



ESVS Guidelines. Invasive Treatment for Carotid Stenosis: Indications, Techniques

C.D. Liapis^{a,*}, Sir P.R.F. Bell^b, D. Mikhailidis^c, J. Sivenius^d,
A. Nicolaides^e, J. Fernandes e Fernandes^f, G. Biasi^g,
L. Norgren^h, on behalf of the ESVS Guidelines Collaborators¹

^a Department of Vascular Surgery, Athens University Medical School, Attikon University Hospital, Rimini 1, 12462 Athens, Greece

^b Faculty of Medicine, Leicester Royal Infirmary, Leicester, UK

^c Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital, Royal Free and University College School of Medicine (University of London), London, UK

^d Department of Neurobiology, University of Kuopio, FIN-70211 Kuopio, Finland

^e Imperial College, London, UK

^f Department of Vascular Surgery, Hospital Santa Maria and Faculty of Medicine, Lisbon, Portugal

^g University of Milano-Bicocca, Department of Surgical Sciences, Vascular Surgery Unit, San Gerardo Hospital, Monza, Italy

^h Department of Surgery, University Hospital, Orebro, Sweden

Submitted 11 August 2008; accepted 7 November 2008

KEYWORDS

Carotid stenosis;
Treatment;
Guidelines;
Angioplasty;
Stenting;
Endarterectomy

Summary The European Society for Vascular Surgery brought together a group of experts in the field of carotid artery disease to produce updated guidelines for the invasive treatment of carotid disease. The recommendations were rated according to the level of evidence. Carotid endarterectomy (CEA) is recommended in symptomatic patients with >50% stenosis if the perioperative stroke/death rate is <6% [A], preferably within 2 weeks of the patient's last symptoms [A]. CEA is also recommended in asymptomatic men <75 years old with 70–99% stenosis if the perioperative stroke/death risk is <3% [A]. The benefit from CEA in asymptomatic women is significantly less than in men [A]. CEA should therefore be considered only in younger, fit

* Corresponding author. C.D. Liapis, Department of Vascular Surgery, Athens University Medical School, Attikon University Hospital, Rimini 1, 12462 Athens, Greece Tel.: +30 210 58 31 343 or +30 210 58 31 552; fax: +30 210 58 31 343.

E-mail address: liapis@med.uoa.gr (C.D. Liapis).

¹ Efthimios D. Avgerinos, Francis Becker, Fabrizio Benedetti Valentini, Jean-Pierre Becquemin, Hans-Christof Diener, Alberto Froio, Peter A. Gaines, Gianfranco Gensini, Grigoris Gerotziakas, Maura Griffin, Weyner Hacke, Maarit A. Heikkinen, Bo Norrving, Janet Powell, John Kakisis, Christos Karkos, Konstantinos Konstantinidis, Thomas Kotsis, Marialuisa Lavitrano, T. Matzsch, Hakan Parsson, Luis Mendes Pedro, Juha-Pekka Salenius, Michael Schachter, Henrik Sillesen, Dafydd J. Thomas.

women [A]. Carotid patch angioplasty is preferable to primary closure [A]. Aspirin at a dose of 75–325 mg daily and statins should be given before, during and following CEA. [A] Carotid artery stenting (CAS) should be performed only in high-risk for CEA patients, in high-volume centres with documented low peri-operative stroke and death rates or inside a randomized controlled trial [C]. CAS should be performed under dual antiplatelet treatment with aspirin and clopidogrel [A]. Carotid protection devices are probably of benefit [C].

© 2008 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.

Introduction

Ischaemic stroke represents a major health problem and is an important cause of long-term disability in several developed countries.^{1–4} Mortality from stroke ranges between 10% and 30%,⁵ and its survivors remain at a high annual risk of recurrent ischaemic events and mortality, both from myocardial infarction (MI) and repeated stroke.⁶ The risk of stroke increases with each decade of life, and the growth in the elderly population will be a source of increasing disability. Atherosclerosis accounts for up to one-third of all strokes. Atherosclerosis from supra-aortic vessels and especially from the common carotid bifurcation is a major cause of recurrent ischaemic stroke, accounting for approximately 20% of all strokes,⁷ while nearly 80% of these may occur without warning, thus emphasising the need for careful patient follow-up.^{8–10}

The pattern of progression of carotid stenosis is unpredictable, and the disease may progress swiftly or slowly or remain stable for many years. Modern medical treatment aims to diminish the progress of the disease and protect from stroke. Antiplatelets have been shown to reduce the incidence of stroke, and statins have been shown to have a stabilising effect on the atheromatous plaque.

Carotid occlusive disease amenable to re-vascularisation accounts for 5–12% of new strokes.^{8–11} The efficacy of carotid endarterectomy (CEA) in preventing stroke in patients with atherosclerotic carotid bifurcation stenosis has been established.^{12,13} CEA is now the standard re-vascularisation therapy, with which carotid artery stenting (CAS) must be compared.

Reduction of risk and the need for specific accreditation of specialists and institutions for the treatment of extracranial carotid disease are now recognised^{14,15} and are vital to ensure the greatest benefit from medical treatment, CEA and CAS.

Selection of the best treatment strategy for both symptomatic and asymptomatic patients is of outmost importance. The impact of the new medications and of the endovascular procedures requires careful re-evaluation of established concepts to provide guidelines for institutions and individual practitioners dealing with extracranial carotid disease.

With many clinical trials having been completed and more still ongoing, the need for guidelines representing the views of the Society combined with the input of specialists from other disciplines dealing with the disease was felt to be of potential benefit for all healthcare professionals, the members of the Society and the public.

Aiming to reach a readership of not only vascular specialists but also physicians in primary health care, the ESVS Guidelines project was launched at the European Society for Vascular Surgery (ESVS) meeting on 17 September 2005 in Helsinki, Finland.

The goals of this project are to provide an abbreviated document, to focus on key aspects of invasive treatment of carotid disease and to update information based on recent publications and the more recent available guidelines. The recommendations are graded according to levels of evidence. It should be emphasised that good practice is based on a combination of the scientific evidence, patients' preferences and local availability of facilities and trained professionals.

This document has been developed with a broad European representation. Specialists were called together in 2005 to form the Carotid Guidelines Working Group on a voluntary basis among the ESVS members and the European Board of Vascular Surgery national representatives. They are all acknowledged vascular experts in the field of carotid artery disease (CAD). In order to produce a credible document, expertise from other disciplines (neurology, radiology, vascular medicine and cardiology) was sought. The working groups reviewed the literature and, after extensive correspondence and meetings, proposed a series of draft documents with clear recommendations for the treatment of CAD. The draft documents were sent to the reviewers for their comments and corrections. The reviewers comments were taken back to the Guidelines Committee, where all of the amendments, additions and alterations suggested were discussed, and the final consensus document was agreed upon. This document was presented to and approved by the ESVS Council and was then presented to the ESVS General Assembly, which approved and endorsed the document.

The article is constructed in such a way that vascular specialists will find most of the information required for everyday practice in patients with carotid stenosis, while health physicians from other disciplines will easily find guidance for referral of patients and the expected outcomes of various treatment options. The reader should keep in mind that the guidelines can be based only on existing published evidence and do not reflect individual preferences or practice of the authors.

Grading of recommendations

The recommendations and selected statements are rated according to the guidance issued by the former US Agency for Health Care Policy and Research,¹⁶ now renamed the Agency for Healthcare Research and Quality:

Grade	Recommendation
A	Based on the criterion of at least one randomised, controlled clinical trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B	Based on well-conducted clinical studies but no good-quality randomised clinical trials on the topic of recommendation.
C	Based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. (i.e., no applicable studies of good quality)

Note that the grade of recommendation is based on the level of available evidence and does not necessarily relate to clinical importance.

A. Indications

The indication to treatment of patients with carotid disease should consider five different aspects:

1. neurological symptomatology,
2. degree of carotid stenosis,
3. medical co-morbidities,
4. vascular and local anatomical features, and
5. carotid plaque morphology.

In routine clinical practice, the indication to treat using invasive techniques is usually based on 1 and 2, while the choice between carotid endarterectomy (CEA) and carotid artery stenting (CAS) is mainly based on 3, 4 and 5.

A1 Neurological Symptomatology and Degree of Carotid Stenosis

A1.1 Neurological symptomatology and degree of carotid stenosis: Cut-off points for CEA

Patients are considered to be symptomatic (according to the most relevant randomised clinical trials (RCTs)) if they have suffered a carotid distribution transient ischaemic attack (TIA) or a non-disabling stroke in the preceding 6 months.^{17,18} Patients with disabling strokes were not included in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and in the European Carotid Surgery Trial (ECST). The degree of stenosis in symptomatic patients is now usually calculated according to the Moneta's (NASCET) criteria: an internal carotid artery to common carotid artery peak systolic velocity (ICA/CCA PSV) ratio of 4 identifies a 70% stenosis.¹⁹ A 70% stenosis calculated according to the NASCET criteria corresponds to an 83% stenosis according to the ECST criteria.

On pooling data from the ECST, NASCET and Veterans Affairs trial, 35 000 patient-years of follow-up were analysed.²⁰ Surgery increased the 5-year risk of ipsilateral ischaemic stroke in patients with less than 30% stenosis ($n = 1746$, absolute risk reduction = 2.2%, $p = 0.05$), had no effect in patients with 30–49% stenosis (1429, 3.2%, $p = 0.6$), was of marginal benefit in those with 50–69% stenosis (1549, 4.6%, $p = 0.04$) and was highly beneficial in

those with 70% stenosis or greater without near-occlusion (1095, 16.0%, $p < 0.001$).

On pooling data from the ECST and NASCET, it has been demonstrated in 5893 patients with 33 000 patient-years of follow-up that the randomisation within 2 weeks after the last ischaemic event increased the effectiveness of surgery ($p = 0.009$).²¹ The number of patients needed to undergo surgery (i.e., the number needed to treat (NTT)) to prevent one ipsilateral stroke in 5 years was five for those randomised within 2 weeks after their last ischaemic event versus 125 for patients randomised after more than 12 weeks.

After 4657 patient-years of observation over a median 2.7 years of follow-up, the Asymptomatic Carotid Atherosclerosis Study (ACAS) estimated that the aggregate 5-year risk of ipsilateral stroke and any perioperative stroke or death was 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53%).²² The expert panel of the American Heart Association (AHA) has therefore assigned a 'grade A recommendation' to the use of endarterectomy in selected asymptomatic patients with high-grade stenosis, provided the rate of perioperative stroke and death is 3% and life expectancy is at least 5 years.¹⁴

The Asymptomatic Carotid Surgery Trial (ACST) randomised 3120 asymptomatic patients between immediate CEA and indefinite deferral of any CEA.²³ Combining the perioperative events and the non-perioperative strokes, the net 5-year risks were 6.4% versus 11.8% for all strokes (net gain 5.4%, $p < 0.0001$), 3.5% versus 6.1% for fatal or disabling strokes (net gain 2.5%, $p = 0.004$) and 2.1% versus 4.2% just for fatal strokes (net gain 2.1%, $p = 0.006$). In asymptomatic patients aged below 75 years with 70% carotid diameter reduction on ultrasound, immediate CEA halved the net 5-year stroke risk from 12% to 6% (including the 3% perioperative hazard). Unlike ACAS, the benefit in ACST was demonstrated for overall, fatal, disabling and non-disabling strokes.

The benefit from CEA for women was not demonstrated in the ACAS. In the ACST study, the absolute risk reduction (ARR) in women was 4.1% (3.4% in the immediate CEA group vs. 7.5% in the deferral one), which was not statistically significant ($p = 0.07$),²⁴ and in men, the ARR was 8.2% (2.4% vs. 10.6%, respectively) with a significant benefit ($p < 0.0001$). The NTT was 12 for men and 24 for women over 5 years. The longer the follow-up, the greater was the benefit from CEA for women: the immediate hazard of death or stroke was 3.7% and the benefit was 1.25% per year; consequently, about 3 years are required to counterbalance the perioperative risk. In men, the benefit is already significant after 1.5 years.

Invasive treatment recommendation 1. Neurological symptomatology and degree of carotid stenosis

- The operative treatment of carotid disease is absolutely indicated in symptomatic patients with >70% (NASCET) stenosis [A] and probably with >50% (NASCET) stenosis [A]. The perioperative stroke/death rate should be <6%. CEA is contraindicated for symptomatic patients with less than 50% stenosis [A].
- CEA should be performed within 2 weeks of the patient's last symptoms [A].
- CEA can be recommended for asymptomatic men below 75 years with 70–99% stenosis if the risk associated with surgery is less than 3% [A].
- The benefit from CEA in asymptomatic women with carotid stenosis is significantly less than in men [A]. CEA should therefore be considered only in younger, fit women [A].

A1.2 The present role of endovascular interventions for symptomatic lesions

Several trials have compared CEA and carotid stenting. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)²⁵ suggests that angioplasty and surgery are equally effective in preventing stroke, and the death and disabling stroke rate is the same following angioplasty and surgery. The hazard ratio for any disabling stroke or death was 1.03 (95% confidence interval (CI): 0.64–1.64, $p = 0.09$), 1.04 (95% CI: 0.63–1.70, $p = 0.9$) for ipsilateral stroke lasting more than 7 days and 1.22 (95% CI: 0.63–2.36, $p = 0.4$) for disabling or fatal ipsilateral stroke (when other causes of treatment-related death were excluded).

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators (SAPPHIRE) trial²⁶ concluded that angioplasty using protection device results in 12.2% 1-year major adverse events, compared to 20.1% for surgery patients, and individual end-points produced better results for angioplasty compared to surgery (death: 6.9–12.6%, stroke: 5.7–7.3%, myocardial infarction (MI): 2.5–7.9%). It should be noted, however, that 70.1% of the patients included in the trial were asymptomatic.

The Endarterectomy Versus Angioplasty in patients with Severe Symptomatic carotid Stenosis (EVA 3S)²⁷ and the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE)²⁸ are the two most recently published trials comparing CAS and CEA in symptomatic patients. The EVA 3S trial was discontinued because the odds ratio of stroke and death was 2.5 times higher in the CAS group. The SPACE trial failed to prove the non-inferiority of CAS compared to surgery. In most end-points there was a trend towards better results with CEA.

An unequivocal advantage of CAS over CEA is the avoidance of cranial nerve injuries. Such injuries can be found on detailed examination by a speech therapist in up to 27.5% of patients undergoing CEA.²⁹ The respective value in the recent randomised trials, in which the usual examination was performed, was 4.9–9%, whereas the incidence of cranial nerve injury in patients undergoing CAS was 0–1.1%.^{25–27}

The most recent meta-analysis by The Cochrane Collaboration of eight randomised trials comparing CEA with CAS (CAVATAS, Kentucky, Leicester, Wallstent, SAPPHIRE, EVA-3S, SPACE and BACASS) showed that surgery is associated with

lower stroke and death rate within 30 days of treatment (odds ratio (OR): 1.39, 95% CI: 1.05–1.84, $p = 0.02$) and higher cranial neuropathy rate (OR: 0.07, 95% CI: 0.03–0.20, $p < 0.01$).³⁰ No significant differences were found in the following outcome comparisons: 30-day stroke, MI or death and stroke during long-term follow-up. The authors conclude that currently available data do not support a change in clinical practice away from recommending CEA as the treatment of choice for suitable carotid artery stenosis. At present, several large RCTs comparing CEA with CAS are in progress for symptomatic patients, and their results are awaited.

Long-term outcomes

In the SAPPHIRE trial, the pre-specified major secondary end-point at 3 years was a composite of death, stroke or MI within 30 days after the procedure or death or ipsilateral stroke between 31 and 1080 days (3 years).³¹ This was reached by 24.6% of patients in the CAS group and 26.9% of patients in the CEA group ($p = 0.71$). Among symptomatic patients, the rates of the composite end-point were 32% and 21.7% in the CAS and CEA groups, respectively. It should be noted, however, that subgroup analysis of the data, based on whether the patient had symptomatic or asymptomatic disease, was problematic, given the small number of patients and the fact that such analysis was not pre-specified.

The mid-term outcomes of EVA-3S and SPACE have recently been published.^{32,33} In EVA-3S, the cumulative probability of peri-procedural stroke or death and non-procedural ipsilateral stroke after 4 years of follow-up was higher with CAS than with CEA (11.1% vs. 6.2%). This difference was largely accounted for by the higher peri-procedural (within 30 days of the procedure) risk of CAS compared with CEA (9.6% vs. 3.9%). After the peri-procedural period, the risk of ipsilateral stroke was low and similar in both treatment groups (4.49% and 4.94% for CAS and CEA, respectively).³² In the SPACE results, the rate of any peri-procedural stroke or death in addition to ipsilateral ischaemic stroke within 2 years was 8.8% in the CEA group, and 9.5% in the CAS group ($p = 0.31$).³³ The absolute number of recurrent ischaemic events after the peri-procedural period up to 2 years was 10 events after endarterectomy (1.9%) and 12 after stenting (2.2%). Excluding those patients who had not received the allocated treatment modality, the results were similar: 7.8% in the endarterectomy and 9.4% in the stenting groups. Thus, the SPACE mid-term results indicate that if a patient has been treated successfully without any complications, the risk of stroke is very small and very comparable between CEA and CAS. The rate of re-stenosis was reported to be considerably higher for the CAS group (10.7% vs. 4.6% in the intention-to-treat population and 11.1% vs. 4.6% in the per-protocol population), but only two incidences of recurrent stenoses after CAS led to neurological symptoms.

Invasive treatment recommendation 2. CAS in symptomatic patients

- The available level I evidence suggests that for symptomatic patients, surgery is currently the best option [A].
- Mid-term stroke prevention after successful CAS is similar to CEA [A].

- CAS should be offered to symptomatic patients, if they are at high risk for CEA, in high-volume centres with documented low peri-procedural stroke and death rates or inside an RCT [C].

Critical issue

- More evidence is required to establish the role of CAS in symptomatic CAD, both in the peri-procedural period as well as in the long term.

A1.3 The present role of endovascular management of asymptomatic carotid disease

Procedural outcomes

One randomised trial specifically compares CAS with CEA in asymptomatic patients. In the SAPHIRE trial²⁶ (see also previous section), 334 patients considered to be at high risk for CEA were randomised between CEA and CAS; of these patients, 70.1% were asymptomatic. The primary end-point at 30 days was a combined incidence of death, stroke and MI, which occurred in 5.4% of the asymptomatic patients who received a stent compared to 10.2% of those who underwent surgery. This was statistically not considered to be different ($p = 0.20$). There was a 4.9% cranial nerve palsy rate in the surgical group.

Another randomised trial, comprising 85 patients, compared CAS and CEA in asymptomatic patients and concluded that both the methods are equally effective and safe.³⁴

There are several other papers comparing CEA and CAS in asymptomatic patients with variable results. Unfortunately, none of these studies was an RCT.

Long-term outcomes

Data on the durability of CAS in asymptomatic patients are limited. The 3-year cumulative end-point in the SAPHIRE trial, combining the 30-day end-point with ipsilateral stroke and death between 31 days and 3 years, was reached by 21.4% of asymptomatic patients receiving a stent and 29.2% of those undergoing endarterectomy.³¹ As previously mentioned, however, this subgroup analysis was not pre-specified in the study design of this RCT.

A recent retrospective investigation of 3179 CAS procedures performed at four European carotid high-volume centres has concluded that CAS is a durable procedure for stroke prevention, with an annual neurological complications rate comparable to that of conventional surgery, both for symptomatic and asymptomatic patients.³⁵ Evidence from RCTs is needed to verify these findings.

Invasive treatment recommendation 3. CAS in asymptomatic patients

- Meanwhile, it is advisable to offer CAS in asymptomatic patients only in high-volume centres with documented low peri-procedural stroke and death rates or within well-conducted clinical trials [C].

Critical issue

- The benefit from CAS in asymptomatic patients with carotid artery stenosis is still to be demonstrated.

A1.4 Neurological symptomatology and degree of carotid stenosis: Carotid stenting at the same cut-off points of CEA?

In several centres, if a patient has a degree of stenosis that requires a surgical treatment (50% or more for symptomatics and 70% or more for asymptomatics), then the patient will be a candidate also for CAS. The point is that no RCT has proved the effectiveness of CAS over a specific cut-off point of the degree of carotid stenosis. An RCT comparing the best medical treatment versus carotid stenting both in symptomatic and asymptomatic patients (equivalent to NASCET/ACST for surgery) is not available. ACST-2 is a new randomised trial that compares CEA with CAS in asymptomatic patients, while another multinational randomised trial, TACIT (Transatlantic Asymptomatic Carotid Intervention Trial), compares optimal medical therapy (OMT) alone, OMT plus stenting and OMT plus CEA in asymptomatic patients.

The lack of standardisation in the indication to treatment of CAS is evident in the ongoing RCTs on CAS, as the cut-off points used are always different. In the Carotid Revascularization Endarterectomy versus Stent Trial (CREST),³⁶ the lowest degree of stenosis was 50% in symptomatic patients and 70% in asymptomatic patients. In the SAPHIRE trial,²⁶ the thresholds were 50% and 80%, respectively. The inclusion criterion for the International Carotid Stenting Study (ICSS) and the SPACE study was a symptomatic carotid stenosis 50% by NASCET criteria.^{37–40} The EVA-3S trial enrolled only symptomatic patients with a 60% stenosis (NASCET criteria).⁴¹

Critical issues

- The assumption that a patient can be treated with CAS when he has an indication to CEA (carotid stenosis greater than 50% in symptomatics or 70% in asymptomatics) has not been validated.
- There is no randomised evidence on the specific threshold in the degree of stenosis over which there is an indication to CAS (neither in symptomatic nor asymptomatic patients).

A2 Medical Co-morbidities and High-risk Patients

The concept of a high-risk patient is very controversial. It appears that when patients meet NASCET/ACAS exclusion criteria, they are automatically defined as high risk.

According to the SAPHIRE trial, a high-risk patient with medical co-morbidities has one of the following features:

- congestive heart failure (New York Heart Association class III/IV) and/or a known severe left ventricular dysfunction;
- open heart surgery needed within 6 weeks;
- recent MI;
- unstable angina (Canadian Cardiovascular Society class III/IV); or
- severe pulmonary disease.

In the SAPHIRE trial,²⁶ the major adverse events (death, stroke and MI) at 1 year were 12.2% in the CAS group

compared to 20.1% for surgically treated patients ($p = 0.053$). However, it is unknown what the major adverse event rate would have been if patients had received best medical treatment alone without any intervention. In this context, it should be noted that there is no indication from the literature that a 'high risk' for surgery patient is also at 'high risk' for stroke if medically treated. Therefore, a peri-interventional stroke or death risk of $>3\%$ in 'high-risk for surgery' patients with asymptomatic carotid stenosis cannot be accepted.

Several authors stratified CEA candidates according to inclusion and exclusion criteria from the SAPHIRE trial. A comparison of high-risk and low-risk CEA cases demonstrated no statistical difference in the major adverse event rate. The authors showed that CEA can be performed in patients at high risk, with cardiac, stroke and death rates well within the accepted standards.^{42–46}

Illig compared outcomes after CEA in patients who would have been excluded from the NASCET and ACAS trials and would have been eligible for the Acculink for Revascularisation of Carotids in High Risk Patients (ARCHeR) study.⁴⁷ No statistically or clinically significant differences were found in the combined 30-day stroke or death rates after CEA in any group defined by previous surgical trials or current ongoing high-risk stent registries.

The age was considered as a risk factor for CEA. One of the inclusion criteria of the SAPHIRE trial was age above 80 years. Nevertheless, it has been demonstrated that octogenarians undergoing CAS are at higher risk than non-octogenarians for peri-procedural complications, including neurological events and death.^{36,48} On the other hand, the most recent papers on surgical treatment of octogenarians demonstrated that the major adverse event rate was similar to that of non-octogenarians.^{49,50}

Invasive treatment recommendation 4. Treatment options influenced by medical co-morbidities

- CEA can be performed in high-risk patients with cardiac, stroke and death rates well within accepted standards [B].
- For asymptomatic patients at 'extremely' high risk (several medical comorbidities at the same time), best medical treatment might be the best option instead of invasive intervention [C].
- CAS is associated to higher risk of embolisation in octogenarians [B]. CEA is performed in octogenarians without increased risk of embolisation and with an acceptable rate of neurological and cardiac complications [C].
- CAS should not be offered to asymptomatic 'high-risk' patients if the peri-interventional complication rate is $>3\%$ [C].

A3 Vascular and Local Anatomical Features

Complex bifurcation disease with long, multifocal lesions or an angulated ICA, extensive aortic or brachiocephalic trunk plaque, severe tortuosity or calcification of the aortic arch vessel, or ring-like, heavy calcifications of the carotid bifurcation are considered relative contraindications to CAS. Only high-volume centres with documented low peri-

procedural stroke and death rate may treat such patients with CAS.

On the other hand, CAS is indicated in patients with contralateral laryngeal nerve palsy and previous radical neck dissection or cervical irradiation and with prior CEA (re-stenosis), because the rate of cranial nerve injuries following surgery is higher in this subset. Moreover, CAS can be offered to patients with high bifurcation or intracranial extension of a carotid lesion, where surgical access could be difficult or in patients at high risk of cerebral ischaemia during carotid clamping (occlusion of the contralateral internal carotid artery and anomalies of the circle of Willis). This is based on experts' opinion and not on RCTs.⁷

It should be noted, however, that none of these conditions is associated with an increased stroke risk, if medically treated, compared with the risk in patients with favourable for surgery anatomy. Therefore, CAS should not be offered if the peri-interventional stroke risk is $>3\%$.

Invasive treatment recommendation 5. Treatment options according to vascular and local anatomical features

- CAS is indicated in case of contralateral laryngeal nerve palsy, previous radical neck dissection, cervical irradiation, with prior CEA (restenosis), with high bifurcation or intracranial extension of a carotid lesion, provided that the peri-interventional stroke or death rate is higher than that accepted for CEA [C].
- CAS is not advisable in patients with extensive aortic and supra-aortic vessel plaques, calcification and tortuosity, unless performed in high-volume centres with documented low peri-procedural stroke and death rate [C].

A4 Carotid Plaque Morphology and the Risk of Embolisation During CAS: Carotid Plaque Echolucency and Ulceration

Echolucent plaques generated a higher number of embolic particles following balloon angioplasty and stenting in an *ex vivo* model.⁵¹ Low GSM plaques have also been found to be independent predictors of stroke during CAS in the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study.⁵² These findings, however, were not reproduced by a subsequent study.⁵³

While several authors have demonstrated in more than 8000 patients that carotid plaque echolucency is an important factor in determining future neurological events,^{54–58} the reproducibility of the technique has been questioned.^{59–61} New imaging modalities as well as biological markers are increasingly used for the identification of the vulnerable carotid plaque. Computed tomography angiography (CTA), especially with the use of multidetector scanners, can measure plaque density and distinguish among plaque features such as calcium, lipid and fibrous stroma, while it can also help in the evaluation of surface irregularities.^{62,63}

Magnetic resonance imaging (MRI) can detect and quantify various plaque components such as the lipid-necrotic core,

fibrous cap, intraplaque haemorrhage or thrombus.^{62,64} MRI with the use of targeted contrast agents is currently under investigation for the characterisation of the cellular biology of the carotid plaque. In this context, targeted contrast agents have been used for the detection of macrophage activity, thrombus, neo-vascularisation, protease activity and apoptosis.^{65,66}

Fluorine-18-labelled fluorodeoxyglucose positron emission tomography (FDG-PET) can detect metabolic activity and, thus, identify inflammation.⁶⁵ Novel techniques, including optical coherence tomography (OCT) and time-resolved laser-induced fluorescence spectroscopy (TR-LIFS), have also been used for the characterisation of vulnerable carotid plaques.^{67,68}

Several cells typical for the atherosclerotic plaque such as monocyte-derived macrophages, T-lymphocytes, activated endothelial cells and proliferating smooth muscle cells produce and secrete molecules that can be measured in the circulation and, thus, can be used as biomarkers of plaque instability and rupture. Such molecules include C-reactive protein, matrix metalloproteinases and their inhibitors, soluble CD40 ligand, cytokines, oxidised LDL, lipoprotein-associated phospholipase A₂, type II secretory phospholipase A₂, myeloperoxidase, monocyte chemo-attractant protein-1, etc.^{69,70}

Identification of a vulnerable carotid plaque by some of these modalities may lead some to opt for CEA rather than CAS, or for a reversal of flow neuroprotection device rather than a filter wire which involves traversing the lesion. However, studies evaluating the modification of the therapeutic strategy according to the instability of the carotid plaque, as assessed by the aforementioned techniques, are lacking in the literature.

Some authors have suggested that increased wall coverage by a closed-cell stent may yield additional stabilisation of a vulnerable plaque and thus increase safety of the procedure. A multicentre study analysing 3179 consecutive patients showed that the late-event rates varied from 1.2% to 3.4% for free-cell areas <2.5 mm² and >7.5 mm², respectively.⁷¹ Post-procedural event rate was 1.3% for closed cells and 3.4% for open cells. All these differences were highly pronounced among symptomatic patients. These findings, however, were countered by a subsequent publication reporting no association between stent design and neurological complications among 1684 patients undergoing CAS in 10 European centres.⁷² None of these studies was randomised.

Invasive treatment recommendation 6. Treatment options according to carotid plaque morphology

- Plaque morphology should be assessed in all cases before invasive treatment [B].
- The plaque at risk of peri-procedural embolisation should be identified by validated imaging (GSM, etc.) or other diagnostic techniques such as biological markers [C].

Critical issues

- The brain protection device (BPD) used during the endovascular procedure cannot protect from late

embolisation. The selection of carotid plaques at lower embolic potential is essential to reduce late complications.

- There is no randomised trial demonstrating the superiority of one stent compared to others (tapered vs. straight, open- vs. closed cell) in the reduction of neurological complications.

B. Techniques

B1 Techniques Of CEA

B1.1 Shunting

Temporary interruption of cerebral blood flow during CEA can be avoided by using a shunt across the clamped section of the carotid artery. This may improve the outcome. Two trials involving 590 patients compared routine shunting with no shunting.^{73,74} Another trial involving 131 patients compared shunting with a combination of electroencephalographic and carotid pressure measurement, with the need to shunt assessed by carotid pressure measurement alone.⁷⁵ For routine versus no shunting, there was no significant difference in the rate of all stroke, ipsilateral stroke or death up to 30 days after surgery, although data were limited. There was no significant difference between the risk of ipsilateral stroke in patients selected for shunting with a combination of electroencephalographic and carotid pressure assessment compared to pressure assessment alone, although again the data were limited.⁷⁶

In one large analysis from the ECST trial,⁷⁷ in 1729 patients, no statistically significant associations between operative risk and the use of shunting, patching, intra-operative EEG monitoring or type of anaesthetic was found.

Invasive treatment recommendation 7. Shunting

- There is no evidence for the routine use of shunts during CEA [A].

Critical issue

- There is still insufficient evidence from RCTs to support or refute the use of routine or selective shunting during CEA. Further, there is little evidence to support the use of one form of monitoring over another in selecting patients requiring a shunt. A large RCT (3000–5000 patients) would be required to assess whether shunting reduces the risk of peri-operative and long-term death and stroke.

B1.2 Patch angioplasty versus primary closure

Carotid patch angioplasty (with either a vein or a synthetic patch) may reduce the risk of carotid artery re-stenosis and subsequent ischaemic stroke when compared to CEA with primary closure.

A Cochrane review⁷⁸ included seven trials;^{79–85} in which, patients were randomised to primary closure, vein patch or synthetic patch groups, resulting in 1127 patients undergoing 1307 operations that are available for analysis. The quality of trials was generally poor. Follow-up varied from hospital

discharge to 5 years. Carotid patch angioplasty was associated with a reduction in the risk of stroke of any type (OR = 0.33, $p = 0.004$), ipsilateral stroke (OR = 0.31, $p = 0.0008$) and stroke or death during the peri-operative period (OR = 0.39, $p = 0.007$) and long-term follow-up (OR = 0.59, $p = 0.004$). It was also associated with a reduced risk of perioperative arterial occlusion (OR = 0.15, 95% CI: 0.06–0.37, $p = 0.00004$) and decreased re-stenosis during long-term follow-up in five trials (OR = 0.20, 95% CI: 0.13–0.29, $p < 0.00001$). The sample sizes are still relatively small, data were not available from all trials and there was significant loss to follow-up. Very few arterial complications, including haemorrhage, infection, cranial nerve injury and pseudo-aneurysm formation, were recorded with either patch or primary closure. No significant correlation was found between the use of patch angioplasty and the risk of either perioperative or long-term all-cause death rates.

One recent RCT⁸⁶ comparing 216 primary closure with 206 polyurethane patch angioplasties confirmed the significant reduction of re-stenosis rate and could not find any difference in perioperative complications.

Invasive treatment recommendation 8. Patch angioplasty

- Evidence suggests that carotid patch angioplasty reduces the risk of occlusion and re-stenosis, as well as the risk of combined stroke/death [A].

B1.3 Patch angioplasty with different materials

Some surgeons who use carotid patching favour using a patch made from an autologous vein, whilst others prefer to use synthetic materials. A Cochrane review⁸⁷ included eight trials^{79,83,88–93} involving 1480 operations. Prior to 1995, all studies had compared vein closure with polytetrafluoroethylene (PTFE) closure,^{79,83,89,90} but three of the later studies compared vein to Dacron patches^{91–93} and one compared Dacron with PTFE.⁸⁸ The treatment allocation was not adequately concealed in two trials, and one only followed up patients to the time of hospital discharge. An intention-to-treat analysis was possible for six trials. In all but two trials a patient could be randomised twice and have each carotid artery randomised to different treatment groups. There were too few operative events to determine whether there was any difference between the vein and Dacron patches for perioperative stroke, death and arterial complications. A study that compared Dacron and PTFE patches found a significant risk of combined stroke and TIA ($p = 0.03$) and re-stenosis at 30 days ($p = 0.01$), a borderline significant risk of perioperative stroke ($p = 0.06$) and a non-significant increased risk of perioperative carotid thrombosis ($p = 0.1$) with Dacron compared with PTFE. Five trials followed up patients for longer than 30 days. During follow-up for more than 1 year, no difference was shown between the two types of patches for the risk of stroke, death or arterial re-stenosis. However, the number of events was small. Based on 15 events in 776 patients in four trials, there were significantly fewer pseudo-aneurysms associated with synthetic patches than with vein (OR = 0.09, 95% CI: 0.02–0.49), but the numbers involved were small and the clinical significance of this finding is uncertain.

One RCT of 273 patients who underwent 276 CEA procedures, using a Dacron patch in 137 operations and vein in 139 operations, has recently been published.⁹² Patch type had no influence on early operative risk, no association with enhanced patterns of thrombogenicity in the early postoperative period and no influence on risk for ipsilateral or any stroke at 3 years. Dacron patches were, however, associated with a significantly higher incidence of recurrent stenosis at 3 years, with most occurring within 6–12 months of surgery.

Data from observational studies indicate that vein-patch rupture is more likely if the vein is harvested from the ankle.^{94–96} Therefore, if a vein patch is to be used, it seems more appropriate to use the proximal part of the saphenous vein from the groin or the thigh.

Critical issue

- As differences between the outcomes with different patch materials are small, more data than currently available would be required to draw firm conclusions.

B1.4 Type of endarterectomy

CEA is conventionally undertaken by a longitudinal arteriotomy. Eversion CEA, which employs a transverse arteriotomy and re-implantation of the carotid artery, is reported to be associated with low perioperative stroke and re-stenosis rates but an increased risk of complications associated with a distal intimal flap.

Five trials^{97–101} were included for a total of 2465 patients and 2589 arteries.¹⁰² Three trials included bilateral CEAs. In one trial, arteries rather than patients were randomised so it was not clear how many patients had been randomised in each group, therefore, information on the risk of stroke and death from this study were considered as a separate analysis. There were no significant differences in the rate of perioperative stroke and/or death (1.7% vs. 2.6%, OR = 0.44, 95% CI: 0.10–1.82) and stroke during follow-up (1.4% vs. 1.7%, OR = 0.84, 95% CI: 0.43–1.64) between eversion and conventional CEA techniques. Eversion CEA was associated with a significantly lower rate of re-stenosis >50% during follow-up (2.5% vs. 5.2%, OR = 0.48, 95% CI: 0.32–0.72). However, there was no evidence that the eversion technique for CEA was associated with a lower rate of neurological events when compared to conventional CEA. There were no statistically significant differences in local complications between the eversion and conventional group. No data were available to define the cost–benefit trade-off of eversion CEA technique. It should also be noted that when only CEA with patch (and not primary closure) was compared with eversion endarterectomy, there was no statistically significant difference between the two techniques in terms of re-stenosis rate.

The Cochrane review concludes that eversion CEA may be associated with low risk of arterial occlusion and re-stenosis.¹⁰² However, the numbers are too small to definitively assess benefits or harms. Reduced re-stenosis rates did not appear to be associated with clinical benefit in terms of reduced stroke risk, either perioperatively or later.

Invasive treatment recommendation 9. Type of endarterectomy

- The choice of the CEA technique should depend on the experience and familiarity of the individual surgeon [A].

B1.5 Local versus general anaesthesia

CEA reduces the risk of stroke in people with recently symptomatic, severe carotid artery stenosis. However, there are significant perioperative risks which may be lessened by performing the operation under local rather than general anaesthesia (GA).

A Cochrane review included six randomised trials^{103–108} involving 554 operations and 41 non-randomised studies involving 25 622 operations.¹⁰⁹ The methodological quality of the non-randomised trials was questionable. Eleven of the non-randomised studies were prospective and 29 reported on a consecutive series of patients. In nine non-randomised studies, the number of arteries, as opposed to the number of patients, was unclear. A meta-analysis of the non-randomised studies showed that the use of local anaesthesia was associated with significant reductions in the odds of death (35 studies), stroke (31 studies), stroke or death (26 studies), MI (22 studies) and pulmonary complications (seven studies) within 30 days of the operation. A meta-analysis of the randomised studies showed that the use of local anaesthesia (LA) was associated with a significant reduction in local haemorrhage (OR = 0.31, 95% CI: 0.12–0.79) within 30 days of the operation, but there was no evidence of a reduction in the odds of operative stroke. However, the trials were too small to allow reliable conclusions to be drawn, and, in some studies, intention-to-treat analyses were not possible because of exclusions.

The GALA (general anaesthesia vs. local anaesthesia) trial is the largest randomised surgical/anaesthetic trial ever performed and included 3526 patients recruited by 95 centres in 24 countries.¹¹⁰ This two-arm, parallel group, multicentre RCT was designed to determine whether the type of anaesthesia influenced perioperative morbidity and mortality (particularly from stroke), quality of life in the short term and stroke and MI-free survival to 1 year.¹¹¹

An analysis of the results¹¹⁰ has shown that primary outcome events (MI, stroke or death) were observed (randomisation: 30 days post-surgery) in 84 of 1752 (4.8%) GA and 80 of 1771 (4.5%) LA patients and this difference was not statistically significant, even when primary outcome events were considered individual. Similarly, there were no differences between LA and GA for patients aged above or below 75 years or for those considered at higher risk from surgery. In 310 patients with contralateral carotid occlusion, there were 23 primary outcome events (15 of 150 (10%) GA vs. 8 of 160 (5%) LA, *P* for interaction is 0.098). Further, neurological events were more likely to occur contralateral to the operated artery (i.e., on the same side as the occlusion) in the GA group (54% vs. 29%). Thus, LA might offer an advantage for patients with a contralateral occlusion. Further, 1-year survival data for GALA patients suggested fewer subsequent events in LA patients (log-rank test *p* < 0.094).

It should be noted that the complication rate for both GA and LA groups was considerably lower than the results of

NASCET and ECST trials, indicating that outcomes of CEA have substantially improved during the recent years.

Invasive treatment recommendation 10. Local versus general anaesthesia

- Both LA and GA are safe. The anaesthetist and surgeon, in consultation with the patient, should determine the method of anaesthesia. Particularly for patients with a contralateral carotid occlusion, LA might offer some benefit [A].

B1.6 Quality control of CEA

CEA deals successfully with carotid atheromatous lesions, thus eliminating a potential source of cerebral emboli. At times, however, residual haemodynamic irregularities may occur as a result of technique imperfection or anatomical variations. These irregularities have been associated with a number of immediate and late postoperative complications, such as recurrent cerebrovascular symptoms and secondary episodes of stroke. For this reason, the detection of flow abnormalities or intimal defects in patients undergoing CEA and the achievement of normal intra-operative and postoperative haemodynamics are essential for the elimination of potentially life-threatening perioperative and late cerebrovascular events.¹¹² Intra-operative quality control after CEA has been advocated to improve the results of surgical treatment of extracranial CAD. The aim of completion study after CEA is to identify potential technical defects or imperfections in the site of endarterectomy (intimal flaps, platelet aggregates, plaque residues, stenosing sutures and patch curves) that may be related to perioperative neurological complications and re-stenosis.^{113,114} Completion angiography was introduced in 1968 by Blaisdell¹¹⁵ to achieve intra-operative quality control. In recent years, duplex imaging, angiography and IVUS have been proposed as alternative, accurate and less-invasive methods. There is no general agreement regarding either the need for routinely performing intra-operative control or the superiority of one method over the others. Routine arteriography following CEA is not suggested.¹¹⁶ A policy of patient individualisation at the surgeon's discretion seems to make the intervention safe.

Invasive treatment recommendation 11. Quality control of CEA

- Completion evaluation of the results of CEA in the form of either ultrasound or arteriography is advisable [B].

B1.7 Perioperative medical treatment

As indicated by the latest Cochrane review, antiplatelet drugs reduce the odds of stroke in patients undergoing CEA.¹¹⁷ It is suggested that antiplatelets may increase the odds of haemorrhage, but there are currently very few data to quantify this effect. Therefore, there is no reason to withhold antiplatelet drugs from patients undergoing CEA. In a double-blinded, placebo-controlled trial,

low-dose ASA (75 mg d⁻¹) reduced the number of post-operative strokes without complete recovery within 1 week.¹¹⁸ The intra-operative bleeding did not differ between the groups. The ACE trial, a double-blind RCT, compared 81, 325, 650 and 1300 mg of aspirin, administered before CEA and continued for 3 months.¹¹⁹ The combined rate of stroke, MI and death was the primary outcome and was lower in the low-dose groups (81 mg and 325 mg) than in the high-dose groups (650 mg and 1300 mg) at 30 days (5.4 vs. 7.0%, $p < 0.07$) and at 3 months (6.2 vs. 8.4%, $p < 0.03$).

Although clopidogrel has defined indications for stroke prevention, it is not clear how to manage this medication at the time of surgery. The role of clopidogrel combined with ASA in reducing cerebral emboli in patients undergoing CEA was studied by Payne et al.¹²⁰ Patients on routine 150-mg ASA were randomised to 75 mg of clopidogrel or placebo. The magnitude of embolisation, by transcranial Doppler, in the first 3 h after surgery was significantly reduced in the clopidogrel group (2.2%) compared with patients receiving placebo (18.5%), representing a 10-fold reduction in the relative risk. However, in the clopidogrel-treated patients, the time from flow restoration to skin closure (an indirect marker of haemostasis) was significantly increased, although there was no increase in bleeding complications or blood transfusions.

For patients who receive anticoagulants (e.g., for atrial fibrillation of mechanical valve), there is a lack of well-designed studies or reports on large populations for accurate risk quantification for those temporarily discontinuing anticoagulation for surgery. Bridging anticoagulant therapy with heparin or low-molecular-weight heparin should be considered for the majority of patients who require temporary interruption of warfarin therapy.¹²¹ In patients who are receiving warfarin therapy with a target International Normalised Ratio (INR) of 2.0–3.0 or 2.5–3.5, stopping warfarin 5 or 6 days, respectively, before surgery will ensure a normal INR at the time of surgery.¹²² INR testing should be performed on the day before surgery to ensure it is normal.

With regard to the effect of perioperative administration of statins to patients undergoing CEA, a study has been undertaken at the Johns Hopkins Medical Institutions during a 10-year period.¹²³ CEA was performed on 1566 patients, including 126 (8%) patients who underwent a combined CEA/coronary artery bypass grafting (CABG) procedure. Statin use was associated with reduction in perioperative strokes (1.2% vs. 4.5%; $p < 0.01$); mortality (0.3% vs. 2.1%; $p < 0.01$) and length of hospitalisation (median 2 days [interquartile range, 2–5] vs. 3 days [interquartile range, 2–7]; $p < 0.05$). Perioperative statin use was found to independently reduce the odds of stroke threefold (OR = 0.35; 95% CI: 0.15–0.85; $p < 0.05$) and of death fivefold (OR = 0.20; 95% CI: 0.04–0.99; $p = 0.05$). The decreased perioperative stroke rate observed with statin use persisted regardless of the year of surgery.

There have been two prospective randomised trials examining the efficacy of perioperative statin therapy among patients undergoing major vascular surgery. The first investigation, carried out by Durazzo et al.,¹²⁴ randomised patients undergoing CEA or other major vascular operation to receive 20 mg atorvastatin or placebo once

a day for 45 days, irrespective of their serum cholesterol concentration. Vascular surgery was performed on an average 30 days after randomisation, and the patients were prospectively followed up over 6 months. Patients taking statins in this trial were found to have a threefold decrease (8% vs. 26%, $p < 0.031$) in the rate of combined cardiovascular events, including acute MI, ischaemic stroke, unstable angina and death from cardiac causes at 6 months. In the other prospective non-randomised clinical trial by Schouten et al.,¹²⁵ statin therapy was administered to patients for 40 days prior to their elective vascular procedure, and the medication was continued when the patients resumed oral intake in the post-operative period. This study demonstrated that statin therapy was associated with a significantly reduced composite end-point of perioperative death and MI (8.8% vs. 14.7%; $p < 0.01$).

Given that statins appear to provide benefit during the perioperative period through both pleiotropic and lipid-lowering mechanisms, it would be reasonable to administer statins to patients as early as possible before their operation.¹²⁶ There are no objective data available at this time to suggest the superiority of one statin medication over the other in the perioperative period.

Invasive treatment recommendation 12. Perioperative medical treatment

- Aspirin at a dose of 75–325 mg daily as along with statins should be given before, during and following CEA [A].

Critical issue

- More data from randomised trials are required to establish the role of clopidogrel during CEA.

B2 Technique of Stenting the Carotid Artery

B2.1 Introduction

This section describes the basic procedural technique and complications and tries to identify those factors that are likely to affect peri-procedural outcomes. It is recognised that there are many variations of the basic technique—this section is not meant to be prescriptive. Data have been obtained from peer-reviewed publications where possible.

B2.2 Basic technique

- The decision to undertake CAS is best taken by a multidisciplinary team.
- Patients should have had their risk factors addressed and should normally be taking dual antiplatelet therapy.¹²⁷
- Access is typically via the common femoral artery, although direct carotid puncture and access via the upper limbs is recognised.¹²⁸
- Heparin 5000–7500 I.U. is delivered (5000 I.U. will provide twice normal ACT for 45 min). Some units monitor the ACT to twice normal.

- A long sheath or guiding catheter is placed below the carotid artery bifurcation.
- In the majority of the cases, mechanical cerebral protection will be used at this stage. Currently, such cerebral protection includes: (a) proximal occlusion (endovascular clamp or reverse flow), (b) distal balloon occlusion and (c) filters. No particular technique has been demonstrated to be superior to the others.¹²⁹
- Atropine (0.6–1.2 mg) or glycopyrrolate (0.6 mg) is delivered to reduce stimulation of the carotid baroreceptors.¹³⁰
- Pre-dilatation of the stenosis is undertaken by some, in cases of pre-occlusive stenosis, to facilitate subsequent stent placement.
- A self-expanding stent is placed to cover the entire lesion. Balloon-expandable stents are no longer used because of the risk of crushing leading to arterial occlusion, and no one type of self-expanding stent has yet been shown to be superior to another.
- Post-dilatation is then performed. Current practice favours under-dilatation to restrict distal embolisation.
- The mechanical cerebral protection device is retrieved.
- Often, arterial closure devices are used at the femoral artery to shorten time of immobilisation.

High-quality imaging is paramount to accurate, safe treatment, and it therefore makes sense that the procedure is undertaken using dedicated digital subtraction angiographic equipment with a mobile table and rotating arm.

A large image intensifier facilitates manipulation across a large field, and on-line measurement ensures that a correct size of protection devices and stents are used. The presence of an anaesthesiologist or another physician capable of maintaining adequate haemodynamic control is mandatory.

B2.3 Complications

Complications related to the cerebral protection systems are frequent.¹³¹ Spasm at the site of filter deployment is common and, in the majority of cases, is minor and does not require intervention. Occasionally, it may be so severe as to cause arrest of flow. Arrest of flow should, therefore, first be managed by moving the filter away from the site of spasm and then by administering an anti-spasmodic drug (e.g., nitrate 200 µg) once some flow has been restored.

Other causes of arrest of flow are dissection, acute stent thrombosis and a filter filled with debris. Flow-limiting dissection is best managed with a further stent. An acute stent thrombosis is extremely rare and would probably be best managed with a Gp IIb/IIIa inhibitor (e.g., Rhexopro) or a lytic agent (e.g., rtPA) with the cerebral protection system in place. If a large embolus is identified within the filter prior to retrieval, this is probably best managed by partially closing and removing the filter, if possible, or else, repeat usage of either a Gp IIb/IIIa inhibitor (e.g., Rhexopro) or a lytic agent (e.g., rtPA) can be attempted.

Occasionally, an acute hemispheric event is witnessed on table. With the use of cerebral protection, this is very rarely due to a visible embolus within the intracranial circulation. If an embolus is visualised on angiography, then mechanical disruption, removal and lysis have all been

successfully employed, and there is currently no suggestion to consider that one technique is better than the other. Usually, however, no embolus is identified. Therefore, the mechanism is probably distal micro-embolisation. This should be confirmed by MRI, and haemorrhage should be excluded. It is then advisable to keep these patients anticoagulated to restrict extension of thrombus.

Hypotension immediately following CAS occurs in 19–51% of patients but is usually transient and rarely symptomatic.^{130,132–135} It may last longer than 24 h in 3–4% of patients. There is currently no consensus as to which patients require vasopressor agents.

Bradycardia is also common, with a reported incidence of 2.3–37% in cases of prophylactic atropine administration^{130,136–138} and 23–62% in cases without the use of prophylactic atropine.^{130,135,139–141} Increased age, symptomatic lesions, presence of ulceration and calcification and carotid bulb lesions have been found to be significant predictors of bradycardia during CAS. Prophylactic placement of a temporary pacemaker is not very popular, while prophylactic administration of atropine is debatable due to its potential side effects, including tachycardia which increases cardiac oxygen demand.

Major access-site complications occur in around 3% of patients and include haemorrhage and arterial occlusion.

Other complications (deterioration in renal function, etc.) are generic to endovascular procedures.

B2.4 Improving the outcome of carotid stenting

Training and experience

Several papers from the ICCS (Italian Consensus Carotid Stenting)/SPREAD group, the American Society of Interventional and Therapeutic Radiology, the American Society of Neuroradiology and the Society for Vascular Surgery have focused on training, competence and credentialing standards in CAS.^{142–144}

A proper training for interventionalists dealing with supra-aortic endovascular engagements should include the following issues:

1. Cognitive training in cerebrovascular disease.
2. Diagnostic angiographic training: virtual reality could be useful.
3. Interventional training: a specific training on individual devices from different manufacturers.
4. Surgical training.

The technical skill should be maintained over time. This can be achieved through maintaining a minimum caseload per year.

It should be noted that there is a wide range of minimum training and credentialing requirements indicated by different society guidelines. The SCAI/SVMB/SVS clinical competence statement on carotid interventions requires that the trainee should have performed at least 15 diagnostic cervicocerebral angiograms as primary operator prior to functioning as a primary stent operator.¹⁴³ The respective value required by the NeuroVascular Coalition Writing Group is 100 appropriately supervised diagnostic cervicocerebral angiograms,¹⁴⁴ whereas the ICCS–SPREAD Joint Committee requests 150 procedures of supra-aortic vessels

engagement (during diagnostic as well as interventional procedures) of which ≥ 100 are as the primary operator.¹³⁶ Similarly, the minimum training to achieve the basic competence and technical skill as the primary operator for performing carotid stenting ranges between 25 carotid stenting procedures (half as primary operator)¹⁴³ and 75 procedures (of which ≥ 50 as primary operator).¹⁴² CAS simulators have proved to be useful both for training and assessment of technical skills, but cannot substitute for live experience.

The diversity of credentialing standards is also reflected in the different thresholds required by the eligibility of RCT participants. The SPACE trial required 25 successful consecutive percutaneous transluminal angioplasty or stent procedures,²⁸ while EVA-3S required at least 12 carotid stenting procedures or at least 35 stenting procedures in the supra-aortic trunks, of which at least five in the carotid artery.²⁷ In the SAPHIRE²⁶ and CREST¹⁴⁵ trials, the experience of interventional physicians had to be equal to or superior to the published results of carotid stenting (i.e., an incidence of peri-procedural stroke or death of less than 6–8%).

Drugs

There has been only one RCT evaluating the effect of dual antiplatelet treatment in CAS.¹⁴⁶ In this study, 75 mg aspirin plus 24-h heparin was compared with 75 mg aspirin plus a loading dose of 300 mg clopidogrel 6–12 h before the procedure. Dual antiplatelet treatment was found to be associated with a significant reduction in the neurological complication rate (25% vs. 0%) without an additional increase in bleeding complications. The optimal dose of aspirin ranges between 75 and 325 mg, while the dose of clopidogrel is 75 mg, both starting at least 3 days before the stenting procedure.^{27,28,147–149} In urgent cases, 300 mg of clopidogrel in a single dose can be given 6–12 h before the procedure. Dual antiplatelet treatment should continue for at least 1 month after carotid stent placement and preferably for 3 months, taking into account that stent endothelialisation is a slow process, needing 28–96 days to complete.¹⁵⁰

Despite the lack of randomised trials for post-CAS antiplatelet therapy, evidence from the CURE and CREDO studies for patients with unstable angina or percutaneous coronary angioplasty suggest that prolonged dual antiplatelet therapy may reduce major ischaemic events in patients after carotid stenting.^{151,152} The demonstration that high-risk subgroups such as diabetics and patients with previous cardiac surgery show magnified benefit with clopidogrel compared with aspirin raises the possibility that these subgroups, in particular, may derive benefit from extended dual antiplatelet therapy.¹⁵³

Considering the beneficial effect of statins on patients undergoing CEA, it is reasonable to advocate their efficacy for patients undergoing CAS. However, no randomised or prospective studies currently exist. In a retrospective review, Groschel et al.¹⁵⁴ identified 180 patients who underwent CAS for high-grade symptomatic carotid artery stenoses. The incidence of all cardiovascular events was 4% among statin users compared to 15% ($p < 0.05$) among those not receiving statins. This included a stroke rate of 4% versus 12%, a mortality rate of 0% versus 2% and an MI

rate of 0% versus 2%. Further investigations are, however, required.

It is likely that drugs intended to block the carotid baroreceptors provide some protection against serious bradycardia and asystole during manipulation in the carotid bulb.¹³⁰

Mechanical cerebral protection systems

No randomised trials attest to the benefits of mechanical cerebral protection systems. However, a systematic review of all studies reporting on the incidence of CAS complications that were published between 1990 and 2002 showed that the combined stroke and death rate within 30 days was 1.8% in patients treated with cerebral protection devices compared with 5.5% in patients treated without cerebral protection devices ($p < 0.001$).¹⁵⁵ The review included 2537 CAS procedures without protection devices and 896 CAS procedures with protection devices. A subsequent report by the Global Carotid Artery Stent Registry documented a 5.3% rate of stroke and procedure-related death in 6753 cases performed without protection, whereas the respective rate in 4221 cases performed with cerebral protection was 2.2%.¹⁵⁶ The publication of these data has led to the almost universal adoption of the routine use of cerebral protection devices during CAS.

Nevertheless, the latest meta-analysis by The Cochrane Collaboration concluded that there is no significant difference in death or any stroke between endovascular treatment with or without cerebral protection (OR = 0.77, 95% CI: 0.41–1.46, $p = 0.43$).³⁰ The meta-analysis included two studies (EVA-3S and SPACE), none of which was a randomised comparison of angioplasty with or without cerebral protection.

The first prospective randomised study of CAS with or without a distal cerebral protection filter was recently published and showed that, contrary to the initial expectations, new MRI lesions developed in 72% of the cerebral protection group compared with 44% in the no cerebral protection group ($p = 0.09$).¹⁵⁷ Most of these lesions were silent, with the stroke rate being equal in the two groups (11%). The major limitation of this study was the small number of cases included (36 stenting procedures in 35 patients), which was due to the reluctance of the patients to participate in a study with no cerebral protection group.

Invasive treatment recommendation 13. Improving the CAS outcome

- CAS should be performed under dual antiplatelet treatment with aspirin and clopidogrel [A].
- Dual antiplatelet treatment should start before CAS and continue for 3 months after the stenting procedure [C].
- Validated training programmes should be developed [B].
- Cerebral protection devices are probably beneficial [C].

Critical issues

- The benefit of cerebral protection devices is not supported by Level A evidence.
- The optimal type of cerebral protection has still to be defined.
- The ideal stent has yet to be developed.

B3 Simultaneous Management of Peripheral Arterial and Carotid Disease

B3.1 Introduction

Peripheral arterial disease (PAD) is a marker of systemic atherosclerotic disease with increased risk of stroke, myocardial infarct as well as cardiovascular death.^{158–161} Arteriosclerosis is a generalised and progressive disease and affects different arterial segments of the body. The prevalence of simultaneous significant carotid artery stenosis in this group of patients is high. Several studies have demonstrated concomitant carotid lesions (>50% stenosis) in up to 33% of patients with symptomatic PAD.^{162,163} This has to be compared with cross-sectional and population-based studies where the incidence of a stenosis >50% seem to be in the range of 0.8–8%. Even higher numbers up to 60% have been reported if stratified for further risk factors such as diabetes, age above 70 years and an ankle/brachial index (ABI) <0.8.^{164,165} The vast majority of these are asymptomatic; however, the clinical management is complicated in terms of the immediate approach as well as secondary prevention.

B3.2 Diagnosis

Careful history taking is important in patients scheduled for interventional treatment of PAD to elucidate symptoms possibly originating from CAD. Clinical and neurological examination is also important, which includes palpation as well as auscultation of the carotid artery. However, it is necessary to be careful in interpreting these findings since a carotid artery bruit does not necessarily demonstrate a significant stenosis. Similarly, the absence of a bruit does not predict a normal artery.¹⁶⁶

In a patient with a recent (<6 months) history of TIA/stroke, a duplex examination of the carotid arteries should be performed. One might also consider a duplex scan in all vascular patients, but such a generalised screening is controversial and the cost-effectiveness remains to be demonstrated. According to a study by Cina et al., an ABI <0.4 in addition to two or more cardiovascular risk factors justify screening in this particular subgroup.¹⁶³

Other diagnostic modalities include magnetic resonance angiography (MRA) and conventional contrast angiography, but these investigations should be limited to cases with inconclusive duplex scans.

B3.3 Clinical management

Risk factor management is mandatory, including diabetes control and treatment of heart failure and hypertension. Antiplatelet drugs and statins are important as adjunctive treatment to reduce the risk of embolisation, and possibly also for plaque stabilisation.

The treatment of PAD should not be delayed due to an asymptomatic carotid artery stenosis. The asymptomatic carotid artery may subsequently be handled according to the centre's policy (Fig. 1).¹⁶⁷

On the other hand, a >70% carotid artery stenosis, causing symptoms within the recent 6 months has priority for treatment before surgery for PAD.

Another possible approach is a simultaneous procedure, however, this approach might be quite demanding to the patient. No scientific proof exists for this kind of management.

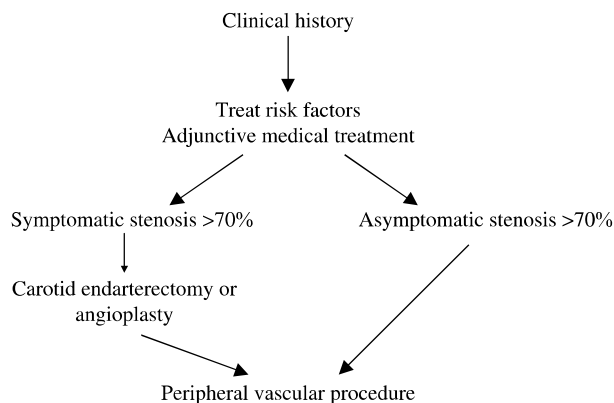


Figure 1 Algorithm for the management of simultaneous carotid artery disease and peripheral vascular disease. Adapted from Clement et al.¹⁶⁷

Invasive treatment recommendation 14. Simultaneous management of peripheral arterial and carotid disease

- A carotid stenosis which has been asymptomatic for 6 months need not delay the operative treatment of peripheral vascular disease [C].

B4 Simultaneous Management of Coronary and Carotid Artery Disease

The incidence of significant carotid stenosis in patients undergoing CABG ranges between 2.8% and 22%,^{168,169} whereas 28–40% of patients undergoing CEA have significant concomitant coronary artery disease.^{170,171} In general, patients with mild or moderate coronary artery disease can undergo CEA with acceptably low perioperative risk. However, in patients with severe coronary artery disease, as manifested by unstable angina or NYHA functional status III or IV, and symptomatic, critical carotid stenosis, the optimal surgical strategy remains debatable. Operating on the carotid lesion first exposes the patient to an increased risk of perioperative morbidity and mortality from MI; operating on the coronary arteries first exposes the patient to an increased risk of perioperative stroke, while conducting both operations simultaneously may result in excessive surgical stress for the patient.

Several meta-analyses have been performed in order to summarise the wealth of divergent data reported in the literature. The most recent meta-analysis,¹⁷² including 97 published studies following 8972 staged or combined operations, concluded that there is no significant difference in outcomes for staged and synchronous procedures. The combined risk of death/stroke or MI was 10–12% for both strategies. However, in the absence of randomised trials, it is impossible to draw definite conclusions regarding the best management strategy. Until a contemporary, totally randomised study resolves the confusion surrounding the appropriate management of patients with concomitant, severe coronary and carotid artery disease, the surgical approach should be individualised, based on the specific risk profile of each patient.

It remains to be proved whether carotid stenting could be the solution for simultaneous management of coronary and carotid artery disease. The SAPPPIRE trial showed that carotid stenting is superior to endarterectomy with regards to cardiac complications in high-risk patients.²⁶ A randomised trial exclusively of patients in need of CABG is needed to provide definite answers.

Invasive treatment recommendation 15. Simultaneous management of coronary and carotid artery disease

- Until data from randomised trials are available, the surgical approach to the patient with simultaneous severe coronary and carotid artery disease should be individualised, based on the specific risk profile of each patient [C].

B5 Developments (Trials Under Way)

The main focal points of the ongoing international multi-centre RCTs concerning the treatment outcomes of carotid artery stenosis are: the role of percutaneous transluminal angioplasty and stenting (endovascular treatment), the optimal treatment of the asymptomatic CAS and CEA under GALA. The other areas of interest are the prevention of postoperative thrombo-embolic stroke and treatment of carotid occlusion.

The following are a few of the studies currently in progress:

- The International Carotid Stenting Study (ICSS), which will compare primary stenting with CEA in the treatment of symptomatic carotid artery stenosis.
- The Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST), which will compare endovascular treatment with endarterectomy in patients with either symptomatic or asymptomatic carotid stenosis.
- The Transatlantic Asymptomatic Carotid Intervention (TACIT), which will compare the best medical therapy combined with carotid stenting or endarterectomy with the best medical therapy alone in the prevention of stroke and death in patients with asymptomatic carotid stenosis,
- The Asymptomatic Carotid Surgery Trial 2 (ACST-2), which will compare carotid endarterectomy and CAS in the treatment of asymptomatic carotid stenosis.
- The Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT I), which will compare endovascular treatment with CEA in patients with severe CAS who have not had symptoms within 180 days.
- The Carotid Occlusion Surgery Study (COSS), which will determine whether surgical anastomosis of the superficial temporal artery to the middle cerebral artery in conjunction with the best medical therapy can reduce the incidence of ipsilateral ischaemic stroke by at least 40% in patients with symptomatic internal carotid artery occlusion.
- The SPACE-2 study, which is a three-armed comparison among up-to-date best medical treatment, CAS and CEA in patients with asymptomatic CAD.

ESVS working groups on indications and treatment of carotid stenosis:

Name	Participation	Discipline
1 K. Balzer		Vascular surgery
2 E. Bastounis		Surgery
3 J. Beard		Vascular surgery
4 J.-P. Becquemin		Vascular surgery
5 F. Benedetti-Valentini		Vascular surgery
6 M. Brown		Neurology
7 P. Cao		Vascular surgery
8 A. Cremonesi		Cardiology
9 P. Dimakakos		Vascular surgery
10 A. Froio		Vascular surgery
11 P. Gaines		Radiology
12 G. Gensini		Cardiology/Internal medicine
13 A. Halliday		Vascular surgery
14 M. Heikkinen		Vascular surgery
15 M. Horrocks		Vascular surgery
16 J. Kakisis		Vascular surgery
17 C. Karkos		Vascular surgery
18 K. Katsenis		Vascular surgery
19 D. Kiskinis		Vascular surgery
20 K. Konstantinidis		Vascular surgery
21 T. Kotsis		Vascular surgery
22 M. Lavitrano		Pathology/immunology
23 T. Mätzsch		Vascular surgery
24 R. Naylor		Vascular surgery
25 B. Norrving	Reviewer	Neurology
26 H. Pärsson		Vascular surgery
27 J. Powell	Reviewer	Vascular medicine
28 D. Raithel		Vascular surgery
29 J. Salenius		Vascular surgery
30 C. Setacci		Vascular surgery

Funding

This work was funded exclusively by the ESVS in the form of travel grants.

Conflicts of Interest

None declared.

Acknowledgements

The Guidelines Committee gratefully acknowledges the assistance and support of the ESVS Council and Executives. The authors are grateful to their colleagues who contributed the information for this report.

References

- 1 Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. American Heart Association Statistics

- Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;**113**:e85–151.
- 2 Kleindorfer D, Panagos P, Pancioli A, Khoury J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke* 2005;**36**: 720–723.
 - 3 White H, Boden-Albala B, Wang C, Elkind MS, Rundek T, Wright CB, et al. Ischemic stroke subtype incidence among whites, blacks, and Hispanics: the Northern Manhattan Study. *Circulation* 2005;**111**:1327–1331.
 - 4 Bonita R, Stewart A, Beaglehole R. International trends in stroke mortality: 1970–1985. *Stroke* 1990;**21**:989–992.
 - 5 Mohr JP, Caplan LR, Melski JW, Goldstein RJ, Duncan GW, Kistler JP, et al. The Harvard Cooperative Stroke Registry: a prospective registry. *Neurology* 1978;**28**:754–762.
 - 6 Robinson RW, Demirel M, LeBeau RJ. Natural history of cerebral thrombosis: 9–19 years follow-up. *J Chronic Dis* 1968;**21**:221.
 - 7 Veith FJ, Amor M, Ohki T, Beebe HG, Bell PR, Bolia A, et al. Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. *J Vasc Surg* 2001;**33**(2 Suppl):S111–6.
 - 8 Bogousslavsky J, Van MG, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke* 1988;**19**:1083–92.
 - 9 Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. *Stroke* 1988;**19**:547–54.
 - 10 Inzitari D, Eliasziw M, Gates P, Sharpe BL, Chan RK, Meldrum HE, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 2000;**342**:1693–700.
 - 11 Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. *Stroke* 1992;**23**:486–91.
 - 12 Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;**339**:1415–25.
 - 13 The European Carotid Surgery Trialists Collaborative Group. Risk of stroke in the distribution of an asymptomatic carotid artery. *Lancet* 1995;**345**:209–12.
 - 14 Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott T, et al. Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the ad hoc committee. *Stroke* 1995;**26**:188–201.
 - 15 Setacci C, Cremonesi A. SPACE and EVA-3s Trials: The need of standards for carotid stenting. *Eur J Vasc Endovasc Surg* 2007;**33**:48–9.
 - 16 AHCPR. United States Department of Health and Human Services. Agency for Health Care Policy and Research. *Acute pain management: operative on medical procedures and trauma*. [107]. Rockville MD: AHCPR; 1993.
 - 17 European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;**351**:1379–87.
 - 18 Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial: Surgical results in 1415 patients. *Stroke* 1999;**30**:1751–8.
 - 19 Moneta GL, Edwards JM, Chitwood RW, Taylor Jr LM, Lee RW, Cummings CA, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. *J Vasc Surg* 1993;**17**:152–9.
 - 20 Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003;**361**:107–16.
 - 21 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 2004;**363**:915–24.
 - 22 Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;**273**:1421–8.
 - 23 Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;**363**:1491–502.
 - 24 ACST Writing Committee, on behalf of the ACST Collaborative Group. ACST: which subgroups will benefit most from carotid endarterectomy? Authors' reply. *Lancet* 2004;**364**:125–126.
 - 25 CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Lancet* 2001;**357**:1729–37.
 - 26 SAPHIRE Investigators (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy). Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;**351**:1493–501.
 - 27 Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al. EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;**355**:1660–71.
 - 28 Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, et al. SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;**368**:1239–47.
 - 29 Liapis CD, Satianni B, Florance CL, Evans WE. Motor speech malfunction following carotid endarterectomy. *Surgery* 1981;**89**:56–9.
 - 30 Ederle J, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev* 2007;**4**:CD000515. doi: 10.1002/14651858.CD000515.pub3.
 - 31 Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, et al. SAPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;**358**:1572–9.
 - 32 Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al. EVA-3S investigators. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008;**7**:885–92.
 - 33 Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;**7**:893–902.
 - 34 Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomised trial in a community hospital. *J Am Coll Cardiol* 2001;**38**:1589–95.
 - 35 de Donato G, Setacci C, Deloosse K, Peeters P, Cremonesi A, Bosiers M. Long-term results of carotid artery stenting. *J Vasc Surg* 2008;**48**:1431–41.

- 36 Hobson 2nd RW, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, et al. CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg* 2004;40:1106–11.
- 37 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.
- 38 Brown MM, Hacke W. Carotid artery stenting: the need for randomised trials. *Cerebrovasc Dis* 2004;18:57–61.
- 39 Ringleb PA, Kunze A, Allenberg JR, Hennerici MG, Jansen O, Maurer PC, et al. Steering Committee of the SPACE Study. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial. *Cerebrovasc Dis* 2004;18:66–8.
- 40 Hacke W, Brown MM, Mas JL. Carotid endarterectomy versus stenting: an international perspective. *Stroke* 2006;37:344.
- 41 Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) Trial. *Cerebrovasc Dis* 2004;18:62–5.
- 42 Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg* 2004;39:958–66.
- 43 Nguyen LL, Conte MS, Reed AB, Belkin M. Carotid endarterectomy: who is the high-risk patient? *Semin Vasc Surg* 2004;17:219–23.
- 44 Ballotta E, Da Giau G, Baracchini C, Manara R. Carotid endarterectomy in high-risk patients: a challenge for endovascular procedure protocols. *Surgery* 2004;135:74–80.
- 45 Pulli R, Dorigo W, Barbanti E, Azas L, Pratesi G, Innocenti AA, et al. Does the high-risk patient for carotid endarterectomy really exist? *Am J Surg* 2005;189:714–9.
- 46 Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. *J Vasc Surg* 2003;37:40–6.
- 47 Illig KA, Zhang R, Tanski W, Benesch C, Sternbach Y, Green RM. Is the rationale for carotid angioplasty and stenting in patients excluded from NASCET/ACAS or eligible for ARChER justified? *J Vasc Surg* 2003;37:575–81.
- 48 Stanziale SF, Marone LK, Boules TN, Brimmeier JA, Hill K, Makaroun MS, et al. Carotid artery stenting in octogenarians is associated with increased adverse outcomes. *J Vasc Surg* 2006;43:297–304.
- 49 Ballotta E, Da Giau G, Militello C, Barbon B, De Rossi A, Meneghetti G, et al. High-grade symptomatic and asymptomatic carotid stenosis in the very elderly. A challenge for proponents of carotid angioplasty and stenting. *BMC Cardiovasc Disord* 2006;6:12.
- 50 Reed AB, Gaccione P, Belkin M, Donaldson MC, Mannick JA, Whittemore AD, et al. Preoperative risk factors for carotid endarterectomy: defining the patient at high risk. *J Vasc Surg* 2003;37:1191–9.
- 51 Ohki T, Marin ML, Lyon RT, Berdejo GL, Soundararajan K, Ohki M, et al. Ex vivo human carotid artery bifurcation stenting: correlation of lesion characteristics with embolic potential. *J Vasc Surg* 1998;27:463–71.
- 52 Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation* 2004;110:756–62.
- 53 Reiter M, Bucek RA, Effenberger I, Boltuch J, Lang W, Ahmadi R, et al. Plaque echolucency is not associated with the risk of stroke in carotid stenting. *Stroke* 2006;37:2378–80.
- 54 Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Thomas DJ, et al. Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Effect of image normalization on carotid plaque classification and the risk of ipsilateral hemispheric ischemic events: results from the asymptomatic carotid stenosis and risk of stroke study. *Vascular* 2005;13:211–21.
- 55 Liapis CD, Kakisis JD, Kostakis AG. Carotid stenosis: factors affecting symptomatology. *Stroke* 2001;32:2782–6.
- 56 Mathiesen EB, Bonna KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: the tromso study. *Circulation* 2001;103:2171–5.
- 57 Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Silleesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* 2001;104:68–73.
- 58 Pedro LM, Pedro MM, Goncalves I, Carneiro TF, Balsinha C, Fernandes e Fernandes R, et al. Computer-assisted carotid plaque analysis: characteristics of plaques associated with cerebrovascular symptoms and cerebral infarction. *Eur J Vasc Endovasc Surg* 2000;19:118–23.
- 59 de Bray JM, Baud JM, Delanoy P, Camuzat JP, Dehans V, Descamp-Le Chevoir J, et al. Reproducibility in ultrasonic characterization of carotid plaques. *Cerebrovasc Dis* 1998;8:273–7.
- 60 Arnold JA, Modaresi KB, Thomas N, Taylor PR, Padayachee TS. Carotid plaque characterization by duplex scanning: observer error may undermine current clinical trials. *Stroke* 1999;30:61–5.
- 61 Montauban van Swijndregt AD, Elbers HR, Moll FL, de Letter J, Ackerstaff RG. Ultrasonographic characterization of carotid plaques. *Ultrasound Med Biol* 1998;24:489–93.
- 62 Maldonado TS. What are current preprocedure imaging requirements for carotid artery stenting and carotid endarterectomy: have magnetic resonance angiography and computed tomographic angiography made a difference? *Semin Vasc Surg* 2007;20:205–15.
- 63 Wintermark M, Jawadi SS, Rapp JH, Tihan T, Tong E, Glidden DV, et al. High-resolution CT imaging of carotid artery atherosclerotic plaques. *AJNR Am J Neuroradiol* 2008;29:875–82.
- 64 Fabiano S, Mancino S, Stefanini M, Chiochi M, Mauriello A, Spagnoli LG, et al. High-resolution multicontrast-weighted MR imaging from human carotid endarterectomy specimens to assess carotid plaque components. *Eur Radiol* 2008;18:2912–21.
- 65 U-King-Im JM, Tang T, Moustafa RR, Baron JC, Warburton EA, Gillard JH. Imaging the cellular biology of the carotid plaque. *Int J Stroke* 2007;2:85–96.
- 66 Howarth SP, Tang TY, Trivedi R, Weerakkody R, U-King-Im J, Gaunt ME, et al. Utility of USPIO-enhanced MR imaging to identify inflammation and the fibrous cap: A comparison of symptomatic and asymptomatic individuals. *Eur J Radiol* 2008; doi:10.1016/j.ejrad.2008.01.047.
- 67 Prabhudesai V, Phelan C, Yang Y, Wang RK, Cowling MG. The potential role of optical coherence tomography in the evaluation of vulnerable carotid atheromatous plaques: a pilot study. *Cardiovasc Intervent Radiol* 2006;29:1039–45.
- 68 Jo JA, Fang Q, Papaioannou T, Qiao JH, Fishbein MC, Beseth B, et al. Diagnosis of vulnerable atherosclerotic plaques by time-resolved fluorescence spectroscopy and ultrasound imaging. *Conf Proc IEEE Eng Med Biol Soc* 2006;1:2663–6.
- 69 Ding S, Zhang M, Zhao Y, Chen W, Yao G, Zhang C, et al. The role of carotid plaque vulnerability and inflammation in the pathogenesis of acute ischemic stroke. *Am J Med Sci* 2008;336:27–31.
- 70 Koenig W, Khuseynova N. Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler Thromb Vasc Biol* 2007;27:15–26.
- 71 Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in

- carotid artery stenting? *Eur J Vasc Endovasc Surg* 2007;33:135–43.
- 72 Schillinger M, Gschwendtner M, Reimers B, Trenkler J, Stockx L, Mair J, et al. Does carotid stent cell design matter? *Stroke* 2008;39:905–9.
 - 73 Sandmann W, Kolvenbach R, Willeke F. Risks and benefits of shunting in carotid endarterectomy (letter). *Stroke* 1993;24:1098.
 - 74 Gumerlock MK, Neuwelt EA. Carotid endarterectomy: to shunt or not to shunt. *Stroke* 1988;19:1485–90.
 - 75 Fletcher JP, Morris JGL, Little JM, Kershaw LZ. EEG monitoring during carotid endarterectomy. *Aust N Z J Surg* 1988;58:285–8.
 - 76 Bond R, Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev*; 2002. Issue 2. Art. No.: CD000190. doi: 10.1002/14651858.CD000190.
 - 77 Bond R, Warlow CP, Naylor AR, Rothwell PM. European Carotid Surgery Trialists' Collaborative Group. Variation in surgical and anaesthetic technique and associations with operative risk in the European carotid surgery trial: implications for trials of ancillary techniques. *Eur J Vasc Endovasc Surg* 2002;23:117–26.
 - 78 Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. *Cochrane Database Syst Rev*; 2006;:1.
 - 79 AbuRahma AF, Khan JH, Robinson PA, Saiedy S, Short YS, Boland JP, et al. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: perioperative (30 day) results. *J Vasc Surg* 1996;24:998–1007.
 - 80 De Vleeschauwer P, Wirthle W, Holler L, Krause E, Horsch S. Is venous patch grafting after carotid endarterectomy able to reduce the rate of restenosis? Prospective randomized pilot study with stratification. *Acta Chirurg Belg* 1987;87:242–6.
 - 81 Eikelboom BC, Ackerstaff RGA, Hoeneveld H, Ludwig JW, Teeuwen C, Vermeulen FE, et al. Benefits of carotid patching: a randomized study. *J Vasc Surg* 1988;7:240–7.
 - 82 Katz D, Snyder SO, Gandhi RH, Wheeler JR, Gregory RT, Gayle RG, et al. Long-term follow up for recurrent stenosis: a prospective randomized study of expanded polytetrafluoroethylene patch angioplasty versus primary closure after carotid endarterectomy. *J Vasc Surg* 1994;19:198–205.
 - 83 Lord RSA, Raj TB, Stary DL, Nash PA, Graham AR, Goh KH. Comparison of saphenous vein patch, polytetrafluoroethylene patch, and direct arteriotomy closure after carotid endarterectomy. Part I: Perioperative results. *J Vasc Surg* 1989;9:521–9.
 - 84 Myers SI, Valentine RJ, Chervu A, Bowers BL, Clagett GP. Saphenous vein patch versus primary closure for carotid endarterectomy: Long term assesment of a randomized prospective study. *J Vasc Surg* 1994;19:15–22.
 - 85 Ranaboldo CJ, Barros D'Sa ABB, Bell PRF, Chant ADBPerry PM for the Joint Vascular Research Group. Randomized controlled trial of patch angioplasty for carotid endarterectomy. *Br J Surg* 1993;80:1528–30.
 - 86 Mannheim D, Weller B, Vahadim E, Karmeli R. Carotid endarterectomy with a polyurethane patch versus primary closure: a prospective randomized study. *J Vasc Surg* 2005;41:403–8.
 - 87 Bond R, Rerkasem K, Naylor R, Rothwell PM. Patches of different types for carotid patch angioplasty. *Cochrane Database Syst Rev*; 2006;:1.
 - 88 AbuRahma A, Hannay S, Khan JH, Robinson PA, Hudson JK, Davis EA. Prospective randomised study of carotid endarterectomy with polytetrafluoroethylene versus collagen-impregnated Dacron (Hemashield) patching: perioperative (30-day) results. *J Vasc Surg* 2002;35:125–30.
 - 89 Gonzalez-Fajardo JA, Perez JL, Mateo AM. Saphenous vein patch versus polytetrafluoroethylene patch after carotid endarterectomy. *J Cardiovasc Surg* 1994;35:523–8.
 - 90 Katz SG, Kohl RD. Does the choice of material influence early morbidity in patients undergoing carotid patch angioplasty? *Surgery* 1996;119:297–301.
 - 91 Hayes PD, Allroggen H, Steel S, Thompson MM, London NJ, Bell PR, et al. Randomized trial of vein versus Dacron patching during carotid endarterectomy: influence of patch type on postoperative embolization. *J Vasc Surg* 2001;33:994–1000.
 - 92 Naylor R, Hayes PD, Payne DA, Allroggen H, Steel S, Thompson MM, et al. Randomized trial of vein versus dacron patching during carotid endarterectomy: long-term results. *J Vasc Surg* 2004;39:985–93.
 - 93 O'Hara PJ, Hertzner NR, Mascha EJ, Krajewski LP, Clair DG, Ouriel K. A prospective, randomized study of saphenous vein patching versus synthetic patching during carotid endarterectomy. *J Vasc Surg* 2002;35:324–30.
 - 94 O'Hara PJ, Hertzner NR, Krajewski LP, Beven EG. Saphenous vein patch rupture after carotid endarterectomy. *J Vasc Surg* 1992;15:504–9.
 - 95 Riles TS, Lamparello PJ, Giangola G, Imparato AM. Rupture of the vein patch: a rare complication of carotid endarterectomy. *Surgery* 1990;107:10–2.
 - 96 Scott EW, Dolson L, Day AL, Seeger JM. Carotid endarterectomy complicated by vein patch rupture. *Neurosurgery* 1992;31:373–7.
 - 97 Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A. Carotid endarterectomy with patch closure versus carotid eversion endarterectomy and reimplantation: a prospective randomized study. *Surgery* 1999;125:271–9.
 - 98 Ballotta E, Renon L, Da Giau G, Toniato A, Baracchini C, Abbruzzese E. A prospective randomized study on bilateral carotid endarterectomy: patching versus eversion. Clinical outcome and restenosis. *Ann Surg* 2000;232:119–25.
 - 99 Balzer K. Eversion versus conventional carotid endarterectomy. In: Horsch S, Ktenidis K, editors. *Perioperative monitoring in carotid surgery*. Darmstadt: Steinkopff Springer; 1998. p. 159–65.
 - 100 Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G, et al and collaborators of the EVEREST Study Group. A randomized study on eversion versus standard carotid endarterectomy: study design and preliminary results: the EVEREST trial. *J Vasc Surg* 1998;27:595–605.
 - 101 Vanmaele RG, Van Schil PE, DeMaeseneer MG, Meese G, Leher PH, Van Look RF. Division-endarterectomy-anastomosis of the internal carotid artery: a prospective randomized comparative study. *Cardiovasc Surg* 1994;2:573–81.
 - 102 Cao PG, De Rango P, Zannetti S, Giordano G, Ricci S, Celani MG. Eversion versus conventional carotid endarterectomy for preventing stroke. [Systematic Review]. *Cochrane Stroke Group Cochrane Database Syst Rev* 2006;1.
 - 103 Forsell C, Takolander R, Bergqvist D, Johansson A, Persson NH. Local versus general anaesthesia in carotid surgery. A prospective, randomised study. *Eur J Vasc Surg* 1989;3:503–9.
 - 104 Kasprzak P, Altmeppen J, Rosin L, Metz CH, Horn M, Jauch KW. Local versus general anaesthesia in carotid surgery—results of a prospective randomised study. *Cardiovasc Surg* 1999;7(Suppl 1). 16 (Abs 4.2).
 - 105 McCarthy RJ, Nasr MK, McAteer P, Horrocks M. Physiological advantages of cerebral blood flow during carotid endarterectomy under local anaesthesia. A randomised clinical trial. *Eur J Vasc Endovasc Surg* 2002;24:215–21.
 - 106 McCleary AJ, Maritati G, Gough MJ. Carotid endarterectomy: local or general anaesthesia? *Eur J Vasc Endovasc Surg* 2001;22:1–12.

- 107 Pluskwa F, Bonnet F, Abhay K, Touboul C, Rey B, Marcandoro J, et al. Blood pressure profiles during carotid endarterectomy. Comparing flunitrazepam/fentanyl/nitrous oxide with epidural anaesthesia (author's translation). *Annales Francaises d'anesthesie et de reanimation* 1989;**8**:26–32.
- 108 Sbarigia E, DarioVizza C, Antonini M, Speziale F, Maritti M, Fiorani B, et al. Locoregional versus general anesthesia in carotid surgery in carotid surgery: is there an impact on perioperative myocardial ischemia? results of a prospective monocentric randomized trial. *J Vasc Surg* 1999;**30**:131–8.
- 109 Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy [Systematic Review] Cochrane Stroke Group. *Cochrane Database Syst Rev* 2004;**2**:CD000126. Doi: 10.1002/14651858.CD000126.pub2.
- 110 GALA Trial Collaborative Group, 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;**372**:2132–42.
- 111 Gough MJ, Bodenham A, Horrocks M, Colam B, Lewis SC, Rothwell PM, et al. GALA: an international multicentre randomised trial comparing general anaesthesia versus local anaesthesia for carotid surgery. *Trials* 2008;**9**:28.
- 112 Liapis CD, Paraskevas KI. Role of residual defects following carotid endarterectomy in the occurrence of cerebrovascular symptoms. *Vasc Endovasc Surg* 2006;**40**:119–23.
- 113 Donaldson MC, Ivarsson B, Manick J, Whittemore AD. Impact of completion angiography on operative conduct and results of carotid endarterectomy. *Ann Surg* 1993;**6**:682–7.
- 114 Kinney EV, Seabrooke G, Kinney LY, Bandyk DF, Towne JB. The importance of intra-operative detection of residual flow abnormalities after carotid endarterectomy. *J Vasc Surg* 1993;**17**:912–22.
- 115 Blaisdell FW, Lim R, Hall AD. Technical results of carotid endarterectomy: arteriographic assessment. *Am J Surg* 1967;**114**:239–46.
- 116 Pratesi C, Dorigo W, Troisi N, Fargion A, Innocenti AA, Pratesi G, et al. Routine completion angiography during carotid endarterectomy is not mandatory. *Eur J Vasc Endovasc Surg* 2006;**32**:369–73.
- 117 Engelter S, Lyrer P. Antiplatelet therapy for preventing stroke and other vascular events after carotid endarterectomy. *Cochrane Database Syst Rev* 2003;**3**:CD001458. doi: 10.1002/14651858.CD001458.
- 118 Lindblad B, Persson N, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. *Stroke* 1993;**24**:1125–8.
- 119 Taylor DW, Barnett HJM, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;**353**:2179–84.
- 120 Payne DA, Jones CI, Hayes PD, Thompson MM, London NJ, Bell PR, et al. Beneficial effects of clopidogrel combined with aspirin in reducing cerebral emboli in patients undergoing carotid endarterectomy. *Circulation* 2004;**109**:1476–81.
- 121 Szeder V, Torbey MT. Prevention and treatment of perioperative stroke. *Neurologist* 2008;**14**:30–6.
- 122 Palareti G, Legnani C. Warfarin withdrawal. Pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 1996;**30**:300–13.
- 123 McGirt MJ, Perler BA, Brooke BS, Woodworth GF, Coon A, Jain S, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. *J Vasc Surg* 2005;**42**:829–36.
- 124 Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leão P, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004;**39**:967–76.
- 125 Schouten O, Kertai MD, Bax JJ, Durazzo AE, Biagini E, Boersma E, et al. Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. *Am J Cardiol* 2005;**95**:658–60.
- 126 Perler B. The effect of statin medications on perioperative and long term outcomes following carotid endarterectomy or stenting. *Semin Vasc Surg* 2007;**20**:252–8.
- 127 Chaturvedi S, Yadav JS. The role of antiplatelet therapy in carotid stenting for ischemic stroke prevention. *Stroke* 2006;**37**:1572–7.
- 128 Feldtman RW, Buckley CJ, Bohannon WT. How I do it: cervical access for carotid artery stenting. *Am J Surg* 2006;**192**:779–81.
- 129 Iyer V, de Donato G, Deloose K, Peeters P, Castriota F, Cremonesi A, et al. The type of embolic protection does not influence the outcome in carotid artery stenting. *J Vasc Surg* 2007;**46**:251–6.
- 130 Cayne NS, Faries PL, Trocciola SM, Saltzberg SS, Dayal RD, Clair D, et al. Carotid angioplasty and stent-induced bradycardia and hypotension: Impact of prophylactic atropine administration and prior carotid endarterectomy. *J Vasc Surg* 2005;**41**:956–61.
- 131 Kwon BJ, Han MH, Kang HS, Jung C. Protection filter-related events in extracranial carotid artery stenting: a single-center experience. *J Endovasc Ther* 2006;**13**:711–22.
- 132 Gupta R, Horowitz M, Jovin TG. Hemodynamic instability after carotid artery angioplasty and stent placement: a review of the literature. *Neurosurg Focus* 2005;**18**:e6.
- 133 Park B, Shapiro D, Dahn M, Arici M. Carotid artery angioplasty with stenting and postprocedure hypotension. *Am J Surg* 2005;**190**:691–5.
- 134 Trocciola SM, Chaer RA, Lin SC, Ryer EJ, De Rubertis B, Morrissey NJ, et al. Analysis of parameters associated with hypotension requiring vasopressor support after carotid angioplasty and stenting. *J Vasc Surg* 2006;**43**:714–20.
- 135 Lin PH, Zhou W, Koungias P, El Sayed HF, Barshes NR, Huynh TT. Factors associated with hypotension and bradycardia after carotid artery angioplasty and stenting. *J Vasc Surg* 2007;**46**:846–54.
- 136 Pappadà G, Beghi E, Marina R, Agostoni E, Cesana C, Legnani F, et al. Hemodynamic instability after extracranial carotid stenting. *Acta Neurochir (Wien)* 2006;**148**:639–45.
- 137 Taha MM, Toma N, Sakaida H, Hori K, Maeda M, Asakura F, et al. Periprocedural hemodynamic instability with carotid angioplasty and stenting. *Surg Neurol* 2008;**70**:279–86.
- 138 Mlekusch W, Schillinger M, Sabeti S, Nachtmann T, Lang W, Ahmadi R, et al. Hypotension and bradycardia after elective carotid stenting: frequency and risk factors. *J Endovasc Ther* 2003;**10**:851–61.
- 139 Harrop JS, Sharan AD, Benitez RP, Armonda R, Thomas J, Rosenwasser RH. Prevention of carotid angioplasty-induced bradycardia and hypotension with temporary venous pacemakers. *Neurosurgery* 2001;**49**:814–22.
- 140 Gupta R, Abou-Chebl A, Bajzer CT, Schumacher HC, Yadav JS. Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. *J Am Coll Cardiol* 2006;**47**:1538–43.
- 141 Nano G, Dalainas I, Bianchi P, Stegher S, Bet L, Malacrida G, et al. Ballooning-induced bradycardia during carotid stenting in primary stenosis and restenosis. *Neuroradiology* 2006;**48**:533–6.
- 142 Cremonesi A, Setacci C, Bignamini A, Bolognese L, Briganti F, Di Sciascio G, et al. Carotid artery stenting: first consensus document of the ICCS-SPREAD Joint Committee. *Stroke* 2006;**37**:2400–9.

- 143 Rosenfield KM. SCAI/SVMB/SVS Writing Committee. Clinical competence statement on carotid stenting: training and credentialing for carotid stenting—multispecialty consensus recommendations. *J Vasc Surg* 2005;41:160–8.
- 144 Connors JJ 3rd, Sacks D, Furlan AJ, Selman WR, Russell EJ, Stieg PE, et al.; NeuroVascular Coalition Writing Group; 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; Society of Interventional Radiology. 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.
- 145 Hobson 2nd RW, Howard VJ, Roubin GS, Ferguson RD, Brott TG, Howard G, et al. CREST. Credentialing of surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg* 2004;40:952–7.
- 146 McKeivitt 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;29:522–7.
- 147 Bates ER, Babb JD, Casey Jr DE, Cates CU, Duckwiler GR, Feldman TE, et al.; American College of Cardiology Foundation; American Society of Interventional & Therapeutic Neuroradiology; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology. 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 (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid Stenting). *J Am Coll Cardiol* 2007;49:126–70.
- 148 Bohannon WT. Technical tips for carotid angioplasty and stenting. *Semin Vasc Surg* 2008;21:3–7.
- 149 Gopalan D, Thomas SM. Pharmacotherapy for patients undergoing carotid stenting. *Eur J Radiol* 2006;60:14–9.
- 150 Grewe PH, Deneke T, Machraoui A, Barmeyer J, Müller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. *J Am Coll Cardiol* 2000;35:157–63.
- 151 CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502.
- 152 Steinhubl SR, Berger PB, Mann III JT, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *J Am Med Assoc* 2002;288:2411–20.
- 153 Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. *Arch Intern Med* 2004;164:2106–10.
- 154 Groschel K, Ernemann U, Schulz JB, Nägele T, Terborg C, Kastrup A. Statin therapy at carotid angioplasty and stent placement: effect on procedure-related stroke, myocardial infarction, and death. *Radiology* 2006;240:145–51.
- 155 Kastrup A, Gröschel 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;34:813–9.
- 156 Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv* 2003;60:259–66.
- 157 Barbato JE, Dillavou E, Horowitz MB, Jovin TG, Kanal E, David S, et al. A randomized trial of carotid artery stenting with and without cerebral protection. *J Vasc Surg* 2008;47:760–5.
- 158 Fowkes FG. Epidemiology of atherosclerotic arterial disease in the lower limbs. *Eur J Vasc Surg* 1988;2:283–91.
- 159 Newman AB, Scovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation* 1993;88:37–45.
- 160 Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, et al. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 2003;163:884–92.
- 161 Simons PC, Algra A, Eikelboom BC, Grobbee DE, van der Graaf Y. Carotid artery stenosis in patients with peripheral arterial disease: the SMARTstudy. *J Vasc Surg* 1999;30:519–25.
- 162 Alexandrova NA, Gibson WC, Norris JW, Maggisano R. Carotid artery stenosis in peripheral vascular disease. *J Vasc Surg* 1996;23:645–9.
- 163 Cina CS, Safar HA, Maggisano R, Bailey R, Clase CM. Prevalence and progression of internal carotid artery stenosis in patients with peripheral arterial occlusive disease. *J Vasc Surg* 2002;36:75–82.
- 164 Colgan MP, Strode GR, Sommer JD, Gibbs JL, Sumner DS. Prevalence of asymptomatic carotid disease: results of duplex scanning in 348 unselected volunteers. *J Vasc Surg* 1988;8:674–8.
- 165 McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, et al. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 2005;162:33–41.
- 166 AbuRahma AF, Robinson PA. Prospective clinicopathophysiologic follow-up study of asymptomatic neck bruit. *Am Surg* 1990;56:108–13.
- 167 Clement DL, Boccalon H, Dormandy J, Durand-Zaleski I, Fowkes G, Brown T. A clinical approach to the management of the patient with coronary (Co) and/or carotid (Ca) artery disease who presents with leg ischaemia (Lis). *Int Angiol* 2000;19:97–125.
- 168 Hertzner NR, Loop FD, Beven EG, O'Hara PJ, Krajewski LP. Surgical staging for simultaneous coronary and carotid disease: a study including prospective randomization. *J Vasc Surg* 1989;9:455–63.
- 169 Schwartz LB, Bridgman AH, Kieffer RW, Wilcox RA, McCann RL, Tawil MP, et al. Asymptomatic carotid artery stenosis and stroke in patients undergoing cardiopulmonary bypass. *J Vasc Surg* 1995;21:146–53.
- 170 Hertzner NR, Young JR, Beven EG, Graor RA, O'Hara PJ, Ruschhaupt 3rd WF, et al. Coronary angiography in 506 patients with extracranial cerebrovascular disease. *Arch Intern Med* 1985;145:849–52.
- 171 Urbinati S, Di Pasquale G, Andreoli A, Lusa AM, Carini G, Grazi P, et al. Preoperative noninvasive coronary risk stratification in candidates for carotid endarterectomy. *Stroke* 1994;25:2022–7.
- 172 Naylor AR, Cuffe RL, Rothwell PM, Bell PR. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg* 2003;25:380–9.