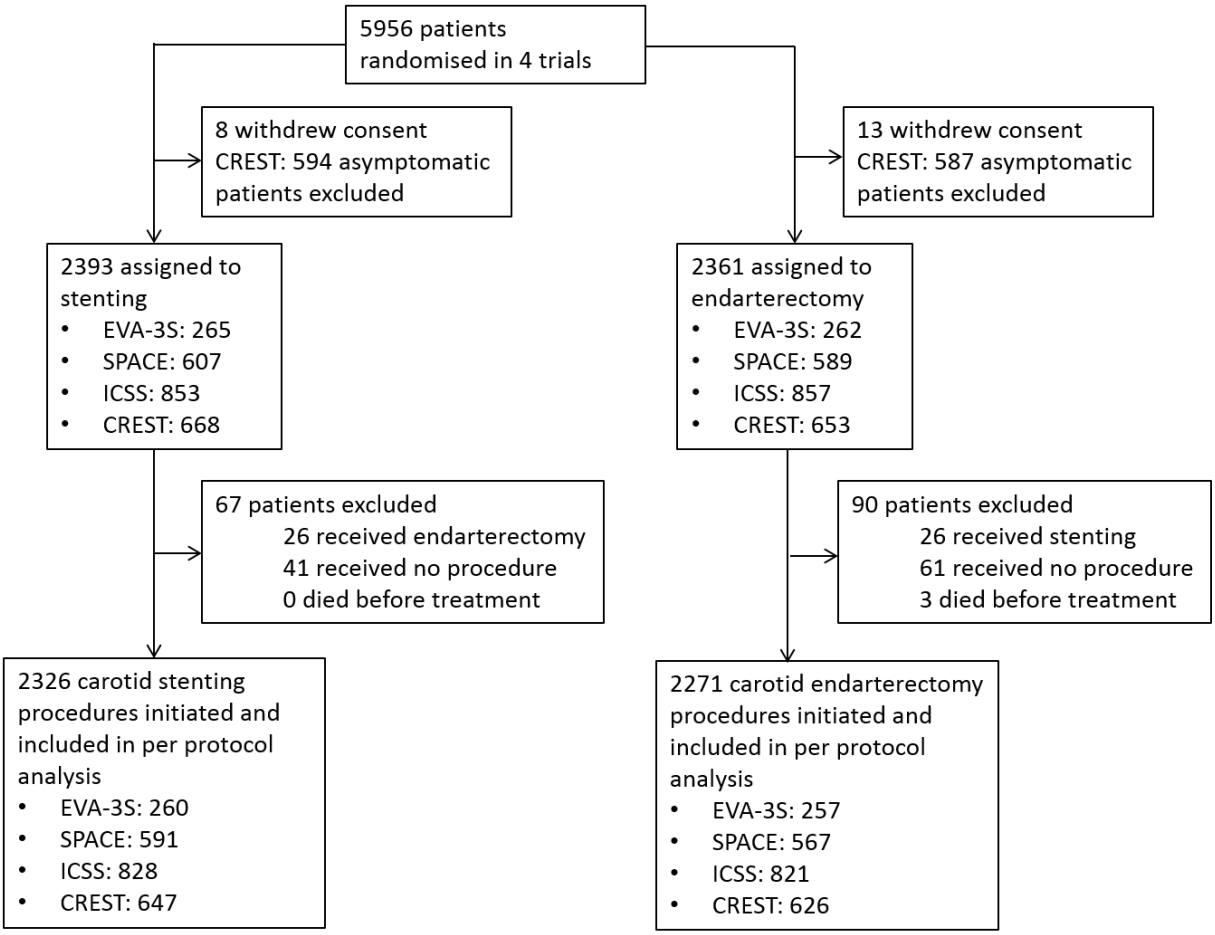
This analysis has important limitations. First, we did not collect information as to the mechanism of stroke across all four contributing trials (e.g. embolic, haemodynamic, stent thrombosis). Second, with regard to events occurring on the day of treatment, we do not know if the events occurred during or after the procedure, as the exact timing of stroke or death was not recorded. Third, all participating trials recruited patients between 2000 and 2008. Since that time, there has been substantial progress in the development of new stent designs, the introduction of cerebral protection devices and new

access routes, all of which may help reduce the risk of immediate procedural complications. Thus, the peri-procedural stroke rate among patients with symptomatic carotid stenosis using current generation CAS technologies and cerebral protection devices may be lower than demonstrated in these 4 trials. Fourth, in order to be able to investigate whether the CAS versus CEA treatment effect differed between the immediate and delayed procedural period by formal tests of statistical interaction, we included all patients in the population at risk for an event between day 1-30, even those who experienced an event on the day of procedure (n=152). However, in a post-hoc analysis excluding these patients from the population at risk for an event between day 1-30, the results remained essentially unchanged.

The fact that the increased risk of stroke or death in the stenting group is limited to the day of procedure demonstrates the need to improve the procedural safety of carotid artery stenting. This may potentially be achieved by technical advances (route of access, stent design and new protection devices) and increased operator skill. However, more data from randomised trials to evaluate these new devices and access routes are needed. Our finding that age is associated with both immediate and delayed procedural events in the stenting group argues against vascular anatomy as the sole mediating factor. Other, currently unknown factors are likely to contribute to this effect and remain to be elucidated.

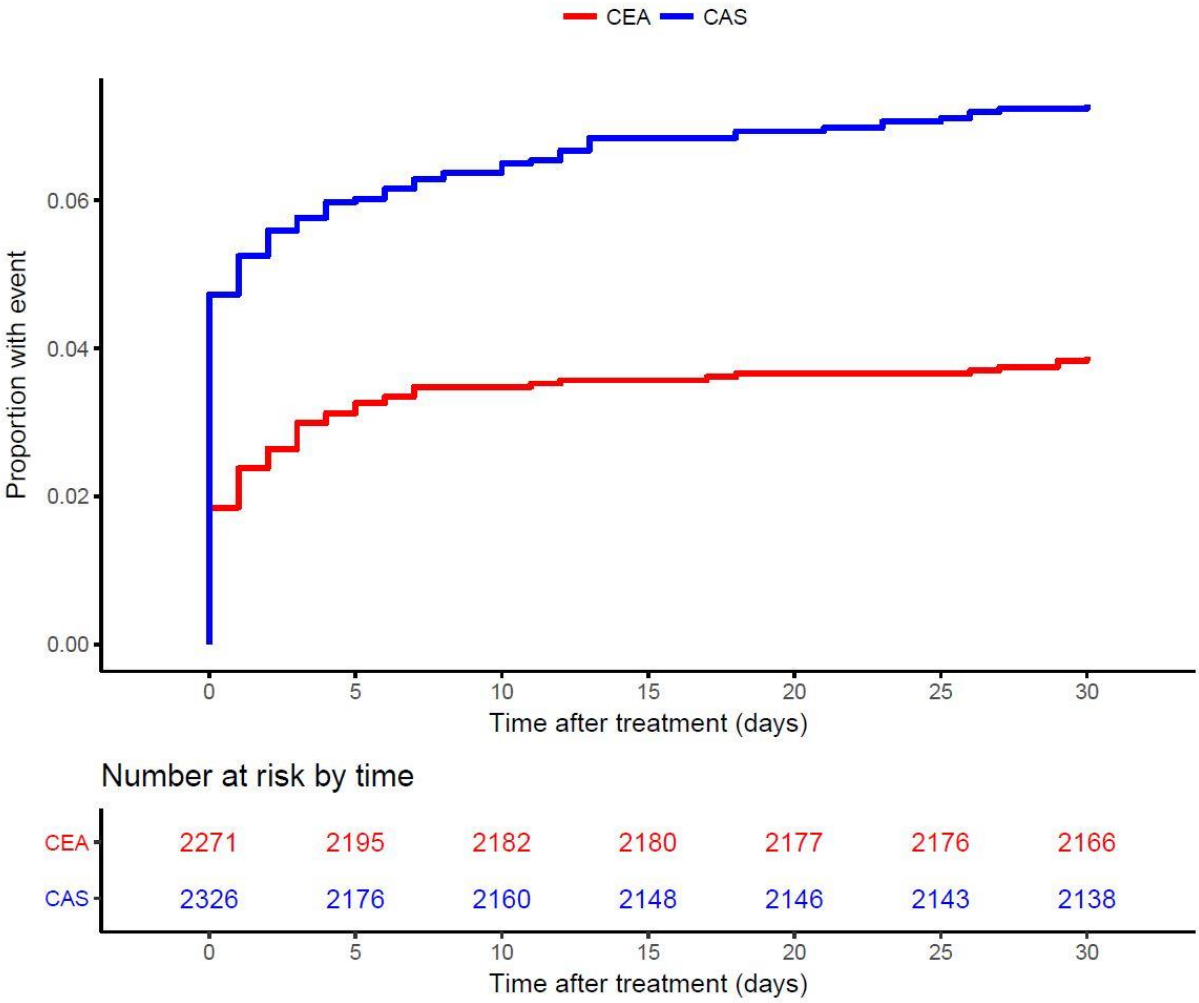
Figures

Figure 13 - Study flow chart.



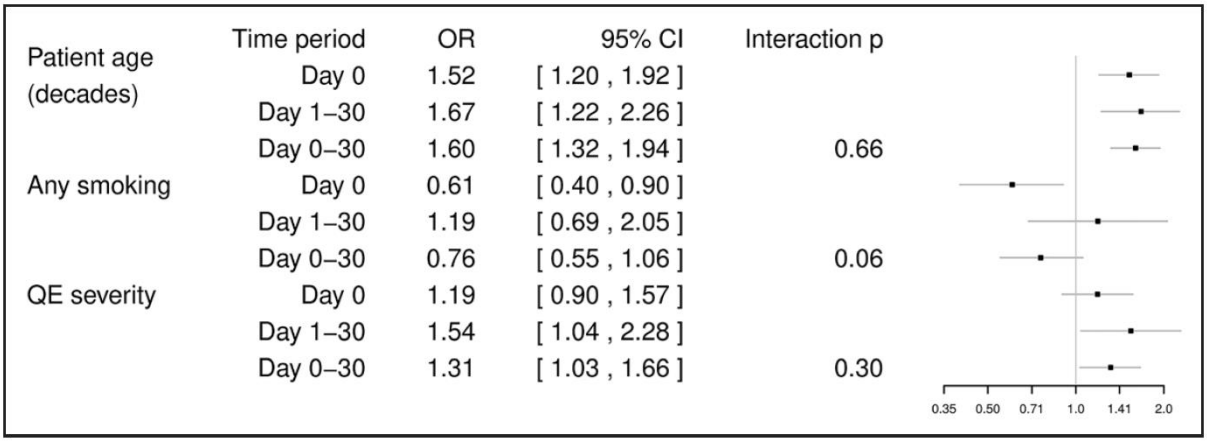
Study flow chart depicting all patients in trials included in meta-analysis as well as events that precluded them from analysis.

Figure 14 - Kaplan-Meier curve.



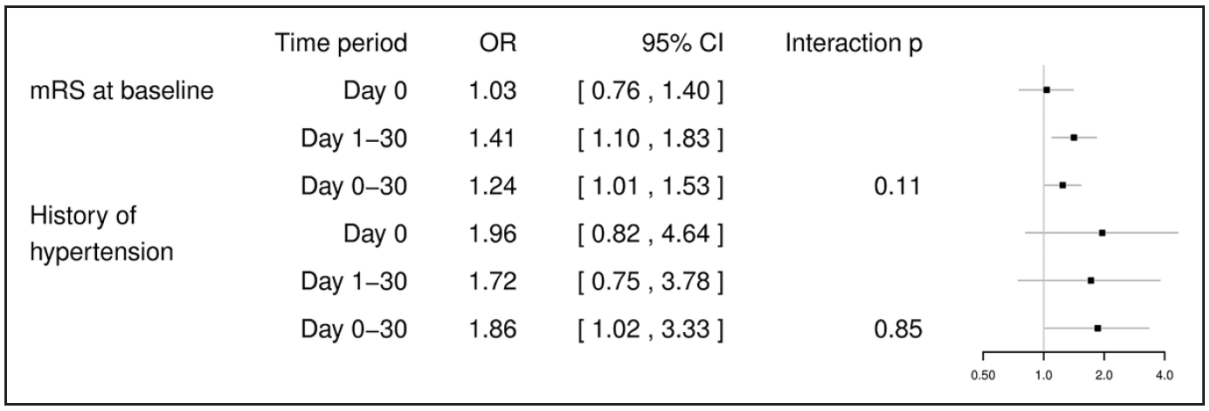
Kaplan-Meier curve of the cumulative incidence of periprocedural stroke or death within 30 days after treatment in the stenting and endarterectomy group seperately. Number of events: 169 events in the CAS group, 87 events in the CEA group. The cumulative incidence of stroke or death was 7.3% in the CAS group and 3.9% in the CEA group.

Figure 15 **- Effects of baseline variables on the risk of stroke or death in patients treated with carotid artery stenting.**



Forest plot showing the odds ratios for the effects of the three baseline variables patient age (in decades), any history of smoking, and qualifying event severity on the incidence of stroke or death on the day of treatment (day 0), between day 1 and 30, or within 30 days in patients treated with stenting. ORs were estimated by three separate GLMMs (one for the day of treatment, one for day 1- 30, and one for the full procedural period), each containing age, any history of smoking, and QE severity (stroke > TIA > ocular ischaemia). CI=Confidence Interval; OR=Odds Ratio; QE=Qualifying event; GLMM=general linear mixed model.

Figure 16 **- Effects of baseline variables on the risk of stroke or death in patients treated with carotid endarterectomy.**



Forest plot showing the odds ratios for the effects of the baseline variable "mRS at baseline", and history of hypertension on the incidence of stroke or death on the day of treatment (day 0), between day 1 and 30, or within 30 days in patients treated with endarterectomy. ORs were estimated by three separate GLMMs (one for the day of treatment, one for day 1-30, and one for the full procedural period). OR=Odds ratio; CI=confidence interval; GLMM=general linear mixed model; mRS=modified Rankin scale

Tables

Table 2 - Patient characteristics at baseline.

	CEA (n = 2271)	**CAS** (n = 2326)
Male *n (%)*	1593/2271 (70.1%)	1615/2326 (69.4%)
Age *years (mean, SD)*	69.4 ± 9.2	69.2 ± 9.2
Systolic blood pressure *mmHg (mean, SD)*	142.8 ± 21	143.9 ± 21
Hypertension *n (%)*	1718/2264 (75.9%)	1743/2264 (75.3%)
Diabetes *n (%)*	576/2270 (25.4%)	575/2325 (24.7%)
Hyperlipidaemia* or LLT *n (%)*	1471/2271 (64.7%)	1462/2326 (62.9%)
LLT	1443/2271 (63.5%)	1439/2326 (61.9%)
Smoking (current or past) *n (%)*	1472/2254 (65.3%)	1489/2308 (64.5%)
Coronary artery disease *n (%)*	630/2218 (28.4%)	626/2276 (27.5%)
mRS at baseline *n (%)*		
0 *n (%)*	1133/2252 (50.3%)	1167/2305 (50.6%)
1 *n (%)*	587/2252 (26.1%)	622/2305 (27.0%)
2 *n (%)*	365/2252 (16.2%)	358/2305 (15.5%)
>2 *n (%)*	167/2252 (7.4%)	158/2305 (6.9%)
Degree of ipsilateral carotid stenosis		
Moderate (50-69%) *n (%)*	443/2271 (19.5%)	441/2326 (19%)
Severe (70-99%) *n (%)*	1828/2271 (80.5%)	1885/2326 (81.0%)
Contralateral stenosis or occlusion	301/2037 (14.8%)	308/2326 (14.8%)
Qualifying event type		
Ocular ischaemia *n (%)*	388/2256 (17.2%)	394/2312 (17.0%)
Transient ischaemic attack *n (%)*	835/2256 (37.0%)	847/2312 (36.6%)
Hemispheric stroke *n (%)*	1033/2256 (45.8%)	1071/2312 (46.3%)
Days from QE to treatment *median (IQR)*†	29.0 (13.0, 67.0)	26.0 (11.0, 61.0)
Treatment within 7 days of QE *n (%)* †	214/1907 (11.2%)	277/1926 (14.4%)

*Baseline data of patients in the stenting and endarterectomy group. Percentages exclude missing data. CEA = carotid endarterectomy; CAS = carotid artery stenting; LLT = lipid lowering therapy: EVA-3S recorded LLT use at baseline but patients were only considered to be taking LLT if started >3months prior to randomisation. SPACE and CREST collected data on LLT use at randomisation. ICSS did not collect information on LLT use at baseline but did collect these data at the one-month follow-up, which were included in the table. QE = qualifying event; SD = standard deviation.*Data were not collected in SPACE. †Date of the qualifying event before randomisation was not collected in the SPACE trial initially, but for the pooled analysis, these dates were gathered where available.*

Table 3 - ***Outcome events occurring on the day of procedure vs. day 1-30 thereafter.***

	CAS (n=2326)		**CEA** (n=2271)		**Total** (n=4597)	
	Day of procedure	**Day 1-30**	**Day of procedure**	**Day 1-30**	**Day of procedure**	**Day 1-30**
Any stroke *n(%)*	109	52	42	43	151	95
Ipsilateral	100 (92%)	47 (90%)	42 (100%)	37 (86%)	142 (94%)	84 (88%)
Non-ipsilateral	9 (8%)	5 (10%)	0 (0%)	6 (14%)	9 (6%)	11 (12%)
Ischaemic stroke *n (%)*	108 (99%)	48 (92%)	41 (98%)	32 (74%)	149 (99%)	80 (84%)
Haemorrhagic stroke *n (%)*	1 (1%)	4 (8%)	1 (2%)	11 (26%)	2 (1%)	15 (16%)
Non-stroke death	1	7	0	3	1	10

Data are numbers and percentages of patients who experienced an outcome event. CAS = carotid artery stenting; CEA = carotid endarterectomy.

6.4. Project 4 - Secular trends in procedural stroke or death risks of stenting versus endarterectomy for symptomatic carotid stenosis – a pooled analysis of randomised trials

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Abstract

Background- Over the past decades, stroke risk associated with carotid disease has decreased, reflecting improvements in medical therapy and a more rigorous control of vascular risk factors. It is less clear whether the procedural risk of carotid revascularization has declined over time.

Methods and Results - We analysed temporal changes in procedural risks among 4,597 patients with symptomatic carotid stenosis treated with carotid artery stenting (CAS; n=2,326) or endarterectomy (CEA; n=2,271) in 4 randomised trials between 2000 and 2008, using generalized linear mixed-effects models with a random intercept for each source trial. Models were additionally adjusted for age and other baseline characteristics predicting treatment risk. The primary outcome event was any procedural stroke or death, occurring during or within 30 days after revascularization. The procedural stroke or death risk decreased significantly over time in all patients (unadjusted OR per year 0.91, 95% CI 0.85-0.97, p=0.006). This effect was driven by a decrease in the CEA group (unadjusted OR per year 0.82, 95% CI 0.73-0.92, p=0.003), whereas no significant decrease was found after CAS (unadjusted OR 0.96, 95% CI 0.88-1.04, p=0.33). CEA patients had a lower procedural stroke or death risk compared to CAS patients, and the difference significantly increased over time (interaction p=0.031). After adjustment for baseline characteristics, the results remained essentially the same.

Conclusions - The risk of stroke or death associated with carotid endarterectomy for symptomatic carotid stenosis decreased over an 8-year period, independent of clinical predictors of procedural risk. No corresponding reduction in procedural risk was seen in patients treated with stenting.

Introduction

Over the past decades the risk of stroke associated with carotid disease appears to have decreased,[102] reflecting improved medical care and risk factor control. In some patients, the risk of stroke under conservative management may be so low that the risks associated with carotid revascularisation are no longer justified. This is of relevance for patients with asymptomatic carotid stenosis but potentially also for patients with symptomatic carotid stenosis. On the other hand, the procedural risk associated with carotid revascularisation may also have decreased over time preserving the net benefit of invasive treatment. The evidence to support or refute such a trend is currently limited.

We conducted an analysis of the temporal change in procedural stroke or death risks associated with CEA and CAS in four large randomised controlled trials which enrolled patients with symptomatic carotid stenosis between 2000 and 2008, using data at individual patient level.[63, 64, 66, 67] We hypothesized that procedural risks associated with carotid artery revascularisation would have declined over time. In addition, we assumed that risks of CAS might have decreased more strongly than CEA risks, due to technical development and increasing experience.

Methods

This meta-analysis includes individual patient data from EVA-3S (NCT 00190398), SPACE (ISRCTN 57874028), CREST (NCT00004732) and ICSS (ISRCTN 25337470) and is based on the same dataset as Project 3 (section 6.3.)[63, 64, 66, 67] The present analysis was pre-specified during one of the regular steering committee meetings of the Carotid Stenosis Trialists' Collaboration by representatives from the involved trials. All four trials randomly allocated patients with symptomatic moderate to severe carotid stenosis (≥50% reduction of lumen diameter measured according to the method used in the NASCET[34]), who were equally suitable for either procedure to CAS or CEA. CREST additionally included

patients with asymptomatic carotid stenosis, but these patients were excluded from the present analysis.

In EVA-3S, SPACE and ICSS any stent with a CE (Communauté Européeene) mark could be used. In CREST the protocol specified the use of *RX Acculink* stent. In EVA-3S the use of distal filter protection devices became mandatory early in the trial.[103] In CREST, the protocol specified the use of the *RX Accunet* embolic-protection device whenever feasible. In ICSS and SPACE the use of protection devices remained optional throughout the trials. Surgeons were allowed to perform standard or eversion endarterectomy under local or general anaesthesia, with or without the use of shunts or patches.

The primary outcome of the present analysis was any stroke or death occurring within 30 days after treatment. Stroke was defined as an acute deficit of focal neurological function, which led to symptoms lasting longer than 24 hours, resulting from intracranial vascular disturbance (ischaemia or haemorrhage).

Statistical analysis

The analysis population included all patients in whom the randomly allocated treatment was initiated (per-protocol analysis).[61] The following baseline characteristics of patients from all 4 source trials were summarized descriptively for an early (2000-2004) and a late enrolment period (2005-2008): sex, patient age, modified Rankin Scale (mRS) at baseline, systolic blood pressure at baseline, history of hypertension, diabetes, lipid-lowering therapy (LLT), smoking (past or present), coronary heart disease, degree of ipsilateral carotid stenosis according to NASCET criteria[6], presence of contralateral carotid stenosis (≥70%) according to NASCET criteria[6] or occlusion, qualifying event (QE) type, and days from QE to treatment.

To investigate whether the risk of stroke or death within 30 days of treatment changed over time, we used GLMMs with binomial error and logit link function, with a random intercept for each source trial.

We fitted one GLMM for all patients, using treatment received (CAS vs. CEA), year of treatment (as continuous variable) and the interaction between treatment received and year of treatment as explanatory variables to investigate if any difference in procedural risk between CAS and CEA changed over time. In addition, a separate GLMM with only year of treatment as explanatory variable was fitted for each treatment group separately. To adjust our models, we identified those baseline patient characteristics which were most strongly associated with procedural risk for stroke or death, using backward model selection based on Akaike's information criterion (AIC), in all patients and in each treatment group separately. We continued dropping variables from the multivariate models as long as the AIC for the reduced model was smaller than the AIC of the former model. Due to the high percentage of missing values, we did not include days from QE to treatment in the backward model selection. The models investigating the effect of time on procedural risk were subsequently adjusted for all baseline characteristics selected in this manner. We performed a post-hoc sensitivity analysis adjusting all models for days from QE to treatment.

Results

In total, 4,775 patients with symptomatic carotid stenosis were enrolled in the contributing trials. The pooled per-protocol analysis set included 4,597 patients, 2,271 of whom received CEA and 2,326 CAS (Figure 13, section 6.3). EVA-3S enrolled patients from 2000-2005, SPACE from 2001-2006, ICSS from 2001-2008, and CREST from 2000-2008. Baseline characteristics were well balanced between treatment groups as previously reported.[63, 64, 66, 67] The proportions of patients with a history of hypertension, coronary heart disease, smoking and severe ipsilateral carotid stenosis were significantly higher in the later enrolment period (2005-2008) compared to the early enrolment period (2000-2004; Table 4). The proportion of patients taking LLT significantly increased from 52.4% in the early enrolment period to 74.1% in the late enrolment period. Level of functional disability measured by the mRS was higher and the time from QE to treatment was shorter in the late enrolment period (Table 4).

Crude percentages of patients with the primary outcome measure per year are shown in Table 5. In the CEA group, crude procedural risks were 7.1% between 2000-2002 and 2.0% between 2007-2008. In the CAS group, crude risks were 8.2% between 2000-2002 and 5.8% between 2007-2008 (Table 5). The risk of stroke or death during the procedural period for both treatments combined decreased significantly over time (unadjusted OR per year 0.91, 95% CI 0.85-0.97, p=0.006). After adjustment for baseline characteristics which were independently associated with the primary outcome in both treatment groups combined (age, mRS, hypertension, diabetes, and severe ipsilateral carotid stenosis), the decline in risk remained essentially unchanged (adjusted OR 0.89, 95% CI 0.83-0.95, p<0.001). In the post-hoc sensitivity analysis additionally adjusting our models for days from QE to treatment, the results remained again essentially the same (OR 0.91, 95% CI 0.84-0.99, p=0.023).

In the CEA group alone, the risk of procedural stroke or death also decreased significantly over time, both in the unadjusted model (OR 0.82, 95% CI 0.73-0.92, p=0.003), in the model adjusted for mRS, hypertension, diabetes, coronary heart disease, ipsilateral severe carotid stenosis, and contralateral stenosis >50% or occlusion (OR 0.82, 95% CI 0.72-0.93, p=0.002), and in the model additionally adjusted for days from QE to treatment (OR 0.81, 95% CI 0.71-0.93, p=0.005).

In the CAS group alone, the change in procedural risk over time was not statistically significant in the unadjusted model (OR 0.96, 95% CI 0.88-1.05, p=0.33), in the model adjusted for age, hypertension, LLT, smoking, and qualifying event type (OR 0.95, 95% CI 0.87-1.05, p=0.28), nor in the model additionally adjusted for days from QE to treatment (OR 0.95, 95% CI 0.86-1.06, p=0.38).

Patients receiving CEA were at lower risk of procedural stroke or death than patients receiving CAS over the entire enrolment period (OR 0.47, 95% CI 0.35-0.62, adjusted for year of treatment; OR 0.46, 95% CI 0.35-0.62, adjusted for year of treatment, age, mRS at baseline, history of hypertension and diabetes, severe ipsilateral carotid stenosis). This difference in procedural risk became more

pronounced over time (unadjusted interaction: OR 1.17, 95% CI 1.02-1.35, p=0.031, adjusted interaction: OR 1.16, 95% CI 1.01-1.34, p=0.038; Figures 17 and 18). The interaction was of similar magnitude but no longer statistically significant when additionally adjusting for days from QE to treatment (OR 1.13, 95% CI 0.96-1.34, p=0.142).

Discussion

In this meta-analysis of individual patient data from 4 RCTs, the risk of stroke or death associated with carotid revascularization for symptomatic carotid stenosis decreased significantly over time. When patients were analysed separately by treatment, the decline in risk over time was only statistically significant in patients treated with carotid endarterectomy. This decrease in risk was independent of clinical risk factors.

Data from the Oxford Vascular Study (Oxvasc) showed a decline in age and sex specific stroke incidence in an unselected population in Oxfordshire, UK between 1981-84 and 2002-04,[104] coinciding with a significant increase in the use of blood pressure lowering, antiplatelet and lipid-lowering medication between the two periods. Likewise, meta-regression analyses suggested a decline in annual stroke risk associated with asymptomatic carotid stenosis over the past 20 years.[102] Indirect evidence on a decline in stroke risk in patients with symptomatic carotid stenosis can be gathered from TIA registries: the 90-day stroke risk after a TIA caused by large artery atherosclerosis was consistently reported to be around 20% in the last decade, [105, 106] but dropped to merely 6% in a recent publication.[107] While some of this decrease may probably have been accounted for by more rapid specialized assessment and early carotid revascularization in selected patients, changes in medical therapy are also likely to be important. A study from Denmark of patients with symptomatic carotid stenosis found a decline in the rate of any recurrent cerebrovascular event prior to carotid revascularization from 29% to 2.5% after introduction of an optimized medical treatment regimen consisting of dual antiplatelet and statin therapy.[108]

In the original European and North American symptomatic carotid endarterectomy trials establishing the benefit of CEA in patients with symptomatic carotid stenosis, only a minority of patients received statins.[8] Since these trials were conducted, medical therapy and risk factor management has improved, not only with more widespread use of statins but also with stricter control of blood pressure and management of other risk factors. A lower stroke risk under conservative management than observed in previous trials may obviate the need for invasive revascularization in many patients with symptomatic or asymptomatic carotid disease. On the other hand, any decline in the procedural risk of stroke or death associated with carotid revascularization would act towards maintaining the net benefit of invasive treatment. Existing literature suggests a decline in procedural risk associated with CEA for asymptomatic carotid stenosis. [109] However, reliable data on procedural risks for symptomatic carotid stenosis have been sparse,[110] and it remained unknown if temporal changes differed between CAS and CEA.

Our findings now provide strong evidence for a decline in procedural stroke or death risk associated with revascularization of symptomatic carotid stenosis over time. The availability of data at individual patient level from several randomised clinical trials yielded important strengths. First, we were able to show temporal changes with greater statistical power than was possible at the level of a single trial. Second, we were able to minimize the risk of confounding of the effect of time on procedural risk by a potential change in the characteristics of patients included in the trials during the course of enrolment. Some of the baseline risk factors which were associated with the procedural risk of stroke or death in both treatment groups combined (history of hypertension, disability measured by the mRS, and degree of ipsilateral carotid stenosis) became more prevalent in the later enrolment period. After adjusting for these risk factors, the results remained essentially the same.

A third strength of our study was that we were able to investigate whether any temporal trend in procedural risks would differ between CEA and CAS, owing to the randomised design of the source trials. Wide-spread use of CAS only started a few years before the start of the trials contributing to this meta-analysis. We therefore hypothesized that technical development and increasing experience would lead to a stronger decline in procedural risk with CAS compared to CEA. Surprisingly, we found the opposite to be true. It is possible that investigators became more selective in the patients they included in the trials as enrolment went on, in terms of characteristics that were not measured. If this was the case, any such selection effect must have had a stronger impact on procedural risks of CEA than on risks of CAS. Previous studies suggest that neurophysiological monitoring and intra-operative assessment of the treated carotid artery during the CEA procedure became more frequent over time and that these factors are associated with a lower short-term stroke or death risk.[111, 112] It is possible that these factors were also of importance in our study population, but the data were not available for the present analysis. For CAS however, with growing experience, interventionists might have accepted patients in the trials with more difficult anatomy, which may have counteracted any learning-curve effect.

The CREST investigators have previously reported a non-significant decline in the procedural stroke or death risk associated with CAS over time, and an initial decrease followed by an increase in CEA risk for which there was no conclusive explanation.[113] Of note, CREST initially included only patients with symptomatic carotid stenosis, but then additionally allowed patients with asymptomatic carotid stenosis in the trial during the course of enrolment. This change in the proportion of the two groups limited the investigation of a temporal trend. In the present, pooled analysis, only patients with symptomatic carotid stenosis were included from the CREST trial. The combined analysis of data from four trials allowed for a more reliable investigation of temporal changes in treatment risks, and whether these differed between CAS and CEA, than was possible at the level of a single trial.

The question whether any change in procedural risk of carotid revascularization over time would be explained by an increased use of lipid-lowering therapy was of particular interest. We found an increase of patients taking LLT from 52% in the early enrolment years to 74% in the late enrolment years. However, LLT did not explain procedural risk in the entire study population or in patients treated with CEA. LLT reduced procedural risk in patients treated with CAS but the temporal change in CAS risk was not statistically significant either unadjusted or adjusted for LLT and other risk factors.

As both risk of stroke and procedural risk of revascularisation appear to be lower than at the time of the initial CEA trials, substantial uncertainty remains as to which patients will still benefit from carotid revascularization in addition to contemporary medical therapy and risk factor management. Several randomised trials are currently investigating this question, including the Second European Carotid Surgery Trial (ECST-2), the Stent Protected Angioplasty versus Carotid Endarterectomy Trial 2 (SPACE-2), the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2), and the Endarterectomy Combined with Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke (ACTRIS) trial.

Our study has important limitations. First, the trials included in this meta-analysis were conducted between 2000 and 2008. The procedural risk associated with carotid revascularization methods might have declined even further since 2008. Particularly in CAS, the most recent technical developments, such as stent designs with very small open area between struts,[114] reverse-flow protection systems,[48] and direct trans-cervical access[115] were only achieved after completion of the 4 trials included in this meta-analysis and many devices used in these trials are now outdated and now longer in use. Second, in the earliest years of enrolment (2000-2002) most patients included in this analysis were enrolled in either EVA-3S or SPACE. In addition, between 2007 and 2008 enrolment only continued in ICSS and CREST while EVA-3S and SPACE had completed their enrolment. However, the adjustment for source

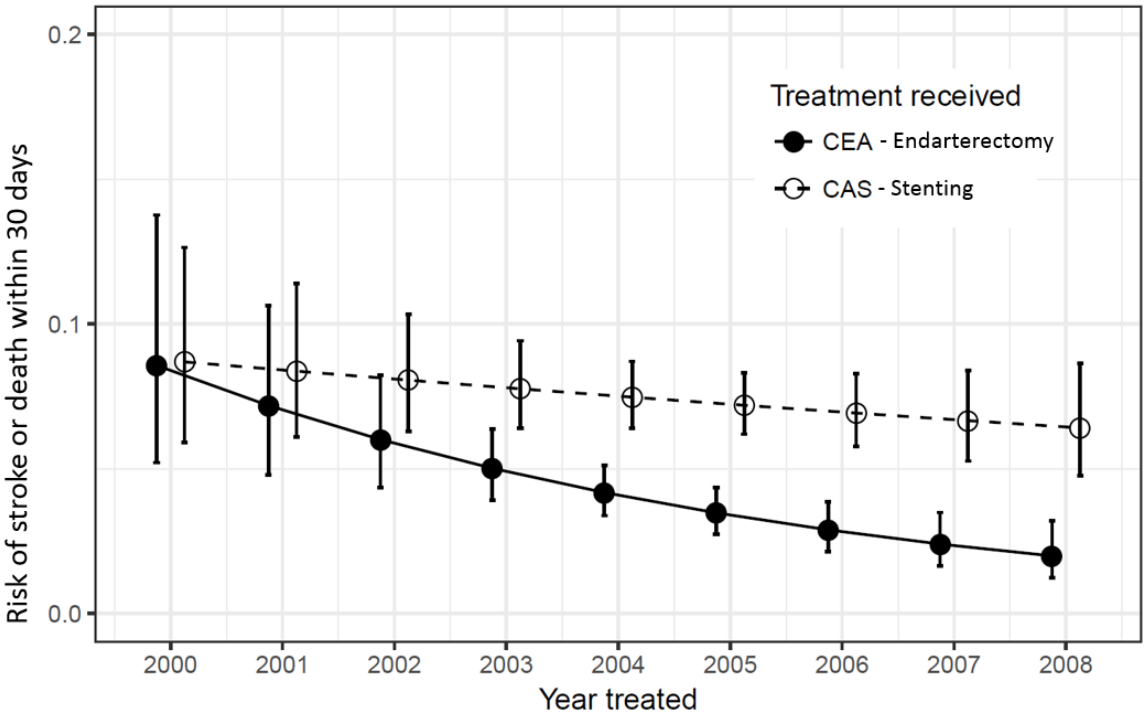
trial included in all of our models should account for any differences between trials. In addition, in a post-hoc analysis in which we excluded all patients from EVA-3S, the results remained essentially unchanged. Third, the results obtained in this analysis cannot necessarily be extrapolated to a decline in procedural risk outside of clinical trials. Fourth, due to the high percentage of missing values, we did not include days from QE to treatment in our initial analysis even though this variable was shown to differentially influence the risk of carotid revascularization.[116]

Conclusions

Treatment of symptomatic carotid stenosis within the examined trials became safer over time. The reduction in stroke or death risk over time was driven by a significant decline in procedural risks in patients treated with endarterectomy. Mechanisms underlying these findings remain to be determined.

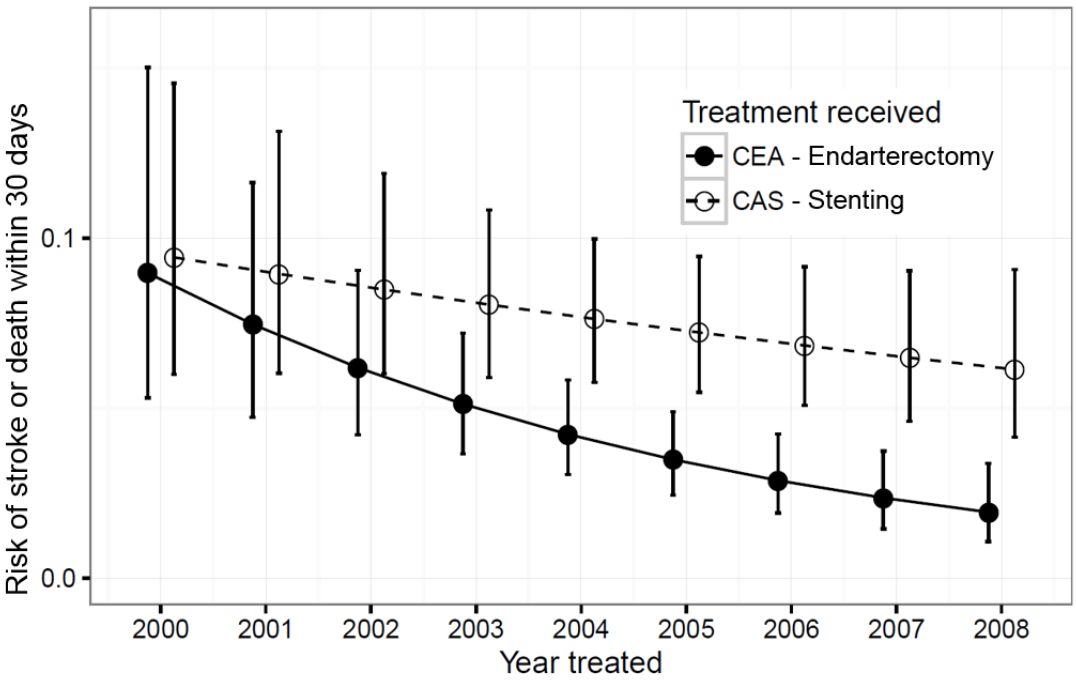
Figures

Figure 17 - Decline in risk of stroke or death over time – unadjusted model.



Modelled risks of stroke or death occurring within 30 days after treatment over time by treatment group in the unadjusted generalized linear mixed-effects model. Open and closed circles represent fitted values from the model. Error bars represent Bayesian 95% credible intervals. The interaction between type of treatment and year of treatment was statistically significant (interaction p=0.031). CEA – carotid endarterectomy; CAS – carotid artery stenting.

Figure 18 - Decline in risk of stroke or death over time – adjusted model.



Modelled risks of stroke or death (fitted values) occurring within 30 days after treatment over time by treatment group in the adjusted generalized linear mixed-effects model. The fitted values are shown for a "model patient" with median age and modified Rankin Scale (mRS) score at baseline, history of hypertension and severe carotid stenosis, but no history of diabetes mellitus. Open and closed circles represent fitted values from the model. Error bars represent Bayesian 95% credible intervals. The interaction between type of treatment and year of treatment was statistically significant (interaction p=0.038). CEA – carotid endarterectomy; CAS – carotid artery stenting.

Tables

Table 4 - Baseline characteristics in the early (2000-2004) and late (2005-2008) enrolment period.

	2000-2004 (n = 2,044)	**2005-2008** (n = 2,553)	**p-value**
Male sex	69.8%	69.8%	ns
Age, *years* (mean, SD)	69.2 ± 9.4	69.3 ± 9.1	ns
Systolic blood pressure at baseline, *mmHg* (mean, SD)	143.7 ± 19.8	143.1 ± 21.9	ns
Hypertension	73.8%	77.0%	0.016
Diabetes	25.8%	24.4%	ns
LLT*	52.4%	74.1%	<0.001
Smoking (current or past)	62.0%	67.3%	<0.001
Coronary heart disease	26.2%	29.3%	0.025
mRS at baseline (median [IQR])	0 (0-1)	1 (0-1)	0.02
Degree of ipsilateral carotid stenosis			<0.001
Moderate (50-69%)	22.4%	16.7%	
Severe (70-99%)	77.6%	83.3%	
Contralateral stenosis or occlusion	14.5%	15.0%	ns
Qualifying event type			ns
Retinal ischaemia	15.7%	18.3%	
Transient ischaemic attack	37.9%	36.0%	
Hemispheric stroke	46.4%	45.8%	
Days from qualifying event to treatment (median [IQR])†	32 (15-68)	26 (11-61)	<0.001

*Baseline characteristics of patients enrolled in the 4 source trials during the early enrolment period (2000-2004) and the late enrolment period (2005-2008). P-values for differences in baseline characteristics between the early and the late enrolment period were calculated using Welch test for continuous variables, Wilcoxon rank sum test for mRS (not normally distributed), and Chi-squared test for categorical variables. SD indicates standard deviation, mRS: modified Rankin Scale, ns: not significant. *LLT: lipid-lowering therapy: EVA-3S recorded LLT use at baseline but patients were only considered to be taking LLT if started >3months prior to randomisation. SPACE and CREST collected data on LLT use at randomisation. ICSS did not collect information on LLT use at baseline but did collect*

these data at the one-month follow-up, which were included in the table. † Date of the qualifying event before randomisation was not collected in SPACE initially, but for the pooled analysis, these dates were gathered where available. As a result, 16.6% of values for this variable are missing.

***Table 5* - Procedural risk for stroke or death expressed as crude risks over time.**

Year of treatment	**All patients** (n = 4,597)		**Endarterectomy** (n = 2,271)		**Stenting** (n = 2,326)	
	N Patients	**N (%)**	**N Patients**	**N (%)**	**N patients**	**N (%)**
2000-2002 *n (%)*	560	43 (7.7%)	280	20 (7.1%)	280	23 (8.2%)
2003 *n (%)*	659	43 (6.5%)	330	18 (5.5%)	329	25 (7.6%)
2004 *n (%)*	825	37 (4.5%)	411	13 (3.2%)	414	24 (5.8%)
2005 *n (%)*	919	58 (6.3%)	439	14 (3.2%)	480	44 (9.2%)
2006 *n (%)*	630	37 (5.9%)	310	13 (4.2%)	320	24 (7.5%)
2007-2008 *n (%)*	1004	39 (3.9%)	501	10 (2.0%)	503	29 (5.8%)
Total	4597	257 (5.6%)	2271	88 (3.9%)	2326	169 (7.3%)

Total numbers of patients recruited, as well as numbers of patients and crude percentages of patients with the primary outcome measure per year for all patients, patients treated with endarterectomy and patients treated with carotid stenting separately. The years 2000-2003 and 2007-2008 were pooled due to the relatively small number of patients enrolled.

7. Discussion and Outlook

The aim of this PhD thesis was to contribute towards enabling personalised treatment decisions for patients with carotid disease by comparing procedural risks and long-term effects of carotid stenting and endarterectomy in patients with symptomatic and asymptomatic carotid stenosis and to explore parameters specifically linked to the mechanisms of stroke occurring as a complication of carotid revascularisation procedures.

7.1. Procedural risks and long-term effects of carotid artery stenting and endarterectomy

To gain a comprehensive overview of the available randomised evidence on treatment of carotid stenosis, we first updated a systematic Cochrane Review including all new evidence, which had become available since the last update in 2012. The main results of this systematic review were that among patients with symptomatic carotid stenosis, CAS carries a higher risk of procedure related stroke or death than CEA.[61] The extra procedural risk associated with CAS is mostly attributed to an increase in minor, non-disabling strokes. In contrast, the risks for myocardial infarction, cranial nerve palsy and access site hematoma are higher with CEA than with CAS. Beyond the procedural period, both treatments are equally effective at preventing recurrent stroke or severe restenosis of the treated artery. For patients with asymptomatic carotid stenosis, high-level evidence is still limited, but suggests that there may also be a small increase in procedure related stroke with CAS compared to CEA.

Thus, the available evidence clearly demonstrates that given the equal long-term durability of CAS and CEA, the choice between the two procedures in individual patients should primarily be informed by minimising procedural risks. We therefore focussed our further research in this PhD programme on risk factors and mechanisms associated with procedure related stroke or death and how these risk factors would influence the relative risk of these complications between CAS and CEA.

7.2. Personalised treatment: age and sex

Our subgroup analyses performed as part of the Cochrane Review revealed that increasing patient age is an important risk factor for procedure related stroke or death in CAS. The risk of death or any stroke in the short-term is similar between CAS and CEA in patients younger than 70 years. In patients who are 70 years or older however, the risk of death or any stroke is significantly higher with CAS than CEA. In contrast, treatment effects were similar in men and women.

Thus, CAS is a safe and effective treatment alternative to CEA for patients younger than 70 years. Patients who are 70 years or older should primarily be treated with CEA. However, there is currently no evidence that the treatment recommendation on the choice of CAS or CEA should differ between men and women.

The mechanisms mediating the interaction between patient age and procedural risk in CAS are currently poorly understood. A discussion of possible underlying mechanisms is provided in section 7.3 and 7.4. of this thesis.

7.3. Personalised treatment: vascular anatomy

In order to prevent procedural complications occurring during CAS and CEA, further knowledge on patient-related risk factors (other than patient age) potentially increasing the risk of complications was needed. Navigation of the endovascular catheter in the vascular tree during CAS may dislodge emboli, which might cause distal embolization and stroke. This might be particularly relevant in patients with difficult configuration of the aortic arch or tortuous supra-aortic vessels.

We therefore systematically assessed vascular anatomy in patients with symptomatic carotid stenosis randomised to CAS or CEA within the ICSS-MRI substudy. We were able to confirm our hypothesis that complex vascular anatomy increases the risk for cerebral ischaemia during CAS but not during CEA. Owing to the use of new DWI lesions on brain MRI as a surrogate outcome measure, we were able to increase the power of our analysis which allowed us to investigate this important research question

despite the comparatively time consuming method used for the systematic assessment of vascular anatomy. Our findings are particularly relevant as our assessment of vascular anatomy was performed on baseline MR- and CT-angiography, which are commonly obtained during routine diagnostic work-up in patients with carotid disease before treatment is initiated.

The results of our update of the Cochrane Review and further previous research had identified older age as an important risk factor for procedural stroke in CAS.[74] Elongation of the aortic arch and supra-aortic arteries were found to be more prevalent in elderly patients. Hence the increased risk of procedural stroke in elderly patients might be mediated by vascular anatomy. However in our analysis, the association between complex vascular anatomy and cerebral ischaemia in CAS remained significant even after correction for age. Thus, complex vascular anatomy seems to be an important risk factor for procedural cerebral ischaemia in CAS independent of the patient's age and should be taken into account when selecting the optimal treatment option for the individual patient.

7.4. Timing of procedural risks

In order to prevent procedural complications of CAS and CEA, further knowledge was needed on their temporal distribution and associated risk factors. We therefore conducted an individual patient-data meta-analysis pooling data from four randomised controlled trials comparing CAS versus CEA in symptomatic patients (EVA-3S, SPACE, ICSS and CREST) to investigate the timing of stroke or death within the 30-day peri-procedural period. We found that the increased occurrence of procedural stroke or death in patients treated with CAS was limited to the day of treatment. For the remainder of the peri-procedural period (day 1-30 after treatment), there was no significant difference in the occurrence of stroke or death between the two treatments. These findings confirm the assumption that the majority of complications occur on the day of the revascularisation procedure. Hence, technical improvements and increased operator skill could potentially lower the procedural risk associated with CAS. Importantly, since the trials included in our meta-analysis were conducted, CAS technology has evolved considerably (alternative access routes, e.g. direct carotid access, newer

protection devices, e.g. flow-reversal, and new stent devices, e.g. membrane covered stents). However, randomised evidence on the benefit of these advances is sparse and it remains to be shown whether CAS using current technologies carries a similar risk to CEA in patients with symptomatic carotid stenosis.

Of note, we identified patient age as an important risk factor for both immediate and delayed stroke or death in the CAS group. This finding argues against vascular anatomy as the sole mediating factor between age and procedural stroke in CAS. Another possible underlying mechanism mediating this association might be that older patients have more unstable atheromatous lesions than younger patients, which may cause thromboembolic strokes not only on the day of treatment, but also during the following days. However, further research elucidating the association between patient age and procedural risk in CAS is needed.

7.5. Secular trends of procedural risks

Owing to improved medical management and better control of vascular risk factors, the risk of stroke under contemporary medical therapy in patients with carotid disease is lower than in the early trials establishing the benefit of CEA compared with medical therapy alone.[102] This raises the question, whether patients with carotid stenosis at low or intermediate risk of stroke still benefit from carotid revascularisation procedures. On the other hand, any decline in the procedural risk of stroke or death associated with CAS and CEA would act towards maintaining the net benefit of invasive treatment. We therefore analysed temporal changes in procedural risk associated with CAS and CEA within a second analysis of the same, pooled dataset of individual patients.

Our analysis revealed that the risk of stroke or death associated with carotid revascularisation procedures has decreased over time. The decline in procedural risk was particularly apparent in patients treated with CEA, while we found no significant decrease in patients treated with CAS. Widespread use of CAS only began a few years prior to the start of the trials contributing to our meta-analysis. We had therefore hypothesized that technical development and increased experience with

this comparatively new procedure would result in a stronger decline in procedural risk in CAS compared with CEA. Surprisingly, we found the opposite to be true.

Our findings provide strong evidence that invasive treatment of symptomatic carotid stenosis has become safer over time. This supports the notion that patients with symptomatic carotid stenosis may still benefit from carotid revascularisation procedures, even though stroke risk associated with carotid disease has declined. However, currently ongoing randomised trials will ultimately answer the question whether patients with carotid disease, who are at low to intermediate risk of stroke and receive contemporary medical therapy as well as risk factor control, still benefit from carotid revascularisation. These trials include the Second European Carotid Surgery Trial (ECST-2) which compares revascularisation by endarterectomy or stenting combined with optimal medical therapy (OMT) versus OMT alone in patients with asymptomatic or low-to-intermediate risk symptomatic carotid stenosis. A specific carotid artery risk score is used to quantify the risk for recurrent stroke in patients with symptomatic carotid stenosis and identify patients eligible to participate. Other currently ongoing randomised trials include the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)[117] and the Endarterectomy Combined with Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke (ACTRIS) trial.[118]

7.6. Outlook and future projects

7.6.1. Vascular anatomy in mechanical thrombectomy for acute ischaemic stroke

Complex anatomy of the supra-aortic vessels might influence the duration of transfemoral endovascular treatment for large vessel occlusion in acute ischaemic stroke.[119-121] Translating our findings from Project 2 (section 6.2.) of this thesis and in collaboration with the Department of Neuroradiology, we hypothesized that elongation of the aortic arch, aortic arch variants, and increased tortuosity of the supra-aortic arteries result in increased technical difficulty and prolongation of

mechanical thrombectomy for acute ischaemic stroke. This may subsequently result in a clinically less favourable outcome.

We performed a retrospective analysis of all patients who have undergone mechanical thrombectomy for acute large vessel occlusion at the University Hospital Basel between January 2014 and December 2017 and systematically assessed the anatomy of the aortic arch and the supra-aortic vessels as described in Project 2 (section 6.2.) of this thesis.

The primary outcome measure is the duration of the intra-arterial mechanical thrombectomy procedure. Secondary outcome measures include the time from femoral artery puncture to time of revascularisation, focal neurological deficits measured according to the National Institute of Health Stroke Scale (NIHSS)[122] at 24 hours compared to NIHSS on admission, and functional disability measured with the modified Rankin Scale (mRS)[58] at 3 months.

Data collection will be finished by the end of this PhD. We plan to perform statistical analysis and to publish our results in 2019.

7.6.2. Proteomics discovery approach to identify candidate biomarkers of atherosclerotic plaque instability

The primary mechanism underlying cerebral ischaemia caused by carotid disease is plaque rupture and subsequent embolism to the brain. This has fostered the concept of the unstable or high-risk plaque, which is prone to rupture and cause ischaemic stroke. Previous research has shown that high-risk plaques associated with ipsilateral stroke can be identified with imaging techniques.[123-125] Plaques showing intra-plaque haemorrhage (IPH) on MRI are associated with an increased risk of cerebral ischaemia compared with plaques without IPH.[126, 127] Of note, the presence of IPH on MRI is a much stronger predictor of stroke risk than established clinical risk factors such as degree of stenosis or symptom status. To date, evidence supporting the use of biomarkers to identify patients with high-risk carotid plaques is limited. Comparison of protein expression patterns by proteomics techniques in imaging-defined high-risk versus low-risk plaques might provide further insight in biological

mechanisms associated with plaque instability and identify potential biomarkers which might be clinically valuable in predicting cerebrovascular events.

In a multicentre cohort study, we aim to study protein expression patterns in endarterectomy specimens from patients with symptomatic carotid stenosis who exhibit imaging markers of plaque instability and compare those with specimens from patients with asymptomatic carotid stenosis without imaging markers of plaque instability.

The results of this study may help define distinct protein signatures associated with plaque instability, which may eventually lead to the discovery of novel serum biomarkers aiding in identifying patients with carotid disease at risk of stroke and thus enabling personalised treatment decisions for the individual patient.

MDM has submitted a grant proposal to the Swiss Heart Foundation applying for funding for this project.

7.6.3. Ultrasound plaque imaging and biomarkers

Previous research demonstrated that visualisation of components of the atherosclerotic plaque with ultrasound is also possible. On B-mode ultrasound of the carotid artery, parts of the plaque appearing dark (echolucent) correspond to necrotic areas with increased lipid content and plaque haemorrhage.[128] Computerised analysis allows for normalization against reference tissues and therefore a quantitative and objective assessment of plaque echolucency, expressed by the grey scale median (GSM), i.e. the median grey scale value in the plaque.[129] Patients with echolucent plaques are at increased risk of stroke.[130]

We analysed duplex ultrasound images obtained at baseline in patients with clinically asymptomatic carotid stenosis randomised in the ACST-2 MRI substudy and aim to investigate possible associations between plaque echolucency, serum biomarkers and the presence of ischaemic brain lesions. Data collection for this project is currently still ongoing and is planned to be completed by the end of 2018.

7.6.4. Ongoing large randomised controlled trials

7.6.4.1. ACST-2 and ACST-2 MRI substudy

Within ACST-2, patients with asymptomatic carotid stenosis who are deemed to require revascularisation are randomly assigned to treatment by CAS or CEA. This large RCT with a planned sample size of 3600 patients is scheduled to keep enrolling patients until the end of 2019 and therefore lay beyond the scope of this PhD project. Within an MRI substudy patients are examined with multimodal MRI of the brain 1-7 days before treatment and 1-3 days after treatment. During this PhD project, 76 patients were enrolled at 7 centres worldwide, resulting in 128 patients in total. We plan to continue enrolment in the substudy until the end of the main ACST-2 trial in 2019 and aim to publish the results of the substudy in 2020. We hypothesise that patients with structural or biological markers of plaque instability are at increased risk of cerebral ischaemia occurring during treatment with CAS compared with CEA.

7.6.4.2. ECST-2

Within this large RCT, patients with symptomatic or asymptomatic carotid stenosis in whom there is uncertainty about the benefit of revascularisation because they are not at high risk of stroke are randomised between optimal medical treatment (OMT) and OMT plus carotid revascularisation by CEA or CAS. We hypothesize that carotid revascularisation will reduce the risk of cerebral ischaemia in patients in whom structural or biological markers of plaque instability are present, while patients with stable plaques experience no additional benefit from revascularisation compared to OMT alone. OMT in both arms consists of antiplatelet therapy, statin or other cholesterol lowering treatment, antihypertensive treatment if required, and modification of cardiovascular risk factors.

Imaging of the carotid plaque by multi-contrast MRI and ultrasound, as well as blood samples for biomarker analysis are prospectively obtained at baseline in a subset of 244 patients who are enrolled in ECST-2. The primary imaging measure for plaque instability is intra-plaque haemorrhage on MRI.

Additionally, multimodal MRI scans of the brain are performed at baseline and at a median of 2-year follow-up to detect new cerebral infarction or haemorrhage.

During this PhD 34 patients were enrolled in ECST-2 in Basel. In total, 363 patients were enrolled worldwide, 164 of whom had plaque MRI performed at baseline. Recruitment is planned to continue until the planned subset sample size of 244 patients is reached.

8. Contributions by the PhD student

During my PhD, I had the opportunity to contribute to the planning and conduct of several research projects and was able to explore my own research ideas towards the end of my PhD.

For the update of the Cochrane Review (Project 1, section 6.1.), I performed a systematic review of the literature identifying over 8,000 possibly relevant studies, conducted a systematic assessment of data quality, extracted outcomes, and performed data synthesis in a meta-analysis. This work provided me with the opportunity to learn about rigorous methodology in the conduct of systematic reviews, pitfalls and strengths of combining data in a meta-analysis, and with the opportunity to gain a comprehensive overview of the available randomised evidence on treatment of carotid stenosis. The skills acquired during my work on the Cochrane Review were of great importance for the conduct of the individual patient data meta-analyses on the temporal distribution of procedure-related outcome events in CAS and CEA and on the development of procedural risk of CAS and CEA over time (Projects 3 and 4, sections 6.3. and 6.4.). For these projects, I drafted the statistical analysis plan with the help of a statistician, helped with data cleaning, interpreted the statistical results, and wrote the manuscripts.

For Project 2 (section 6.2.), I contributed to the planning of the study, systematically assessed the configuration of the aortic arch, anatomy of the supra-aortic vessels and pre-defined stenosis characteristics in all 184 patients included in the analysis, performed statistical analysis, and wrote the manuscript.

Besides my work on our research projects, my responsibilities also consisted of the recruitment, randomisation and follow-up of patients in ongoing RCTs of patients with carotid disease (ACST-2, ECST-2, PRECISE-MRI). During my PhD, we recruited 86 patients in all three trials combined. I acquired the necessary skills to perform carotid duplex ultrasound and subsequently followed all trial patients clinically and with duplex ultrasound. During the three years as a PhD student, I performed approximately 280 ultrasound examinations.

As study coordinator for the ACST-2 MRI substudy, I was the main contact person for issues concerning the substudy, managed all participating centres, recruited new centres, and worked closely with the Clinical Trial Unit adjusting the electronic database and setting up a screening log. I additionally took part in regular Collaborators' Meetings reporting on the progress of the substudy and helped conduct site initiation visits for new centres in Switzerland. I was additionally involved in setting up and maintaining a biobank for blood samples obtained as part of our biomarker projects. Moreover, I was responsible for collecting and inventorying MRI images obtained at the collaborating centres within the ACST-2 MRI substudy.

During the last year of my PhD, I was involved in the supervision of two Masters Students, both of whom are currently working in two of the ongoing research projects (7.6.1. Vascular anatomy in mechanical thrombectomy for acute ischaemic stroke and 7.6.3. Ultrasound plaque imaging and biomarkers).

As an original spin-off of our study on the influence of vascular anatomy on the risk of CAS and CEA and in collaboration with the Department of Diagnostic and Interventional Neuroradiology, I was able to translate our findings into the field of endovascular therapy of large vessel occlusion in acute ischaemic stroke (Project 7.6.1.). I had a substantial role in the conception and planning of this project, including writing the ethics proposal, coordination of the study group, development of the statistical analysis plan, and data collection.

During the last year of my PhD, I was able to pursue a new research idea with the aim to improve identification of unstable carotid plaques by investigating protein expression patterns in endarterectomy specimens (Project 7.6.2.). For this project, I submitted a grant proposal to the Swiss Heart Foundation as main applicant.

Throughout my PhD, I drafted and revised manuscripts, ethics proposals and one grant proposal with the help of my primary supervisor and the input from our co-authors. I regularly presented our work and our findings at national and international conferences and received four national awards.

9. Conclusion and closing remarks

Our update of the Cochrane Review on carotid stenting versus endarterectomy for treatment of carotid stenosis yielded high-quality evidence for the comparison of short-term risk of stroke or death in patients with symptomatic carotid stenosis, which clearly favours endarterectomy over carotid stenting. Beyond 30 days after treatment, stenting is as effective in preventing recurrent stroke as endarterectomy. However, combining procedural safety and long-term efficacy in preventing recurrent stroke still favours endarterectomy over carotid stenting. For patients with asymptomatic carotid stenosis, the available evidence showed a strong trend towards endarterectomy showing a lower short-term risk of stroke or death. However, there was only moderate quality evidence and more data from ongoing randomised trials are needed. Concerning the durability of stenting in patients with asymptomatic carotid stenosis, only limited data are available and these do not yet allow any firm conclusions.

In our second project, we identified complex vascular anatomy as an important predictor for cerebral ischaemia in patients with symptomatic carotid stenosis treated with stenting. Stenting should therefore be avoided in patients with symptomatic carotid stenosis and difficult configuration of the aortic arch or increased tortuosity of the internal carotid artery.

Furthermore, we were able to show that the excess occurrence of stroke or death associated with stenting is limited to the day of treatment. This finding demonstrates the need to improve procedural safety of carotid stenting. It remains to be determined whether recent advances in stenting technology (new devices, direct carotid access, new protection systems) improve the safety of this procedure.

Our analysis of temporal trends in procedural risks of stenting and endarterectomy revealed that the risk of stroke or death associated with carotid revascularisation procedures has decreased over time. The decline in stroke or death risk was particularly apparent in patients treated with endarterectomy. As stroke risk associated with carotid disease has also decreased, currently ongoing randomised trials

will ultimately answer the question whether patients with carotid stenosis who are at low or moderate risk of stroke still benefit from carotid revascularisation procedures.

10. References

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