Carotid Artery Disease

16

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Key Points

- In patients with carotid artery stenosis, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking should be evaluated and treated aggressively.
- The use of prophylactic aspirin is recommended in all patients with carotid artery stenosis.
- Patients with an asymptomatic carotid stenosis should be educated about possible symptoms of transient ischemic attacks and should immediately contact a physician in case a transient ischemic attack occurs.
- In patients with an asymptomatic carotid stenosis, prophylactic carotid endarterectomy (CEA) can be recommended only in highly selected patients with high-grade stenosis (>70%) performed by surgeons with established perioperative morbidity and mortality rates of <3%. With regard to carotid angioplasty and stenting (CAS), there is currently a lack of data comparing this treatment modality with contemporary best medical therapy alone. If considered, CAS should be performed only by operators with established perioperative morbidity and mortality rates of <3%.
- Carotid endarterectomy should be considered in patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (>70%) carotid artery stenosis. CAS is an indicated alternative to CEA in younger patients with a symptomatic severe (>70%) carotid artery stenosis, whereas patients older than approximately 70 years of age should preferentially be treated with CEA. Both procedures should be performed only by surgeons or interventionalists with established perioperative/peri-interventional morbidity and mortality rates of <6%.
- In patients with a recently symptomatic carotid artery stenosis, surgery or interventional treatment should ideally be performed within 2 weeks.

16.1 Introduction

Stroke is one of the leading causes of morbidity and mortality in North America, affecting over half a million patients at a cost of over $30 billion a year. Depending on the population studied, extracranial internal carotid artery stenosis accounts for approximately 10–15% of ischemic strokes. Aside from these symptomatic cases, large population-based studies indicate that the prevalence of asymptomatic carotid artery stenosis is approximately 0.5% in the sixth decade and increases up to 10% in persons over 80 years of age [1].

Carotid stenoses may result in brain ischemia either through direct hemodynamic impairment of the cerebral blood circulation or, more commonly, as a source of thromboembolic material arising from symptomatic carotid plaques. These mainly develop in regions of low vessel-wall shear stress such as the carotid bulb and are characterized by increased cellular proliferation, lipid accumulation, calcification, ulceration, hemorrhage, and thrombosis. Symptomatic carotid artery disease is commonly manifested by transient contralateral symptoms or ipsilateral monocular blindness and then detected during further diagnostic workup, whereas patients with an asymptomatic carotid stenosis are most commonly found by physical examination of a carotid bruit.

The main approaches for treating patients with carotid artery disease include the stabilization of the carotid plaque

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through risk factor modification and medication as well as the removal of the stenosis through carotid endarterectomy (CEA) or carotid angioplasty and stenting (CAS).

16.2 Diagnostic Testing

Obtaining a history and performing general medical (including auscultation of the neck for carotid bruits and transmitted murmurs) and neurological (to correlate neurological symptoms with an ischemic territory) examinations are crucial steps in selecting proper treatment for patients with carotid artery disease. The approach of any patient with carotid artery disease should also involve recognition of this disease as a specific manifestation of a generalized arteriopathy. Therefore, a thorough search should be made for other evidence of atherosclerosis, including cardiac and peripheral vascular disease. A clear separation between symptomatic and asymptomatic carotid artery stenosis is critical. Symptoms of a carotid artery stenosis typically include contralateral weakness or numbness, dysphasia, ipsilateral monocular blindness (amaurosis fugax), and, in rare instances, syncope, confusion, or seizures. Specific signs of left hemisphere ischemia include aphasia, while right hemisphere ischemia may be manifest by apraxia or visuospatial neglect. All of these symptoms may be transient, representing TIAs, or permanent, resulting in cerebral infarction. Non-specific symptoms such as a blurred vision or a subjective generalized weakness should not be considered as a symptomatic event. Laboratory testing should be performed to determine the presence of cardiovascular risk factors (e.g., unknown diabetes mellitus and hyperlipidemia). It is also useful in ruling out metabolic and hematologic causes of neurological symptoms such as hypoglycemia, hyponatremia, and thrombocytosis.

Patients with an asymptomatic carotid stenosis are most commonly found by physical examination of a carotid bruit. Although carotid bruits only have a limited value for the diagnosis of carotid artery disease, carotid auscultation should be part of the routine physical examination of patients with cardiovascular risk factors. While carotid auscultation is a sufficient screening test for asymptomatic patients, all patients with a TIA or stroke must be evaluated with duplex ultrasonography either alone or supplemented with digital subtraction angiography (DSA), computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or contrast-enhanced MRA. *Duplex ultrasonography is the imaging tool of choice to screen for carotid artery stenosis*.

To date, conventional or digital subtraction cerebral angiography is still considered to be the gold standard for imaging the carotid arteries. In the large clinical trials, cerebral angiography was used to evaluate the entire carotid system, including the intracranial collateral circulation, and served as standard for defining the degree of carotid stenosis and for defining morphological features of the offending plaque. Usually, the degree of a carotid artery stenosis is determined with the North American method (NASCET method), which measures the minimal residual lumen at the level of the more distal internal carotid artery. It is based on the formula: stenosis = $(1 - N/D) \times 100\%$, where N is the diameter at the point of maximum stenosis and D is the diameter of the arterial segment distal to the stenosis where the arterial walls fist become parallel. Using this method a hemodynamically significant carotid stenosis would correspond to a 60% diameter stenosis.

Digital subtraction angiography, however, is invasive and expensive and is associated with a risk of serious neurological complications or death of approximately 0.5–1%. Therefore, it has largely been replaced by CTA or MRA. Nowadays, the latter techniques are mainly used as confirmatory tests after results of an ultrasound examination are suggestive of the presence of a carotid stenosis in most centers. Carotid duplex ultrasound is a noninvasive, safe, and inexpensive technique that has a high sensitivity and specificity in detecting a significant stenosis of the ICA. On the other hand, the accuracy of carotid ultrasound relies heavily upon the experience and expertise of the examiner and may be limited by features such as calcified, tortuous arteries, or far distal stenoses. In these cases, CTA may be particularly useful. With this technique, three-dimensional reconstruction allows relatively accurate measurements of the residual lumen diameter. MRA images are either based on two- or three-dimensional time-of-flight (TOF) or gadolinium-enhanced sequences. The contrast-enhanced techniques produce higher quality images that are less prone to artifacts. While MRA is less operator dependent than ultrasound, it is more expensive and time-consuming and may not be performed if the patient has claustrophobia, a pacemaker, or ferromagnetic implants.

16.3 Medical Treatment

The estimated annual risk of stroke in patients with an asymptomatic stenosis is approximately 1–2% [2] and 4–6% in patients with a symptomatic carotid stenosis [3], respectively. Aside from considering a surgical removal or an interventional therapy for a carotid stenosis, primary and secondary medical therapies are clearly indicated, all the more considering that 20% of patients undergoing CEA for symptomatic carotid artery stenosis and 45% of patients undergoing CEA for asymptomatic carotid artery stenosis subsequently have strokes related to other etiologies [4]. While the concept of "best medical therapy" for patients with asymptomatic or symptomatic carotid artery disease

mainly consisted of "stop smoking" and "take aspirin" in the large trials comparing CEA with medical therapy, major advances have been made in the past two decades regarding statin, antiplatelet, and antihypertensive therapies. Although several cardiovascular risk factor modifications and medical therapies have not been specifically evaluated in patients with severe carotid artery stenosis, they are generally recommended to limit progression of atherosclerosis and decrease clinical events, irrespective of carotid revascularization.

In patients with an asymptomatic carotid stenosis, antiplatelet therapy with aspirin is indicated for primary prevention mainly of cardiovascular events [5]. In patients with symptomatic carotid stenosis current recommendations are based on the results of large stroke prevention studies with mixed patient populations and include the use of aspirin, clopidogrel, or a fixed combination of aspirin with extended-release dipyridamole [6, 7]. There is no data to support the use of aspirin in doses greater than 325 mg day. Clopidogrel might be a more potent antiplatelet agent than aspirin, but due consideration must also be given to the risk of excess bleeding should the patient require surgery.

Although not specifically tested for in patients with carotid artery disease, there is a general consensus that a stringent control of blood pressure is the cornerstone of therapy to modify atherogenic risk factors, and the benefits of antihypertensive therapy extend to all patient subgroups, especially diabetic patients. For primary stroke prevention, a large meta-analysis found that regardless of the agent used, a 10 mmHg reduction in systolic blood pressure produced a 31% relative risk reduction for stroke [8]. For secondary stroke prevention, proven agents include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and the combination of a thiazide diuretic with an angiotensin-converting enzyme inhibitor [6, 7]. Although there is emerging evidence that some antihypertensive medications may exert their beneficial effect in ways other than by reducing blood pressure, the primary goal of blood pressure therapy should be to achieve values of <140/90 mmHg for nondiabetic patients and < 130/80 mmHg for patients with diabetes. The selection of drugs should therefore primarily be influenced by the presence of comorbid conditions such as diabetes mellitus, renal failure, or left ventricular dysfunction. Many patients will require multiple medications to achieve optimal blood pressure values.

Statins have assumed a prominent role in cerebrovascular and cardiovascular risk modification [9, 10]. The SPARCL trial, which randomized 4732 patients with recent stroke or TIA to atorvastatin 80 mg/day or placebo, reported a 16% relative risk reduction (RRR) in future stroke [10]. In a subgroup analysis of 1007 patients with documented carotid stenosis patients taking atorvastatin 80 mg daily, the RRR for future stroke was 33%, 42% for major coronary events, and 56% for the need of carotid revascularization [11]. In a review of 180 patients undergoing CAS, a significantly higher 30-day rate of stroke, MI, or death was identified among patients who were not taking preprocedural statin therapy [12]. A similar result was obtained for symptomatic patients undergoing CEA [13]. In a further study of patients receiving medical treatment for severe carotid artery disease, statin use was associated with significantly lower rates of stroke, MI, or death [14].

Smoking, physical inactivity, and eating habits are also important modifiable risk factors for the development and progression of carotid artery disease. While preventive medications are easy to prescribe, lifestyle modification should be considered as equally important. A combination of nicotine replacement therapy, social support, and skills training, for instance, has been shown to be effective in treating tobacco dependence.

In patients with carotid artery stenosis, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking should be evaluated and treated aggressively.

16.4 Carotid Endarterectomy in Patients with Symptomatic Carotid Stenosis

The superiority of CEA over medical treatment in the management of symptomatic high-grade (>70% angiographic stenosis) atherosclerotic carotid artery stenosis has been established in two, large randomized trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [3] and the European Carotid Surgery Trial (ECST) [15]. A third trial was stopped prematurely when the results of NASCET were announced [16].

In NASCET and ECST, all surgeons were screened for an acceptable operative record. Entry criteria for these trials included carotid artery stenosis (>30% reduction in the luminal diameter on conventional angiogram) and ipsilateral TIA, non-disabling stroke, or retinal infarction within 4–6 months. The main exclusion criteria included a probable cardiac source of embolism, serious disease likely to cause death within 5 years, or intracranial disease that was more significant than the carotid lesion. Both trials used different methods to measure carotid stenosis. While NASCET used the residual lumen diameter at the most stenotic portion of the vessel and compared this to the lumen diameter in a normal portion of the internal carotid artery distal to the stenosis to determine the degree of stenosis (see above), ECST used the lumen diameter at the most stenotic portion of the vessel and compared this to the estimated probable original diameter at the most stenotic portion of the vessel. In the meantime, equivalent measurements for the two methods have been determined: a 50% stenosis with the NASCET method is equivalent to a 75% for ECST, and a 70% stenosis with the NASCET method is equivalent to an 85% stenosis for ECST.

In NASCET and for patients with symptomatic carotid stenosis of 70–99% (measured by the NASCET method), CEA reduced the 2-year risk of ipsilateral stroke from 26% in the medical group ($n = 331$) to 9% in the surgical group ($n = 328$), yielding an absolute risk reduction of 17% ($p < 0.001$). The number needed to treat (NNT) to prevent one stroke was 6 (NNT = 12 at 1 year). A 5.8% incidence of perioperative stroke or death was reported for patients in the surgical arm. In patients with moderate degrees of stenosis (50–69%), the 5-year ipsilateral stroke risk was 22.2% in the medical arm and 15.7% in the surgical arm ($p < 0.045$). The NNT to prevent one stroke was 15 (NNT = 77 at 1 year). Benefit in the 50–60% stenosis group was best achieved in patients presenting with hemispheric, not retinal symptoms, with stroke rather than TIA, male sex, and intracranial carotid artery stenosis. In this group of patients, subgroup analysis did not demonstrate a benefit of CEA in women (NNT = 125 to prevent one major ipsilateral stroke in 5 years). Patients with <50% stenosis did not benefit from surgery.

The ECST reported a similar efficacy of CEA in the secondary prevention of stroke for patients with a high-grade carotid stenosis. In this trial, the frequency of a major stroke or death at 3 years was 26.5% in the control group ($n = 220$) versus 14.9% in the surgical group ($n = 356$), so that surgery was associated with an absolute benefit of 11.6% ($p < 0.001$). The NNT to prevent one stroke annually was 21. A 7.4% incidence of perioperative stroke or death was reported for patients in the surgical arm. The risk of these complications was not related to the severity of the stenosis.

Although NASCET and ECST have clearly demonstrated the superiority of CEA combined with medical therapy over medical management alone for symptomatic patients with carotid artery stenosis of >70% (NASCET) [3] or >80% (ECST) [15], several post hoc analyses have been performed to identify subsets of patients who are most likely to benefit from surgery. In fact, the decision to treat individual patients with carotid artery disease surgically should not be exclusively based on the stenosis severity, but should also take into account age, gender, neurological symptoms, and other determining factors for subsequent stroke or surgical risk. In addition, patients who have severe comorbidities, patients with persistent disabling neurological deficits, and those with a total occlusion of the carotid artery are unlikely to benefit from CEA and should thus be treated with medical therapy.

The benefit of CEA increases steadily from 50% to 99% (NASCET method) as a consequence of an enhanced risk of ipsilateral stroke, proportional to the severity of the stenosis, while surgery-related morbidity does not vary substantially with the degree of stenosis [17]. A patient with a 90–99% symptomatic stenosis derives twice the benefit from CEA than one with a 70–79% stenosis.

Other factors that can be used to estimate the absolute risk of ipsilateral stroke for individual patients with symptomatic carotid stenosis who are candidates for CEA include patient age, gender, type of presenting event, plaque morphology, and time since last event [18].

In a subgroup analysis of NASCET, the benefit of CEA for patients with a symptomatic carotid stenosis aged 75 years or older was compared with that for those aged 65–74 years and less than 65 years [19]. Among medically treated patients with 70–99% carotid stenosis, the risk of ipsilateral ischemic stroke at 2 years was highest (36.5%) in patients aged 75 years or older. The rates of perioperative stroke and death were 7.9, 5.5, and 5.2% in patients younger than 65 years, 65–74 years, and >75 years, respectively. Because patients aged 75 years or older had the highest risk with medical treatment, the absolute risk reduction by CEA was greatest in this subgroup (28.9%). Only three patients had to undergo surgery to prevent one ipsilateral ischemic stroke at 2 years. Thus, elderly patients profited more from CEA than younger patients in this trial. Likewise, the ECST data has indicated that increasing age is associated with a greater benefit from CEA for symptomatic carotid stenosis [20].

Men gain more benefit from CEA than women. The stroke risk reduction with CEA is highest in patients presenting with hemispherical TIAs or minor strokes compared to retinal symptoms. Plaque ulceration also confers an increased stroke risk on medically treated patients. Patients with recently symptomatic stenoses are at the highest risk of subsequent stroke and thus derive a substantial benefit from surgery. *Patients with a recently symptomatic carotid artery stenosis have a high early risk for subsequent stroke, so that expedited evaluation and surgery are of utmost importance to maximize benefit of treatment.*

In a combined 5-year analysis of the NASCET and ECST patients with a symptomatic carotid stenosis (≥50%, NASCET method), the NNT to prevent one stroke was 9 for men and 36 for women, 5 for age ≥75 years and 18 for <65 years, and 5 if randomized within 2 weeks of the last TIA and 125 if randomized >12 weeks after the last TIA [21].

According to current guidelines, CEA should be considered in patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (>70%, NASCET method) carotid artery stenosis [6, 7]. In patients with recent symptomatic moderate (50–69%, NASCET) carotid stenosis, CEA should be considered in men, in patients older than 74 years of age, and in patients with hemispheric symptoms rather than transient monocular blindness (Fig. 16.1). Since the medical management has greatly improved in the past few years, current guidelines advise proceeding with CEA only if the perioperative morbidity and mortality risk is estimated to be <6% [6].

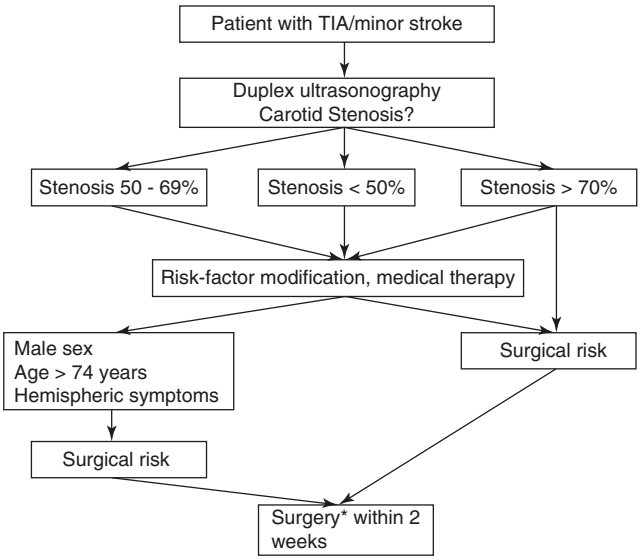

Fig. 16.1 Algorithm for CEA considerations

16.5 Carotid Endarterectomy in Patients with Asymptomatic Carotid Stenosis

Altogether, there have been five randomized trials comparing endarterectomy with medical treatment in patients with asymptomatic extracranial carotid artery stenosis.

The Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin (CASANOVA) trial included 410 patients with an asymptomatic internal carotid artery stenosis of 50–90%, based on cerebral angiography [22]. Patients with more than 90% stenosis were excluded from this trial. All patients were treated with 330 mg aspirin daily and 75 mg dipyridamole three times daily. After a minimum of 3 years of follow-up for each patient, statistical analysis found no significant difference in the number of neurological deficits and deaths between both groups.

The Veterans Affairs Asymptomatic Carotid Endarterectomy Trial compared the outcomes of 211 surgically versus 233 medically treated patients with an asymptomatic angiographically proven carotid stenosis of 50–99% [23]. While the combined outcome of stroke and death was not significantly different between both treatment groups, the study showed a reduction in the relative risk of ipsilateral neurological events with surgery when TIA and stroke were included as composite endpoints.

The Mayo Asymptomatic Carotid Endarterectomy (MACE) trial was terminated early due to a significantly higher number of TIAs and myocardial infarctions in the surgical group compared with the medical group, likely reflecting the avoidance of aspirin in the surgical group [24].

The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated the efficacy of endarterectomy in patients with a >60% diameter reduction (determined either by angiography or by Doppler ultrasound scanning) in asymptomatic carotid stenosis [25]. Patients were aged 40–79 years and had a life expectancy of at least 5 years. Approximately 30% of patients had other cerebrovascular symptoms. The event rate in surgically treated patients for the primary endpoint (ipsilateral stroke, perioperative stroke, or death) was 5.1% over 5 years. This included a 1.2% risk of angiography-related complications among the 424 patients undergoing postrandomization angiograms and an exceedingly low 1.1% surgical risk (2.3% aggregate perioperative stroke risk). The corresponding rate in medically treated patients was 11% (5.9% absolute risk reduction; NNT = 17; $p = 0.004$). The NNT to prevent one event was 83 at 1 year. The risk of major ipsilateral stroke or any perioperative stroke or death was not significantly different between both treatment groups (6.5% in the medical group versus 3.4% in the surgical group, $p = 0.12$). The benefits of CEA were greater for men than women (relative risk reduction in men 66% versus 17% in women, respectively), and perioperative complications were higher among women than men (3.6% versus 1.7%).

The Asymptomatic Carotid Surgery Trial (ACST) confirmed the marginal benefit of CEA in patients with asymptomatic severe stenoses [26]. In this study, 3120 asymptomatic patients with >60% carotid stenosis identified during ultrasonography were assigned to immediate CEA or deferral of surgery and were followed for a mean period of 3.4 years. The risk of stroke or death within 30 days of CEA was 3.1% in the CEA group and 0.8% in the deferral group, whereas 5-year risks of non-preoperative stroke were 3.1 and 11% ($p < 0.0001$). When the preoperative and non-perioperative stroke risk were combined, a significant 5.4% absolute risk reduction occurred, very similar to the ACAS results. The benefits were similar in males and females and were not substantially different with varying degrees of carotid stenosis. However, patients 75 years of age and older did not benefit. Despite the relatively low perioperative complication rate in ACST, the net benefit of CEA was delayed for about 2 years after surgery, so that CEA in asymptomatic patients should be considered a long-term investment.

In both the ACAS and the ACST, an extremely low perioperative stroke rate was achieved, without which there would be no benefit from surgical management of asymptomatic carotid artery stenoses. A combined analysis of ACAS and ACST suggests that CEA in asymptomatic patients with >60% carotid stenosis leads to a small but significant overall benefit if the surgery can be performed with low preoperative morbidity and mortality rates [26]. Especially in patients with an asymptomatic carotid stenosis, the benefit of CEA is highly dependent on a low risk of procedural neurological complications and is eliminated when

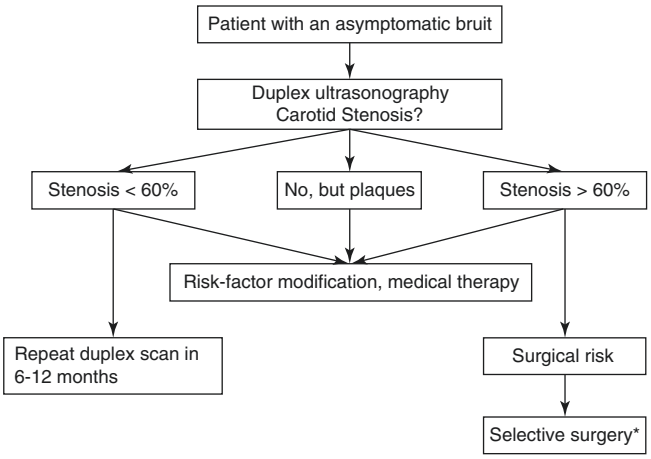

Fig. 16.2 Algorithm for the management of patients with an asymptomatic carotid stenosis

the combined 30-day stroke and death rates exceed approximately 3% [27, 28]. It should also be considered that the benefits of CEA in asymptomatic patients may generally be overestimated. In a subgroup analysis of NASCET, the causes of stroke on the asymptomatic side of 1800 patients were determined during follow-up. Nearly 50% of the strokes were lacunar or cardioembolic in origin and were thus not preventable by CEA [2].

According to current guidelines, all patients with an asymptomatic carotid stenosis should receive low-dose aspirin and a statin [5]. Prophylactic CEA can be recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity and mortality rates. Patient selection should be guided by an assessment of comorbid conditions and especially life expectancy and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences (Fig. 16.2).

16.6 Carotid Angioplasty and Stenting

While CEA is currently the accepted standard for the treatment of patients with high-grade symptomatic and for the treatment of selected patients with an asymptomatic internal carotid artery stenosis, carotid angioplasty and stenting (CAS) has emerged as a treatment alternative to CEA for the primary and secondary prevention of stroke related to carotid stenosis. Potential advantages over surgery include avoiding a surgical incision and its complications, including cranial nerve palsies and wound hematoma. Unlike CEA, which is limited to the cervical carotid artery, CAS can be performed in patients with distal or even intracranial lesions. It has also been argued that CAS does not require general anesthesia and may be associated with shorter hospitalization and thus lower costs. On the other hand, CAS has the major disadvantage of producing more emboli to the brain than CEA [29].

In the past few years, several large randomized single or multicenter trials comparing CAS with CEA and large stent registries have been published. In the large stent registries encompassing many thousands of patients, the 30-day stroke, myocardial infarction, and death rates have varied from approximately 2 to 8% in mixed populations of asymptomatic and symptomatic patients [30, 31]. The very first, prospective, randomized trial comparing CAS with CEA was performed at a single university teaching hospital in Leicester and was stopped early by the Steering Committee after inclusion of only 17 patients with a symptomatic carotid stenosis (≥70%) due to an excessive complication rate in the CAS arm trial (5 out of 7 CAS patients developed a stroke) [32].

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first completed, prospective multicenter trial comparing endovascular ($n = 251$, mainly angioplasty alone) versus surgical treatment ($n = 253$) of patients with symptomatic (96.4%) and asymptomatic carotid stenosis [33]. Periprocedural stroke (symptoms >7 days) and death rates were similar for endovascular treatment and surgery (10.0% versus 9.9%). After 3 years the rate of any stroke or death after 3 years was 14.3 in the endovascular group versus 14.2% in the surgical group indicating that the long-term results are also comparable between both procedures [33].

The Wallstent study was a multicenter randomized trial comparing CAS ($n = 107$) with CEA ($n = 112$) in patients with a symptomatic carotid stenosis of at least 60% [34]. The cumulative incidence of ipsilateral stroke and procedure related or vascular death within 1 year was 12.1% for the stent group versus 3.6% for the endarterectomy group ($p < 0.05$). The incidence of any stroke or death within 30 days was significantly higher after CAS than CEA (12.2% versus 4.5%, $p < 0.05$).

Two prospective, single-center, randomized trials performed in a community hospital with either patients with a symptomatic carotid stenosis (CEA $n = 51$ versus CAS $n = 53$) or with an asymptomatic carotid stenosis (85 patients randomly assigned to CAS or CEA) have been published [35, 36]. In the trial dealing with symptomatic patients, the composite outcome of any stroke or death within 30 days was 2% in patients treated with CEA and 0% in those treated with CAS, whereas no strokes or deaths occurred in both treatment arms of the asymptomatic trial.

The multicenter Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study compared CEA with protected CAS in patients with a moderate to severe carotid stenosis (exceeding 80% in asymptomatic patients or 50% in symptomatic patients who also had comorbid conditions that might increase the risk of

surgery (e.g., recent myocardial infarction, congestive heart failure, severe pulmonary disease, advanced age, and contralateral carotid occlusion) [37]. Excluded patients (n = 404) were entered into a registry and not randomized. The trial was terminated early after randomization of 334 patients because of an abrupt slowing in the pace of patient enrollment. The primary endpoint (composite of stroke, myocardial infarction, or death within 30 days or ipsilateral stroke between 31 days and 1 year) occurred in 20 CAS patients versus 32 CEA patients (12.2% versus 20.1%, p = 0.004 for non-inferiority and p = 0.053 for superiority). With respect to the subgroup of symptomatic patients, the primary endpoint was similar between CAS and CEA (16.8% versus 16.5%).

The Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study compared CAS (n = 261) with CEA (n = 259) in patients with a symptomatic (amaurosis fugax, hemispherical transient ischemic attack, or minor stroke in the previous 120 days) carotid stenosis of 60–99% according to NASCET criteria [38]. The trial was stopped prematurely after the inclusion of 527 patients due to increased complication rates in the CAS group. The 30-day incidence of any stroke or death was 3.9% in surgical patients versus 9.6% in patients treated with CAS ($p < 0.05$). Thirty-day mortality was similar in both groups. The 30-day incidence of disabling stroke or death was 1.5% after CEA compared with 3.4% after CAS. The main prespecified secondary outcome (any periprocedural stroke or death and any ipsilateral stroke occurring in up to 4 years of follow-up) was also significantly higher with CAS than with CEA (11.1% versus 6.2%, $p < 0.05$). This difference was largely driven by the higher periprocedural complications rates associated with CAS, demonstrating a low risk of ipsilateral stroke after the periprocedural period, which was similar in both treatment groups.

The Stent-Protected Angioplasty Versus Carotid Endarterectomy in Symptomatic Patients (SPACE) study compared CAS (n = 605) with CEA (n = 595) in symptomatic patients with a carotid stenosis of at least 70% (according to ECST criteria, corresponding to a stenosis of ≥50% according to NASCET) [39]. High-risk patients with uncontrolled hypertension or severe concomitant disease and a poor prognosis were excluded from this trial. The use of embolic protection devices was optional (eventually 26.6% of the patients were treated with embolic protection devices during CAS). The primary endpoint was ipsilateral stroke (ischemic stroke or intracerebral hemorrhage or both, with symptoms lasting longer than 24 h) or death of any cause between randomization and 30 days after treatment. Using a predefined non-inferiority margin of 2.5% or more, this trial aimed to show that CAS is not worse than CEA. The primary endpoint occurred in 41 CAS patients versus 37 CEA patients (6.84% versus 6.34%, p = 0.09 for non-inferiority). Therefore, SPACE failed to prove the non-inferiority of CAS compared with CEA, expressed as the rate of ipsilateral stroke or death within 30 days. The rate of any stroke or death within 30 days was 7.68% in CAS patients compared to 6.51% in CEA patients. In a subgroup analysis, older age in the CAS group was significantly associated with an increased risk for ipsilateral stroke [40]. At 2 years follow-up, there was no statistically significant difference between CAS and CEA with respect to the composite endpoint of any periprocedural stroke or death and ipsilateral ischemic stroke (9.4% versus 7.8% using a per protocol analysis). However, recurrent carotid stenoses were significantly more frequent in the CAS group.

The International Carotid Stenting Study (ICSS) compared CEA (n = 858) with CAS (n = 855) in patients with a recently symptomatic carotid artery stenosis ≥50% [41, 42]. *The primary outcome measure of this trial was the 3-year rate of fatal or disabling stroke in any territory. In the first 120 days after randomization, the CAS group had significantly greater incidences of stroke, death, or MI (8.5%* vs. *5.2%; hazard ratio: 169, 116–2.45), any stroke (65* vs. *35 events; HR 1.92, 1.27–2.89), and all-cause death (19* vs. *7 events; HR 2.76; 1.16–6.56) compared to the CEA group* [41]. *After a median follow-up period of 4.2 years, the number of fatal or disabling strokes (52* vs. *49), as well as the cumulative 5-year risk, did not differ significantly between the CAS and CEA groups (6.4%* vs. *6.5%; p = 0.77)* [42]. *In the CAS group the 5-year cumulative risk for any stroke was significantly higher than in the CEA group (15.2%* vs. *9.5%, p < 0.001), but these were mainly non-disabling strokes* [42]. A preplanned meta-analysis of individual patient data of EVA-3S, SPACE, and ICSS showed that the rates of any stroke or death within 120 days after randomization were significantly higher after CAS (8.9%) than after CEA (5.9%) ($p < 0.001$) [43].While there was no significant difference in the outcome between CEA and CAS in patients <70 years of age, the rates of stroke and death at 120 days among patients aged ≥70 years were significantly higher after CAS (12%) than after CEA (5.9%) ($p < 0.01$) in these trials.

The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST), performed in the United States and Canada, compared CAS with CEA in 2502 patients with a symptomatic carotid stenosis >50% (by angiography) or with an asymptomatic carotid stenosis >60% [44]. Nearly half of the patients had been treated for an asymptomatic stenosis in this trial. With respect to the primary composite endpoint (perioperative stroke, death, myocardial infarction, and ipsilateral stroke within 4 years of randomization), there were no significant differences between the CAS and CEA groups (7.2% vs. 6.8%, p = 0.5) proving the non-inferiority of CAS compared to CEA. However, when only the perioperative endpoints were compared, the incidences of stroke where higher in the CAS group than in the CEA group (4.1% vs. 2.3%, p = 0.01), whereas surgery was associated with higher rates of MI than stenting (2.3% vs. 1.1%, p = 0.03).

Prespecified analyses did not show a modification of the treatment effect by symptomatic status. In asymptomatic patients, the 4-year rate of the primary composite endpoint was 5.6% with CAS and 4.9% with CEA ($p = 0.056$). In symptomatic patients, the rates were 8.6% with CAS versus 8.4% with CEA ($p = 0.69$). In contrast, there was a significant interaction between age and treatment efficacy. Comparable with the results of the large European trials (EVA-3S, SPACE, and ICSS [43]), CEA showed a greater efficacy than CAS in patients older than approximately 70 years of age. In CREST there was no difference in the incidence of restenosis between CEA and CAS at 2 years as measured with a standardized ultrasound protocol [45].

In an updated review of the Cochrane Stroke Group comprising 16 trials and a total of 7572 patients, the risk of any stroke or death within 30 days in symptomatic patients was significantly higher after CAS than after CEA (OR 1.72; 95% CI 1.29–2.31), whereas the subsequent risk of ipsilateral stroke during long-term follow-up was comparable between both treatment groups [46].

Based on the results of the randomized trials summarized above, current guidelines have incorporated CAS as a *treatment alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is <6%* [6]. In addition it has been recommended to consider patient age in choosing between CAS and CEA in the sense that patients older than approximately 70 years of age should preferentially be treated with CEA [6].

With the exception of CREST and until the recent publication of the Asymptomatic Carotid Trial (ACT) in 2016, there was paucity of data comparing CEA with CAS in patients with an asymptomatic carotid stenosis. ACT randomized 1453 patients younger than 79 years of age and with a ≥70% carotid stenosis who were asymptomatic (i.e., no stroke, TIA, or amaurosis fugax within the last 180 days) [47]. The primary endpoint was a composite of stroke, death, or MI within 30 days postprocedure or ipsilateral stroke within 1 year postprocedure. CAS was non-inferior to CEA with similar event rates (3.8% vs. 3.4%). The rate of stroke and death within 30 days was 2.9% in the stenting group and 1.7% in the surgical group ($P = 0.33$). From 30 days to 5 years after treatment, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group ($P = 0.51$).

While ACT has provided evidence that CAS is non-inferior to CEA in patients with a high-grade asymptomatic carotid stenosis, there was a lack of a treatment group that received contemporary medical treatment only. With modern medical therapy, observational studies have indicated that the annual risk of a stroke is likely less than 1% per year in patients with an asymptomatic carotid stenosis [48], questioning the benefit of any revascularization procedure.

16.7 Summary

The approach to any patient with carotid artery disease should always involve recognition of this disease as a specific manifestation of a generalized arteriopathy.

In patients with a carotid artery disease, best medical management should be given scrupulous attention including control of blood pressure, reduction of atherogenic lipoproteins, glycemic control, smoking cessation, and control of heart disease if it develops. All patients should receive antithrombotic medication in the form of aspirin.

From an evidence-based point of view, CEA currently remains the treatment of choice for patients with a symptomatic carotid stenosis and selected patients with an asymptomatic carotid stenosis. Especially in patients younger than 70 years of age, CAS is an alternative to CEA. However, the overall benefits of both procedures strongly depend on the surgical or interventional risks. Therefore, appropriate patient selection remains a key issue for any physician to consider. Acceptable guidelines for operative/interventional risk are 3% for asymptomatic patients and 6% for those patients with a TIA or stroke due to a carotid stenosis. Current guideline recommendations and the positive data of the large surgical trials should not be used to justify performing CEA or CAS without a clear medical indication or in centers with little experience and poor outcome data. Against the background of a continuously improving "best medical treatment" and the lack of trial data comparing CAS or CEA with contemporary medical therapies in asymptomatic patients, the potential advantages of revascularization in these patients still needs to be determined in further randomized trials.

16.8 Case Study

A 54-year-old man presented with two transient episodes of right-sided hemiparesis mainly involving the upper extremity combined with some slurring of his speech as well as difficulty finding appropriate words. Both episodes had occurred in the last 2 days and had lasted less than 10 min each. There were no further episodes of transient or permanent focal neurological deficits. The patient was taking no medications. He had a history of smoking (45 pack years). Except for a bruit in the left side of the neck, the neurological examination was normal on admission.

A computed tomography scan showed no signs of ischemia, whereas a diffusion-weighted MRI scan revealed

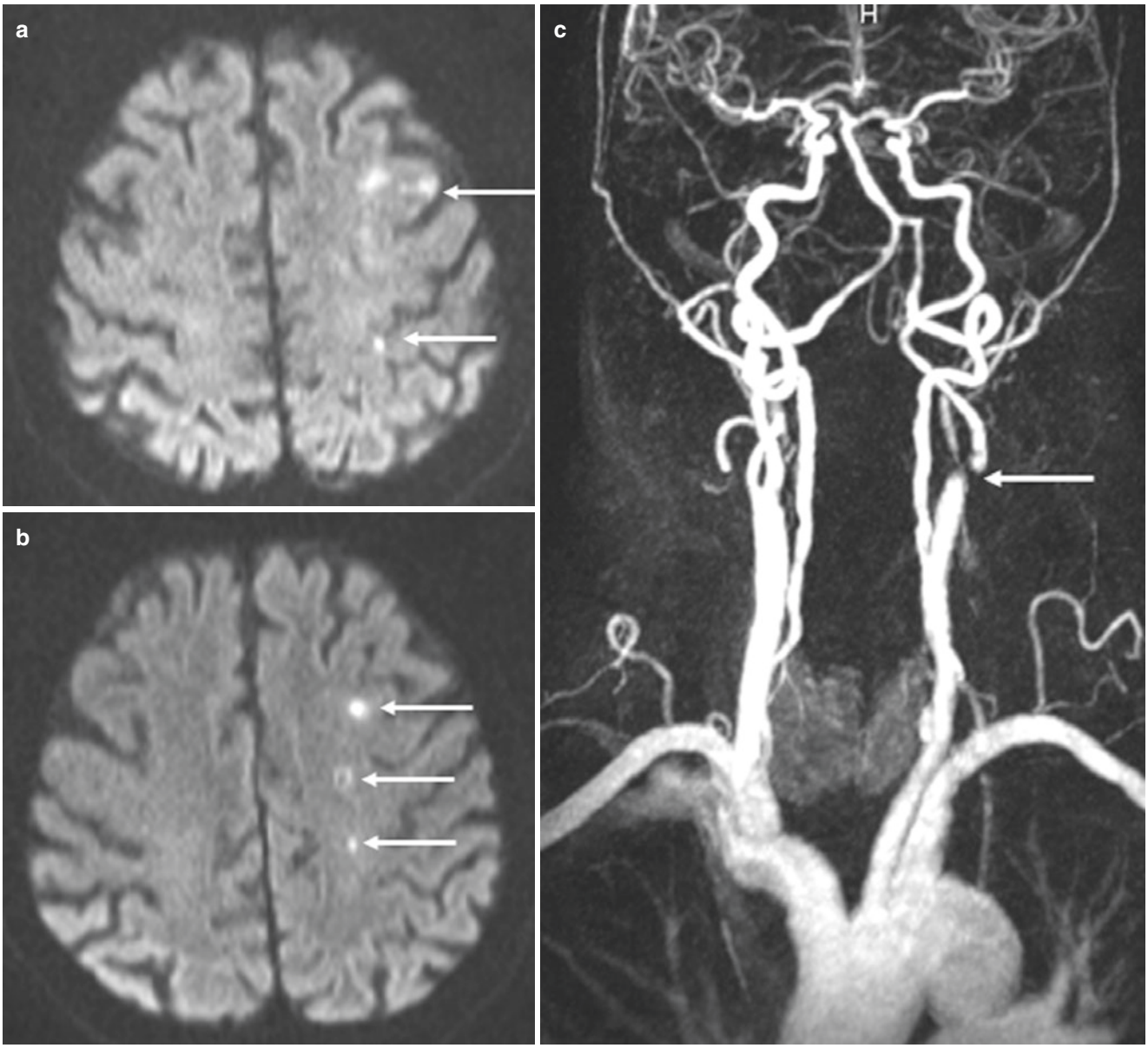

Fig. 16.3 Diffusion-weighted MR images (**a**–**c**) showing multiple embolic lesions throughout the left hemisphere (arrows), partially involving hemodynamic border zones. Contrast-enhanced magnetic resonance angiogram revealing a high-grade stenosis at the origin of the left internal carotid artery

multiple cortical signal abnormalities throughout the left hemisphere, as well as internal border zone regions consistent with multiple ischemic lesions of embolic and possibly also hemodynamic origin (Fig. 16.3). An extracranial Doppler and duplex sonography showed a severely ulcerated high-grade stenosis at the origin of the left internal carotid artery (ICA) (approximately 90%), which was confirmed by a contrast-enhanced magnetic resonance angiography. A post-stenotic flow pattern was seen in the left main segment of the middle cerebral artery with transcranial duplex sonography, all other detectable intracranial vessels revealed normal and symmetric flow signals. A cardiac source of embolism was ruled out by performing a 24-h electrocardiogram and transthoracic echocardiography. Diabetes mellitus and hyperlipidemia were ruled out.

Based on the clinical presentation and the results of the workup, the diagnosis of a symptomatic high-grade stenosis of the left ICA with a lumen reduction of about 80–90% was made. The current American Heart Association guidelines for the care of patients with a TIA or minor stroke due to a high-grade carotid stenosis recommend risk factor modification, the use of antithrombotic medications, and endarterectomy. The risks and potential benefits of surgical removal of the ICA stenosis were discussed extensively with the patient

and his family. Three days after admission, the patient underwent uneventful carotid endarterectomy and was given aspirin indefinitely. In addition, he was encouraged to change his lifestyle (smoking cessation, regular exercise, and avoidance of excessive alcohol consumption).

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