Title page

Title: Management of atherosclerotic extracranial carotid artery stenosis

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Summary

Atherosclerosis leading to stenosis of the internal carotid artery is the underlying cause in about 10-15% of ischaemic strokes (symptomatic carotid stenosis). About 1-2% of the adult population have asymptomatic carotid stenosis. Clinical trials in patients with symptomatic carotid stenosis revealed a higher procedural risk of non-disabling stroke with stenting compared to endarterectomy, but a higher risk of myocardial infarction, cranial nerve palsy, and access site hematoma with endarterectomy. Apart from procedural complications, both treatments are equally effective in preventing stroke and recurrent severe carotid stenosis in the medium to long-term. Endarterectomy has a modest effect in preventing stroke among patients with asymptomatic carotid stenosis, whereas the role of stenting remains to be established. With advances in medical therapy against atherosclerosis, benefit from invasive therapy has become uncertain. Risk modelling including brain and carotid plaque imaging will become increasingly important in selecting patients for interventions.

Introduction

Atherosclerotic carotid artery disease is the underlying cause of about one in five ischaemic strokes and transient ischaemic attacks (TIA).(1) The global prevalence of carotid stenosis is estimated to be 1.8% of all men and 1.2% of all women between 30-79 years of age.(2) Among males, the prevalence ranged from 0.5% in 30-34 year olds to 6.9% in 75-79 year olds, and among females from 0.3% to 4.3%.

Despite a wealth of existing evidence, many questions in the management of symptomatic and asymptomatic carotid disease remain unanswered. Improved medical therapy has lowered atherosclerosis related morbidity and mortality, raising questions about the benefit of carotid revascularisation in many patients. Imaging of atherosclerotic plaque morphology beyond measuring degree of stenosis have improved the identification of patients at risk for stroke, who are likely to benefit from carotid revascularisation, including some not previously considered to be at risk. Finally, while the choice between carotid endarterectomy and stenting for symptomatic carotid stenosis is informed by evidence from numerous randomised trials, important technical advances in carotid artery stenting have taken place in the last decade since these trials were performed. The role of stenting in asymptomatic carotid stenosis remains uncertain. There is concern that many patients are receiving carotid revascularisation without good evidence of benefit. We therefore considered that a review of the scientific basis of practice in the management of carotid atherosclerosis was timely. We discuss the existing evidence on medical and invasive therapy, highlight advances in risk prediction and treatments, and point out areas of remaining uncertainty and ongoing research, providing a basis for individualised treatment decisions now and in the future. Non-atherosclerotic diseases of the carotid artery, such as dissection or fibromuscular dysplasia, or intracranial atherosclerosis will not be covered in this review.

Pathophysiology

Atherosclerosis mostly occurs at the carotid bifurcation, involving the distal common and the proximal internal carotid artery and less often the origin of the common carotid artery and the cavernous segment of the intracranial carotid artery. The most important mechanism by which carotid stenosis causes stroke or TIA is rupture of the atherosclerotic plaque with subsequent embolism of locally formed thrombus or plaque debris (figure 1). Inflammation in the plaque plays an important role in this process.(3) Other recognized stroke mechanisms include propagation or embolization of thrombus from an occluded extracranial internal carotid artery or hemodynamic impairment, i.e. a reduction in cerebral perfusion. Carotid disease has traditionally been inferred as a potential cause for a stroke or TIA in the presence of at least 50% stenosis associated with ipsilateral carotid territory symptoms. However, atherosclerotic plaques with lesser degrees of stenosis may also cause embolic stroke or TIA. Carotid stenosis is commonly defined as symptomatic if it has caused ischaemic events in the ipsilateral eye (transient monocular blindness or *amaurosis fugax*, or retinal infarcts) or cerebral hemisphere (TIA or stroke) in the previous 6 months. Large-artery atherosclerosis, when identified as the underlying cause of TIA, incurs the highest risk of early recurrent stroke among all aetiologies.(4)

Management

Optimal medical therapy

Optimal medical therapy and lifestyle modification are the cornerstone of effective management of carotid artery disease and apply to all patients (table 1). It is reasonable to recommend low-dose aspirin therapy in patients with asymptomatic carotid stenosis in order to prevent cardiovascular events as a whole.(5) A combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin was shown to be superior to aspirin monotherapy for long-term prevention of stroke and other cardiovascular events in patients with stable atherosclerotic disease, including those with asymptomatic carotid stenosis.(8, 9)

Patients with symptomatic carotid stenosis causing recent minor stroke or TIA benefit from urgent dual antiplatelet therapy with a combination of aspirin and clopidogrel for three weeks to three months after the initial event, or aspirin and ticagrelor for 30 days after the initial event, followed by antiplatelet monotherapy.(10-12) Dual antiplatelet therapy with ticagrelor and aspirin appeared to be more effective in symptomatic large artery atherosclerosis compared with other stroke etiologies,(13) while this was not the case for clopidogrel-aspirin combination.(14) Co-existing atrial fibrillation (AF) and carotid artery disease augmented the risk of stroke in study populations without control of medication.(15) However, in the ROCKET-AF trial comparing rivaroxaban versus warfarin in patients with AF, co-existing carotid artery disease did not increase the risk of stroke.(16) Thus, there is no

evidence to support the addition of aspirin to oral anticoagulation in patients with AF and concomitant asymptomatic carotid stenosis. However, individual patients with symptomatic carotid stenosis and concomitant atrial fibrillation who have high risk of athero-embolism (e.g., evidenced by repetitive ipsilateral emboli clinically or on imaging, or imaging features of plaque instability) may benefit from adding antiplatelet therapy to OAC temporarily to prevent early recurrent stroke before carotid revascularisation.

Guidelines on lipid-lowering therapy consider both asymptomatic and symptomatic carotid stenosis as manifest atherosclerotic cardiovascular disease (ASCVD), conferring “very high” cardiovascular risk.(17, 18) Among patients with symptomatic carotid stenosis, ASCVD is already documented by the presence of stroke or TIA. Yet even “significant carotid plaque” in patients with asymptomatic carotid stenosis is considered an ASCVD equivalent.(18) It is unclear if patients with minor degree of asymptomatic carotid stenosis (<50% narrowing) benefit from aggressive cholesterol lowering in the absence of other cardiovascular disease history, and whether imaging features of plaque instability confer additional benefit in such patients. Current European guidelines recommend an LDL-cholesterol target of 1.4 mmol/L in patients at very high risk, whereas American guidelines recommend high statin intensity irrespective of serum cholesterol levels.(17, 18) The PCSK-9 inhibitors evolocumab and alirocumab were shown to prevent cardiovascular events among patients with stable atherosclerotic disease by lowering baseline LCL-cholesterol by about 60% on top of established statin therapy.(19, 20) Data on PCSK-9 inhibitors in patients with carotid artery disease are lacking.

Blood pressure control in antihypertensive patients, glycaemic control in diabetics, smoking cessation and weight reduction are other important elements in the medical management of carotid disease.(21) Most patients with carotid stenosis will tolerate blood pressure lowering. In case of symptoms attributable to haemodynamic impairment with antihypertensive therapy, a higher blood-pressure target may be selected in individual patients, or the patient referred for carotid artery revascularisation based on individual judgement.

Advances in medical therapy, in particular widespread use of statins and other agents to achieve low cholesterol levels, more strict adherence to blood pressure targets, and improved control of other risk factors, appear to have lowered the risk of stroke in patients with asymptomatic and symptomatic carotid stenosis treated conservatively.(22) Indeed, the observed 90-day stroke risk after a TIA caused by large artery atherosclerosis declined from 20% in registries published in the last decade,(23, 24) to 6% in a large registry published in 2016.(4) While some of this decline may have been accounted for by more rapid specialised assessment and early carotid revascularisation in selected patients, changes in medical therapy are also likely to have contributed.

Revascularisation for symptomatic carotid stenosis

The benefit of carotid endarterectomy in patients with symptomatic carotid stenosis was established in the final two decades of the last century. In The *North American Symptomatic Carotid Endarterectomy Trial* (NASCET), the two-year risk of any ipsilateral stroke (including peri-operative events) in patients with severe symptomatic carotid stenosis (≥70% narrowing of the lumen) was reduced from 26% to 9% ($p<0.001$).(25) Modest benefit was also seen in patients with moderate stenosis (50-69%) by a reduction of stroke risk from 22.2% to 15.7% ($p=0.045$) after 5 years.(26) In the *European Carotid Surgery Trial* (ECST), endarterectomy prevented stroke only in patients with symptomatic carotid stenosis of ≥80%,(27) but the measurement of the degree of stenosis on angiography differed between the trials. In a pooled analysis of NASCET, ECST and a smaller trial where ECST angiograms were reanalysed using the NASCET method, the absolute 5-year risk reduction from endarterectomy was 15.9% in patients with severe (≥70%) stenosis and 4.6% in patients with moderate (50-69%) stenosis.(28) Thus, six patients with severe symptomatic stenosis or 22 patients with moderate symptomatic stenosis had to be operated on to prevent one ipsilateral stroke after 5 years (number needed to treat, NNT). Extracranial-intracranial bypass surgery is not effective to prevent stroke in patients with carotid artery occlusion.(29)

Endovascular treatment with stents, usually with access through the femoral artery, is an alternative option. Risks and benefits of carotid stenting versus endarterectomy for symptomatic carotid stenosis have been compared in several randomised trials. The *Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis* (EVA-3S) trial was stopped after inclusion of 527 patients, because the procedural (30-day) stroke or death risk in the stenting group (9.6%) exceeded that in the endarterectomy group (3.9%).(30) The *Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy* trial (SPACE) including 1214 patients reported more similar risks of procedural stroke or death, 7.4% in the stenting group and 6.6% in the carotid endarterectomy group, but the trial was unable to prove non-inferiority of stenting according to its design.(31, 32) The *International Carotid Stenting Study* (ICSS) including 1713 patients reported a significantly higher risk of procedural stroke or death in the stenting group (7.4%) than in the endarterectomy group (3.4%) in an interim analysis.(33) Among the 1321 patients with symptomatic carotid stenosis enrolled in the *North American Carotid Revascularization Endarterectomy vs. Stenting Trial* (CREST), procedural stroke or death risks in the stenting group (6.0%) were lower than in the previous trials, but still higher than in the endarterectomy group (3.2%, $p=0.02$).(34)

The 2020 update of the Cochrane systematic review and meta-analysis includes data from 8 trials, including the large trials cited above. Analysis of a total of 5184 patients with symptomatic carotid stenosis demonstrated an average risk of procedural stroke or death of 7.3% with stenting and 4.4%

with endarterectomy, resulting in a random-effects odds ratio [OR] of 1.74 (95% confidence interval 1.30-2.33, p=0.0002), favouring endarterectomy in the overall population included in the trials.(35) Subgroups in which stenting appears as safe as endarterectomy are discussed below.

Revascularisation for asymptomatic carotid stenosis

In patients with *asymptomatic* carotid stenosis of 60% or higher, carotid endarterectomy consistently reduced the cumulative 5-year stroke risk from about 11% under medical therapy to about 6% in the *Asymptomatic Carotid Atherosclerosis Study* (ACAS) and the *Asymptomatic Carotid Surgery Trial* (ACST), (36, 37) resulting in a NNT to prevent one stroke of 20.

Among the 1181 patients with asymptomatic carotid stenosis enrolled in CREST, there was no significant difference in the risk of procedural stroke or death between stenting and endarterectomy (2.5% vs 1.4%).(34) The *Asymptomatic Carotid Trial 1* (ACT-1) including 1453 patients reported procedural stroke or death risks of 2.9% in the stenting group and in 1.7% in the endarterectomy group, a difference which was not statistically significant.(38) The report of the initial results of the *Second Asymptomatic Carotid Surgery Trial* (ACST-2) in August 2021, in which 3625 patients with asymptomatic carotid stenosis were recruited, more than doubled the evidence on stenting versus endarterectomy for asymptomatic carotid stenosis.(39) The risk of procedural stroke or death was 3.7% in the stenting group and 2.7% in the endarterectomy group. The risks of procedural disabling stroke or death were 0.9% and 1.0%, respectively. In general, post-procedural stroke risks did not differ between stenting and endarterectomy in these trials (see section below headed 'Long-term durability of treatment').

Reductions in stroke risk under modern medical therapy may obviate the need for revascularisation in many patients with asymptomatic carotid stenosis,(41) and possibly also among some patients with symptomatic carotid stenosis. On the other hand, the procedure-related risks of carotid revascularisation have also declined.(42) This has led to several ongoing trials investigating the current benefit of carotid revascularisation versus medical therapy alone in the context of optimal medical therapy (table 4).

Technical aspects of revascularisation

A randomised trial showed no significant difference in procedural risks of endarterectomy performed under local anaesthesia compared with general anaesthesia,(43) while in real-world conditions, local anaesthesia appears to be safer.(44)

Around two thirds of procedural strokes counted within 30 days of carotid stenting occur on the day of the procedure, mostly at the time of stent deployment or post-stent balloon dilation.(45) Passage of the stenosis with the catheter, shortening of self-expanding stents after deployment and

compressing the struts of the stent against the atheromatous plaque during balloon dilatation might dislodge plaque debris or local thrombus. Cerebral protection devices were therefore developed with the aim of preventing cerebral embolisation during carotid stenting. A pooled analysis of the EVA-3S, SPACE and ICSS trials showed no significant difference in procedural stroke or death risk between stenting with use of a protection device (mostly of the filter type) and unprotected stenting.(47) While filter-type protection devices might capture some emboli during stent deployment, it is possible that crossing the stenosis with the device before the filter is deployed might also dislodge thrombus material from the plaque. A different approach to cerebral protection involves flow reversal during the procedure using devices placed proximal to the stenosis which was shown to prevent some emboli compared with distal filter devices.(50, 51)

Another possible cause of stroke during catheterisation using the standard access route is dislodgement of thrombus or plaque debris from atherosclerosis of the aortic arch and proximal access vasculature, particularly among patients with difficult vascular anatomy.(52) To avoid navigating the aortic arch, direct puncture of the common carotid artery with prior surgical incision (trans-carotid artery [TCAR] access) has been tested with relatively low risks of peri-procedural stroke or death in prospective single-arm studies,(53-55) and subsequently confirmed in larger registries.(56-58) However, TCAR has mostly been used in asymptomatic or low risk for recurrent stroke symptomatic patients.(59) Its value in recently symptomatic patients has yet to be proven. Trans-brachial access also avoids aortic arch related complications.(60)

The design of carotid stents also affects procedural risk. So-called closed-cell stents (where the open area between stent struts is ≤5.0 mm^2 and all stent struts are interconnected) are associated with a lower risk of peri-procedural stroke or death than an open-cell designs.(47, 61) The tight meshes of closed-cell stents might be better suited to sealing off the atherosclerotic plaque and prevent appositional thrombus at the surface of the plaque or plaque debris escaping into the blood stream during the procedure. This concept has sparked the development of multi-layered stents with very small open areas.(62, 63)

Other procedure-related complications

Cerebral embolism during carotid revascularisation may occur without overt clinical symptoms. In a substudy of 231 patients in ICSS, 50% of patients in the stenting group and 17% in the endarterectomy group had new ischaemic brain lesions on diffusion-weighted MRI after the procedure, 85% of which were clinically silent (OR 5.21, 95% CI 2.78-9.79, p<0.0001).(64) Silent infarcts on MRI may serve a surrogate outcome measures for the procedural safety of carotid revascularisation.(65)

Procedure-related clinically manifest myocardial infarction (MI) is rare in comparison with stroke, occurring in 0.3% to 0.5% with stenting and in 0.6% to 0.9% with endarterectomy. (30, 33, 38, 39) The incidence was higher in the CREST trial, in which patients were routinely screened with enzyme measurement and electrocardiogram (ECG) before and after treatment, and MI was defined by a rise in cardiac enzymes together with either typical chest pain or ECG changes consistent with myocardial ischaemia.(34) The risks of peri-procedural biochemical MI according to this definition were 1.1% in the carotid stenting arm and 2.3% in the carotid endarterectomy arm. 15 of 42 peri-procedural MIs (36%) occurring in the CREST study population as a whole were asymptomatic.(66)

Cranial nerve injury occurred in 5.6% of patients treated with endarterectomy versus 0.4% of patients treated with stenting in RCTs.(35) Cranial nerve palsies usually result from surgical traction on the nerve and the majority are temporary, while only a very small proportion remain permanent. Table 2 summarises the peri-procedural and post-procedural complications of carotid revascularisation.

Long-term durability of treatment

Stroke prevention

Clinical trials consistently showed that among patients with symptomatic carotid stenosis, long-term rates of recurrent stroke excluding procedure-related events were remarkably low after revascularisation and did not significantly differ between endarterectomy and stenting.(32, 67-69) In ICSS, for example, the 5-year ipsilateral stroke risks were 4.7% in the stenting group and 3.4% in the endarterectomy group.(68) Among patients with symptomatic carotid stenosis included in the CREST trial, the 10-year rates of ipsilateral stroke were 6.9% in the stenting group and 5.6% in the endarterectomy group.(69) In a pooled analysis of the four largest trials comparing stenting versus endarterectomy for symptomatic carotid stenosis, annual risk of post-procedural ipsilateral stroke was 0.6% in both treatment groups.(70)

In the CREST trial, the post-procedural event rates were identical among patients with symptomatic and asymptomatic carotid stenosis and did not differ between stenting and endarterectomy, either, demonstrating that initial symptom status is relevant for the risk of procedural stroke, but not for the long-term risk of recurrent stroke after revascularisation.(69) Similarly, long-term stroke rates did not differ between stenting and endarterectomy among patients with asymptomatic carotid stenosis in the ACT-1 and the ACST-2 trials.(38)(39) In ACST-2, the post-operative stroke rates were very low, with cumulative 5-year risk of ipsilateral fatal or disabling stroke of 0.6% in both arms, and of ipsilateral stroke of any severity of 2.1% in the stenting group and 1.0% in the endarterectomy group.(39)

Restenosis

Evidence on recurrent stenosis after treatment is available from follow-up of patients with duplex ultrasound at regular intervals in RCTs. (67, 69, 71) While there were differences in ultrasound criteria, the majority of these trials found no significant difference in the occurrence of severe restenosis or occlusion between stenting and endarterectomy in the long term, with cumulative risks 5 to 10 years after treatment ranging from 5% to 12% in the stenting group and from 8% to 10% in the endarterectomy group. Moderate or greater restenosis (≥50%), on the other hand, is more common and occurred more often in patients treated.(67, 72)

Restenosis typically occurs in the first 1-2 years after carotid revascularisation and is most often caused by neo-intimal hyperplasia, a proliferation of smooth muscle cells which appears to be less prone to cause thrombo-embolic events than recurrent atherosclerosis.(73) Nonetheless, there is some evidence that carotid artery restenosis increases the risk of stroke.(74) This increase in stroke risks appears to be more pronounced with restenosis following endarterectomy than with restenosis after stenting,(72, 75) hinting at possible differences in pathogenesis. However, the annual risk of stroke in patients with severe restenosis after treatment of symptomatic carotid stenosis is only about 1%, which is roughly the same as expected in a patient with severe asymptomatic carotid stenosis not undergoing revascularisation under current medical therapy.(72)

Selection of patients and procedures

Prediction of stroke risk with medical therapy alone

Estimation of the risk of stroke under medical therapy is key to selecting patients likely to benefit from revascularisation of carotid stenosis, particularly in light of emerging evidence that stroke risks have declined both for symptomatic and asymptomatic carotid stenosis with advances in medical management of atherosclerotic disease.(4, 22-24) A clinical model that estimated the risk of ipsilateral stroke from carotid stenosis treated with medical therapy alone was originally derived using data from patients included in the control (avoid surgery) arm of ECST and validated using data from NASCET.(76) This model estimated the five-year risk of ipsilateral stroke in a patient with symptomatic carotid stenosis based on sex, age, degree of stenosis, type of and time since the presenting ischaemic event, plaque surface irregularity or ulceration on catheter angiography, as well as vascular risk factors and comorbidities. Applying the model to data from the NASCET trial demonstrates that only patients with a predicted 5-year stroke risk of >20% can be expected to have clear benefit from surgery. A recalibrated model was used to select patients for the *Second European Carotid Surgery Trial* (ECST-2), which tests the hypothesis whether modern medical therapy alone obviates the need for carotid revascularisation among patients with symptomatic or asymptomatic carotid stenosis with a predicted 5-year stroke risk of less than 20%.

Several prospective observational studies demonstrated that certain imaging features of the carotid plaque are associated with an increased risk for future cerebrovascular events.(77) For patients with symptomatic carotid stenosis, the best evidence is currently available for the presence of haemorrhage visualised in carotid plaques on magnetic resonance imaging using specialised MR sequences. Patients with recently symptomatic carotid stenosis and presence of intra-plaque haemorrhage face an eleven-fold increase in risk of ipsilateral stroke, even after adjustment for previously identified clinical risk factors including degree of stenosis.(78) Importantly, the risk of recurrent stroke is also increased among patients with intra-plaque haemorrhage causing less than 50% stenosis, many of whom would have previously been considered to have cryptogenic stroke or stroke of uncertain origin and who are not currently considered candidates for carotid revascularisation (figure 2). Positron emission tomography (PET) is able to visualize plaque inflammation-related metabolism by uptake of 18F-fluorodeoxyglucose (FDG), which has been demonstrated to predict early recurrent stroke among patients with recently symptomatic carotid stenosis.(79, 80)

For patients with asymptomatic carotid stenosis, a number of features on duplex ultrasound have been associated with increased risk of cerebrovascular event, including degree and progression of stenosis,(81-85) echolucent plaque,(86) and in particular echolucent areas near the surface of the plaque.(87) In addition, the presence of micro-embolic signals detected by transcranial Doppler (TCD) ultrasound in the middle cerebral artery ipsilateral to an asymptomatic carotid stenosis increases the risk of stroke about six-fold.(88) Reduced cerebrovascular reserve distal to severe symptomatic or asymptomatic carotid stenosis assessed by TCD also increases the risk for cerebrovascular events.(89, 90) The current European Society for Vascular Surgery guideline recommends consideration of revascularisation in patients with asymptomatic carotid stenosis only if one or more imaging or clinical features associated with increased risk of stroke are present.(5) However, the value of these investigations in selecting patients has not been demonstrated in the context of a clinical trial, and outside research studies, few clinicians currently utilise plaque imaging to select patients for revascularisation. We anticipate that this will change in the future.

Selection for carotid stenting or endarterectomy

Combining randomised data from several trials allows adequately powered subgroup analyses to investigate if the relative effect of stenting versus endarterectomy differs between patient groups. A pooled analysis of individual patient data from four major trials within the Carotid Stenosis Trialists' Collaboration comparing the two treatments in patients with symptomatic carotid stenosis demonstrated that the risk of procedural stroke or death strongly increases with age in patients treated with stents, while this was not the case with endarterectomy.(91, 92) In contrast, age had surprisingly little effect on the risk of stroke occurring beyond the procedural period.(92) The reasons

why higher age increases procedure-related stroke risk in carotid stenting are not completely clear; more difficult vascular anatomy, increased burden of atherosclerosis in the aortic arch and supra-aortic arteries, more unstable plaques,(93) or less capacity to compensate for peri-procedural embolism at higher age are possible mechanisms. Current guidelines therefore advise against stenting in patients with symptomatic carotid stenosis above the age of 70, except in specific conditions when surgery is not feasible, or the risk of complications with surgery is deemed high, as summarised below.(5) In younger patients, carotid stenting is a suitable option to offer patients so long as no other contra-indications to stenting are present.

Anatomical features of supra-aortic arteries may also increase the risk of stroke during stenting. For example, angulation in the course of the stenotic internal carotid artery by ≥60 degrees quadrupled the risk of peri-procedural brain infarction in the ICSS-MRI substudy, but had no significant effect on the risk of endarterectomy.(52)

Timing of revascularisation in patients with symptomatic carotid stenosis

An individual patient data meta-analysis of RCTs clearly demonstrated that the benefit of CEA in patients with symptomatic carotid stenosis was most pronounced amongst those who were randomised within two weeks of the index neurological event.[9] In patients with severe (70-99%) stenosis, benefit was still present up to 12 weeks; in contrast, among patients with moderate degree of stenosis (50-69%), the benefit of surgery was no longer present after 14 days. Although some evidence suggests increased procedure-related risks for urgent carotid endarterectomy performed within 2 days of the presenting event,(94) early surgery thereafter is safe, including suitable patients initially treated with thrombolysis for acute stroke.(95, 96) Despite advances in medical therapy, there is still a considerable risk of early recurrent stroke in patients with symptomatic carotid stenosis awaiting revascularisation.(97) Current guidelines therefore recommend operating patients with symptomatic carotid stenosis who are deemed to require revascularisation as soon as possible, preferably within 14 days of the first ischaemic event.(98, 99)

A pooled-analysis by the Carotid Stenosis Trialists' Collaboration also yielded some evidence that the extra risk of peri-procedural stroke or death associated with stenting compared with endarterectomy in patients with symptomatic carotid stenosis is increased when treating patients within the first week after the symptomatic event.(100) It is possible that in the first days after an initial event plaques are particularly unstable and vulnerable to peri-procedural thromboembolic complications. It has to be emphasised that the effects of age and timing of intervention are supported by trial evidence dating back from more than ten years ago and may be less pronounced in the current era, owing to advances in stent and catheter technology, medication (combined antiplatelet therapy) and increased

experience with stenting. Table 3 summarises current indications for endarterectomy and stenting in patients with symptomatic and asymptomatic carotid stenosis according to current guidelines.(5, 98)

Carotid revascularisation in patients at high surgical risk

Stenting might be the preferred option if revascularisation of the carotid artery is warranted in individual patients with a stenosis at a surgically inaccessible site, or patients with stenosis after previous cervical irradiation therapy, in whom the risk for transient cranial nerve palsy following endarterectomy is increased.(101) Patients undergoing redo surgery for restenosis after previous endarterectomy are at increased risk for wound and patch infection, and hence might also be better candidates for stenting.

Stenting might also have advantages over endarterectomy in patients who are at increased risk for cardiovascular complications with surgery. The *Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy* trial (SAPPHIRE) included 334 patients with concomitant cardiopulmonary disease, contralateral carotid occlusion, stenosis occurring after neck irradiation or previous endarterectomy, or other criteria thought to increase surgical risk.(102) In these patients, stenting was non-inferior to surgery with regard to the primary composite outcome of death, stroke, or myocardial infarction within 30 days after the intervention, or death or ipsilateral stroke between 31 days and 1 year,(102) and there was no difference in ipsilateral stroke risk up to three years after treatment.(103) Of note, more than 70% of patients in the SAPPHIRE trial had asymptomatic carotid stenosis. In patients with asymptomatic carotid stenosis and severe cardiopulmonary disease, most clinicians would opt for conservative therapy.

Conclusions and future directions

Atherosclerotic stenosis of the internal carotid artery, typically located at the site of the carotid bifurcation at the neck, is a common cause of ischaemic stroke. Early trials demonstrated a substantial reduction in stroke risk with carotid endarterectomy in patients with severe symptomatic carotid stenosis, and a modest benefit in patients with moderate symptomatic stenosis, as well as in patients with asymptomatic carotid stenosis. Advances in medical therapy for atherosclerosis and improved risk factor control might have diminished the benefit of surgery. Selection of patients at increased risk of stroke under medical therapy, especially among those with moderate symptomatic or asymptomatic stenosis, is essential to optimise the choice of the optimal strategy for long term stroke prevention. Imaging of carotid plaque composition using MRI and other modalities is likely to play an increasingly important role in patient selection.

Among patients with symptomatic carotid stenosis, randomised controlled trials have consistently demonstrated that the risk of peri-procedural stroke or death is greater in stenting compared with

endarterectomy. However, this was mainly caused by a higher risk of minor stroke occurring with stenting, and the extra events largely occurred in elderly patients. Conversely, stenting reduces the risk of procedure-related myocardial infarction, cranial nerve palsy and access site hematoma. Excluding peri-procedural events, stenting and endarterectomy work equally well to prevent recurrent stroke or recurrence of stenosis. Where both stenting and endarterectomy are feasible in individual patients with symptomatic carotid stenosis, the choice of treatment should therefore primarily be based on an assessment of procedural risks. In addition, stenting may be considered in symptomatic patients at increased risk for complications with surgery, patients in whom the stenosis occurred after previous surgery or radiation therapy to the neck and if the stenosis is not surgically accessible, so long as these patients are considered to benefit from revascularisation. Stenting should not be routinely used to treat asymptomatic carotid stenosis but may be suggested in asymptomatic patients in whom revascularisation is considered to be appropriate and who are less suitable for surgery.(98)

Future research should be directed at improving the selection of patients with carotid stenosis who are at risk of stroke and benefit from revascularisation, based on risk models enriched with imaging data. New trials are needed to demonstrate if the recent technological advances in carotid artery stenting have improved procedural safety to the level achieved with endarterectomy. Finally, emerging antithrombotic and lipid-lowering medications may further reduce the overall risk of stroke and other vascular events in patients with carotid disease.

Search strategy and selection criteria

We searched databases including MEDLINE, Science Citation Index, the Cochrane Central Register of Controlled Trials and on-going trials registries up to August 2021. Search terms were: carotid artery disease, carotid stenosis, symptomatic, asymptomatic, prevalence, age, sex, stroke, transient ischaemic attack, transient monocular blindness, amaurosis fugax, aspirin, clopidogrel, ticagrelor, anticoagulation, lipid-lowering therapy, stenting, embolism, protection devices, flow reversal, stent design, trans-carotid, endarterectomy, anaesthesia, randomised controlled trials, patient selection, magnetic resonance imaging, Positron emission tomography, ultrasound. We selected studies with a randomised trial design and systematic reviews thereof, large observational registries, and reports of technical developments in carotid revascularisation. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Authors' contributions statement

LB performed the literature review and wrote the first draft of the manuscript. The other authors contributed to the editing of the text. MB initiated the review and takes final responsibility for the content. All authors contributed to editing and commenting on the text.

Declaration of interests

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Tables and Figures

Table 1: Optimal medical management of carotid artery disease

Antithrombotic therapy	Asymptomatic carotid stenosis Aspirin, aspirin plus dipyridamole, or clopidogrel**(5)** Low-dose rivaroxaban (2.5 mg twice daily) plus aspirin**(8, 9)** Symptomatic carotid stenosis causing minor stroke or TIA Aspirin plus clopidogrel for 3 weeks to 3 months**(10, 11)** Aspirin plus ticagrelor for 30 days(12) Oral anticoagulation if otherwise indicated (e.g. in patients with atrial fibrillation)
Lipid-lowering therapy	Target LDL cholesterol ≤1.4 mmol/L(18) using a healthy diet plus: A statin, with or without ezetimibe Ezetimibe PCSK9 inhibitors
Antihypertensive therapy	Target blood pressure ≤140/90 mmHg measured in clinic or ≤135/85 mmHg measured at home
Glycaemic control in type 2 diabetes	Target HbA1c ≤6.5%
Life-style modification	Smoking cessation Weight reduction Regular exercise (150 minutes of moderate aerobic activity per week)

Table 2: Main procedural and post-procedural complications of carotid revascularization

Procedural (≤ 30 days)	- Intraoperative stroke - Postoperative stroke - Death - Myocardial infarction - Postendarterectomy hypotension - Postendarterectomy hypertension - Cerebral hyperperfusion syndrome - Bleeding/ wound haematoma - Cranial nerve injury - Silent cerebral ischaemic lesions - Wound infection - Internal carotid artery occlusion - Residual stenosis - Allergic reactions to contrast medium
Late complications (>30 days)	- Restenosis - Patch infection - Pseudo-aneurysm

Table 3: Indications for carotid endarterectomy and stenting

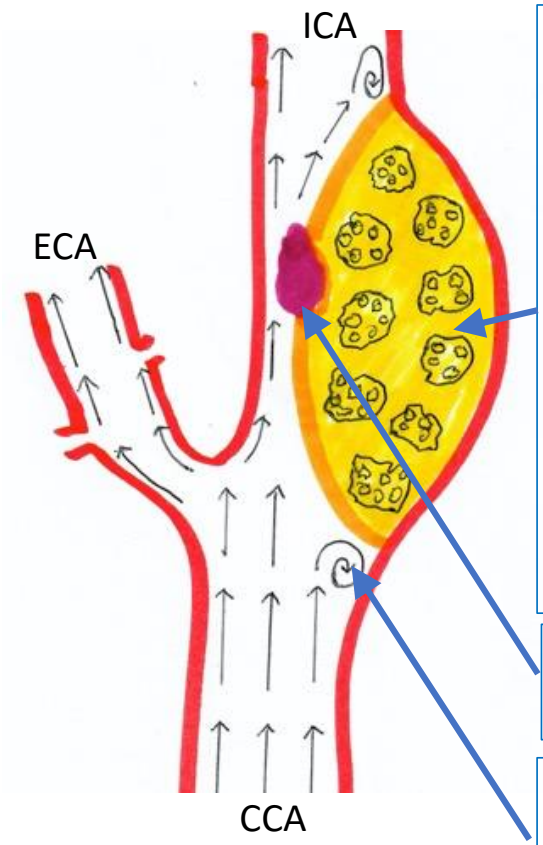
	Carotid endarterectomy	Carotid artery stenting
Symptomatic carotid stenosis	• Recommended for severe stenosis (70-99%) • Suggested for moderate stenosis (50-69%) • Not recommended for minor stenosis (<50%) • Recommended within 14 days of the first ischaemic event	• Suggested as an alternative to endarterectomy in patients <70 years old • Not recommended in patients with severe atherosclerosis of the aortic arch or tortuosity of supra-aortic vessels
Asymptomatic carotid stenosis	• Recommended for 60-99% stenosis in patients at increased stroke risk	• Not routinely recommended • Possible option in selected patients unsuitable for surgery, provided they benefit from revascularisation

Legend: Recommendations for carotid endarterectomy and stenting, according to current guidelines.(5, 98)

Table 4: Ongoing randomised trials of carotid revascularisation

Trial	Comparison
Second Asymptomatic Carotid Surgery Trial (ACST-2)	Stenting versus endarterectomy for asymptomatic carotid stenosis. Recruitment of 3625 patients from 2008 to 2020, follow-up ongoing. 130 study sites in 33 countries. Trial registration ISRCTN21144362.
Second European Carotid Surgery Trial (ECST-2)	Revascularisation versus optimised medical therapy alone for asymptomatic or low-to-intermediate risk symptomatic carotid stenosis. Recruitment of 429 patients from 2012 to 2019, follow-up ongoing. 23 study sites in Europe and Canada. Trial registration ISRCTN 97744893.
Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)	Two parallel trials: carotid artery stenting versus best medical therapy alone, and carotid endarterectomy versus best medical therapy alone, for asymptomatic carotid stenosis. Recruitment ongoing since 2014, target population 2480 patients. 157 study sites in the U.S., Canada, Israel and Spain. Trial registration NCT02089217.
Endarterectomy Combined With Optimal Medical Therapy (OMT) vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-than-average Risk of Ipsilateral Stroke (ACTRIS)	Endarterectomy versus optimal medical therapy alone in patients with asymptomatic carotid stenosis and presence of imaging features associated with increased stroke risk. Recruitment ongoing since 2019, target population 700 patients. 23 study sites in France. Trial registration NCT02841098.

Figure 1: Pathophysiology of embolic stroke originating from carotid artery stenosis



Atheromatous plaque develops at site of low shear stress
- LDL accumulates in intima
- Oxidised LDL activates endothelial cells and attracts monocytes
- Monocytes take up oxidized LDL and secrete pro-inflammatory cytokines and proteases
- Haemorrhage from neo-vessels also activates inflammation
- Thinning of fibrous cap leads to plaque ulceration or rupture

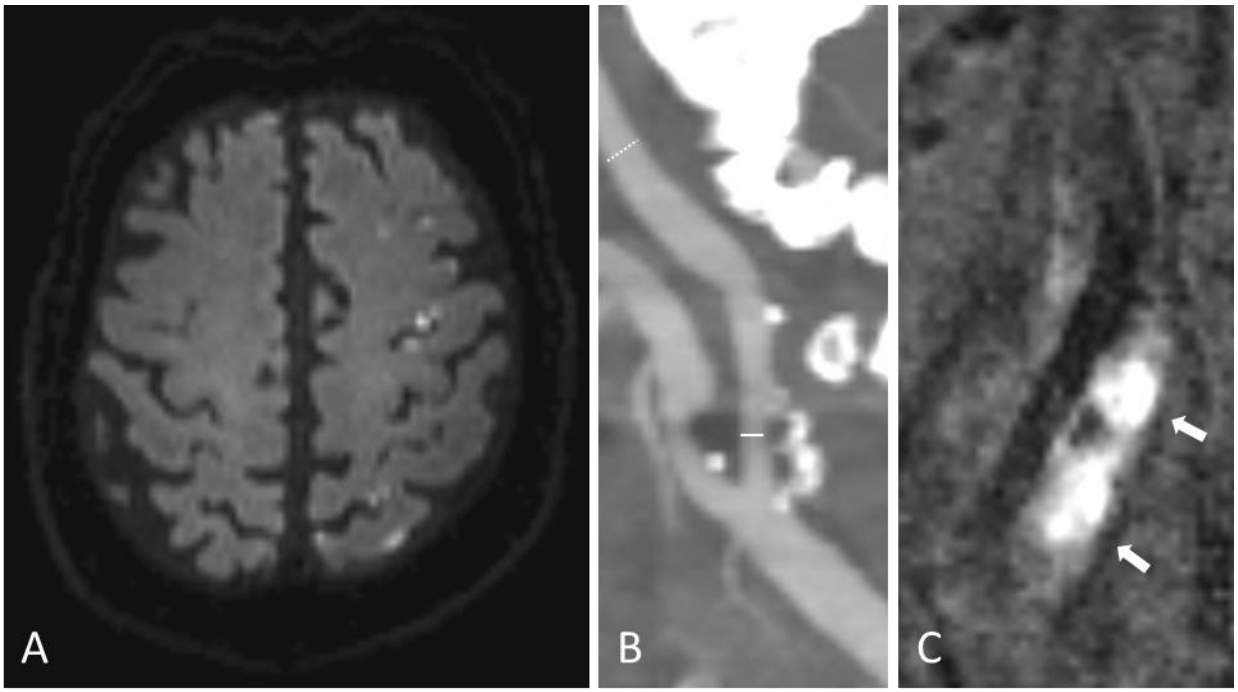
Thrombosis on ulcerated or ruptured plaque

Turbulence created by stenosis:
- Activates platelets
- Might contribute to thrombosis

TIA and stroke result from one or more of the following mechanisms:
1. Embolism of thrombus to intracranial arteries
2. ICA occlusion with propagation of thrombus intracranially
3. Reduction in perfusion pressure from severe stenosis or occlusion

Legend: ICA, internal carotid artery; ECA, external carotid artery, CCA, common carotid artery; LDL, low-density lipoprotein; TIA, transient ischaemic attack.

Figure 2: Role of carotid plaque MRI in a patient with symptomatic carotid artery stenosis



Legend: Example of a patient with recurrent left-hemispheric transient ischaemic attacks. (A) Diffusion-weighted MRI shows multiple embolic lesions in the vascular borderzone between the left middle and anterior cerebral arteries. (B) CT angiography shows mixed calcified and soft plaque at the origin of the left internal carotid artery causing 40% narrowing of the lumen according to the method of measuring stenosis used in the NASCET trial; hereby the diameter at the site of maximum narrowing (straight line) is compared with the diameter of the distal, non-diseased artery where the walls run parallel (dashed line). (C) The MPRAGE sequence of Plaque MRI shows elevated signal in the carotid plaque signifying intra-plaque haemorrhage (arrows). The lumen of the internal carotid artery appears dark (asterices). This patient is at increased risk of stroke and may benefit from carotid revascularisation despite the stenosis measuring <50%. MRI, magnetic resonance imaging. CT, computer tomography. NASCET, North American Symptomatic Carotid Endarterectomy Trial. MPRAGE, magnetization-prepared rapid acquisition with gradient echo.

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