REVIEW

Controversies in cardiovascular medicine series

Carotid artery stenting vs. endarterectomy

Marco Roffi[1]*, Debabrata Mukherjee[2], and Daniel G. Clair[3]

[1]Interventional Cardiology Unit, Division of Cardiology, University Hospital, Rue Micheli-du-Crest 24, 1211 Geneva, Switzerland; [2]Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, KY, USA; and [3]Department of Vascular Surgery, Heart and Vascular Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Randomized clinical trials have demonstrated that carotid endarterectomy (CEA) is superior to medical management for stroke prevention in patients with symptomatic and, to a lesser degree, asymptomatic internal carotid artery stenosis. However, large-scale registries have shown that the adverse event rates following CEA are commonly higher than observed in the trials. In the last decade, carotid artery stenting (CAS) has emerged as a less invasive alternative to surgery. In order to address the efficacy of CAS, we performed a meta-analysis of 10 randomized trials comparing CAS with CEA in 4648 mainly symptomatic patients. The analysis showed that CAS was associated with a statistically significant increased death or stroke rate at 30 days compared with CEA (odds ratio 1.60, 95% confidence interval 1.26–2.02). However, most of the trials had inadequate requirements in terms of endovascular expertise and did not mandate the use of emboli protection devices. Beyond 30 days, long-term follow-up of the trials previously reported suggest that both revascularization techniques are equivalent in terms of stroke prevention. Conversely, large-scale high-quality CAS registries—mostly with independent neurological assessment and clinical event committee adjudication—have reported results in the range of current recommendation for CEA in over 20 000 patients, despite the fact that the majority of patients were at high risk for surgery. Until further data become available, the performance of CAS should be limited to protocols or centres of excellence and targeted especially to patients at high risk for surgery.

Keywords   Carotid artery stenting • Carotid endarterectomy • Meta-analysis • Carotid artery stenosis • Randomized trials
• Emboli protection

Introduction

In Western countries, stroke is the third most frequent cause of death, behind cardiac disease and cancer, and is the number one condition associated with permanent disability. An atherosclerotic lesion of the internal carotid artery may be responsible for 10–20% of all ischaemic strokes or transient ischaemic attacks (TIAs).[1] Large-scale randomized trials have established the benefit of carotid endarterectomy (CEA) over medical management in patients with symptomatic and, to a lesser degree, asymptomatic carotid artery disease. In the last decade, carotid artery stenting (CAS) has been increasingly advocated as less invasive treatment to surgery. This review focuses on the current role of both revascularization techniques.
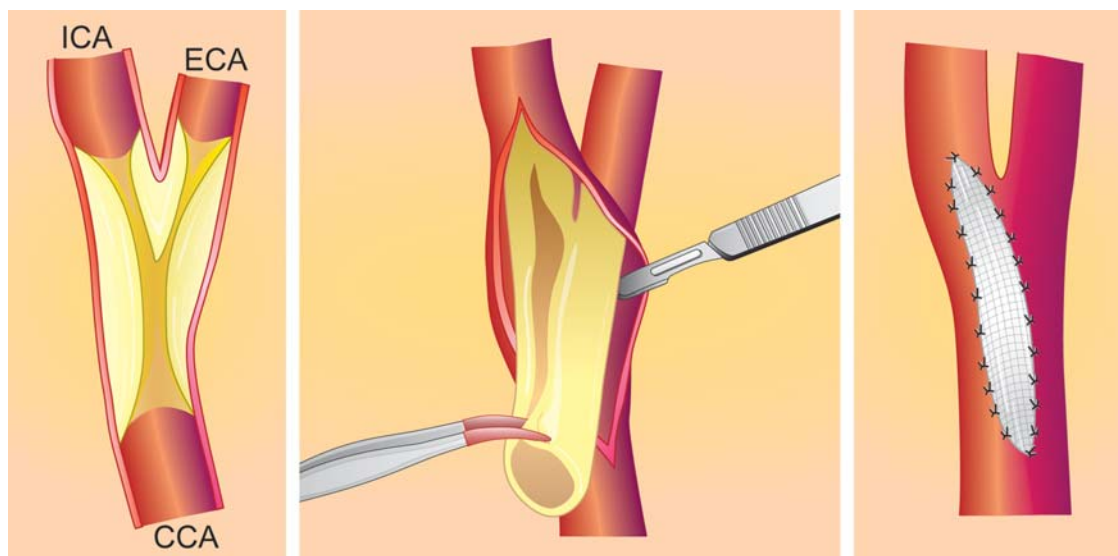
Carotid endarterectomy

Impact of technique on outcomes

The performance of carotid CEA has undergone significant revision and modification over the last 50 years. Improvements in the technique and post-procedural care have made CEA a relatively simple surgery characterized by a low stroke risk, limited morbidity, and rapid recovery. Typically, patients are operated while on aspirin 100–325 mg/day. The operation is performed under regional or, more commonly, general anaesthesia. The General Anesthesia vs. Local Anesthesia for carotid surgery (GALA) trial randomized 3526 patients undergoing CEA to the two forms of anaesthesia and found no difference in stroke or mortality rates.[2]

Surgery is usually started by means of an oblique incision along the anterior border of the sternocleidomastoid muscle, which is then retracted posteriorly exposing the common carotid artery, the carotid bifurcation, the external carotid artery, the superior thyroid artery, and the internal carotid artery (*Figure 1*). Thereafter, intravenous heparin is administered to achieve full anticoagulation, and the internal, external, and common carotid arteries are clamped. If needed, a shunt is placed at that time. Following a longitudinal incision from the common carotid artery into the internal carotid artery, the plaque is removed and the arteriotomy is

---

Figure 1 Technique of carotid endarterectomy. An atherosclerotic lesion involving the common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) is demonstrated on the left panel. The middle panel demonstrates plaque removal following a longitudinal incision of the vessel. The right panel shows the arteriotomy repair with the use of a patch.

Table 1 Randomized controlled trials evaluating medical management vs. carotid endarterectomy for ipsilateral stroke prevention in patients with carotid artery stenosis

	Degree of stenosis (%)	Medical Rx	CEA (%)	Medical Rx (%)	RRR/ARR (%)	NNT	Endpoint*
Symptomatic population							
NASCET[6]	70–99	Aspirin 1300 mg daily	9.0	24.5	65/15.5	6	2-year stroke risk
NASCET[7]	50–69	Aspirin 1300 mg daily	15.7	22.2	29/6.5	15	5-year stroke risk
ECST[8]	70–99	Not specified	7.0	19.9	65/12.9	8	3-year stroke risk
Asymptomatic population							
VA[11]	50–99	Aspirin 650 mg twice daily	4.7	9.4	50/4.7	23	5-year stroke risk
ACAS[9]	60–99	Aspirin325 mg daily	5.1	11.0	53/5.9	17	5-year stroke risk
ACST[10]	60–99	Antiplatelet drugs	6.4	11.8	46/5.4	18	5-year stroke risk

CEA, carotid endarterectomy; Rx, treatment; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat to prevent one stroke; VA, Veteran's Administration Cooperative Study; ASA, aspirin; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Symptomatic Trial.
*Kaplan-Meier estimates.

repaired with the use of a patch. Although primary closure of the endarterectomy site is still performed by a number of surgeons, there is strong evidence in favour of routine patch placement for the reduction of acute stroke risk and recurrent stenosis.[3] An alternate to standard approach, endarterectomy can also be performed using an eversion technique. Eversion and conventional endarterectomy have been proved to be associated with similar outcomes in a randomized comparative trial involving 1353 patients.[4] Following CEA, the patient is usually monitored in a post-anaesthesia care unit. Although the mean length of hospital stay may vary in different countries, a discharge on post-operative day 1 or 2 has proved to be feasible and safe.[5]

Randomized trials on carotid endarterectomy vs. medical management

The current treatment of extracranial cerebrovascular disease has been based on major randomized controlled trials comparing medical management and CEA on the occurrence of stroke or death. In symptomatic patients, CEA offered a profound benefit over medical therapy as demonstrated in North American Symptomatic Carotid Endarterectomy Trial (NASCET)[6,7] and European Carotid Symptomatic Trial (ECST)[8] (Table 1). NASCET reported a dramatic benefit of surgery in terms of stroke prevention for symptomatic carotid stenosis ≥70% with an absolute risk

reduction (ARR) of 16.5% over 2 years and a significant but less marked advantage in patients with 50−69% carotid stenosis (ARR 6.5% over 5 years).[6,7] Similarly, ECST reported an ARR of stroke of 12.9% over 3 years associated with CEA for patients with symptomatic carotid stenosis ≥70% (measured according to the ECST method and approximately equivalent to ≥50% stenosis as measured in NASCET).[8]

The benefit of CEA in asymptomatic individuals has been less impressive. Three major trials have evaluated surgery in comparison with medical treatment in this setting, namely ACAS (Asymptomatic Carotid Atherosclerosis Study),[9] ACST (Asymptomatic Carotid Surgery Trial),[10] and VA (Veterans Administration Cooperative Study).[11] The minimum degree of stenosis to qualify for the study was 50% in the VA study and 60% in ACST and ACAS. In the trials, the 30-day stroke and mortality rate was ∼3% in surgically treated patients. Since the stroke rate among asymptomatic patients medically treated in ACAS and ACST was low, ∼2% per year, the ARR conferred by CEA in these trials was in only the range of 1% per year despite an RRR in the range of 50%. This translates into number needed to treat in the range of 100 to prevent one stroke per year with surgery.[3,7]

Limitations of randomized clinical trials

The role of revascularization in asymptomatic patients has been challenged because of outdated medical regimen used in the randomized trials, and specifically the lack of statin therapy. ACST was the only trial in which patients were at least in part treated with a lipid-lowering agent (17% at the time of randomization, 70% at their last follow-up visit).[10] Indeed, aggressive lipid-lowering treatment could further reduce the benefit of surgery in asymptomatic patients, eliminating the benefit of intervention in some cases.[12] However, although for most patients with asymptomatic carotid artery stenosis the yearly risk of stroke may be in the range of 1−2%,[9,10] the risk may increase to 3−4% per year in elderly patients or in the presence of contralateral carotid stenosis or occlusion, carotid plaque heterogeneity, poor collateral blood supply, generalized inflammatory states, or cardiac or medical illnesses.[13] Therefore, the benefit of revascularization may have been underestimated in selected subgroups of patients.

Finally, it is unknown whether the surgical results observed in the randomized trials may apply to the large proportion of patients who fall outside the inclusion criteria for the trials or for surgeons and centres not involved in the studies. For example, in both ACAS and NASCET patients beyond the age of 79 years, with a life expectancy of <5 years, surgery in the last month, unstable angina, cardiac valvular disease, symptomatic heart failure, pulmonary failure, renal failure, and cancer were excluded from enrolment. Anatomic exclusion criteria included previous ipsilateral CEA, tandem lesions, radical neck surgery, and prior neck radiation therapy.[6,14] Patient's characteristics known to increase the surgical risk are reported in *Table 2*. Another limitation on the generalization of the trials' results is that surgeons in these studies were vetted prior to initiating enrolment, were well experienced with the procedure, outcomes were monitored carefully throughout the studies, and enrolment was limited or even discontinued at poorly performing sites.

Therefore, results of CEA observed in the clinical trials may not represent everyday clinical practice. An analysis involving 10 561 patients undergoing CEA across different states in the USA documented a 30-day mortality of 1.5% and a stroke or mortality rate of 5.2%.[15] The mortality rate was 1.6% in symptomatic patients and 1.1% in asymptomatic patients. The stroke or mortality rate was 7.5% in symptomatic patients and 3.7% in asymptomatic patients, both beyond the thresholds recommended by the American Heart Association (AHA) guidelines, described in what follows.[16] Similar results were observed in a registry from Ontario Canada documenting a 30-day death or stroke rate of 6.0% among 6038 patients undergoing surgery, with an event rate of 7.3% among symptomatic and of 4.7% among asymptomatic patients.[17]

Guidelines and consensus documents on carotid endarterectomy

Numerous groups have outlined recommendations regarding the performance of CEA. The most widely quoted guidelines are

Table 2 Conditions associated with an increased operative risk for carotid endarterectomy

Anatomic factors	Medical factors
Prior CEA	Class III or IV heart failure
Prior neck surgery	Non-revascularized left main or multivessel coronary disease
Prior neck irradiation	Class III or IV angina
Symptomatic ICA lesion	Myocardial infarction within 30 days
High ICA lesion	Severe renal insufficiency
Low CCA lesion	Age ≥80
Tracheostomy	Severe pulmonary disease
Contralateral laryngeal nerve palsy	Female sex
Contralateral ICA occlusion	Concomitant cardiac surgery
Intraluminal thrombus	Recent implantation of a coronary drug eluting stent
Long subtotal ICA occlusion (string sign)	

CEA, carotid endarterectomy; ICA, internal carotid artery; CCA, common carotid artery.

those produced by the AHA, likely because they are multidisciplinary, involving neurologists, surgeons, and cardiologists.[16] Across the different documents, there is agreement on the strong evidence in favour of performing CEA in symptomatic patients with ≥70% stenosis, provided the surgical risk of stroke or death is kept at <6%. For symptomatic patients with <50% stenosis, there is no benefit from surgery. In patients with symptomatic 50–69% stenosis, a moderate benefit from CEA is present, and the decision to proceed should be based on the surgical risk and life expectancy of the patient as well as on the local surgical expertise. According to the AHA guidelines, there are no proven but only acceptable indications for CEA for symptomatic patients with an estimated peri-operative risk of stroke or death >6%. Those indications include TIA or mild-to-moderate stroke within a 6-month interval and ≥70% carotid stenosis; recurrent TIA while on anti-platelet therapy with ≥50% ulcerated carotid stenosis; crescendo TIA with ≥50% carotid stenosis; and evolving stroke in the presence of ≥70% carotid stenosis with large ulceration.[16]

Guidelines recommend CEA in asymptomatic patients for patients with ≥60% stenosis.[16,18] However, the benefit is moderate and present only if the surgical risk of death or stroke is kept at <3% and life expectancy of the patient is at least 5 years. Lesion, patient, and surgeon characteristics should be taken into account in the decision process involving asymptomatic individuals. The 2005 guidelines of the American Academy of Neurology recommend revascularization in eligible asymptomatic patients only up to the age of 75 years.[18]
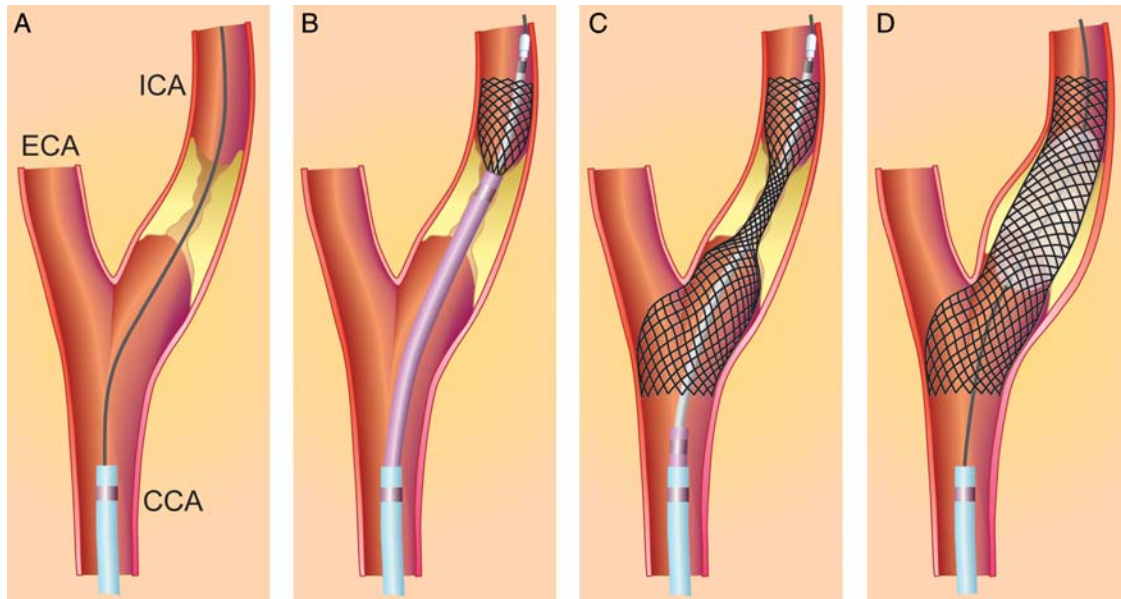
Carotid artery stenting

Patients undergoing CAS are commonly pre-treated with aspirin and clopidogrel. Aspirin is continued lifelong and clopidogrel given for at least 1 month after the procedure. The concept of dual antiplatelet therapy came from the coronary experience and was immediately embraced by part of the interventional community also for the endovascular treatment of the carotid arteries. Small randomized trials comparing single with double antiplatelet therapy for CAS followed but had to be prematurely terminated due to high stent thrombosis and neurological event rates in the aspirin-only group.[19,20] Anticoagulation, commonly with unfractionated heparin, is limited to the time of the procedure.

The common carotid artery is engaged with a guiding catheter or a long sheath. At this time, an emboli protection device (EPD) is deployed. Three types of EPDs are available: filter-based, distal balloon occlusion and the proximal occlusion EPD—with or without flow reversal (*Figure 2*). Although the use of EPDs has never been investigated in a randomized fashion, there is broad—though not unanimous—consensus that these devices should be used during CAS.[21–23] A systematic review documented a 30-day death or stroke rate of 5.5% among 2357 patients undergoing CAS without the use of EPDs and of 1.8% among 839 individuals treated with these devices (*P* < 0.001).[24] A benefit from EPDs was also suggested in a large-scale prospective registry documenting an in-hospital death or stroke rate of 2.1% among 666 patients undergoing CAS with adjunctive EPDs and of 4.9% in
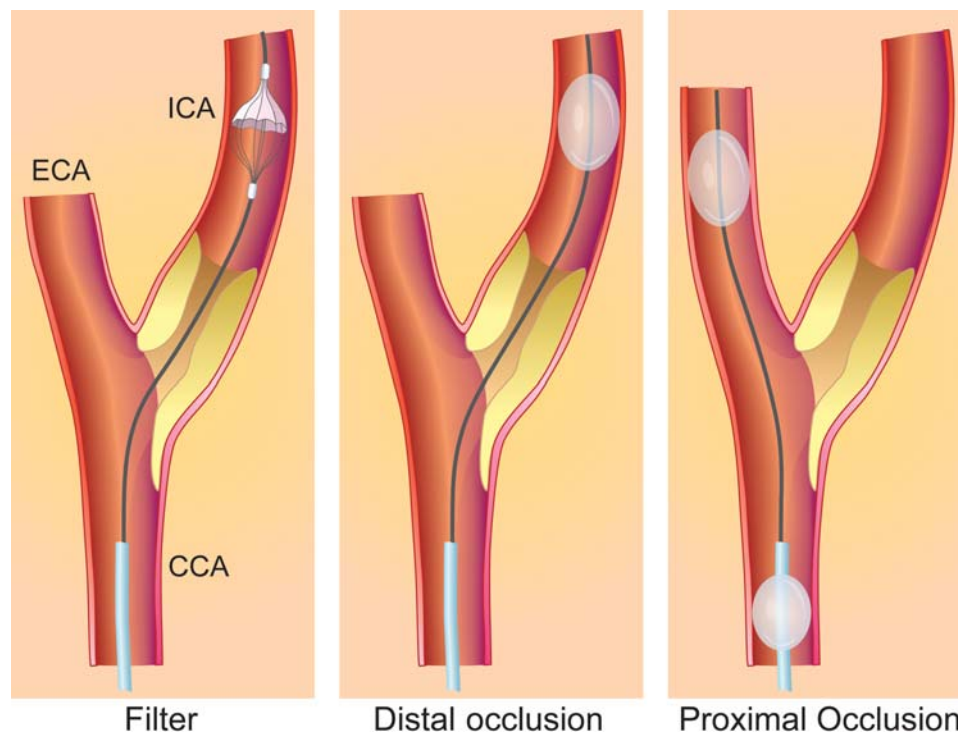
Figure 2 Strategies for emboli protection devices in carotid artery stenting. On the left panel, a filter device is demonstrated; in the middle, a distal balloon occlusive device; and in the right panel, a proximal occlusive device. CCA, common carotid artery; ICA, internal carotid artery; ECA, external carotid artery.

Figure 3 Carotid artery stenting procedure. Following engagement of the common carotid artery (CCA) with a guiding catheter or long sheath, the lesion in the internal carotid artery (ICA) is passed with a wire or with the filter emboli protection device (A). Subsequently, a self-expanding stent is deployed, usually covering the carotid bifurcation (B and C). Thereafter, a balloon post-dilatation is performed to achieve good stent expansion (D). ECA, external carotid artery.

the group of patients ($n = 789$) treated without protection ($P = 0.004$).[25] In the same study, the use of EPDs was identified in the multivariate analysis as an independent protective factor for this endpoint [adjusted odds ratio (OR) 0.45; $P = 0.026$]. Similar findings were observed in a prospective multicentre feasibility trial enrolling 261 patients.[26] Accordingly, the 1 year major ipsilateral stroke rate was 0% among patients undergoing CAS with adjunctive EPDs and 2.3% in patients undergoing unprotected CAS ($P = 0.05$). As a confounding variable, EPDs have been used more recently and therefore likely at a later stage of the operator's learning curve. Nevertheless, even in centres with large CAS experience prior to the introduction of these devices, the use of EPDs did affect outcomes positively.[27,28] The complication rate associated with EPD use appears to be low ($<1\%$).[29] In the USA, CAS without the use of EPDs is not reimbursed. Filter-based systems are the most widely used type of EPDs on both sides of the Atlantic.

Although no randomized study has compared carotid angioplasty vs. stenting, virtually all endovascular carotid procedures currently performed are stent-based (*Figure 3*). Carotid stents are self-expanding and the vast majority of them are made of nitinol. With respect to stent design, carotid stents are available in closed-cell and open-cell designs. Although from a conceptual perspective closed-cell design may confer better plaque coverage than open-cell design and be advantageous for the treatment of symptomatic lesions, no randomized comparison has been performed so far, and the existing reports are conflicting.[30,31] Following stent deployment, a post-inflation of the stent with a balloon catheter is mandatory. Subsequently, the EPD system and then the guiding catheter/sheath are removed.

Strengths and limitations of carotid artery stenting

The main advantages of CAS over CEA are that the procedure is less invasive, performed under local anaesthesia, and is less influenced by the co-morbidities of the patient, while the outcomes are determined mainly by anatomical or procedural variables.[32–34] In addition, patients are usually discharged the day following the procedure. Factors associated with an increased risk or being considered a contraindication for CAS are listed in *Table 3*. As for CEA, CAS carries a higher risk of stroke if performed in symptomatic patients compared with asymptomatic patients.[32,33] In addition, octogenarians have been identified as a high-risk subgroup in CAS and age has been detected as independent predictor of adverse events in large-scale registries.[33,35] The likely explanation for this finding is that older patients have more advanced atherosclerotic disease and complex anatomy at the level of the aortic arch and supra-aortic vessels, such as a steep aortic arch or severe tortuousity of the common carotid arteries. As a result, the engagement of the common carotid artery with guiding catheters or sheaths may be more cumbersome and cause distal embolization. Nevertheless, a recent single-centre experience has demonstrated that in selected octogenarians with favourable anatomy, CAS can be accomplished at a complication rate below the standard recommended for CEA in the general population.[36]

An additional advantage of CAS over CEA is that the endovascular approach allows for the treatment of lesions not accessible to surgery, such as those located high in the internal carotid artery or low in the common carotid artery. However, this disease pattern affects only a

Table 3 Conditions associated with increased procedural risk and contraindications for carotid artery stenting

Increased risk
Age $\geq$ 80 years
Symptomatic ICA lesion
Severe renal insufficiency
Severely diseased and/or steep aortic arch
Severely diseased and/or tortuous CCA
Severely diseased and/or tortuous distal ICA
Long subtotal ICA occlusion (string sign)
Poor femoral access
Major stroke within 4–6 weeks
Extensive intracranial microvascular disease
Contraindications
Intolerance to aspirin and/or clopidogrel
Circumferential ICA calcification
Intraluminal thrombus
Chronic ICA occlusion
Intracranial aneurysm or AVM requiring treatment

CCA, common carotid artery; ICA, internal carotid artery; AVM, arteriovenous malformation.

minority of patients. Conversely, CEA may be the treatment of choice for patients with poor or no femoral access. Accordingly, although CAS may be performed using a radial or brachial approach, the access and engagement of the common carotid arteries are complex and likely associated with higher complication rates.

Since EPDs are believed, as discussed previously, to improve outcomes in CAS, the inability to place such a device should also be considered a relative contraindication to stenting. However, this is rarely the case because of the different types of EPDs available. Commonly recognized contraindications to CAS include a severe circumferential calcification at the level of the carotid lesion, which may limit stent expansion, and the presence of a thrombus.[21] Finally, on the basis of the critical role of dual antiplatelet therapy in CAS, in patients with proven intolerance to aspirin or clopidogrel, surgery should be preferred.

Like in any other endovascular or surgical procedure, common sense suggests a major impact of operator skills and experience on CAS outcomes. However, these variables are difficult to investigate other than in a simulator setting.[37] Nevertheless, in the PRO-CAS registry, the procedural stroke and death rates decreased over time and differed according to the level of experience with a 5.9% stroke/death rate in centres with less than 50 interventions per year and a 3.0% rate in those with more than 150 interventions per year.[32] Similarly, centres reporting less than 50 interventions per year in a randomized trial had a stroke/mortality rate of 4.6%, whereas those performing more than 50 procedures had a stroke/mortality rate of 2.9%.[38] In the CASES-PMS registry, in which investigators underwent a comprehensive training programme prior to patient enrolment, no difference in outcomes was observed in relation to the baseline CAS

experience.[39] This suggests that such a programme may help in lessening the learning curve.

Randomized trials of carotid endarterectomy vs. carotid artery stenting

Five major, i.e. including more than 300 patients, randomized trials have compared endovascular and surgical carotid revascularization. Whereas the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy) trial[40] focused on patients—both symptomatic and asymptomatic—at high risk for surgery, CAVATAS (CArotid and Vertebral Artery Transluminal Angioplasty Study),[41] SPACE (Stent protected Percutaneous Angioplasty of the Carotid artery vs. Endarterectomy),[42] EVA-3S (Endarterectomy vs. Angioplasty in patients with Symptomatic Severe carotid Stenosis),[43] and ICSS (International Carotid Stenting Study)[44] enrolled exclusively symptomatic patients.

The CAVATAS study, performed in the late 1990s, randomized 504 symptomatic patients at low-to-moderate risk for surgery to CEA or carotid angioplasty.[41] The incidence of death or stroke at 30 days was 10.0% in the endovascular group and 9.9% in the surgical group. The outcomes among the two groups remained comparable at 3 years.

The SAPPHIRE study is the only randomized trial comparing CEA and CAS performed with the systematic use of EPDs.[40] The trial included symptomatic and asymptomatic patients at high risk for surgery and was designed to prove the non-inferiority of the endovascular approach. The study was terminated prematurely because of slow enrolment owing to competing CAS registries. Among the 334 patients randomized (29% of them being symptomatic), major adverse events at 1 year occurred in 12.2% in the CAS group and in 20.1% in the CEA group ($P = 0.053$). In the actual treatment analysis, the observed difference reached statistical significance ($P = 0.048$). The difference was mainly driven by a reduction in the rate of myocardial infarction (at 30 days 0.6% in the CAS group vs. 4.3% in the CEA group; $P = 0.04$). No cranial nerve injury was observed in the CAS group, whereas this complication occurred in 5.3% of the CEA patients ($P < 0.01$). The durability of CAS was documented by a comparable cumulative percentage of major (1.3% for CAS vs. 3.3% for CEA) and minor (6.1% for CAS vs. 3.0% for CEA) ipsilateral strokes at 3 years as well as by a low rate of repeat revascularization during the same period of time (3.0% for CAS vs. 7.1% for CEA).[45]

The SPACE study sought to prove the non-inferiority of CAS compared with CEA among symptomatic patients. The use of EPDs in the CAS arm was left at the discretion of the treating physician and was used in 27% of cases. Although the required sample size based on interim analysis was 2400 patients, the trial had to be terminated following the inclusion of 1200 patients because of slow enrolment and lack of funding. The incidence of ipsilateral stroke or death at 30 days was the primary endpoint of the study and did not differ between the groups, occurring in 6.8% of cases in the endovascular group and in 6.3% of patients in the surgical arm.[42] At 2-year follow-up, no difference in adverse events between the two groups could be detected.[46]

The EVA-3S was a randomized non-inferiority trial comparing CAS with CEA in patients with a ≥60% symptomatic carotid artery stenosis. The primary endpoint was the cumulative incidence of any stroke or death within 30 days after treatment.[43] The protocol did not mandate the use of EPDs. The performance of CAS without EPD protection in the study was rapidly halted following the observation that 4 out of 15 patients treated without protection suffered a stroke, whereas the proportion of patients treated with protection was 5 out of 58 [OR 3.9; 95% confidence interval (CI) 0.9–16.7].[47] The entire trial was then stopped prematurely after the inclusion of 527 patients because of significantly increased event rates in the CAS arm (death or stroke 9.6% in the CAS arm and 3.9% in the CEA arm; $P = 0.01$). At 6 months, the incidence of any stroke or death was 11.7% in the CAS group and 6.1% in the CEA group ($P = 0.02$). At 4-year follow-up, the death or stroke rate still favoured CEA, driven by the 30-day events. Beyond 30 days, no difference was observed.[48]

The International Carotid Stenting Study (ICSS) randomized 1710 symptomatic patients to CAS or CEA.[44] The primary endpoint is the long-term survival free of disabling stroke. The use of EPDs was not mandatory. Although follow-up is ongoing and expected to be completed in 2011, the 30-day safety results were recently presented.[49] The incidence of death, stroke, or periprocedural myocardial infarction was 8.5% in the CAS group and 5.1% in the CEA group ($P = 0.004$). No difference was observed in the survival free of disabling stroke at 120 days.

Limitations of randomized clinical trials

Current randomized data comparing CAS and CEA have several limitations. First of all, the data on asymptomatic patients are limited since all but one trial included only symptomatic patients. Second, the use of EPDs was mandatory in just one trial. Third, the minimal endovascular experience required per protocol was in most of the trials incredibly low, raising important questions on the ethics of the studies and applicability of the results (Table 4). This despite the observation that in the first randomized trial, a single-centre study, the inexperience of the operator (just eight CAS procedures) had catastrophic results on CAS outcomes.[50] Out of seven patients undergoing CAS, five had a stroke, and the study was prematurely discontinued. Of note, in all but one large-scale trial, tutoring was allowed.

In CAVATAS, training in neuroradiology and angioplasty (but not necessarily in the carotid artery) was required, and tutor-assisted procedures were allowed for investigators with little skill in cerebrovascular angioplasty.[41] In SAPPHIRE, the most demanding in terms of previous endovascular experience, investigators had to submit their procedures to an executive review committee, and the CAS peri-procedural death or stroke rate had to be <6% and no tutor-assisted procedures were allowed.[40] With respect to the SPACE trial, the main publication described a minimum of 25 successful consecutive percutaneous transluminal angioplasty or stenting procedures.[42] However, a second publication reveals that during the trial, an amendment of the protocol allowed for tutoring of interventionalists who had a total experience of at least 10 CAS procedures.[51]

In the French EVA-3S study, the minimal endovascular requirement was 12 CAS procedures. Alternatively, a minimum of five interventions was deemed to be sufficient to enrol if the operator had performed in his lifetime at least 35 stenting procedures of the supra-aortic trunks. Finally, for investigators not meeting those requirements, it was possible to perform the procedure under the supervision of an experienced tutor—defined as someone with an experience of at least 12 CAS procedures.[43,52] In a later correspondence, the EVA-3S investigators stated that in the trial, only 16% of patients were treated by interventionalists having performed more than 50 CAS procedures in their lifetime, and 39% of patients were treated by physicians in training.[53] Indirect evidence of the suboptimal endovascular treatment of patients in EVA-3S is derived from the incomplete coverage with dual antiplatelet therapy (83% pre-procedure and 85% post-procedure), as well as the high rate of emergent conversion from CAS to CEA (5%), an exceedingly rare complication. A critical question is how interventionalists could have gathered sufficient experience at all if, in France, CAS was never reimbursed. In ICSS, a minimum of 50 total stenting procedures, of which at least 10 had to involve the carotid artery, was required.[44] Tutor-assisted procedures were allowed for interventionalists with insufficient experience.

It remains unanswered why these soft requirements with respect to endovascular experience were proposed by the trial leaderships and accepted by Ethical Committees. Other than SAPPHIRE, none of the randomized trials would have satisfied the minimum recommended experience according to a multispecialty CAS clinical competence statement.[54] The least to say, in the

Table 4 Requirements in terms of endovascular expertise in randomized trials enrolling more than 300 patients and comparing carotid endarterectomy and stenting

CAVATAS[41]	Training in neuroradiology and angioplasty (but not necessarily in the carotid artery) required. Tutor-assisted procedures allowed
SAPPHIRE[40]	Procedures submitted to an executive review committee; CAS peri-procedural death or stroke rate had to be <6% No tutor-assisted procedures allowed
SPACE[42,51]	At 25 successful CAS cases or assistance of a tutor for interventionalists having performed at least 10 CAS cases
EVA-3S[43]	12 or more CAS cases or 5 or more CAS cases and 30 or more cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centres not fulfilling minimal requirements
ICSS[44]	A minimum of 50 total stenting procedures, of which at least 10 should be in the carotid artery. Tutor-assisted procedures allowed for interventionalists with insufficient experience

CAS, carotid artery stenting.

design of the trials, the main purpose of randomized testing of a new procedure was missed, namely to show that the therapy is efficacious in the hands of the most skilled operators on selected (favourable) patients. In this respect, early testing of CEA against medical therapy was properly conducted. In ACAS for example, patients at high risk for surgery were excluded from the trial, and both the centres and the individual surgeons had to demonstrate a 30-day death or stroke rate of <3.0% to be able to enrol. In addition, during the study, the surgeons were audited in the presence of more than one complication and were allowed to continue enrolment only if no operator-related problem was observed.[9,14]
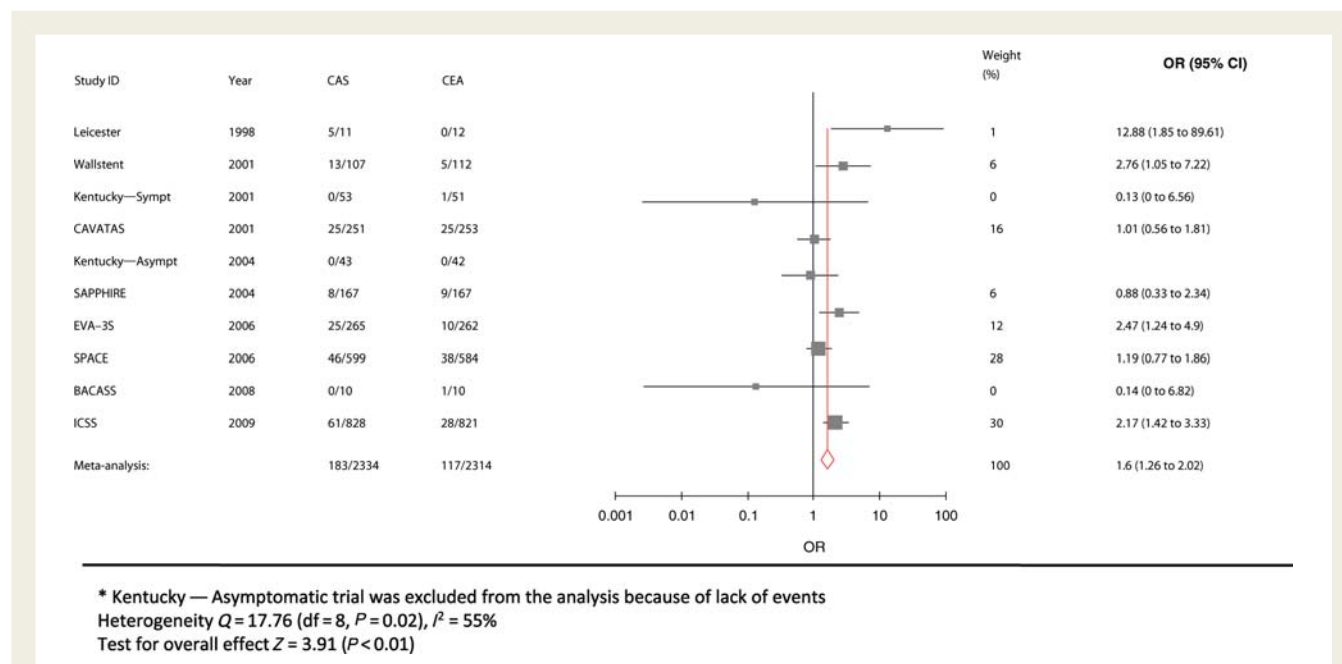
Meta-analysis of the randomized trials

In order to define the current data on the efficacy of CAS vs. CEA, we performed a meta-analysis of the randomized trials comparing CEA and CAS and addressed the 30-day death or stroke rate. To that purpose, we searched MEDLINE (January 1980–July 2009), the Cochrane databases (January 1980–July 2009), EMBASE (January 1980–July 2009), CINAHL (January 1982–June 2009), the US Food and Drug Administration website (http://www.fda.gov), and BIOSIS Previews (January 1980–July2009), using database-appropriate terms for the following: carotid artery disease, carotid angioplasty, carotid stenting, CEA, and carotid revascularization. In addition, we sought studies by reviewing the reference lists of eligible studies and relevant review articles. Finally, major meeting abstract databases (AHA, American College of Cardiology, European Society of Cardiology, Euro-PCR, Transcatheter Cardiovascular Therapeutics, American Stroke Association conference, and European Stroke Conference) were searched using the search terms listed here. A study was

included if it randomized patients with carotid artery disease to CAS or CEA and provided the 30-day death or stroke rate per intention-to-treat analysis. Information was abstracted using a standardized form that included data on the study population and the mentioned outcome.

The analysis was performed with the software provided by MIX meta-analysis.[55,56] The Peto fixed-effect model was used to calculate ORs and 95% CIs. Probability values <0.05 were considered significant. Heterogeneity among trials was tested using Q and I^2 test, and $P < 0.1$ was considered statistically significant for this analysis. A total of 4648 patients, 2334 randomized to CAS and 2314 allocated to CEA, were enrolled in 10 trials. The Chinese TESCAS-C trial enrolling 166 patients was not included because it did not report death or stroke at 30 days.[57] In ICSS, the analysis was restricted to patients in which allocated treatment was initiated. Patients undergoing CAS has a significant increase in 30-day death or stroke compared with patients treated surgically (OR 1.60, 95% CI 1.26–2.02) (*Figure 4*). Statistical tests showed significant heterogeneity in outcomes among the trials (heterogeneity $P = 0.02$). As pointed out in a recent Cochrane review, randomized data of CAS vs. CEA are difficult to interpret because of the heterogeneity among the trials and because several trials were stopped early—a factor that may have led to an overestimation of the endovascular risk.[58] A further limitation of this analysis is the inclusion—for the sake of completeness—of smaller, single-centre, non-controlled, randomized trials.

The added value of the present meta-analysis compared with recent similar report is that it included the largest study of CAS vs. CEA so far performed (ICSS). The recent Cochrane document provided an excellent review of the randomized data but was published before the results of ICSS were made available.[58]

Figure 4 Meta-analysis of the randomized trials comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA). The trials are Leicester,[50] Wallstent,[68] Kentucky-symptomatic,[69] CAVATAS,[41] Kentucky-asymptomatic,[70] SAPPHIRE,[40] EVA-3S,[43] SPACE,[42] BACASS,[71] and ICSS.[49]

Brahmanandam et al.[59] included two non-randomized studies in their analysis, and the strength of the report of Gurm et al.[45] was the presentation of long-term outcomes of the two revascularization strategies.

Large-scale registries

The results of seven CAS registries enrolling more than 1000 patients have been published, for a total of 20 105 patients (Table 5). All but one were performed in the USA, included patients at high risk for surgery, and the majority of patients included were asymptomatic. The good quality of the studies is demonstrated by the high proportion of mandatory neurological assessment pre- and post-procedure (four out of seven) and clinical event committee adjudication of adverse events (five out of seven). The use of EPDs was mandatory in five studies and used in the majority of patients in the remaining two.

The PRO-CAS registry enrolled in German patients with variable risk for surgery and reported an in-hospital death or stroke rate of 3.6%.[32] Symptomatic and asymptomatic patients had an event rate of 4.3 and 2.7%, respectively. In the CAPTURE registry, the 30-day stroke/mortality rate was 5.7% among 3500 patients, with symptomatic individuals experiencing a stroke rate of 8.9% and asymptomatic patients a rate of 4.1%.[60] The CASES-PMS registry-recorded outcomes in 1493 high-risk patients treated with CAS utilizing EPDs reported a stroke/mortality rate of 4.5%, with a stroke rate of 5.3% in symptomatic patients and 3.4% in asymptomatic individuals.[39] The SAPPHIRE Worldwide registry reported a 30-day stroke or death rate of 4.0% in 2001 high-risk patients, with a higher event rates in symptomatic compared with asymptomatic patients (adjusted OR 2.4).[61]

The SVS registry reported 30-day outcomes among 1450 patients who underwent CAS and 1368 patients treated with surgery.[62] In this analysis, the CAS group had significantly higher event rates than CEA (death, stroke, or myocardial infarction rate 6.4 vs. 2.6%). This analysis was limited by the marked imbalances among the groups, the <50% collection of 30-day events, the lack of systematic neurological assessment, and event adjudication as well as the different definition of myocardial infarction among the centres.

The results of two large-scale registries enrolling patients at high risk for surgery, the EXACT (n = 2145) and the CAPTURE 2 (n = 4175) studies, were recently reported.[63] The overall 30-day death and stroke rate in the two studies were 4.1 and 3.4%, respectively. In the population comparable with AHA guidelines (age <80 years), the pooled analysis of the two registries denoted a death or stroke rate within current recommendations for CEA, namely 5.3% for symptomatic patients and 2.9% for asymptomatic patients. In patients ≥80 years of age, the death and stroke rates in symptomatic and asymptomatic patients were 10.5 and 4.4%, respectively.

Guidelines, consensus documents, and reimbursement

Guidelines of the AHA and the American Stroke Association published in 2006 stated that in symptomatic patients with severe stenosis (>70%) in whom the lesion was difficult to access surgically, medical conditions were present that greatly increase the risk for

Table 5 Thirty-day event rates in carotid artery stenting registries enrolling more than 1000 patients

Name	Year	n	Industry sponsored	Surgical high risk	EPDs	Sympt patients (%)	Neurologist[a]	CEC adjud.	D/S (%)	D/S/MI (%)	D/S sympt (%)	D/S asymp (%)
CAPTURE[60]	2007	3500	Yes	Yes	Mandatory	14	Yes	Yes	5.7	6.3	10.6	4.9
CASES PMS[39]	2007	1493	Yes	Yes	Mandatory	22	Yes	Yes	4.5	5.0	NA	NA
PRO-CAS[32]	2008	5341	No	No	75%	55	70	No	3.6[b]	NA	4.3[b]	2.7[b]
SAPPHIRE -W[61]	2009	2001	Yes	Yes	Mandatory	28	No[c]	Yes	4.0	4.4	NA	NA
SVS[62]	2009	1450	No	Yes	95%	45	No	No	NA	5.7	NA	NA
EXACT[63]	2009	2145	Yes	Yes	Mandatory	10	Yes	Yes	4.1	NA	7.0	3.7
CAPTURE 2[63]	2009	4175	Yes	Yes	Mandatory	13	Yes	Yes	3.4	NA	6.2	3.0

EPDs, emboli protection devices; sympt, symptomatic; asymp, asymptomatic; CEC adjud, clinical event committee adjudication; D, death; S, stroke; MI, myocardial infraction.
[a]Neurologist: independent pre- and post-procedural assessment by a neurologist.
[b]In-hospital events.
[c]Neurological assessment performed by a stroke-scale-certified staff member.

surgery, or when other specific circumstances existed such as radiation-induced stenosis or restenosis after CEA, CAS was not inferior to CEA and may be considered.[64] In addition, they stated that CAS was reasonable when performed by operators with established peri-procedural morbidity and mortality rates of 4–6%. The American Society for Vascular Surgery proposed CAS as a potential alternative for symptomatic patients with high peri-operative risk.[65] Although there was consensus agreement among the authors regarding parameters defining high anatomic risk, no consensus was reached with respect to the definition of high-risk medical criteria. In addition, the authors of the guidelines recommended against the use of CAS for asymptomatic stenosis, a 'low-quality' recommendation based on the lack of randomized data in this setting. According to the 2009 guidelines of the European Society of Vascular Surgery (ESVS), CAS should be performed only in high-risk CEA patients, in high-volume centres with documented low peri-operative stroke and death rates or inside a randomized controlled trial.[22]

An American consensus paper endorsed by cardiological, radiological, as well as vascular medicine societies stated that (i) CAS could be considered as an alternative to CEA in patients with symptomatic stenosis at high risk for CEA, and (ii) CAS was reasonable when performed by operators with established peri-procedural morbidity and mortality rates of 4–6%.[21] A position paper of the German Cardiology Society and German Angiology Society extended the use of CAS also to patients not at high risk for surgery.[66] An Italian consensus involving cardiologists, vascular surgeons, radiologists, and neurologists stated that CAS should be used instead of CEA for patients at high risk for surgery, and CAS may be performed in patients not at high risk for surgery if the complications rates are within the AHA recommendations for CEA.[23]

Several other CAS consensus documents, on both sides of the Atlantic, have focused more on credentialing, highlighting the 'turf battles' that have plagued the advancement of this intervention since its inception and technological development.[23,54,67] All groups recommended specific training not limited to catheter skills but including all aspects of carotid disease management. Although, in Europe, CAS is reimbursed in most but not all countries, in the USA, the Centers for Medicare and Medicaid Services' reimbursement for CAS is limited to: (i) patients at high risk for surgery with symptomatic stenosis >70% treated in qualified institutions by qualified physicians using Food and Drug Adminitration-approved stents and EPDs, and (ii) patients at high risk for surgery with symptomatic stenosis >50% or asymptomatic stenosis >80% enrolled in Investigational Device Exemption trials or post-approval studies.

Conclusions

The results of our meta-analysis of the randomized trials comparing CAS with CEA and enrolling almost exclusively symptomatic patients show that CAS is inferior to CEA in terms of stroke or death at 30 days. Beyond 30 days, long-term follow-up of the trials previously reported suggest that both revascularization techniques are equivalent in terms of stroke prevention. As a major limitation, the majority of the randomized studies had inadequate

requirements in terms of endovascular expertise and did not mandate the use of EPDs. Conversely, large-scale high-quality registries have reported results in the range of current recommendation for CEA even in patients at high risk for surgery. Until further data become available, the performance of CAS should be limited to protocols or centres of excellence and targeted especially to patients at high risk for surgery.

Conflict of interest: none declared.

References

1. Fairhead JF, Rothwell PM. The need for urgency in identification and treatment of symptomatic carotid stenosis is already established. *Cerebrovasc Dis* 2005;**19**: 355–358.
2. Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D, Dellagrammaticas D, Horrocks M, Liapis C, Banning AP, Gough M, Gough MJ. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. *Lancet* 2008;**19**:2132–2142.
3. Bond R, Rerkasem K, Naylor AR, Aburahma AF, Rothwell PM. Systematic review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. *J Vasc Surg* 2004;**40**:1126–1135.
4. Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G, Palombo D, Peinetti F, Spartera C, Stancanelli V, Vecchiati E. Eversion versus conventional carotid endarterectomy: late results of a prospective multicenter randomized trial. *J Vasc Surg* 2000;**31**:19–30.
5. Cikrit DF, Larson DM, Sawchuk AP, Lalka SG, Shafique S, Dalsing MC. Short-stay carotid endarterectomy in a tertiary-care Veterans Administration hospital. *Am J Surg* 2004;**188**:544–548.
6. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;**325**:445–453.
7. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;**339**:1415–1425.
8. ESCT Investigators. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379–1387.
9. ACAS Investigators. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;**273**:1421–1428.
10. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491–1502.
11. Hobson RW, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;**328**:221–227.
12. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, Messig M, Welch KM. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke* 2008; **39**:3297–3302.
13. Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, Barnett HJ. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. *N Engl J Med* 2000;**342**:1693–1700.
14. ACAS Investigators. Study design for randomized prospective trial of carotid endarterectomy for asymptomatic atherosclerosis. *Stroke* 1989;**20**:844–849.
15. Kresowik TF, Bratzler D, Karp HR, Hemann RA, Hendel ME, Grund SL, Brenton M, Ellerbeck EF, Nilasena DS. Multistate utilization processes outcomes of carotid endarterectomy. *J Vasc Surg* 2001;**33**:227–234.
16. Biller J, Feinberg WM, Castaldo JE, Whittemore AD, Harbaugh RE, Dempsey RJ, Caplan LR, Kresowik TF, Matchar DB, Toole JF, Easton JD, Adams HP, Brass LM, Hobson RW, Brott TG, Sternau L. Guidelines for carotid endarterectomy: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1998;**97**:501–509.
17. Tu JV, Wang H, Bowyer B, Green L, Fang J, Kucey D. Risk factors for death or stroke after carotid endarterectomy: observations from the Ontario Carotid Endarterectomy Registry. *Stroke* 2003;**34**:2568–2573.
18. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, Cote R, Hess D, Saver J, Spence JD, Stern B, Wilterdink J. Carotid endarterectomy—an

evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2005;**65**: 794–801.

19. Dalainas I, Nano G, Bianchi P, Stegher S, Malacrida G, Tealdi DG. Dual antiplatelet regime versus acetyl-acetic acid for carotid artery stenting. *Cardiovasc Intervent Radiol* 2006;**29**:519–521.

20. McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. *Eur J Vasc Endovasc Surg* 2005;**29**:522–527.

21. Bates ER, Babb JD, Casey DE, Cates CU, Duckwiler GR, Feldman TE, Gray WA, Ouriel K, Peterson ED, Rosenfield K, Rundback JH, Safian RD, Sloan MA, White CJ. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2007;**49**:126–170.

22. Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes E, Fernandes J, Biasi G, Norgren L. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. *Eur J Vasc Endovasc Surg* 2009;**37**:1–19.

23. Cremonesi A, Setacci C, Bignamini A, Bolognese L, Briganti F, Di Sciascio G, Inzitari D, Lanza G, Lupattelli L, Mangiafico S, Pratesi C, Reimers B, Ricci S, de Donato G, Ugolotti U, Zaninelli A, Gensini GF. Carotid artery stenting: first consensus document of the ICCS-SPREAD Joint Committee. *Stroke* 2006;**37**: 2400–2409.

24. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke* 2003;**34**:813–819.

25. Zahn R, Mark B, Niedermaier N, Zeymer U, Limbourg P, Ischinger T, Haerten K, Hauptmann KE, Leitner ER, Kasper W, Tebbe U, Senges J. Embolic protection devices for carotid artery stenting: better results than stenting without protection? *Eur Heart J* 2004;**25**:1550–1558.

26. Ouriel K, Wholey MH, Fayad P, Katzen BT, Whitlow P, Frentzko M, Kuntz RE, Wechsler L, Hopkins N, Satler L, Mishkel G, Yadav JS. Feasibility trial of carotid stenting with and without an embolus protection device. *J Endovasc Ther* 2005; **12**:525–537.

27. Boltuch J, Sabeti S, Amighi J, Dick P, Mlekusch W, Schlager O, Ahmadi A, Minar E, Schillinger M. Procedure-related complications and early neurological adverse events of unprotected and protected carotid stenting: temporal trends in a consecutive patient series. *J Endovasc Ther* 2005;**12**:538–547.

28. McKevitt FM, Macdonald S, Venables GS, Cleveland TJ, Gaines PA. Complications following carotid angioplasty and carotid stenting in patients with symptomatic carotid artery disease. *Cerebrovasc Dis* 2004;**17**:28–34.

29. Cremonesi A, Manetti R, Setacci F, Setacci C, Castriota F. Protected carotid stenting: clinical advantages and complications of embolic protection devices in 442 consecutive patients. *Stroke* 2003;**34**:1936–1941.

30. Schillinger M, Gschwendtner M, Reimers B, Trenkler J, Stockx L, Mair J, Macdonald S, Karnel F, Huber K, Minar E. Does carotid stent cell design matter? *Stroke* 2008;**39**:905–909.

31. Jansen O, Fiehler J, Hartmann M, Bruckmann H. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. *Stroke* 2009;**40**:841–846.

32. Theiss W, Hermanek P, Mathias K, Bruckmann H, Dembski J, Hoffmann FJ, Kerner R, Leisch F, Mudra H, Schulte KL, Sievert H. Predictors of death and stroke after carotid angioplasty and stenting: a subgroup analysis of the Pro-CAS data. *Stroke* 2008;**39**:2325–2330.

33. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, Hopkins LN, Atkinson R, Raabe R, Barnwell S, Green R. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv* 2007; **70**:1025–1033.

34. Stingele R, Berger J, Alfke K, Eckstein HH, Fraedrich G, Allenberg J, Hartmann M, Ringleb PA, Fiehler J, Bruckmann H, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Zeumer H, Hacke W. Clinical and angiographic risk factors for stroke and death within 30 days after carotid endarterectomy and stent-protected angioplasty: a subanalysis of the SPACE study. *Lancet Neurol* 2008;**7**:216–222.

35. Zahn R, Ischinger T, Hochadel M, Zeymer U, Schmalz W, Treese N, Hauptmann KE, Seggewiss H, Janicke I, Haase H, Mudra H, Senges J. Carotid artery stenting in octogenarians: results from the ALKK Carotid Artery Stent (CAS) Registry. *Eur Heart J* 2007;**28**:370–375.

36. Chiam PT, Roubin GS, Panagopoulos G, Iyer SS, Green RM, Brennan C, Vitek JJ. One-year clinical outcomes, midterm survival, and predictors of mortality after carotid stenting in elderly patients. *Circulation* 2009;**28**:2343–2348.

37. Gallagher AG, Cates CU. Approval of virtual reality training for carotid stenting: what this means for procedural-based medicine. *JAMA* 2004;**292**:3024–3026.

38. Fiehler J, Jansen O, Berger J, Eckstein HH, Ringleb PA, Stingele R. Differences in complication rates among the centres in the SPACE study. *Neuroradiology* 2008; **50**:1049–1053.

39. Katzen BT, Criado FJ, Ramee SR, Massop DW, Hopkins LN, Donohoe D, Cohen SA, Mauri L. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. *Catheter Cardiovasc Interv* 2007;**70**:316–323.

40. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;**351**:1493–1501.

41. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;**357**:1729–1737.

42. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;**368**:1239–1247.

43. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;**355**:1660–1671.

44. Featherstone RL, Brown MM, Coward LJ. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis* 2004;**18**:69–74.

45. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Ansel G, Strickman NE, Wang H, Cohen SA, Massaro JM, Cutlip DE. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;**358**:1572–1579.

46. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, Hennerici M, Stingele R, Fiehler J, Zeumer H, Jansen O. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;**7**:893–902.

47. Mas JL, Chatellier G, Beyssen B. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial. *Stroke* 2004; **35**:e18–e20.

48. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, Bossavy JP, Denis B, Piquet P, Garnier P, Viader F, Touze E, Julia P, Giroud M, Krause D, Hosseini H, Becquemin JP, Hinzelin G, Houdart E, Henon H, Neau JP, Bracard S, Onnient Y, Padovani R, Chatellier G. Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008; **7**:885–892.

49. Brown MM. Safety results of the ICSS Study. *Presented at the European Stroke Conference*, Stockholm, May 2009.

50. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, Lloyd AJ, London NJ, Bell PR. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg* 1998;**28**:326–334.

51. Ringleb PA, Hacke W. Stent and surgery for symptomatic carotid stenosis. SPACE study results. *Nervenarzt* 2007;**78**:1130–1137.

52. EVA-3S Investigators. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) Trial. *Cerebrovasc Dis* 2004;**18**:62–65.

53. Maree AO, Rosenfield KA. Endarterectomy versus stenting for carotid stenosis. *N Engl J Med* 2007;**356**:306–307.

54. Rosenfield K, Babb JD, Cates CU, Cowley MJ, Feldman T, Gallagher A, Gray W, Green R, Jaff MR, Kent KC, Ouriel K, Roubin GS, Weiner BH, White CJ. Clinical competence statement on carotid stenting: training and credentialing for carotid stenting—multispecialty consensus recommendations: a report of the SCAI/SVMB/SVS Writing Committee to develop a clinical competence statement on carotid interventions. *J Am Coll Cardiol* 2005;**45**:165–174.

55. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. *BMC Med Res Methodol* 2006;**6**:50.

56. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM. MIX: comprehensive free software for meta-analysis of causal research data. Version 1.7. 2008. http://mix-for-meta-analysis.info.

57. Ling F, Jiao LQ. Preliminary report of trial of endarterectomy versus stenting for the treatment of carotid atheroclerosis in China (TESCAS-C). *Chinese J Cerebrovasc Dis* 2006;**3**:4–8.

58. Ederle J, Featherstone RL, Brown MM. Randomized controlled trials comparing endarterectomy and endovascular treatment for carotid artery stenosis: a Cochrane systematic review. *Stroke* 2009;**40**:1373–1380.

59. Brahmanandam S, Ding EL, Conte MS, Belkin M, Nguyen LL. Clinical results of carotid artery stenting compared with carotid endarterectomy. *J Vasc Surg* 2008;**47**:343–349.

60. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, Hopkins LN, Atkinson R, Raabe R, Barnwell S, Green R. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv* 2007;**69**:341–348.

61. Massop D, Dave R, Metzger C, Bachinsky W, Solis M, Shah R, Schultz G, Schreiber T, Ashchi M, Hibbard R. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHIRE Worldwide Registry first 2,001 patients. *Catheter Cardiovasc Interv* 2009;**69**:129–136.

62. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. *J Vasc Surg* 2009;**49**:71–79.

63. Gray WA, Charturvedi S, Verta P. 30-Day outcomes for carotid artery stenting in 6320 patients from two prospective, multicenter, high surgical risk registries. *Circ Cardiovasc Intervent* 2009;**2**:159–166.

64. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006;**113**:e409–e449.

65. Hobson RW, Mackey WC, Ascher E, Murad MH, Calligaro KD, Comerota AJ, Montori VM, Eskandari MK, Massop DW, Bush RL, Lal BK, Perler BA. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. *J Vasc Surg* 2008;**48**:480–486.

66. Mudra H, Buchele W, Mathias K, Schuler G, Sievert H, Theiss W. Interventional treatment of extracranial carotid stenoses: current status, requirements and indications. *Vasa* 2006;**35**:125–131.

67. Connors JJ III, Sacks D, Furlan AJ, Selman WR, Russell EJ, Stieg PE, Hadley MN. Training, competency, and credentialing standards for diagnostic cervicocerebral angiography, carotid stenting, and cerebrovascular intervention: a joint statement from the American Academy of Neurology, American Association of Neurological Surgeons, American Society of Interventional and Therapeutic Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, AANS/CNS Cerebrovascular Section, and Society of Interventional Radiology. *Radiology* 2005;**234**:26–34.

68. Alberts MJ. Results of a multicenter prospective randomized trial of carotid stenting vs. carotid endarterectomy (Wallstent Trial). *Stroke* 2001;**32**:325–32d.

69. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 2001;**38**:1589–1595.

70. Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery* 2004;**54**:318–324.

71. Hoffmann A, Engelter S, Taschner C, Mendelowitsch A, Merlo A, Randue EW, Lyrer P, Kisrch EC. Carotid artery stenting versus carotid endarterectomy—a prospective randomised single-centre trial with long-term follow-up (BACASS). *Schweiz Arch Neurol Psychiatr* 2008;**159**:84–89.