An Overview About Treatment of Extracranial Atherosclerotic Disease for Stroke Prevention

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Abstract
Stroke is a leading cause of adult mortality and disability worldwide. Extracranial atherosclerotic disease (ECAD), primarily, carotid artery stenosis, accounts for approximately 18%–25% of ischaemic stroke. Recent advances in neuroimaging, medical therapy and interventional management have led to A significant reduction of stroke from carotid artery stenosis. The current treatment of ECAD includes optimal medical therapy, carotid endarterectomy (CEA) and carotid artery stenting (CAS). The selection of treatments depends on symptomatic status, severity of stenosis, individual factors, efficacy and risk of complications. The aim of this paper is to review current evidence and guidelines on the management of carotid artery stenosis, including the comparison of medical and interventional therapy (CAS and CEA), as well as future directions.
Keywords: Extracranial Atherosclerotic stroke, Treatment

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Introduction

Stroke is the leading cause of adult mortality and disability worldwide. Extracranial atherosclerotic disease (ECAD), primarily, carotid artery stenosis, accounts for approximately 18%–25% of ischaemic stroke.[1 2] ECAD can be managed with optimal medical therapy (OMT), carotid endarterectomy (CEA), and carotid artery stenting (CAS). Treatment options largely depend on the presence of symptoms, severity of stenosis, individual factors, efficacy and risk of complications.

Symptoms and severity of carotid stenosis

Symptomatic carotid artery stenosis is defined as focal neurological symptoms that are sudden in onset and referable to ipsilateral carotid atherosclerotic pathology, including one or more transient ischaemic attack (TIA) or ischaemic stroke within the previous 6 months.[3] The risk of recurrent ipsilateral stroke in patients with symptomatic moderate to severe carotid stenosis varies from 2.7% within the first day to 18.8% within 90 days after symptoms onset,[4] significantly higher

than those with asymptomatic stenosis with annual risk of stroke ranging from 0.34% to 2%.[5] Despite conflicting results on the association between severity of carotid artery stenosis and risk of stroke,[4 6] linear correlation between the benefit from CEA and degree of stenosis has been confirmed by previous research. Data of 6092 patients with 35 000 patient-years of follow-up showed that the absolute risk reduction (ARR) from CEA was −2.2% in patients with <30% stenosis, 3.2% with 30%–49% stenosis, 4.6% with 50%–69% stenosis and 16.0% with 70%–99% stenosis.[7] Therefore, the presence of symptoms and severity of stenosis serve as main factors for selection of treatment.

Age

Subgroup analysis of Carotid Revascularisation Endarterectomy vs Stent Trial (CREST) showed increased periprocedural stroke/MI/death by 1.77 times in patients older than 70 years treated with CAS, whereas no evidence of increased risk in CEA-treated patients.[8] A meta-analysis of 4 randomised controlled trials (RCTs) also demonstrated significantly increased risk of stroke or death within 30 days after CAS in patients older than 70 and 80 years of age compared with those under 60 years of age (OR, 4.01 and 4.15, respectively).[9] This association, however, was not found in patients undergoing CEA. Notably, even though CEA may be generally preferable to CAS in patients over 70 years old due to lower periprocedural rate of stroke or death,[9] CAS is a reasonable choice in elderly patients with unfavourable anatomy for CEA, radiation-induced stenosis or restenosis after CEA.

Gender

Pooled data from ECST (European Carotid Surgery Trial) and NASCET (North American Symptomatic Carotid Endarterectomy Trial) found greater benefit from surgery in men with the number needed to treat to prevent ipsilateral stroke in 5 years being 9 for men vs 36 for women in patients with 50% or higher stenosis.[9] In addition, the 30-day perioperative risk of death was significantly higher in women than in men (2.3% vs 0.8%, p=0.002).[10] Combined analysis of NASCET and the ASA and Carotid Endarterectomy (ACE) trial found no benefit from CEA in women (ARR=3.0%, p=0.94), contrary to men (ARR=10.0%, p=0.02) in 50%–69% carotid stenosis. In contrast, with 70% to 99% stenosis, CEA was beneficially in both men and women with similar 5-year ARR in stroke (17.3% vs 15.1%).[10] Therefore, CEA is effective for stroke prevention in symptomatic severe carotid stenosis (≥70%) regardless of genders, while may be only beneficial in men and selected women (eg, high risk of stroke) with moderate stenosis (50%–69%).

Lesion features

Signs of unstable plaques—including rapidly progressing lesions, intraplaque haemorrhage, irregular/ulcerated surface, inflammation and microvascularization—have been increasingly reported as an independent predictor of stroke.[1 11–14] Latest European Society of Cardiology (ESC) guideline also recommends targeting revascularisation in a subgroup of patients with risky clinical and/or imaging features, including ipsilateral silent infarction, stenosis progression, large plaques, echolucent plaques, lipid-rich necrotic core and so on.[15]

Bilateral carotid stenosis

Various degrees of bilateral carotid stenosis are not rare in patients with atherosclerotic disease. For severe stenosis, staged rather than simultaneous approach is recommended due to risks of respiratory failure or fluctuating blood pressure.[16] If surgery is indicated, then the symptomatic side is generally treated first. For bilateral asymptomatic stenosis, more severe stenosis is recommended to be addressed first. If the degree of stenosis is similar on both sides, then the artery supplying the dominant hemisphere can be considered for treatment first. Analysis of NASCET showed higher periprocedural complications of CEA in patients with contralateral carotid occlusion,[17] while the outcome after CAS seemed to be less affected according to a review of 1375 patients.[18]

Tandem lesions

The reported prevalence of stenosis of the internal carotid artery and ipsilateral common carotid is 4.3%.[19] Treatment of tandem lesions is challenging with up to 20% perioperative mortality rate with CEA.[20] Hybrid repair comprising CEA of the carotid bifurcation and retrograde endovascular repair of common carotid artery has been frequently reported with lower combined stroke and death rate than CEA alone.[21] Research with a small sample size has also reported the use of endovascular therapy for the treatment of tandem lesions.[22]

Chronic carotid artery occlusion

Patients with symptomatic chronic carotid artery occlusion and haemodynamic cerebral ischaemia are at high risk for subsequent stroke when treated medically.[23] However, the Carotid Occlusion Surgery Study (COSS) showed that EC-IC bypass surgery plus medical therapy compared with medical therapy alone did not reduce the risk of recurrent ipsilateral ischaemic stroke at 2 years. Medical treatment continues to be the current standard of care for carotid occlusion. Recently, emerging small sample studies have demonstrated the efficacy of reopening of chronically occluded carotid artery.[24–26] These studies indicate that the reopening of chronic carotid artery occlusion may be effective for patients with chronic carotid artery occlusion. However, randomised clinical trials are required to confirm the safety and benefit. In addition to treating culprit artery, contralateral CEA has been reported in patients with carotid occlusion and compromised cerebral haemodynamic reserve.[27]

Some other reported factors include type of symptoms (TIA, minor or major stroke; ocular or hemispheric symptoms), time since last symptomatic event and recurrence of symptoms.[28]

Medical management

Patients with ECAD can benefit from OMT consisting of antiplatelet agents, stains, and risk factor control.[29]

(1) Antiplatelet agents: although the benefit of single antiplatelet agent for stroke prevention in asymptomatic carotid stenosis has not been confirmed by RCTs,[30] current guidelines recommend lifelong low-dose aspirin as part of OMT to reduce the risk of stroke and other cardiovascular events.[15] Dual antiplatelet therapy has been recommended during the periprocedural period and for at least 1 month after CAS.[31]

(2) Statins: statins have been routinely used in RCTs and clinical settings. A meta-analysis of 26 studies reported efficacy of statin with a dose-dependent protective effect,[32] which was consistent with findings from 2 RCTs done afterwards.[33 34]

(3) Risk factor control: hypertension is an important risk factor for ECAD, and the goal of blood pressure (BP) in non-diabetic patients with asymptomatic carotid stenosis is recommended below 140/90 mm Hg.[35] Patients with concomitant diabetes are at particularly increased risk of cerebrovascular events, for whom a diastolic BP ≤85 mm Hg has been recommended by the latest ESC guidelines.[15]

Previous studies have shown up to 26% risk of ipsilateral ischaemic stroke over 2 years in patients with symptomatic severe carotid artery stenosis despite OMT.[5] It is therefore pivotal to consider more effective intervention.

nterventional management

Interventional management consisting mainly of CEA and CAS has been shown to decrease the stroke rate in patients with carotid artery stenosis.[3 24 25 31–35]

Carotid endarterectomy

ECST, NASCET and VA309 (Veterans Affairs 309) trials have demonstrated significant benefit of surgical intervention over medical treatment for secondary stroke prevention in patients with ipsilateral 50%–99% symptomatic carotid artery stenosis, with maximal efficacy in patients with 70%–99% carotid stenosis.[3 36 37] Of note, pooled analysis of these trials showed no benefit of CEA for patients with 0%–49% stenosis.[7]

For asymptomatic carotid stenosis, ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST-1 (Asymptomatic Carotid Surgery Trial) established the benefit of CEA over medical therapy alone in patients with 60%–99% carotid stenosis.[38 39] However, both studies started before the era of modern OMT, the widespread use of which has reduced the annual stroke rate significantly since the 1990s.[40] In ACST-1, for example, the percentage of statin use has increased from 10% in the early period of recruitment to 80% by the end of follow-up.[41] As such, it may be reasonable to consider OMT first for some patients who were considered surgical candidates in the past.

CEA versus CAS

CEA was first described in 1975 by DeBakey and has since become a conventional treatment for severe ECAD.[42] As an alternative to CEA, CAS emerged in 1989 and has proven to be effective and safe for carotid artery stenosis. A number of RCTs have been done to compare the two interventional therapies [43–58] Most studies have shown a higher rate of periprocedural stroke from CAS and a higher incidence of myocardial infarction (MI) with CEA. Similar findings have also been reported by a Cochrane review of 7572 patients, including 16 trials in 2012,[59] and a meta-analysis of 6526 patients from 5 RCTs in 2017.[60] Similar long-term outcomes, including the rate of ipsilateral ischaemic stroke or death with CAS and CEA, have been reported by most of the studies. CEA is preferable to CAS in patients over 70 years old.[9]

Carotid Angioplasty and Stenting

CAS has shown varying outcome differences when compared to CEA based on different patient factors. CAS appears to be a good alternative to CEA in certain patient groups, such as those with unfavorable surgical anatomy (noted previously). When performed with an embolic protection device (EPD), the risk associated with CAS may be lower compared to that of CEA in patients with increased risk for surgical complications.

Carotid Angioplasty and Stenting

CAS has been reported to have superior outcomes when compared to CEA in high surgical risk patients. In a selected group of asymptomatic patients with unfavorable surgical anatomy and significant co-morbidities, it is reasonable to recommend CAS over CEA when intervention is indicated. High surgical risk patients were defined as having one or more of following criteria:[43]

- New York Heart Association class III or IV heart failure
- Chronic obstructive pulmonary disease
- >50% contralateral carotid artery stenosis
- Prior CEA or CAS
- Prior coronary artery bypass graft surgery

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPHIRE) trial randomized high-risk patients into CEA and CAS with EPD groups, with an inclusion criteria of symptomatic stenosis >50% or asymptomatic stenosis >80%. The primary endpoint was defined as death, stroke or MI within 30 days plus death due to neurological causes or ipsilateral stroke between 31 days and 1 year. The secondary endpoint was defined as the primary endpoint events plus death or ipsilateral stroke between 1 and 3 years. Technical success was achieved in 95.6% of patients who underwent CAS. However, the study incurred a selection bias by excluding patients from the CEA arm who were considered a priori to have exceedingly high risk for complication. The trial was stopped before completion, after randomizing 334 patients, due to a sharp decline in enrolment rate. Three-year follow up data were available in only 85.6% of patients. In asymptomatic patients, the occurrence of the primary endpoint was greater after CEA (21.5%) versus after CAS (9.9%). The peri-procedural death, MI or stroke rate was also greater after CEA (10.2%) versus after CAS (5.4%). The 3-year stroke rates were comparable between CEA and CAS, at 9.2% and 10.3%, respectively.[44]

CAS does not appear to be superior to CEA in asymptomatic patients with conventional surgical risk for intervention. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was a multicenter, randomized trial comparing CAS to CEA in both symptomatic (carotid stenosis >50%) and asymptomatic patients (carotid stenosis >60%). Among 2502 patients followed for 2 years, the estimated 4-year rate of stroke, death of MI was similar in both CAS and CEA (7.2% and 6.8%, respectively; stenting HR: 1.11, 95% CI: 0.81–1.51, p=0.51). However, peri-procedural stroke alone was more frequent after CAS (4.1% versus 2.3%, p=0.01), while peri-procedural MI alone was more frequent after CEA (2.3% versus 1.1%, p=0.03). In the subgroup of asymptomatic patients, the 4-year stroke and death rates were higher after CAS (4.5% and 2.7%,

respectively; HR: 1.86, p=0.07). In addition, CREST also showed that quality of life was significantly impacted by major and minor stroke but not by MI, based on quality of life studies done at 1 year. The outcomes with CEA and CAS also appeared to be affected by age, with a crossover occurring at approximately 70 years. CEA showed greater efficacy at older ages and CAS at younger ages. The comparative primary results did not vary by sex or symptom status. As seen in previous randomized trials, cranial nerve palsy was more common after CEA. [45]

Carotid Angioplasty and Stenting in Symptomatic Patients

In symptomatic patients, CEA has been reported to have superior outcomes over CAS in both conventional- and high surgical risk patients. In high surgical risk symptomatic patients, SAPHIRE showed that despite a similar occurrence of the primary endpoint at 1 year (CAS 16.8% versus CEA 16.5%), the secondary endpoint at 3 years was higher after CAS (32% versus 21.7%). Of note, only a smaller portion of symptomatic patients underwent 3-year follow-up compared to asymptomatic patients. [46]

Other studies comparing CAS to CEA in symptomatic patients with conventional surgical risk for intervention include the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which was a multicenter, randomized trial comparing CAS with CEA. A total of 504 patients were randomized, 90% of whom were symptomatic. Of note, EPDs were not used and only 22% of CAS patients were stented. The combined stroke and death rate at 30 days was similar in both groups (10%). However, cranial neuropathy occurred more frequently in CEA patients (8.7% versus 0%, p <0.0001). Major incisional hematoma after CEA occurred more frequently than access site hematoma after CAS (6.7% versus 1.2%, p <0.0015). The rate of ipsilateral stroke after 3 years of follow up was similar in both groups (adjusted hazard ratio=1.04, 95% CI 0.63–1.70, p=0.9). However, the 8-year incidence and HR for ipsilateral non-perioperative stroke was 11.3% versus 8.6% (HR 1.22, 95% CI 0.59–2.54). There was also a higher rate of restenosis associated with CAS, with an estimated 5-year incidence of 30.7% compared to 10.5% after CEA. The investigators found that several factors were associated with the higher incidence of restenosis, including longer segments of stenosis at baseline and performing a balloon angioplasty alone without stenting.

The Endarterectomy Versus Angioplasty in Symptomatic Severe Carotid Stenosis (EVA-3S) trial randomized patients with a completed stroke or TIA within the past 120 days and an ipsilateral carotid stenosis >60%.Patients with disabling stroke were excluded from the trial [mRS score >3]. After randomizing 520 patients, the trial was stopped before completion due to both safety and futility reasons. The 30-day incidence of stroke or death was 9.6% after CAS versus 3.9% after CEA, with a RR of 2.5 (95% CI 0.5–4.2). However, there were several factors in the EVA-3S trial, which may have confounded its results, including inadequate training requirements for operators performing CAS and no uniform requirement for the use of EPDs. In addition, 5 different carotid stent devices and 7 EPDs were used. While experts have agreed that the EVA-3S trial results should not affect management guidelines, the trial has highlighted the importance of rigorous and standardized training criteria required for interventionalists performing carotid stent placement. [49]

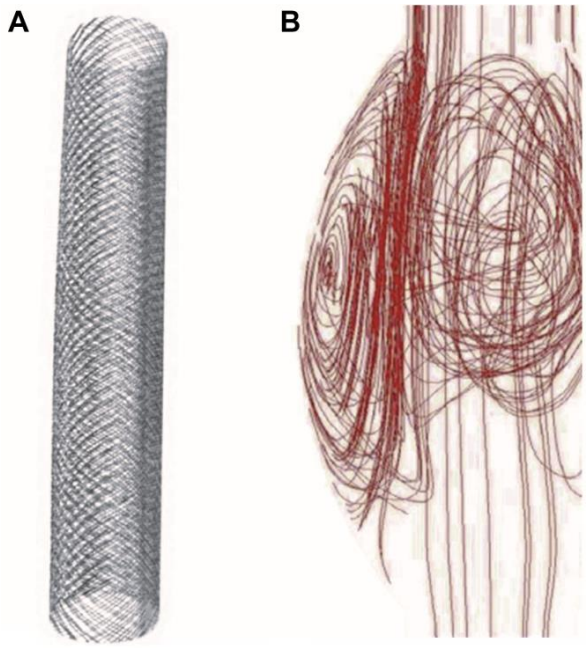

Fig 1

A, Multilayer flow modulator (MFM), an uncovered, self-expanding stent with high radial force and flexibility constructed of braided fatigue- and corrosion-resistant cobalt alloy wire (Phynox). **B,** Graphics showing flow dynamics within stent and aneurysm sac.

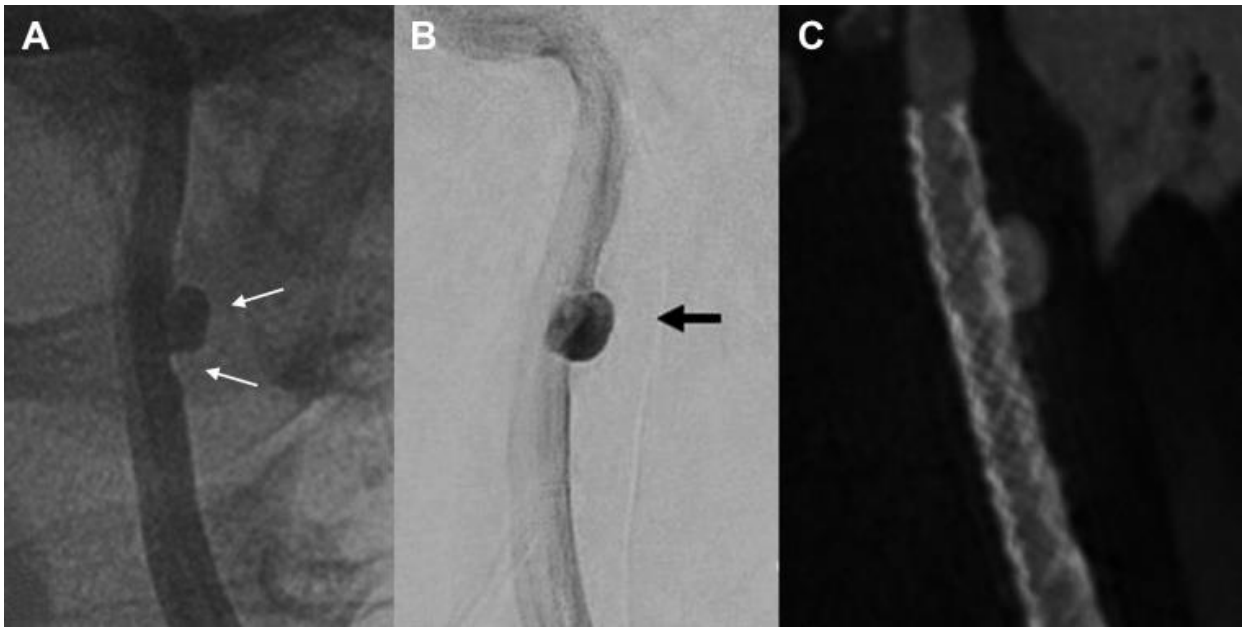

Fig 2 Patient 3, preprocedure and postprocedure images. **A,** Digital subtraction angiography (DSA) showing the dissected internal carotid artery (ICA) segment with associated aneurysm and vessel wall irregularity (*arrows*). **B,** DSA showing stagnation within the aneurysm sac after treatment (*arrow*). **C,** Postprocedure images with XperCT software showing correct location of the stent in place, properly attached to the arterial walls, covering the neck of the aneurysm.

Cerebral Embolism Prevention

The outcomes associated with the use of EPDs have not been studied in randomized trials. Several observational studies have suggested that EPDs when used by experienced operators lead to reduced rates of adverse events, including major and minor strokes. An international survey involving 53 sites with a total of 11392 CAS procedures performed by experienced operators reported a combined stroke and death rate of 2.8% when EPDs were used and 6.2% when they were not. [49] Several other studies have also shown an improvement in outcome with the use of EPDs.

Future direction

Due to significant advances in medical therapy, risk reduction and endovascular technology in recent years, there is renewed discussion regarding the superiority of CEA over CAS and interventional management over the best medical therapy, especially in asymptomatic carotid stenosis. Several studies are being conducted to address these issues.

ACST-2 is an RCT comparing immediate and long-term safety and efficacy of CEA versus CAS in a patient with severe asymptomatic stenosis.[61] The primary endpoint is 30-day MI, stroke and death, with subgroup analysis emphasising health economic aspects including procedural and stroke-related healthcare costs and quality of life. This study is recruiting patients from over 20 countries currently with 3600 patients planned to be enrolled by 2019.

SPACE 2 is a three-arm RCT designed to compare current OMT with CAS and CEA in addition to conservative treatments in patients with asymptomatic carotid artery stenosis. The study was halted after enrolling 513 patients. The 30-day rate of stroke/death was 2.54%, 1.97% and 0% in CAS, CEA and OMT groups, respectively.[62 63]

CREST-2 is an undergoing three-arm RCT to compare current OMT, OMT plus CEA, and OMT plus CAS for asymptomatic severe carotid stenosis, which enables a direct comparison of CAS and CEA. The primary endpoint is any stroke/death within 44 days after randomisation or ipsilateral ischaemic stroke within 4 years. This study is estimated to be completed by 2020.[64]

ECST-2 (ISRCTN 97744893) is an international RCT aimed to investigate the optimal treatment in patients with symptomatic or asymptomatic moderate or severe carotid stenosis at low or intermediate risk of stroke, in which patients will be randomised to OMT versus CAS or CEA. The primary endpoint is any stoke at any time or non-stroke death within 30 days after surgery. This trial is currently recruiting participants and estimated and estimated to be completed by 2022.

No Conflict of interest.

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