Diagnosis and management of carotid atherosclerosis

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Carotid atherosclerosis is a pathological thickening of the common or internal carotid intima, typically into focal areas known as plaques (or atheroma). Although atheroma can remain stable for many years, surface rupture of unstable (vulnerable) plaques leads to local thrombus formation, with subsequent embolisation to the ipsilateral ophthalmic, middle cerebral, or anterior cerebral artery territories. The resultant symptoms are ipsilateral amaurosis fugax or retinal infarction and contralateral body transient ischaemic attack (TIA) or stroke. This review discusses the risk factors, clinical presentation, investigations, and treatment options for symptomatic and asymptomatic carotid atherosclerosis. All references to stenosis use consensus North American Symptomatic Carotid Endarterectomy Trial (NASCET) measurements. All recommendations reflect current UK guidelines, unless stated otherwise.

Who is at risk of carotid atherosclerosis?
Moderate to severe asymptomatic carotid atherosclerotic stenosis is found in 2–5% of European women and 2–8% of European men over 60 years. However, prevalence is much higher in high risk groups (table 1).

The Framingham cohort study found that the following baseline risk factors predicted degree of stenosis over 12 years1:
- Age (odds ratio 1.6–1.7/10 year increase in age)
- Cigarettes smoked (1.3–1.5 per 10 cigarettes smoked a day)
- Systolic blood pressure (1.2 per 10 mm Hg increase)
- Total cholesterol (1.1–1.2 per 0.5 mmol/L increase).

An independent cohort study confirmed that these risk factors were more common at baseline in those with carotid stenosis.2

How does carotid atherosclerosis present clinically?
Patients with carotid atherosclerosis may present with symptoms or be identified solely on imaging. Symptomatic patients can present with ipsilateral amaurosis fugax, retinal infarction (which may affect an area of monocular vision (branch occlusion) or the entire retina (central occlusion)), contralateral body TIA, or stroke. Typically, the ipsilateral anterior cerebral circulation is affected, resulting in contralateral (to the artery and cerebral hemisphere) homonymous hemianopia; visuospatial neglect; or weakness or paraesthesia of the face, arm, or leg. In left sided carotid atherosclerosis, dysphasia may result from involvement of language centres typically found in the left cerebral hemisphere. Visuospatial neglect can occur in patients with intact visual fields, typically through involvement of the right temporoparietal cortex.

Transient hemispheric or ocular symptoms can recur in rapid succession, a situation termed “crescendo.” In the presence of carotid atherosclerosis this suggests ongoing embolisation from an unstable atheroma.

Carotid stroke is caused by embolisation of surface thrombus from fibrous cap rupture to the ipsilateral anterior circulation, rather than exercise induced flow limitation (as in claudication). Hence, with an adequate circle of Willis, an occluded internal carotid artery may remain asymptomatic. Diffusion weighted magnetic resonance imaging elegantly

SUMMARY POINTS
Carotid ultrasound is recommended within 24 hours of a new carotid territory transient ischaemic attack, non-disabling ischaemic stroke, ipsilateral amaurosis fugax, or retinal artery infarction
Consider symptomatic patients with 50-99% carotid stenosis for carotid endarterectomy within one week of symptom onset, and ideally within 48 hours
Consider symptomatic patients with high bifurcation, symptomatic restenosis, and post-radiotherapy stenosis for stenting
Bruits are an unreliable marker of stenosis and ultrasound is preferred
Screening for asymptomatic carotid atherosclerosis is not recommended in the UK
Revascularisation for asymptomatic carotid atherosclerosis should be performed as part of a randomised trial in the UK

<table>
<thead>
<tr>
<th>Table 1</th>
<th>High risk populations for carotid atherosclerosis</th>
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<tbody>
<tr>
<td>Population</td>
<td>Approximate prevalence of asymptomatic 50-99% carotid stenosis (%)</td>
</tr>
<tr>
<td>People with peripheral arterial disease30</td>
<td>25</td>
</tr>
<tr>
<td>People over 60 years with 3 cardiovascular risk factors41</td>
<td>16</td>
</tr>
<tr>
<td>Those with coronary arterial disease77</td>
<td>15</td>
</tr>
<tr>
<td>Those with aortic aneurysmal disease79</td>
<td>12</td>
</tr>
<tr>
<td>People with contralateral symptomatic carotid atherosclerosis84</td>
<td>6</td>
</tr>
</tbody>
</table>

General European population over 60 years2 2.7–5.5

SOURCES AND SELECTION CRITERIA
We search PubMed using the keywords “carotid AND athero* OR stenosis OR plaque”. Key randomised controlled trials and cohort studies were identified.

We searched the Cochrane Library using the keyword “carotid”. The UK fourth national clinical guideline for stroke 2012, UK carotid endarterectomy audit round 4, European Society for Vascular Surgery carotid guidelines parts A–C, and European Society for Cardiology fifth guideline on cardiovascular disease prevention were consulted, along with relevant references from these articles.
What initial assessment is appropriate in symptomatic carotid atherosclerosis?

Careful history taking in a patient who has had a TIA or stroke can help establish whether the presenting symptoms are referable to one or other carotid territory and if the patient is likely to benefit from carotid revascularisation. A history of neck trauma, frontal headache, or connective tissue disease may suggest carotid dissection, which is generally managed with antiplatelet agents or anticoagulation alone.\(^5\)

The ABCD score is commonly used to triage TIA,\(^2\) but it cannot predict the presence of carotid stenosis or the benefit of revascularisation.\(^6\) Establish the patient’s handedness, because this may effect the laterality of language centres and the disability caused by infarction in a dominant hemisphere. Assess the patient’s modifiable risk factors, including blood pressure, cholesterol, glycaated haemoglobin, smoking history, and exercise habits to facilitate secondary prevention.

Which investigations help rule out alternative pathologies?

Among the basic stroke investigations,\(^7\) the most useful investigations for identifying alternative causes of embolic stroke are electrocardiography, prothrombin time on the day of event for patients taking warfarin, and erythrocyte sedimentation rate if arteritis is suspected. If the clinical territory of symptoms is uncertain after initial cerebral computed tomography, diffusion weighted cerebral magnetic resonance imaging may help identify ischaemic lesions in a single carotid territory and rule out bilateral or posterior circulation ischaemic lesions found with other embolic sources (fig 1). In hyperacute stroke, a randomised imaging study showed that this test had a sensitivity of 91\%(95\% confidence interval 88\% to 94\%), specificity of 95\%(75\% to 100\%), and inter-reader \(k\) of 0.84 for acute infarct detection, compared with 61\%(52\% to 70\%), 65\%(50\% to 100\%), and 0.51, respectively, for computed tomography.\(^8\)

How is carotid atherosclerosis diagnosed?

The UK national stroke strategy suggests that clinicians refer patients with ipsilateral anterior circulation transient ischaemic attack, non-disabling stroke, amaurosis fugax, or retinal infarction for carotid duplex ultrasound within 24 hours of presentation.\(^12\) A carotid atheroma is diagnosed on ultrasound as a focal structure encroaching into the arterial lumen by at least 0.5 mm, although some other conditions can mimic it (box).\(^13\) Colour duplex ultrasound has the benefits of speed, safety, and portability. It can also characterise the atheroma and quantify luminal stenosis (fig 2). Stenosis is measured using the Doppler principle to measure the increase in blood velocity at the point of greatest stenosis, which is converted into equivalent digital subtraction arteriogram (DSA) measurements. One recommended method of grading stenosis is to use peak systolic velocity.\(^1\) A peak systolic velocity of more than 125 cm/s corresponds to greater than 50\% stenosis and one of more than 230 cm/s corresponds to greater than 70\% stenosis, although there 

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**Fig 1** | Diffusion weight magnetic resonance imaging of the brain showing acute embolic infarcts (yellow arrow) in the left middle cerebral artery territory, associated with atheroma thromboembolism

**Fig 2** | Echolucent internal carotid artery atheroma (yellow arrow) causing 70\% NASCET equivalent stenosis.

CCA=common carotid artery, ECA=external carotid artery, ICA=internal carotid artery, STA=superficial temporal artery.

Analysis of atheroma characteristics on ultrasound is an area of research for future stroke prediction.
accuracy of non-invasive imaging for detecting 70–99% angiographic NASCET stenosis (table 3). The study found 86% (79% to 91%) inter-sonographer agreement for 70–99% stenosis on ultrasound. Improvements in multidetector computed tomography technology have led to improved diagnostic accuracy, which looked similar to contrast enhanced magnetic resonance angiography and DSA in two blinded case series. Moderate symptomatic carotid atherosclerosis is more problematic, because measurement of stenosis is less accurate.

When choosing imaging modalities, ease of access, cost, contralateral occlusion, the presence of a pacemaker, extensive calcification, and renal failure must be considered. An analysis of imaging strategies in 2009 and their effect on number of strokes saved suggested that an ultrasound-only strategy was as effective as adding a second modality in the 70–99% stenosis group when surgery was performed within 14 days. There is no ideal modality, but most institutions (and current US guidelines) initially use duplex ultrasound to identify 70–99% stenosis, with ultrasound being repeated before surgery by a more experienced sonographer. In borderline cases, moderate stenosis, or in patients who present late (in whom surgical benefit is marginal), multidetector computed tomographic angiography or contrast enhanced magnetic resonance angiography can reduce the number of unnecessary endarterectomies performed.

Who should be referred for consideration of endarterectomy?

Urgently refer patients with 50–99% stenosis on duplex ultrasound to a vascular surgeon, preferably through a multidisciplinary neurovascular meeting, for consideration of confirmatory imaging and endarterectomy. The fourth UK clinical guideline for stroke recommends that surgery is performed within one week, and ideally within 48 hours, when stroke is most common and benefit from endarterectomy is greatest. Those who are currently unfit for surgical or endovascular revascularisation, or who have severe disability, may be reassessed after one week regarding referral for carotid ultrasound.

In the UK, asymptomatic patients with 50–99% NASCET stenosis can be randomised to revascularisation versus medical therapy as part of the ongoing randomised European Carotid Surgery-2 Trial or to surgery versus stenting in the Asymptomatic Carotid Surgery-2 Trial. In the US, revascularisation is commonly used to treat asymptomatic patients with 70–99% stenosis.

Patients with stable neurology and complete carotid occlusion are unsuitable for carotid endarterectomy because they are not at risk of embolisation through an occluded artery. However a subset of patients with insufficient collaterals experience hypoperfusion after occlusion, leading to an annual rate of ipsilateral stroke of 5.9% (4.3% to 7.5%). Patients with previous cardiac disease are at increased risk of perioperative stroke. Patients with severe or disabling symptoms do not benefit from surgery, unless they experience hypoperfusion after occlusion.

Which other factors are important when considering endarterectomy?

Clinicians should consider a patient’s fitness for intervention and any previous cardiac disease. They should also...
look for coexistent aortic aneurysm and peripheral arterial disease (table 1). Examination should include assessment of neck extension and the location of the carotid bifurcation (using ultrasound) in relation to the angle of the mandible, because this has relevance for surgical access to the internal carotid. In cases of stroke, document the level of disability (table 4) because endarterectomy is of known benefit only for those with non-disabling stroke.31 32

Previous neck radiotherapy or surgery may complicate endarterectomy and require an alternative strategy such as medical treatment, stenting, or bypass.33 Previous endarterectomy is relevant because restenosis within the first year may result from myointimal hyperplasia rather than atherosclerosis.34 The presence of connective tissue disease such as Marfan’s syndrome, Ehlers-Danlos syndrome, or fibromuscular dysplasia is important because it predisposes to dissection, which is generally managed non-operatively. For patients who have received stroke thrombolysis, four small case series suggest that early carotid endarterectomy can still be performed safely.35-37

Table 4 | Disability levels in stroke as measured by the modified Rankin scale

<table>
<thead>
<tr>
<th>Modified Rankin scale</th>
<th>Functional disability</th>
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<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>No serious disability</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities but independent</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requires some help but able to walk independently</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk independently and unable to attend to bodily needs without help</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent, fully dependent</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Who benefits most from endarterectomy?
Carotid endarterectomy can precipitate as well as prevent stroke. For symptomatic patients, several factors predict surgical benefit: increasing stenosis (from 50-99%), male sex, early intervention, and increasing age.31 32 These effects were consistent across two large randomised controlled trials.31 32

QUESTIONS FOR FUTURE RESEARCH
Can ultrasound based atheroma analysis and microemboli detection reduce the number of unnecessary endarterectomies performed?
What is the benefit of revascularisation versus modern medical treatment in symptomatic patients with moderate (50-69%) stenosis?
What are the clinical outcomes of asymptomatic patients with 70-99% stenosis on contemporary medical therapy versus revascularisation?
What are the stroke rates in patients with asymptomatic 70-99% carotid stenosis undergoing cardiac bypass?

For example, the absolute ipsilateral stroke risk reduction for a patient with 50-69% symptomatic stenosis treated within two weeks is 14.8% but if left beyond 12 weeks surgery, in fact, becomes harmful.35

For asymptomatic patients with an incidental 70-99% carotid stenosis, three randomised controlled trials provided evidence of a 1% absolute risk reduction each year with endarterectomy over and above medical treatment of that era, particularly in those under 75 years.36 However because of falling background stroke rates, the small risk reduction with surgery, a prerequisite need for national case finding, and the large number of people with preclinical atherosclerosis, surgery is currently recommended for these patients only as part of a trial in the UK.37

How is surgery made safer?
UK registry data show a perioperative stroke or death rate of 2%, myocardial infarction rate of 0.6%, neck haematoma rate of 3%, and cranial nerve palsy rate of 4%.38 A systematic review found that early surgery (less than one week from symptoms) does not increase perioperative stroke or death, with the exception of emergency surgery for stroke in evolution or crescendo TIAs.39

A 2004 meta-analysis found no significant difference for 30 day stroke or death between endarterectomy under local or general anaesthesia (odds ratio 0.85, 0.63 to 1.16; I²=0.0%).40 However, shunt insertion (to preserve internal carotid blood flow intraoperatively using a plastic tube) is needed less often with local anaesthesia (0.27, 0.23 to 0.31; I²=91%), because patients’ neurology can be monitored directly. The 2004 Cochrane meta-analysis of patch angioplasty versus primary closure found a significant reduction in medium term ipsilateral stroke with patching (0.32, 0.16 to 0.63; I²=0%).41

In the week after surgery, blood pressure must be tightly controlled. A pooled analysis of case series found an increased incidence of intracerebral haemorrhage when a postoperative systolic pressure of 150 mm Hg is exceeded.42

Should a bruit prompt referral?
In the past, a bruit over the carotid bifurcation was thought to be the first sign of carotid atherosclerosis. However,
several large studies have found bruits to be an unreliable marker of the presence and severity of carotid atherosclerosis. In NASCET, an ipsilateral carotid bruit had a sensitivity of 63% and specificity of 61% for 70–99% stenosis. This was confirmed in a smaller British study which found a sensitivity of 57% and specificity of 70% for ipsilateral 70–99% stenosis. This low diagnostic accuracy led to auscultation for bruits being replaced with carotid ultrasound.

**Should patients be screened for asymptomatic carotid atherosclerosis?**

A large US cohort study found only a 0.5% prevalence of surgically treatable 70–99% asymptomatic carotid atherosclerosis in people over 65 years, with an ipsilateral five year stroke rate of only 5%. In line with this, current UK guidance now recommends that opportunistic case finding (including those with an asymptomatic bruit) is unnecessary for asymptomatic carotid atherosclerosis. US guidelines discourage screening but state that those with a bruit, or those on an intensive risk factor modification regimen, are reasonable candidates for carotid ultrasound.

**What is the natural course of asymptomatic carotid atherosclerosis?**

Patients may be identified with asymptomatic carotid atherosclerosis on carotid ultrasound and may seek advice. Recent cohort studies have found that ipsilateral stroke rates associated with asymptomatic carotid stenosis are currently less than 1% a year, compared with greater than 2% 10 years ago. These patients are at greater risk of death from ischaemic heart disease, so should be referred to a local clinician with an interest in risk factor modification.

**How is carotid disease managed medically?**

People with carotid atherosclerosis are classified by the European Society of Cardiology as having a very high risk of death from cardiovascular disease. For symptomatic patients in the UK, the Royal College of Physicians currently recommends lifelong antiplatelet drugs (clopidogrel 75 mg daily is recommended despite carotid atherosclerosis being an exclusion criteria to the CAPRIE study that this recommendation is based on), blood pressure control (less than 130/80 mm Hg after the acute phase), statins to reduce low density lipoprotein to less than 2.0 mmol/L, multimodal smoking cessation support, and 2.5 hours of moderate intensity exercise a week. In the US, corresponding targets are: blood pressure less than 140/90 mm Hg and low density lipoprotein less than 2.6 mmol/L.

International consensus statements also exist for the medical management of asymptomatic carotid atherosclerosis. New anti-atherosclerotic drugs under investigation include dalcetrapib for modulating high density lipoprotein concentrations and the next generation of P2Y<sub>12</sub> platelet inhibitors.

**What is the current evidence for carotid stenting?**

Figure 4 illustrates the principles of carotid stenting. A 2012 review analysed outcomes for symptomatic and asymptomatic patients treated with carotid angioplasty and stenting versus endarterectomy. In 16 trials of 7572 symptomatic patients, stenting was associated with a significantly worse risk of 30 day stroke or death (odds ratio 1.72, 1.29 to 2.31; I<sup>2</sup>=27%), particularly in people over 70 years. The long term rates of ipsilateral stroke were similar for both interventions. Stenting was associated with less myocardial infarction (0.44, 0.23 to 0.87; I<sup>2</sup>=0%) and cranial nerve palsy (0.08, 0.05 to 0.14; I<sup>2</sup>=0%). International experts recommend that until perioperative stroke or death rates improve with stenting, endarterectomy remains the procedure of choice for symptomatic carotid atherosclerosis. However, in the US, stenting is considered an alternative to endarterectomy if the institution’s perioperative stroke rate is less than 6%.

In asymptomatic patients, no significant differences were seen in 30 day stroke or death risks between surgery and stenting groups. The term outcomes for the two groups also showed no significant difference. Further trials are assessing outcomes in asymptomatic people with intervention versus medical treatment and surgery versus stenting.

**Cardiovascular risk factors in asymptomatic carotid stenosis.**

32% of patients with a normal carotid ultrasound had a low risk and 7% had a very high risk. The remainder were placed in intermediate categories.

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**Contributors**

AT and AH conceived the idea; all authors helped write the article and critically revised the drafts; AT and AM prepared the figures; AHD is guarantor.

**References**