Chapter 10

Large Artery Occlusive Disease

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Additional information is available at the end of the chapter

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Abstract

Extracranial and intracranial large artery atherosclerosis is often identified as a potential etiologic cause for ischemic stroke and transient ischemic attack (TIA). Given the high prevalence of large artery atherosclerosis in the general population, optimally treating each patient to minimize future stroke risk is paramount. To optimally define treatment, as based upon the individual patient's history, examination, and anatomical imaging findings, clinicians can compartmentalize this disease entity into four distinct clinical scenarios: 1(a) asymptomatic and 1(b) symptomatic extracranial carotid stenosis, (2) intracranial atherosclerosis, and (3) atherosclerotic vertebrobasilar disease. In this chapter, we work to provide a framework for clinicians evaluating and treating such patients.

Keywords: ischemic stroke, large artery atherosclerosis, risk factors, prevention, treatment, extracranial, intracranial, atherosclerosis, carotid stenosis, carotid endarterectomy, carotid angioplasty, stenting

1. Introduction

Large artery atherosclerosis (LAA) of the head and neck is responsible for approximately 15% of all ischemic strokes. The identification and appropriate treatment of such atherosclerotic lesions is an essential skill for all physicians diagnosing and treating stroke patients. Broadly, LAA lesions can be classified into four distinct clinical scenarios as based upon the individual patient's anatomical and clinical findings, and these include the following: 1(a) asymptomatic and 1(b) symptomatic extracranial carotid stenosis, (2) intracranial atherosclerotic disease, and (3) atherosclerotic disease of the vertebrobasilar system. While each of these scenarios' anatomical lesion locations differs, it is important to note that they all share the same risk-factor profiles and somewhat overlapping treatment options. In short, continuous vascular

risk-factor optimization via sustained behavioral modifications and intensive medical therapy is critical to prevent stroke in the setting of LAA. In fact, specific to the settings of intracranial and vertebrobasilar atherosclerosis, as well as asymptomatic carotid atherosclerosis, risk-factor modification is the *primary* treatment option. In symptomatic patients with extracranial atherosclerosis treatment, options also include revascularization procedures including carotid endarterectomy (CEA) and carotid artery stenting (CAS). Appropriate patient selection and timing of such revascularization procedures must be considered. Options in symptomatic intracranial occlusive disease also include stenting vs. medical therapy, but again medical therapy is the primary treatment modality. Across each of these four clinical situations, the results of numerous randomized and nonrandomized clinical trials have led to periodically updated meta-analyses and consensus guidelines that provide evidence-based recommendations for practicing clinicians. While each of these four clinical situations could easily be (and are often) the subject of independent reviews, in this chapter we aim to provide a framework for clinicians evaluating and treating patients across these four clinical scenarios, emphasizing key considerations, clinical trial evidence, and the most recent professional and societal guidelines.

2. Common considerations across all cases of large artery atherosclerosis

Clinical presentation: Defining an ischemic stroke or transient ischemic attack (TIA) as causally related to LAA lesion can be difficult, as each individual patient's symptomatology and workup results can be quite varied. First, it is important to determine if the identified LAA lesion is proximal to a vascular territory that corresponds to the patients' stroke on imaging or symptoms in the setting of a TIA. For example, vague TIA symptoms such as 'transient dizziness or lightheadedness' could potentially infer a posterior circulation etiology but do not necessitate this fact. Such symptoms could also occur in the setting of cardiac arrhythmias or dehydration. More definitive symptoms such as transient diplopia or dysmetria increase the likelihood of a posterior circulation TIA. Again, vague symptoms such as 'transient dizziness or lightheadedness' should also not be utilized to classify a patient as 'symptomatic' for the purposes of managing anterior circulation carotid artery stenosis. To optimize anatomical localization (anterior vs. posterior circulation) in the setting of both stroke and TIA, clinicians must take a detailed history asking about symptoms (e.g., weakness, sensory changes, vision changes, balance problems, etc.) and whether these occurred in isolation or previously, both over the near and long term. Positive imaging demonstrating a clearly defined stroke can make the LAA etiologic diagnosis easier, assuming that the stroke is located in a vascular territory distal to a highly stenosed vessel and/or an irregularly calcified plaque. Stroke in a 'watershed' pattern distal to an LAA lesion might infer a hypoperfusional etiology, which may be related to acute changes in blood pressure (BP). However, similar imaging findings can also be seen in the setting of acute changes to an LAA plaque morphologically via plaque rupture or an embolus from a more proximal source reducing lumen diameter; such situations can impede flow distally resulting in reduced perfusion. Tandem lesions in the same vascular territory can also yield brain regions more at risk for hypoperfusion, as often there

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are sequential pressure drops across each LAA lesion. Such findings complicate management, as predicting whether an acute intervention would help reduce risk becomes more difficult. Further, guideline recommendations in such settings are limited. In summary, LAA can lead to two primary mechanisms of ischemic symptomatology: embolic phenomena and regional brain hypoperfusion. Clearly embolic phenomena should be considered as symptomatic, necessitating clinicians to consider the potential revascularization procedures as to be discussed later in this chapter. Stroke in the setting of LAA hypoperfusional states, while symptomatic, offers additional choices such as intensive medical therapy or permissive hypertension (HTN), thereby allowing the individual patient time to develop improved collateral circulatory pathways, potentially reducing the need for a revascularization procedure.

Workup: All stroke and suspected TIA patients warrant an expedited evaluation that can be simply defined as from '*heart to head*.' In other words, evaluations of the heart, the proximal aorta, the vasculature of the head and neck, as well as clinical and laboratory testing related to vascular risk factors, should be performed on an *inpatient* basis. While it is beyond the scope of this chapter to provide detailed testing recommendations, ideally a transthoracic echocardiogram (TTE) and vessel imaging of the head and neck by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) should be performed in all stroke and TIA patients. If LAA disease is identified, further testing to better define the severity of the stenosis should be considered; such testing might include carotid Doppler studies to determine flow velocities or a gadolinium (GAD)-enhanced magnetic resonance angiography (MRA) of the vasculature in question, among others. While a catheter-based cerebral angiogram can be considered, this invasive test has its own procedural risk and should be reserved for select patients, potentially including those with an 'intention to treat' via CAS. Of note, there is considerable clinical interest and ongoing research regarding the stability and embolic potential of LAA lesions, this in an effort to identify those patients at the greatest risk for stroke. Currently employed techniques include transcranial Doppler (TCD) microembolus detection, ulceration assessment using three-dimensional ultrasound, plaque echolucency measures, intraplaque hemorrhage on MRI, and plaque inflammation evaluations via hybrid-imaging techniques combining positron emission tomography (PET) and MRI [1]. Of these, TCD embolus detection is a relatively straightforward test that can be utilized to assist in individual patient risk stratification.

Vascular risk factors: Across all locations of LAA discussed in this chapter, continuous lifelong vascular risk-factor optimization via sustained behavioral (lifestyle) modifications and intensive medical therapy is critical for stroke prevention. This point cannot be emphasized enough. Over approximately the last 10 or so years, our understanding of the importance of medical management in the setting of atherosclerosis has markedly improved. Population-wide improved control of hypertension, dyslipidemia, and diabetes coupled with a reduction in tobacco use has resulted in a decline in stroke mortality from the third leading cause of death to the fifth cause of death in the USA [2]. Clinicians should take pride in these facts, as these improvements are based upon their efforts implementing professional societal position statements and guidelines. As such, maintaining a working knowledge of these evolving

guidelines and position statements is a critical tool for physicians and other health professionals working to reduce stroke risk. The reduction of cardiovascular disease (CVD) and stroke related to lifestyle management, treatment of blood cholesterol, and management of obesity was the focus of statements in 2013 by the American College of Cardiology (ACC) and the American Heart Association (AHA) [3–6]. They also released a statement regarding hypertension management in collaboration with the Centers for Disease Control (CDC) [7]. Other professional societies, including the Eighth Joint National Committee (JNC 8) and the American Society of Hypertension/International Society of Hypertension, released separate statements about minimizing cardiovascular risk and complications with optimization of blood pressure [8, 9]. The American Heart Association and the American Stroke Association (ASA) also released new Guidelines for the Primary Prevention of Stroke in 2014 [10] and Guidelines for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack [11]. These recent stroke-prevention guidelines offer individualized approach to lifestyle modification including physical activity, diet and nutrition, smoking cessation, obesity, and dyslipidemia. Taken in aggregate, these new guidelines offer up-to-date comprehensive evidence-based recommendations for the primary and secondary prevention of stroke, including those related to LAA. While it is beyond the scope of this chapter to cover all the current recommendations regarding vascular risk-factor control in detail, a few specifics as related to LAA are warranted.

3. Vascular risk-factor control via intensive medical therapy

Based upon the results of numerous recent clinical trials, and as incorporated into the aforementioned recent guidelines, 'intensive (or best) medical therapy' is emphasized for all LAA patients. While the precise definition of intensive medical therapy can be debated, **Table 1** (adapted from [12]) summarizes the key elements. Intensive medical therapy includes smoking cessation, diet, exercise, and control of blood pressure (including diagnosis of the physiological drivers of resistant hypertension by measuring plasma renin and aldosterone [13], dual antiplatelet therapy, and intensive lipid-lowering therapy, not just achieving a target level of fasting low-density lipoprotein (LDL) cholesterol). Overall, the goals of these therapies are to first stop, and then reverse plaque progression. Such regimens clearly are effective. One study demonstrated that by implementing a regimen similar to that as outlined in **Table 1**, they were able to reduce the risk of stroke and myocardial infarction by more than 80% among patients with asymptomatic carotid stenosis [14]. Similarly, the Stenting and Aggressive Medical Management for Prevention of Recurrent Stroke in Intracranial Stenosis (SAMPPRIS) trial [15] demonstrated that "aggressive" medical therapy resulted in better outcomes than with stenting among patients with intracranial stenosis. Several other examples exist.

Antiplatelet agents, including aspirin and clopidogrel, are routinely used for primary and secondary stroke prevention in the setting of LAA. In higher-risk individuals, whose 10-year risk of stroke is greater than 10% and whose risk of stroke outweighs the risks associated with aspirin therapy, the new Guidelines for the Primary Prevention of Stroke recommend the daily use of aspirin [10]. A cardiovascular risk calculator to assist in estimating 10-year risk can be found online at http://my.americanheart.org/cvriskcalculator. Of note, in lower-risk individu-

als, aspirin is not recommended for primary stroke prevention, or in individuals with diabetes that do not have other high-risk factors. For those using aspirin, the faithful daily use of low-dose aspirin is deemed sufficient. Since coated aspirin is less efficacious than uncoated aspirin in ~40% of individuals, uncoated aspirin is recommended [16]. Clopidogrel alone reduces stroke by only 1.7% greater than aspirin [17] and is thus only marginally better than aspirin, whereas combined aspirin/dipyridamole is no better than clopidogrel [18]. The SAMPPRIS study indicated that the combination of clopidogrel and aspirin is more efficacious for secondary stroke prevention than aspirin alone, with a reduction of stroke by 32% (hazard ratio (HR): 0.68; 95% confidence interval (CI): 0.57–0.81; $p < 0.001$) and no increase in major hemorrhage [19]. More recently, the CHANCE investigators demonstrated that the early benefit of clopidogrel-aspirin treatment in reducing the risk of subsequent stroke persisted after 1 year of follow-up [20]. Again, there was no difference in moderate or severe hemorrhage in the combined treatment group vs. the aspirin-alone group (0.3 vs. 0.4%, respectively; $p = 0.44$) [21]. Dual antiplatelet therapy with aspirin and clopidogrel was also used in the SAMPPRIS trial of intracranial arterial stenosis, which demonstrated that aggressive medical management was superior to percutaneous transluminal angioplasty and stenting [15]. Of note, the CHANCE study was performed in China, but the results are thought to be generalizable in Western populations; this hypothesis is currently being evaluated in the ongoing POINT trial [22].

Several recent studies utilizing transcranial Doppler evaluations to evaluate for microemboli found that dual antiplatelet therapy is more efficacious than aspirin alone in the reduction of microemboli for both intracranial [21] and extracranial arterial stenosis [23]. While dual antiplatelet therapy is commonly used for risk reduction in the setting of coronary disease, particularly in the setting of cardiac stenting, it is not widely used in carotid disease as related to the results of one study in which there was an excess of bleeding in the dual therapy group [24]. To reduce the risk of intracerebral hemorrhage (ICH) in the setting of dual therapy, effective blood pressure control is critical, as evidenced by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in which effective blood pressure control reduced ICH to 0.4% of strokes [25]. Gastrointestinal hemorrhages could theoretically be reduced by the identification and treatment of *Helicobacter pylori* infections prior to dual therapy, although this has yet to be definitively proven. In summary, dual antiplatelet therapy should at least be considered across most settings of LAA, including both symptomatic and asymptomatic carotid stenosis. The optimal duration of therapy remains a topic of study and debate, but as consistent with the SAMPPRIS study, 3 months of dual antiplatelet therapy is reasonable while working to optimize vascular risk factors.

Treatment of dyslipidemia has drastically shifted away from strict LDL goals in accord with the 2013 "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" [5]. The guidelines now promote calculating an estimated 10-year risk for atherosclerotic CVD than determining the intensity of statin therapy. Although the new guidelines shift focus away from specific lipid targets, values for total cholesterol, high-density lipoprotein (HDL), age, sex, race, systolic blood pressure (SBP), hypertension treatment, diabetes mellitus (DM), and cigarette smoking are incorporated into the cardiovas-

cular risk calculator (see previously listed link). Statins are the only lipid-modifying therapy with established benefit on ischemic stroke risk. This has been supported by meta-analysis of 78 trials with 266,973 patients demonstrating an odds ratio (OR) of 0.85 [95% CI: 0.78–0.92] for decreased risk of total stroke; however, diet, fibrates, and other treatments did not demonstrate benefit with OR of 0.92 [95% CI: 0.69–1.23], 0.98 [95% CI: 0.86–1.12], and 0.81 [95% CI: 0.61–1.08], respectively [26].

Measure	Intervention
Lifestyle modification	
•All	Show patients images of their plaque, compare the patient's plaque burden with that of healthy persons of the same age and sex, describe the risks associated with that degree of plaque burden and progression and the possibility of plaque regression
•Smoking cessation	Counseling, liberal nicotine replacement, varenicline or bupropion (depending on history of depression)
•Mediterranean diet	Counseling, provision of a booklet-summarizing advice, and providing recipes and links to Internet sites; repeated at follow-up visits as necessary
•Obesity	Counseling on caloric restriction, referral to dietician, bariatric surgery in refractory patients with severe obesity and diabetes or insulin resistance
•Exercise	Recommendations for moderate exercise at least 30 min a day, with advice tailored to the patient's disabilities if any
•Blood pressure	Advice on how to reduce salt intake, limit alcohol intake, avoid licorice, decongestants
Medical therapy	
•Blood pressure control	Physiologically individualized therapy for resistant hypertension based on renin/aldosterone profile 3; switch NSAIDs to sulindac4
•Lipid lowering	Statins dosed according to plaque progression to the highest dose tolerated (with use of CoQ10 to minimize myopathic symptoms), then addition of ezetimibe, and as needed for low HDL/high triglycerides, addition of fibrates and/or niacin
•Antiplatelet agents	Low-dose aspirin, with addition of clopidogrel in patients with severe stenosis or other indicators of high risk
•Anticoagulation	In patients with atrial fibrillation or other potential cardiac sources of emboli
•Insulin resistance	Pioglitazone, reinforcement of lifestyle issues
•Diabetes	Reinforcement of lifestyle changes, referral to diabetes clinic
Other considerations	
•Obstructive Sleep Apnea	Causes night-time high blood pressure. Referral for sleep study and faithful CPAP use.
•Poor dentition	Induces systemic inflammation that can destabilize atherosclerotic plaques. Dental evaluation.
•Gout	Induces systemic inflammation that can destabilize atherosclerotic plaques. Diagnose and treat.

Table 1. Key elements of intensive medical therapy (adapted from Spence [12]).

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While a detailed discussion of all lipid-modifying medications is beyond the scope of this review, recent data regarding niacin use are worth mentioning. Niacin has several favorable properties, including increases in HDL cholesterol (HDL-C), decreased plasma levels of lipoprotein(a) (Lp(a)), inhibition of hepatic production of very-low-density lipoprotein (VLDL), and consequently its metabolite LDL [27]. It raises high-density lipoprotein cholesterol (HDL-C) levels by as much as 30–35%, both by reducing lipid transfer of cholesterol from HDL to VLDL and by delaying HDL clearance [27, 28]. While some early trials of niacin suggested secondary prevention benefits, recent large randomized trials of niacin have raised serious concerns about its safety and efficacy in combination with statin therapy, and by extension concerns about niacin monotherapy. AIM-HIGH found no additional benefit with the addition of extended release niacin to patients treated with a statin with cardiovascular disease, decreased HDL-C levels, and increased triglyceride levels [29]. Notably, the placebo arm received 100–200 mg of niacin daily resulting in HDL-C level increase, which may have reduced the ability to detect a statistically significant benefit. Second, the HPS2-THRIVE trial randomly assigned 25,673 adults aged 50–80 with vascular disease to receive extended-release niacin 2 g daily plus laropiprant (a prostaglandin D2 signal blocker used to reduce flushing from niacin) or placebo; all patients received simvastatin 40 mg daily, and if LDL-C reduction was inadequate with simvastatin, ezetimibe of 10 mg daily was added [30]. Patients in this trial had a long run-in phase demonstrating that they could tolerate simvastatin and then the addition of niacin/laropiprant. After a median follow-up of 3.9 years, there was no reduction with niacin/laropiprant in the primary end point of first major vascular event (13.2 vs. 13.7%; risk ratio [RR]: 0.96, 95% CI: 0.90–1.03) and there was also no benefit for this end point in the subgroup of patients with low HDL-C and elevated triglycerides. Despite the run-in period, there was also an increase in serious adverse events in those receiving niacin/laropiprant including myopathy (RR: 3.54), gastrointestinal side effects, and worsened glucose control with both an increase in new cases of diabetes (RR: 1.32) and serious disturbance in diabetes control (11.5 vs. 7.5%, RR: 1.55; most of these led to hospitalization). Given these results, it advised not to administer niacin to most patients receiving statin therapy. Patients who are unable to take other lipid-lowering therapies may consider long-term niacin therapy if their LDL-C is significantly elevated and is lowered substantially by a trial of niacin treatment.

Hypertension (HTN) is a well-documented and highly prevalent modifiable risk factor for stroke. In general, the most effective stroke prevention measure across all populations is the treatment of hypertension. Despite this, the optimal blood pressure (BP) target has not been elucidated and remains a subject of debate. While decreased BP is associated with reduced stroke risk, but this may not be ubiquitous across all patient populations, specifically those with flow limiting LAA, DM, or advanced age. Interestingly, a lack of definitive benefit from BP clinical trials among older populations was used as the basis to raise the systolic BP treatment goal recommendation from 140 to 150 mmHg in the JNC-8 guidelines [31]. Regardless of this highly controversial change, HTN is often undertreated and an individualized, multifaceted approach including lifestyle changes and medical therapy is emphasized.

Diabetes mellitus (DM) is a well-established risk factor for stroke. Optimal glucose control is achieved by reinforcing lifestyle changes (e.g., dietary, regular exercise, and weight loss) and

through consistent use of medications. As related to LAA, the Atherosclerosis Risk in Communities (ARIC) Study demonstrated that the presence of DM was a predictor of carotid intima-media thickness (cIMT) progression ($p < 0.01$) [32]. In NOMAS, the duration of diabetes was independently associated with ischemic stroke risk when adjusting for risk factors [33]. The investigators found that the risk increased 3% each annually, and tripled among those with diabetes ≥10 years. Therefore, optimal glucose control is essential to reduce the risk of stroke.

Other emerging factors for LAA have been identified, including elevated homocysteine, fibrinogen, lipoprotein (a), and C-reactive protein levels [34]. Other risk factors implicated include obstructive sleep apnea [35], gout [36, 37], and poor dentition [38]. Future studies should work to verify the results of these preliminary reports while considering any implications for preventative strategies. From a genetic standpoint, a recently published study by the National Institute of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) Genetics Network (SiGN) details the largest and most comprehensive genome-wide association (GWA) study of stroke and its subtypes ever performed [39]. This study verified several previous genetic associations with ischemic stroke and identified a new risk locus on chromosome 1p13. Of the replicated loci, it is notable that this report confirms the association between the *HDAC9* locus and LAA ischemic stroke. Interestingly, this same locus (and the same specific variant) that was also reproducibly associated with coronary artery disease suggests a shared underlying causal gene and mechanism. The novel locus identified by SiGN was detected near *TSPAN2* and was also found to be associated with LAA. TSPAN2 is a scaffolding protein expressed in large arteries. This locus has not been reproducibly associated with coronary artery disease in GWA studies, suggesting that *TSPAN2* is potentially specific to ischemic stroke and might therefore provide insight into the pathophysiology of LAA ischemic stroke, rather than just generic atherosclerosis. Studies regarding the mechanistic links between both *HDAC9* and *TSPAN2* with LAA stroke are ongoing. Given the rapid evolution of genomic medicine, it is anticipated that in the near future we will be able to genetically determine disease susceptibility within individuals, families, and populations, thereby allowing preventive stroke therapies as based on individualized genotype.

In summary, the most recent guidelines emphasize intensive medical therapy with a focus on optimal vascular risk-factor control, but now in a more patient-centered approach than in the past. Given that the results from multiple clinical trials drive these recommendations, the applicability of these results at the level of the individual can be confusing, particularly if an individual does not fulfill the clinical trial inclusion criteria driving the recommendations. As such, physicians should consider each patient on an individual basis, working to optimize their risk-factor profile over the long term as based on ever-changing guidelines and information. With so much ongoing research, the optimization of stroke prevention for individuals requires physician diligence to identify risk factors as they emerge and physician maintenance of knowledge to optimally control risk factors in the safest, expeditious, and cost-effective manner possible. While the described multifaceted approach of intensive medical therapy reduces stroke risk in all patients with LAA, broadly classifying LAA patients into one of four clinical scenarios as based upon the individual patient's history, examination, and anatomical imaging findings is a useful way to clarify individual treatment options. These four scenarios

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are discussed now and include the following: 1(a) asymptomatic and 1(b) symptomatic extracranial carotid stenosis, (2) intracranial atherosclerosis, and (3) atherosclerotic vertebrobasilar disease.

4. Cervical extracranial carotid atherosclerosis

Carotid atherosclerosis accounts for ~10% of ischemic stroke cases. Although carotid artery stenosis is a risk factor for stroke, not every carotid stenosis carries the same risk for future stroke. Assuming a relevant stenosis is identified, key factors to consider include the degree of stenosis and the stability of the plaque, this in the setting of the individual patient. Clinicians should be geared toward answering two questions: (1) Which patients should opt for revascularization procedures (vs. intensive medical therapy alone) and (2) Which is the appropriate revascularization procedure (carotid endarterectomy [CEA] vs. carotid artery stenting [CAS])?

Assessment of carotid stenosis: When carotid stenosis produces a pressure drop across the lesion and/or a flow reduction distal to the lesion that is hemodynamically significant, this typically equates to 60% diameter reducing stenosis on catheter angiography via the North American method [10]. The formula is Stenosis = $(1 - N/D) \times 100\%$ (N = diameter at the point of maximum stenosis, D = diameter of the diameter of the arterial segment distal to the stenosis where the arterial walls first become parallel) [10]. This is contrasted with the European method, which estimates the stenosis at the internal carotid bulb. Catheter angiography, considered the 'gold standard' for assessing stenosis, historically carried a ≈1% risk of causing a stroke in patients with atherosclerotic disease; however, the complication rate has been dropping with the stroke complication rate now <0.2% [40]. Duplex ultrasound is the most commonly used method to screen the extracranial carotid artery for atherosclerotic stenosis and carries the lowest risks and costs. Of note, Duplex ultrasound may be insensitive to differentiate between high-grade stenosis from complete occlusion, with additional testing required in such situations. MRA, with or without contrast, is another noninvasive method for evaluating arterial anatomy and has the advantage of providing images of both the cervical and intracranial portions of the carotid artery and its proximal intracranial branches. Time of flight (TOF) MRA without contrast may overestimate the degree of stenosis, as such a GAD-enhanced MRA may be more useful, particularly when working to differentiate high-grade stenosis from total occlusion. Clinicians should be mindful that nephrogenic systemic fibrosis is a rare complication among patients with poor renal function in the setting of GAD use. CTA is yet another method that can be used to evaluate both the extracranial and intracranial carotid circulation. CTA disadvantages include radiation exposure and the need for intravenous injection of a contrast material, with a creatinine greater than 1.7 being a common limiting factor. Additionally, atherosclerotic calcifications with similar density to the contrast material may confound accurate measurements of the stenosis. On physical examination, a carotid bruit can reflect an underlying carotid stenosis; however, sensitivity is limited as evidenced by the NOMAS trial, in which auscultation had a sensitivity of 56% and a specificity of 98% [41].

4.1. Asymptomatic extracranial carotid stenosis

All patients with carotid stenosis have atherosclerosis that warrants intensive medical therapy that should be implemented as soon as possible. As mentioned, several methods exist to identify those patients with carotid stenosis who are at the greater risk for future events. Transcranial Doppler (TCD) embolus detection is a well-validated methodology exemplified by Spence et al. [42], where 10% of the 319 patients with asymptomatic carotid stenosis who have two or more microemboli in 1 h had a 1-year stroke risk of 15.6%. This was much higher than the complication rates of stenting and endarterectomy. Another telling result from that study was that a 1% one-year stroke risk was seen in 90% of patients without microemboli on TCD. This finding was replicated in a 2010 report of 468 patients [14], and further verified in the Asymptomatic Carotid Emboli Study (ACES) [43], among 467 patients. As mentioned previously, other methods exist to identify high-risk patients. As a general guideline, population screening for asymptomatic carotid artery stenosis is not recommended by the US Preventive Services Task Force, which found "no direct evidence that screening adults with duplex ultrasonography for asymptomatic stenosis reduces stroke [44]." In general, since ~2005, the risk of ipsilateral stroke with intensive medical therapy is much lower than the risk of CEA or CAS, this even in the carefully controlled clinical trials to be discussed. As such, in real-world practice the risk of an intervention would be even higher than in a clinical trial, meaning that CEA or CAS is *not indicated* for asymptomatic carotid stenosis, less the few patients at high risk of ipsilateral stroke that are potentially identifiable using TCD.

Endarterectomy for asymptomatic carotid stenosis: The Asymptomatic Carotid Atherosclerosis Study (ACAS) (see **Table 2**) was the first large-scale trial to compare CEA with best medical therapy vs. best medical therapy alone [45]. The study included 1662 patients from 34 centers and examined the composite of any stroke or death occurring in the perioperative period and ipsilateral cerebral infarction thereafter as its primary outcome. The trial was stopped early because of a clear benefit in favor of CEA. A contrast angiography showed diameter-reducing lesions of ≥60% based on the North American method for those patients randomized to surgery. The aggregate 5-year risk for ipsilateral stroke, any perioperative stroke, and death was 5.1% for the surgical patients compared to 11% for the medical patients (RR reduction, 53%; 95% CI, 22–72). The 30-day stroke morbidity and all-cause mortality for CEA, including a 1.2% rate of stroke with catheter angiography, were 2.3%. The rationale for including complications of angiography as part of the risk of surgery was that an angiogram otherwise would not have been performed if surgery was not considered.

The Asymptomatic Carotid Surgery Trial (ACST) (see **Table 2**) included 3120 patients with asymptomatic carotid stenoses of ≥60% as measured by duplex ultrasonography and compared patients undergoing immediate CEA vs. those with an indefinite deferral of the operation [46]. The trial used perioperative stroke, MI, or death, and non-perioperative stroke as the primary end points, which differed from those used in the aforementioned ACAS. Stroke risks were 4.1 vs. 10.0% at 5 years for immediate vs. deferred CEA, respectively, when excluding perioperative events and non-stroke mortality; this resulted in a gain of 5.9% (95% CI: 4.0–7.8). The 10-year stroke risks were 10.8 vs. 16.9% for immediate vs. deferred CEA, respectively; this

resulted in a gain of 6.1% (95% CI: 2.7–9.4). Subgroup analysis demonstrated that the benefits of CEA were confined to patients <75 years of age.

Some caveats regarding these trials should be considered. First, it should be noted that both ACAS and ACST were conducted at times when best medical management was far less than the intensive medical therapy as outlined earlier in this chapter. Second, the surgeons were subject to intense screening, as such their skills may not be generalizable to the community at large. For instance, the complication rate of 30-day stroke and death for CEA in ACAS drops to 1.54% when angiography complications are removed from the analysis [47]. More recently, complication rates from the CREST trial were reported with CEA in asymptomatic patients carrying a combined risk of stroke and death of 1.4% [48]. These complication rates appear lower than what is seen in standard practice. In general, current surgical best practice restricts surgery for asymptomatic carotid stenosis to patients with ≥70% carotid stenosis if the surgery can be performed with ≤3% risk of perioperative complications. Further research regarding this topic is ongoing via the National Institute of Neurological Disorders and Stroke-sponsored Carotid Revascularization of Primary Prevention of Stroke (CREST-2) trial (see **Table 2**) which compares centrally managed patients receiving intensive medical therapy with or without CEA [49, 50].

Endovascular treatment for asymptomatic carotid stenosis: Carotid angioplasty and stenting (CAS) was initially evaluated in patients thought to be at high risk for CEA. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial (see **Table 2**) evaluated CAS vs. CEA. The outcome measures included a composite of stroke, MI, or death within 30 days or death resulting from neurological cause or ipsilateral stroke between 31 and 365 days. The results showed that CAS was not inferior to CEA (within 3%; $p = 0.004$) [51]. Approximately, 70% of the subjects had an asymptomatic stenosis. The rates of stroke, MI, or death were 5.4% with CAS and 10.2% with CEA at 30 days ($p = 0.20$). The same composite outcome measures as above occurred in 9.9% of the CAS patients and 21.5% of the CEA patients after 1 year ($p = 0.02$). CAS had a significantly higher death rate (20.0%) than stroke rate (10.1%) after 3 years [52], raising questions about the long-term value of the procedure in this high-risk cohort. One glaring limitation to this study was the lack of a medically treated control group because the high complication rates in both Carotid Artery Stenosis (CAS) and CEA raise questions about the benefit of either intervention over medical therapy alone.

The CREST study (see **Table 2**) enrolled patients technically eligible for CEA or CAS with both symptomatic and asymptomatic carotid stenosis [53]. The inclusion criteria for asymptomatic patients were stenosis of ≥60% on angiography, ≥70% on ultrasonography, or ≥80% on CTA or MRA if the stenosis on ultrasonography was 50–69%. Composite of stroke, MI, or death resulting from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization was the primary end point. The estimated 4-year occurrence of the composite primary end point between CAS (7.2%) and CEA (6.8%) demonstrated no difference (HR, 1.11; 95% CI, 0.81–1.51; $p = 0.51$). Symptom status showed no significant heterogeneity. The CREST study did, however, show an interaction of age on the primary end point. Patients aged >70 years showed a significant benefit for CEA over CAS. Patients >64 years old who

Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
1. Cervical carotid atherosclerosis			
1a. Asymptomatic carotid stenosis			
ACAS: Endarterectomy for Asymptomatic Carotid Artery Stenosis [45] Enrollment Period: 12/1987–12/1993 Publication Year: 1995	**Arms**: Carotid endarterectomy (CEA) vs. aspirin and risk-factor modification (medical management). **Population**: Patients with at least 60% carotid stenosis and no stroke/TIA. **Outcome**: Primary end points were perioperative stroke and/or death or stroke in the study artery territory after the perioperative period.	-Primary end point was measured in the CEA arm 5.1 vs. 11.0% for medical therapy alone. -Patients who were good surgical candidates with at least 60% carotid stenosis showed decreased 5-year risk of stroke in the study carotid artery. They had 3% perioperative morbidity and mortality.	- Predominantly white males with ≥60% asymptomatic extracranial carotid stenosis benefited from CEA vs. medical management alone. - It is reasonable to perform CEA in asymptomatic patients who have more than 60% stenosis of the internal carotid artery and it was shown to be superior to medical management alone.
ACST: 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis: a multicenter randomized trial [46] Enrollment Period: 1993–2003 Publication Year: 2010	**Arms**: Immediate carotid endarterectomy (CEA) vs. deferral of any carotid procedure. **Population**: Patients with at least 60% carotid stenosis and no stroke/TIA within 6 months were eligible. **Outcome**: Primary end points were perioperative mortality/morbidity and non-perioperative stroke.	-Perioperative stroke risk or death within 30 days of CEA was 3.0%. -Non-perioperative stroke risk was 4.1 vs. 10.0% at 5 years and 10.8 vs. 16.9% at 10 years for immediate CEA vs. deferral of any carotid procedure, respectively. -The net risk was 6.9 vs. 10.9% at 5 years and 13.4 vs. 17.9% at 10 years for immediate CEA vs. deferral of any carotid procedure, respectively. -Patients with effective antihypertensive, antithrombotic, and lipid-lowering therapy and with little likelihood of death from other causes within 10 years had an absolute 10-year stroke reduction of 5%, with a number needed to treat of 20.	-The risk of CEA is greatest in the perioperative period, but in the long term it leads to decreased risk of non-perioperative stroke and shows an overall favorable net risk vs. deferral of CEA. - It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery.
SAPPHIRE: Protected Carotid-Artery Stenting vs. Endarterectomy in High-Risk Patients [51] Enrollment Period: 8/2000–7/2002 Publication Year: 2004	**Arms**: Carotid artery stenting (CAS) with embolic protection device vs. carotid endarterectomy (CEA). **Population**: Patients who presented with asymptomatic carotid stenosis with at least 80% carotid stenosis. **Outcome**: Non-inferiority study. Primary end point was cumulative major cardiovascular events at 1 year. This was composed of death, stroke, or MI within 30 days of intervention or stroke in the territory of the study vessel between days 31 and 1 year.	- For all comers (symptomatic and asymptomatic carotid stenosis), the primary end point was 12.2 (CAS) vs. 20.1% (CEA). Not statistically different for superiority but significant for non-inferiority. - For all comers, the 1-year revascularization rate was 0.6 (CAS) vs. 4.3% (CEA). - Asymptomatic carotid stenosis showed cumulative incidence of the primary end point at 1 year was 9.9 (CAS) vs. 21.5% (CEA), statistically significant. - Periprocedural stroke, MI, or death was 5.4 (CAS) vs. 10.2% (CEA), not statistically different, for asymptomatic carotid stenosis.	-CAS with embolic protection device was non-inferior to CEA in patients ≤80 years old with at least 80% asymptomatic extracranial carotid stenosis; however, subgroup analysis showed CAS to be superior to CEA at 1 year. - As an alternative to CEA, CAS with embolic protection device is indicated for patients at low or average surgical risk who have an anticipated rate of periprocedural stroke or mortality is less than 6% who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram); should undergo CEA within 6 months.

Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
CREST-2: The Carotid Revascularization Endarterectomy vs. Stenting Trial 2 [49] Enrollment Period: Ongoing Publication Year: Pending	**Arms**: Intensive medical management alone vs. Carotid endarterectomy (CEA) + medical management vs. Carotid stenting (CAS) + medical management. **Population**: Enrollment goal is 2480 patients. Men and women 35 years and older who have at least 70% carotid narrowing in at least one carotid artery. **Outcome**: Composite of stroke plus death within 44 days after randomization and ipsilateral stroke thereafter up to 4 years.	Ongoing.	Ongoing.
1b. Symptomatic carotid stenosis			
NASCET: North American Symptomatic Carotid Endarterectomy Trial [25] Enrollment Period: 1/1988–2/1991 (stopped early) Publication Year: 1991	**Arms**: Medical therapy vs. CEA. **Population**: Patients with symptomatic carotid stenosis greater than or equal to 30% were randomized to medical therapy vs. CEA. **Outcome**: Cumulative risk of any ipsilateral stroke at 2 years.	- After a mean follow-up of 2 years, patients with *severe* stenosis showed a dramatic risk reduction of any ipsilateral stroke from 26% in the medical arm to 9% in the CEA arm. The absolute risk reduction was 17% ($p < 0.001$), which translated to a number needed to treat six. - Among patients with *moderate* stenosis, CEA showed a lower, but significant, risk reduction from 22.2% in the medical arm to 15.7% in the CEA arm. The absolute risk reduction was 6.5% ($p = 0.045$), resulting in a number needed to treat 15.5 - Patients with *mild* stenosis of 30–49% did not achieve a significant risk reduction of any ipsilateral stroke following CEA.	- CEA + medical management showed lower risk of death and stroke compared to medical management alone in patients with symptomatic ICA stenosis 70–99%. - Based on NASCET and ECSS, the American Heart Association recommends that it is reasonable to perform CEA, when indicated, for patients with stroke or TIA within 2 weeks, rather than delaying surgery. - Surgery within 2 weeks may be contraindicated for patients who have very large infarctions at high risk of hemorrhagic conversion, or already have hemorrhagic conversion of their infarctions.
ECST: European Carotid Surgery Trial [54] Enrollment Period: 1981–1994 Publication Year: 1998	**Arms**: Carotid endarterectomy (CEA) vs. control (i.e., delay surgery if at all possible) with crossover from the control group. **Population**: Patients with some degree of ICA stenosis who had one or more carotid territory ischemic episodes within the previous 6 months. **Outcomes**: Primary end point was major stroke or death.	- Major stroke or death in 37.0 vs. 36.5% for CEA vs. control group, respectively. - For 2–3 years after randomization, severity of stenosis above 70–80% increased the risk of major ischemic stroke ipsilateral to the unoperated symptomatic carotid artery. - Kaplan-Meier estimates of the frequency of a major stroke or death at 3 years was 26.5 vs. 14.9 for control vs. CEA, respectively; thus, the absolute benefit of CEA was 11.6%.	- For patients at low or average surgical risk who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months.

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Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
VACS: Carotid Endarterectomy and Prevention of Cerebral Ischemia in Symptomatic Carotid Stenosis [55] Enrollment period: 7/1988–2/1991 Publication Year: 1991	**Arms**: Carotid endarterectomy (CEA) and best medical therapy vs. best medical therapy alone. **Population**: Men who presented within 120 days of TIA or small ischemic stroke who had angiography confirmed carotid stenosis great than 50% ipsilateral to the presenting symptoms. **Outcome**: Crescendo TIA in the study vessel distribution or infarction or death within 30 days of randomization.	- Primary end point shown in 7.7 vs. 19.4% for CEA vs. medical therapy alone. - Further analysis revealed that there was an absolute risk reduction of 17.7% for those undergoing CEA in ICA stenosis of at least 70%. This benefit was apparent within 2 months of surgery.	- For patients at low or average surgical risk who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months.
CREST: The Carotid Revascularization Endarterectomy vs. Stenting Trial [48] Enrollment Period: 12/2000–7/2008 Publication Year: 2010	**Arms**: Carotid endarterectomy (CEA) vs. Carotid artery stenting (CAS). **Population**: The study evaluated both symptomatic and asymptomatic carotid stenosis. Symptomatic carotid stenosis was defined as TIA, amaurosis fugax or minor non-disabling stroke in the distribution of the study artery within 180 days of randomization. For symptomatic patient the carotid artery stenosis had to be >50% by angiography, ≥70% by Ultrasound or ≥70% by CTA or MRA if US was 50–69%. Asymptomatic patients had to have stenosis of >60% by angiography, >70% by US or ≥80CTA or MRA if US 50–69%. Patients with previous disabling stroke or chronic atrial fibrillation were not included. **Outcome**: Primary end point was the occurrence of any stroke, MI, or death during the periprocedural period or ipsilateral stroke thereafter up to 4 years.	- There was no significant difference in primary end point between CAS and CEA (7.2 vs. 6.8%). - Periprocedural stroke occurred 4.1 vs. 2.3% for CAS vs. CEA. Periprocedural MI occurred 1.1 vs. 2.3% for CAS vs. CEA. Both were significant differences. There was no significant difference between CAS and CEA for ipsilateral stroke. - Risk for stroke and death was significantly higher for CAS in symptomatic patients but NOT asymptomatic.	- Older patients (>70) had better outcomes after CEA and younger patients (<70) had better outcomes after CAS. Patients had more strokes after CAS and more MIs after CEA. - For patients at low or average surgical risk who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months. - For patients at low or average surgical risk who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months. - As an alternative to CEA, CAS is indicated for patients at low or average surgical risk who have an anticipated rate of periprocedural stroke or mortality is less than 6% who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months.

Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
SAPPHIRE: Protected Carotid-Artery Stenting vs. Endarterectomy in High-Risk Patients [51] Enrollment Period: 8/2000–7/2002 Publication Year: 2004	**Arms**: Carotid artery stenting (CAS) with embolic protection device vs. carotid endarterectomy (CEA). **Population**: Patients who presented with symptomatic carotid stenosis with at least 50% carotid stenosis. **Outcome**: Non-inferiority study. Primary end point was cumulative major cardiovascular events at 1 year. This was composed of death, stroke, or MI within 30 days of intervention or stroke in the territory of the study vessel between days 31 and 1 year.	- For all comers (symptomatic and asymptomatic carotid stenosis) the primary end point was 12.2 (CAS) vs. 20.1% (CEA). Not statistically different for superiority but significant for non-inferiority. - For all comers, the 1-year revascularization rate was 0.6 (CAS) vs. 4.3% (CEA). - The cumulative incidence of primary end point in symptomatic carotid stenosis was 16.8 (CAS) vs. 16.5% (CEA), not statistically different. - Post-procedural incidence of primary end point in symptomatic carotid stenosis within 30 days was 2.1 (CAS) vs. 9.3% (CEA), not statistically different.	-CAS with embolic protection device was non-inferior to CEA in patients ≤80 years old with symptomatic carotid stenosis. - As an alternative to CEA, CAS with embolic protection device is indicated for patients at low or average surgical risk who have an anticipated rate of periprocedural stroke or mortality is less than 6% who have non-disabling stroke or TIA in the presence of ipsilateral ICA stenosis (≥70% by US/MRA/CTA or ≥50% by catheter angiogram) should undergo CEA within 6 months.
CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study: a randomized trial Endovascular vs. surgical treatment in patients with carotid stenosis in *CAVATAS: a randomized trial* [63] Enrollment Period: 3/1992–7/1997 Publication Year: 2001	**Arms**: Endovascular therapy (balloon angioplasty or stenting) vs. carotid endarterectomy (CEA). **Populations**: Patients with symptomatic carotid stenosis. **Outcome**: Primary outcome is any stroke or death within 30 days of treatment.	- Disabling stroke or death within 30 days occurred in 6.4 vs. 5.9% for endovascular procedure vs. CEA, respectively, not statistically significant. - Any stroke lasting more than 7 days or death occurred in 10.0 vs. 9.9% for endovascular therapy vs. CEA, respectively, not statistically significant. - Of the endovascular procedures, 26% underwent stenting and 74% underwent balloon angioplasty. - Cranial neuropath occurred in 8.7% of CEA patient but 0% in endovascular procedures, statistically significant. - The survival analysis up to 3 years after randomization showed no significant difference in rate or ipsilateral stroke.	- There was no significant difference in the major risks or effectiveness on ipsilateral stroke prevention in endovascular procedures compared to CEA.
2. Intracranial atherosclerosis			
WASID: Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis [69] Enrollment Period: 2/1999–7/2003 Publication Year: 2005	**Arms**: Warfarin (INR 2.0–3.0) vs. Aspirin 1300 mg daily. **Population**: Patients with TIA or ischemic stroke caused by angiography verified 50–99% stenosis in a major intracranial artery. **Outcome**: Ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke.	- Death 9.7 vs. 4.3% in warfarin vs. aspirin arms. - Major hemorrhage 8.3 vs. 3.2% in warfarin vs. aspirin arms. - MI or sudden death 7.3 vs. 2.9% in warfarin vs. aspirin arms. -Primary end point occurred in 22.1 vs. 21.8% (not statistically significant) for aspirin vs. warfarin.	- Warfarin demonstrated no benefit over aspirin in the primary outcome of this trial and was associated with significantly higher major adverse events. - Aspirin should be used for treatment of intracranial arterial stenosis.

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Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
SAMMPRIS: Stenting vs. Aggressive Medical Therapy for Intracranial Arterial Stenosis [15] Enrollment Period: 11/2008–4/2011 Publication Year: 2011	**Arms**: Aggressive medical management alone vs. aggressive medical management plus percutaneous transluminal angioplasty and stenting. **Population**: Patients with recent TIA or stroke due to major intracranial artery stenosis (70–99%). **Outcome**: Stroke or death within 30 days of enrollment or after revascularization or stroke in the territory of the qualifying artery.	- Primary end point occurred in 20.0 vs. 12.2% for stenting vs. medical management, respectively. - Thirty-day stroke rate or death was 14.7 vs. 5.8% in stenting vs. medical management group.	- Aggressive medical management is superior to percutaneous transluminal angioplasty and stenting in patients with symptomatic carotid stenosis. - The risk of early stroke after stenting was high. - The risk of stroke with aggressive medical therapy alone was low.
3. Extracranial vertebral artery disease			
CAVATAS: Carotid and Vertebral Artery Transluminal Angioplasty Study: a randomized trial *Treatment of Vertebral Artery Stenosis in CAVATAS* [79] Enrollment Period: 12/1987–12/1993 Publication Year: 1995	**Arms**: Endovascular therapy (balloon angioplasty or stenting) vs. best medical treatment alone. **Populations**: 2. Patients with symptomatic vertebral artery stenosis. **Outcome**: Recurrent vertebrobasilar stroke after intervention.	- Only eight patients were randomized to each arm. - Two patients had TIA during endovascular treatment, but there were no perioperative deaths or strokes within 30 days of the procedure. - No patient in either group experienced a vertebrobasilar territory stroke. Three patients in each arm died as a result of either MI or carotid territory stroke.	- The trial did not show benefit of endovascular therapy for vertebral artery stenosis, but the sample size of 16 was small. - Patients were more likely to have carotid territory stroke or MI during the trial's follow-up period than vertebrobasilar stroke. - Patients with vertebrobasilar disease require reduction of vascular risk factors.
OXVASC: Oxford Vascular Study. Incidence and prognosis of ≥50% symptomatic vertebral or basilar artery stenosis: prospective population-based study [80] Enrollment Period: 3/1992–7/1997 Publication Year: 2007	**Arms**: Posterior circulation vs. carotid territory events. **Populations**: Population based study of 91,000 individuals in and around Oxford, UK. **Outcome**: 90-day recurrent stroke or TIA.	-The frequency of ≥50% vertebrobasilar stenosis is greater than the prevalence of ≥50% carotid stenosis in carotid territory events. - In patients with posterior circulation events, vertebrobasilar stenosis ≥50% was associated with multiple TIAs at presentation and significantly higher 90-day event rates.	- The presence of ≥50 vertebrobasilar stenosis is associated with an increased risk of early recurrent TIA or strokes.

Topic/Trial Name/Years performed and published	Arms/Population/Primary outcome measure(s)	Results	Summary and implications on clinical practice
VAST: Vertebral Artery Stenting Trial – A phase 2 trial randomly allocating patients in a 1:1 ratio to stenting plus best medical treatment or best medical treatment [81] Enrollment Period: 1/2008–4/2013 Publication Year: 2015	**Arms**: Vertebral artery stenting vs. medical treatment alone. **Populations**: Patients with symptomatic extracranial or intracranial vertebral artery stenosis ≥50% and vertebrobasilar transient ischemic attack or ischemic stroke in previous 6 months (n = 115, target n = 180†). **Outcome**: Vascular death, myocardial infarction, or any stroke within 30 days.	- Of the 57 patients randomly assigned to vertebral artery stenting, 50 underwent stent placement of which eight were placed in the intracranial vertebral artery. - Three (5%) of 57 patients had the primary outcome in the stenting group. - One (2%) of 58 patients had the primary outcome in the medical treatment group. - Median follow-up of 3 years revealed seven patients (12%) in the stenting group and four patients (7%) in the medical management group had strokes in the symptomatic vertebral artery distribution.	- Symptomatic vertebral artery stenosis was associated with periprocedural complications in about 5% of patients while medical therapy showed low risk in terms of major vascular complications as well as recurrent stroke. - Medical therapy is the preferred treatment of symptomatic vertebral artery stenosis.
VIST: Vertebral Artery Ischaemia Stenting Trial [82] Enrollment Period: 10/2008–2/2015 Publication Year: PENDING	**Arms**: Vertebral artery stenting/angioplasty vs. best medical therapy alone. **Populations**: Patients age 20 or older who have >50% vertebral artery stenosis and non-disabling stroke or TIA within 3 months of randomization. Total recruitment was 182 patients. **Outcome**: Perioperative risk and long term efficacy (not otherwise specified).	Completed; results pending.	

Table 2. Large artery atherosclerosis studies.

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underwent CAS had a higher periprocedural stroke/death rate. Therefore, age is an important factor to consider when deciding between the two procedures. The results were further evaluated by comparing periprocedural rates stroke and MI for CAS vs. CEA. There was a significant difference (p = 0.01) for periprocedural stroke, which was higher in patients undergoing CAS (4.1%) vs. CEA (2.3%). The periprocedural rate of MI, however, was significantly lower (p = 0.03) for CAS (1.1%) compared with CEA (2.3%). However, CAS had significantly higher (p = 0.03) overall estimated 4-year rate of any periprocedural stroke or death or post-procedural ipsilateral stroke when compared to CEA with a HR, 1.50 (95% CI, 1.05–2.15). Both procedures had relatively low point estimates (2.5% in CAS vs. 1.4% for CEA, p = 0.15) for rates of any stroke or death in the periprocedural period among asymptomatic patients. There was a trend favoring CEA over CAS in symptomatic (HR, 1.37; 95% CI: 0.90–2.09; p = 0.14) and asymptomatic (HR, 1.86; 95% CI: 0.95–3.66; p = 0.07) patients, but the study was not powered for this evaluation. The advantage of revascularization over medical therapy by itself was not addressed by CREST, which did not randomize a group of asymptomatic subjects to medical therapy without revascularization. Unfortunately, as consistent with several of these trials, the lack of medically treated control groups complicates their interpretation. The ongoing National Institute of Neurological Disorders and Stroke-sponsored CREST-2 trial (**Table 2**) will be comparing centrally managed, intensive medical therapy with or without carotid stenting with embolic protection [49, 50].

In summary, the vast majority (~90%) of patients with asymptomatic carotid stenosis would be better served by intensive medical therapy than by endarterectomy or stenting. The ~10% who could possibly benefit from intervention can be identified by microemboli detection on transcranial Doppler or other techniques. Routine intervention for asymptomatic stenosis without such risk stratification is unwarranted. Most of the high-risk patients (~10%) would be better served by CEA than by CAS. The patients who are most appropriate for CAS within the high-risk group would be those at high risk of stroke and who have anatomical features that make CEA difficult. High-risk patients are those with severe cardiac, lung, and renal morbidities and changing anatomy. The specific details are listed in the AHA/ASA guidelines [11]. While anatomic high risk has generally been accepted, improving anesthetic and critical care management may alter medical high-risk criteria.

4.1.1. Asymptomatic carotid stenosis: recommendations (adapted from [10, 11])

1. Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted.

2. In patients who are to undergo CEA, aspirin is recommended peri- and postoperatively unless contraindicated.

3. CEA is a reasonable consideration in asymptomatic patients with >70% stenosis of the internal carotid artery (ICA) if the risk of perioperative stroke, MI, and death is <3%. The data that support this recommendation did not include the current standard for best medical management.

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4. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis of >50%.

5. The effectiveness of prophylactic CAS compared to medical therapy alone in asymptomatic carotid stenosis is not well established, but it can be considered in highly selected patients.

6. In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization vs. medical therapy alone is not well established.

7. Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended.

4.2. Symptomatic carotid stenosis

Over the last half century, numerous clinical trials have compared CEA plus medical therapy to medical therapy alone in the setting of symptomatic carotid stenosis. Again, most of these studies predate the intensive medical therapy now recommended. Surgical techniques have also evolved. Furthermore, carotid angioplasty and stenting (CAS) has emerged as an alternative treatment for stroke prevention in patients in this setting.

Endarterectomy for symptomatic carotid stenosis: Three major randomized trials (see **Table 2**) have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with a high-grade (>70% angiographic stenosis) atherosclerotic carotid stenosis, and include (1) the European Carotid Surgery trial (ECST) [54], (2) the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [25], and (3) the Veterans Affairs Cooperative Study Program (VACS) [55]. Symptomatic patients included those who had >70% ipsilateral carotid stenosis with a non-disabling stroke, TIA, or transient monocular blindness. A pooled analysis of ECST, NASCET, and VACS found a 30-day stroke and death rate of 7.1% in surgically treated patients [56]. In patients with a *70–99% (severe)* stenosis, NASCET found that for every six patients treated, one major stroke would be prevented at 2 years (i.e., a number needed to treat (NNT) of six). Additionally, these three seminal trials showed that patients with stenoses *<50% (mild)* did not have benefit in terms of stroke risk reduction with surgical intervention. The role of CEA was less clear among patients with symptomatic stenosis in the *50–69% (moderate)* range. NASCET evaluated 858 symptomatic patients with a stenosis of 50–69%, and in the surgically treated patients the 5-year rate of any ipsilateral stroke was 15.7% compared with 22.2% in those treated medically ($p = 0.045$) [25]. Thus, the number needed to treat was 15 (i.e., 15 patients would have to undergo CEA to prevent one ipsilateral stroke during the 5-year follow-up period). Therefore, CEA is justified only in appropriate cases when the risk-benefit ratio is favorable for the patient when evaluating surgical and anesthesia risks. In NASCET, the rate of perioperative stroke or death was 6.7%, with more recent population-based studies reporting a rate of 6% [57]. Given that medical management has improved since NASCET, current guidelines advise proceeding with CEA

in the setting of symptomatic stenosis only if the surgeon's rate for perioperative stroke or death is <6% [10, 11].

Patient-selection criteria influencing surgical risk often include gender and age. There is some concern, as based on the NASCET subgroup analyses, that CEA may not be beneficial in women with symptomatic carotid stenosis. Although women were not well represented and the effect of gender was not overwhelming [25], these data did demonstrate a significant difference (p = 0.008) suggesting that woman are more likely to have poorer outcomes as compared to men when undergoing CEA [58]. The surgical mortality, neurological morbidity, and recurrent carotid stenosis were 14% in women and 3.9% in men (p = 0.008) [58]. Notably, CREST was designed with pre-planned subgroup analysis intended to evaluate the effects of gender and age on the primary outcome end point. CREST included both symptomatic and asymptomatic patients, and found no significant interaction in the primary end point by gender. However, CREST did show superior results for CEA as compared with CAS in patients aged >70 years old [53, 59]. Of note, there are limited age-related data on the safety and efficacy of carotid revascularization because patients 80 years old or older were often excluded from trials, including NASCET. However, safe CEA in patients ≥80 years of age has been documented in case series [60]. Some studies comparing CAS and CEA have focused specifically on patients considered at high risk for surgical intervention and will be discussed in greater detail in the upcoming section on CAS. In summary, outcome differences in age and gender, along with medical comorbidities, should be considered when deciding whether or not to proceed with carotid revascularization. *The optimal timing of carotid revascularization via CEA* after a completed non-disabling stroke has been defined to be within 2 weeks if there are no contraindications. This time period is driven by data from the three major randomized controlled trials (RCTs) mentioned above, among others [25, 53, 59]. In these trials, patients were randomized to surgery within 2–14 days (median) and a third of the perioperative strokes occurred during this same time period. The first 2 weeks represented the greatest stroke risk in medically treated patients. After 2–3 years, the annual rate of stroke among the medically treated patients approached the rate observed for asymptomatic patients. Further analysis of patients with ≥70% carotid stenosis in ECST and NASCET showed a reduction in attributable risk from 30 to 18% when surgery occurred within 2 weeks vs. at 2–4 weeks, then to 11% for surgery at 4–12 weeks for any ipsilateral stroke or any stroke or death within 30 days of trial surgery [61]. These three trials included only patients with non-disabling stroke or TIA and reported low rates of ICH associated with surgery (0.2%). The risk for perioperative ICH may be increased with early surgery in patients with major cerebral infarction via a hyper- or reperfusion syndrome, this because of the sudden increase in perfusion of the vasculature distal to stenosis. Optimal control of blood pressure during and post-procedure is emphasized.

Endovascular treatment for symptomatic carotid stenosis: CAS has emerged as a therapeutic alternative to CEA for the treatment of extracranial carotid artery occlusive disease. The theoretical advantages of being a less invasive procedure resulting in decreased patient discomfort and a shorter recovery period were indeed born out in CREST, with an improved health-related quality of life in the perioperative period, although this difference was not sustained at 1 year [62]. As mentioned above in the asymptomatic carotid section, the historical

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use of CAS was typically reserved for patients considered at high risk for CEAs. Many of the reported trials have been industry sponsored and evaluated the efficacy of a single-stent/neuroprotection system in an effort to garner Food and Drug Administration (FDA) approval. The first large randomized trial was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS—see **Table 2**) [63]. CAVATAS randomized patients suitable for either stenting or surgery, and if patients were unsuitable for surgery, they were randomized to either stenting or medical management. The results showed that CAS and CEA had comparable results with 30-day rate of stroke or death of 6% in both groups. Preliminary analyses demonstrated no stroke rate differences 3 years after randomization. The major limitations were that a minority (55 of the 251 patients) in the endovascular group was treated with a stent and embolic protection devices were not used. Of note, embolic protection devices are now required in endovascular procedures reimbursed by the Centers for Medicare & Medicaid Services. Such devices aim to reduce periprocedural stroke rates. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE – see **Table 2**) had the primary objective of comparing the safety and efficacy of CAS with an embolic protection device to CEA; 334 symptomatic and asymptomatic high-risk patients were randomized [51]. The outcomes by which they studied safety included the cumulative incidence of stroke, myocardial infarction, or death. In the periprocedural period, the rate was 4.8% in patients assigned to receive a stent vs. 9.8% assigned to undergo endarterectomy in an intention-to-treat analysis ($p = 0.09$). Those patients who actually underwent stenting and CEA had primary outcomes incidence of 4.4 and 9.9%, respectively ($p = 0.06$). The 1-year rates of the aforementioned primary end point in addition to ipsilateral stroke or death of neurological causes within 31 days to 1 year were 20.1% for CEA and 12.2% for CAS ($p = 0.05$). The conclusion from the trial was that CAS was non-inferior to CEA in this specific high-risk patient cohort in spite of the fact that these differences primarily represented differences in periprocedural MI rates. Overall, the post-procedure morbidity and mortality for asymptomatic patients in both CAS and CEA were high enough to question the benefit of either procedure compared with medical management.

There have been several other RCTs comparing CEA and CAS for symptomatic patients. These trials include EVA-3S (Endarterectomy vs. Angioplasty in Patients with Symptomatic Severe Carotid Stenosis), SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy), and ICSS (International Carotid Stenting Study) trials [64]. In a meta-analysis of these studies, the rate of stroke and death at 120 days after randomization was significantly higher for CAS (8.9%) compared to CEA (5.8%) with HR 1.53 ($p = 0.0006$). Notably subgroup analyses revealed a higher rate of stroke or death at 120 days for CAS (12.0%) vs. CEA (5.9%) among patients aged ≥70 (HR, 2.04; $p = 0.0053$). No significant difference was observed in patients younger than 70 years of age [65].

CREST is an important recent RCT that compared the efficacy of CAS with that of CEA [48, 53]. In CREST, 2502 symptomatic and asymptomatic patients with carotid stenosis were recruited from the US and Canadian centers. Carotid stenosis was defined as >70% by ultrasonography or >50% by angiography. The primary outcome was a composite measure of 30-day rate of stroke, death, and MI and 4-year ipsilateral stroke. The primary outcome was

observed at a rate of 7.2% in CAS and 6.8% in CEA (p = 0.51). The 4-year rate of the primary end point in asymptomatic patients was 5.6% with CAS vs. 4.9% with CEA (HR 1.17; 95% CI: 0.69–1.98; p = 0.56). By comparison, the rates were 8.6% with CAS vs. 8.4% with CEA in symptomatic patients (HR 1.08; 95% CI: 0.74–1.59; p = 0.69). Analysis of symptomatic and asymptomatic patients together showed an interaction between age and treatment efficacy (p = 0.02). The HR for the primary outcome increased (CAS compared to CEA) when stratifying by age; HR was 0.6 (95% CI, 0.31–1.18) for patients <65 years of age, 1.08 (95% CI, 0.65–1.78) for patients 65–74 years old, and 1.63 (95% CI, 0.99–2.69) for patients aged ≥75 years. The risk of MI did not increase with age for either CEA or CAS. The effect of age was primarily driven by stroke risk, with greater stroke risk by age, with this effect stronger in the CAS group as compared to the CEA group. The HR became 1.0 at ≈70 years old for the primary outcomes and 64 years old for stroke. Gender was examined for periprocedural events, there was a trend for fewer events in women undergoing CEA compared to CAS; no periprocedural differences were seen in men. Periprocedural complication rates were lower in CREST as compared to prior trials. In the first 30 days, the rate of any stroke, MI, or death was 5.2% with CAS vs. 4.5% with CEA (HR 1.18; 95% CI: 0.82–1.68). Analyses regarding the type of periprocedural complications identified important differences. First, patients who had CAS had lower rates of MI than patients who had CEA (1.1% vs. 2.3%; HR: 0.50; 95% CI: 0.26–0.94) but higher rates of stroke (4.1% vs. 2.3%; HR: 1.79; 95% CI: 1.14–2.82). Second, complication rates also differed according to the surgical indication; asymptomatic patients had a rate of 3.5% for CAS vs. 3.6% with CEA, and symptomatic patients had a rate of 6.7% with CAS and 5.4% with CEA [48, 53].

Other considerations: strong evidence regarding follow-up imaging and re-stenosis after CEA or CAS is lacking. The Asymptomatic Carotid Atherosclerosis Study (ACAS) trial demonstrated that risk for re-stenosis after CEA was highest in the first 18 months after surgery (7.6%). The incidence decreased to 1.9% in the next 42 months. These data are comparable to the CEA arm of the CREST trial 18-month estimates which showed 6.3% risk of re-stenosis (>70% stenosis) after 24 months of observation. Other smaller studies have variable re-stenosis rates after CEA, but there are many limitations to these studies including the imaging technique utilized, length of follow-up, stenosis criterion, patient loss rates, and case mix. According to a recent narrative review, the rate of hemodynamically significant re-stenosis after CEA is probably 5–7% during variable periods of follow-up [53]. In older trials, the rates of re-stenosis were reportedly higher after CAS than after CEA. In the SPACE trial [64], the rate of re-stenosis (≥70% luminal occlusion) was 10.7% for CAS compared with 4.6% for CEA after 2 years. In CAVATAS, the rates after 5 years were 30.7% for CAS as compared with 10.5% for CEA. In a relatively recent review of 2191 CREST patients with follow-up at 2 years, highly standardized ultrasonography data were used to examine the incidence of re-stenosis and found no differences [66], although independent predictors of re-stenosis including DM, hypertension, and female sex were identified. Smoking was also an independent predictor for re-stenosis, but only with CEA, not CAS. In summary, the most current data suggest that rates of re-stenosis are similar between CEA and CAS. Moreover, there is no clear association between re-stenosis and increased risk for stroke. Therefore, routine surveillance for re-stenosis in asymptomatic patients is not well established.

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Extracranial-intracranial bypass. The International Cooperative Study of Extracranial/Intracranial Arterial Bypass (EC/IC Bypass Study) was the first major trial of EC/IC bypass surgery. The trial randomized 1377 patients within 3 months of a TIA or minor ischemic stroke to either surgery or best medical care [67]. Patients who were eligible for inclusion in the study had narrowing or occlusion of the ipsilateral middle cerebral artery (MCA), stenosis of the (surgically inaccessible) ipsilateral distal internal carotid artery (ICA) or the occlusion of the ipsilateral mid-cervical ICA. The primary outcome was fatal or nonfatal stroke. After nearly 5 years, the primary outcome was more common in patients who underwent surgery. A later trial [68] selected a high-risk group to examine with the goal to evaluate the effectiveness of EC/IC bypass for the prevention of ipsilateral stroke. The trial enrolled 195 patients who had evidence on positron emission tomography (PET) scanning of hemodynamic cerebral ischemia distal to a symptomatic ipsilateral carotid occlusion [68]. TIA or ischemic stroke within 4 months of randomization, such as the previous study, was required for eligibility. The trial was terminated early for futility given a 30-day rate of ipsilateral stroke of 14.4% in the surgical group and 2.0% in the non-surgical group. The same outcome at 2 years was similar in both groups, 21.0% in the surgical group and 22.7% in the nonsurgical group ($p = 0.78$).

4.2.1. Symptomatic extracranial carotid disease: recommendations (adapted from [10, 11])

1. CEA is recommended for patients with a TIA or ischemic stroke within the past 6 months who have severe ipsilateral (70–99%) carotid artery stenosis when the perioperative morbidity and mortality risk is estimated to be <6%.

2. CEA is recommended for patients with patient-specific factors (i.e., age, sex, medical comorbidities) when they have had a recent TIA or ischemic stroke as well as moderate ipsilateral (50–69%) carotid stenosis and the perioperative morbidity and mortality risk is estimated to be <6%.

3. When the *degree of stenosis is <50%*, CEA and CAS are not recommended.

4. When revascularization is indicated for patients with TIA or minor, non-disabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery if there are no contraindications to early revascularization.

5. CAS can be considered as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the anticipated rate of periprocedural stroke or death is <6%.

6. Age should be considered when deciding which procedure is appropriate in symptomatic carotid stenosis. CEA was associated with improved outcomes in patients older than 70 years especially when anatomy is unfavorable for CAS. The periprocedural risk due to stroke, MI, or death and long-term risk for ipsilateral stroke are equivalent for CAS and CEA in younger patients.

7. In patients at high of complications of surgery due to anatomical or medical factors, CAS is a reasonable alternative compared to CEA for patients with symptomatic severe stenosis (>70%).

8. The accepted periprocedural stroke and mortality rates for symptomatic carotid stenosis are <6% for operators performing CAS and/or CEA.

9. Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended.

10. For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, EC/IC bypass surgery is not recommended.

11. EC/IC bypass is considered investigational in patients on optimal medical therapy with recurrent/progressive ischemic symptoms ipsilateral to a stenosis/occlusion of surgically inaccessible portions of the carotid artery.

12. Optimal medical therapy including antiplatelet therapy, statin therapy, and risk-factor modification is recommended for all patients with carotid artery stenosis and a TIA or stroke.

5. Intracranial atherosclerosis

Intracranial atherosclerosis is a common cause of stroke carrying a high risk for recurrence. To date, there have only been a few large, multicenter randomized trials evaluating stroke-preventive therapies for this disease, the two primary trials include WASID [69] and SAMPP-RIS [15] (see **Table 2**).

The WASID study was a double-blind trial that included 569 patients. Patients included in the study were required to have stroke or TIA attributable to 50–99% intracranial stenosis of the MCA, intracranial ICA, intracranial vertebral artery, or basilar artery. The patients were randomized to receive either aspirin 1300 mg or warfarin with a target international normalized ratio (INR) between 2 and 3. WASID was stopped early because of higher rates of death and major hemorrhage in the warfarin arm. The primary end point, the composite rate of ischemic stroke, brain hemorrhage, and non-stroke vascular death occurred in 22% of patients in both treatment arms over a mean follow-up of 1.8 years. The 1- and 2-year rates of stroke in the territory of the stenotic artery occurred in the aspirin arm 12 and 15% at 1- and 2-years, respectively. The 1- and 2-year rates of stroke in the warfarin arm were 11 and 13%, respectively. Both arms demonstrated higher rates of stroke in the territory of the stenotic artery with higher degrees of intracranial stenosis. For patients with ≥70% stenosis, the stroke rate at 1 year was 18% and the rate was 7–8% in patients with 50–69% stenosis [70]. This was supported by a multivariate analysis, which demonstrated that the risk of stroke in the territory of the stenotic artery was highest for severe stenosis (≥70%) and for patients enrolled early (≤17 days, which was the median time to enrollment in the trial) after their qualifying event. Analyses also showed that women appeared to be at increased risk. No subgroup in the post hoc analyses benefited from warfarin. Controlling BP and LDL-C may reduce the risk of subsequent stroke based on WASID results. Contrary to the argument that BP lowering may impair cerebral blood flow and thus increase stroke risk in patients with large artery stenosis, post hoc analysis

showed that patients with mean SBP of ≥140 mmHg had a significantly increased risk of recurrent stroke compared with patients with mean SBP of <140 mmHg (HR 1.63; $p = 0.01$) [71]. Additionally, the patients with high LDL-C levels (mean ≥100 mg/dL) were 1.72 times more likely ($p = 0.03$) to have stroke compared to lower LDL-C levels (mean <100 mg/dL). A low rate of vascular events was observed in the small subset of patients with LDL-C of <70 mg/dL [72].

The SAMMPRIS trial compared endovascular therapy with medical therapy for the prevention of recurrent stroke in patients with symptomatic intracranial arterial stenosis [15]. In SAMMPRIS, patients with TIA or stroke within the past 30 days related to 70–99% stenosis of a major intracranial artery were randomized to aggressive medical management alone or aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS, self-expanding Wingspan stent). Intensive medical therapy was aspirin of 325 mg/d, clopidogrel of 75 mg/d for 90 days after enrollment, intensive risk-factor management that primarily targeted SBP of <140 mmHg (<130 mmHg in patients with DM) and LDL-C of <70 mg/dL, and a lifestyle modification program. Enrollment was stopped early after 451 patients because the primary end point of stroke and death was significantly higher in the PTAS arm at 30 days ($p = 0.002$), 14.7% in PTAS arm and 5.8% in medical arm. The rate of the primary end point at 1 year was also significantly higher in the PTAS arm (20.0%) vs. 12.2% for the medical arm ($p = 0.009$). These 1-year event rate differences were driven by the increased 30-day events in the PTAS arm. Periprocedural ischemic strokes were associated with older age, diabetes mellitus, basilar stenosis, and non-smoking. Of the strokes that occurred within 30 days, 10 of 33 (30.3%) in the PTAS arm and none of 12 (0%) in the medical arm were symptomatic brain hemorrhages ($p = 0.04$). Estimated 1-year rates of major hemorrhage (any brain hemorrhage or major non-stroke-related hemorrhage) were 9.0% in the stenting arm and 1.8% in the medical arm ($p < 0.001$). Of note in SAMMPRIS, the event rates in the PTAS arm (14.7%) were significantly higher than anticipated from the Wingspan stent registry (4.5%) [73]. The results of the medical arm demonstrated better than expected event rates as compared with WASID at 1 month (5.8% observed rate in SAMMPRIS vs. 10.7% expected based on WASID) and at 1 year (12.2% observed vs. 25% expected). These improved outcomes were deemed related to the intensive medical therapy utilized in the trial. Importantly, 284 of the 451 patients (63%) enrolled in SAMMPRIS had their qualifying event while undergoing antithrombotic therapy. In this subgroup of the SAMMPRIS cohort, the rates of the primary end point were 16.0% in the stenting arm and 4.3% in the medical arm at 30 days. At 1 year, the rates were 20.9 and 12.9% for the stenting and medical arms, respectively ($p = 0.028$) [74]. These results indicate that stenting (with the Wingspan system) is *not* a safe or effective rescue treatment for patients who experience a TIA or stroke while already being treated with antithrombotic therapy. Results from extended follow-up of the SAMMPRIS cohort were published in 2014 and demonstrated persistence of the early benefit of medical management over stenting with the Wingspan device [75]. In comparison, patients in the WASID trial were treated with aspirin of 1300 mg/d. In the SAMMPRIS trial, the medical arm used aspirin of 325 mg/d (in combination with clopidogrel of 75 mg/d) and achieved favorable rates of stroke outcome compared with the intervention arm. Lower doses of aspirin were effective in other large trials of secondary prevention, most of which enrolled patients with more heterogeneous subtypes of stroke. In aggregate, these data suggest that doses lower than 1300 mg/d are probably effective in patients

with intracranial stenosis and that dual antiplatelet therapy while optimizing vascular risk-factor control is reasonable. Of note, the SAMMPRIS results are a major contributor to the current recommendations regarding the intensive medical therapy now recommended in many societal and professional stroke-prevention guidelines [76].

A subsequent detailed analysis of the 30-day events in the SAMMPRIS PTAS arm revealed that a large number of the ischemic strokes occurred from occlusion of perforators (basilar perforators to the pons or lenticulostriate perforators from the middle cerebral artery) with the PTAS occluding the perforator 'takeoffs' (i.e., ostium). Other periprocedural risks demonstrated by SAMMPRIS included those associated with wire-vessel perforation causing subarachnoid hemorrhage (SAH) and ICH as associated with dual antiplatelet therapy in the setting of increased perfusion of an ischemic vascular bed. Balloon angioplasty alone without stenting has been proposed as a method to reduce perforator strokes; however, no randomized trials have compared angioplasty against intensive medical management. Re-stenosis rates after angioplasty alone or PTAS in this setting are uncertain.

One other notable study in the setting of intracranial stenosis is the previously described International Cooperative Study of Extracranial/Intracranial Arterial Bypass (EC/IC Bypass Study) [67]. This study included patients with MCA stenosis and ICA stenosis above the second cervical vertebra in addition to the symptomatic patients with extracranial carotid occlusion. The patient population included 109 patients with ≥70% MCA stenosis and 149 patients with ≥70% ICA stenosis. These groups were randomized to bypass surgery or medical treatment with aspirin of 1300 mg/d. The mean follow-up was 55.8 months. The rates of stroke during follow-up in patients with ≥70% MCA stenosis were significantly lower in the medical arm (23.7%) compared to the bypass arm (44%). There was no statistically significant difference in patients with ≥70% ICA stenosis above C2 between the medical arm (36.1%) and bypass arm (37.7%). The results of this study have led to EC/IC bypass being largely abandoned as a treatment for intracranial stenosis.

5.1. Intracranial atherosclerosis: recommendations (adapted from [10, 11])

1. For patients with a stroke or TIA caused by 50–99% stenosis of a major intracranial artery, aspirin of 325 mg/d is recommended in preference to warfarin.
2. For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70–99%) of a major intracranial artery, the addition of clopidogrel of 75 mg/d to aspirin for 90 days might be reasonable.
3. There are insufficient data for the usefulness of clopidogrel alone, aspirin + dipyridamole or cilostazol alone in patients with stroke or TIA attributable to 50–99% stenosis of a major intracranial artery.
4. For patients with a stroke or TIA attributable to 50–99% stenosis of a major intracranial artery, the maintenance of SBP below 140 mmHg and high-intensity statin therapy are recommended.

5. Angioplasty or stenting is not recommended in patients with stroke or TIA attributable to moderate stenosis (50–69%). Medical management is the recommended treatment.

6. Irrespective of whether a patient is on antithrombotic therapy at the time of the stroke or TIA, the Wingspan stent system is not recommended as the initial treatment for patients with severe stenosis (70–99%).

7. For patients with stroke or TIA attributable to severe stenosis (70–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational.

8. In patients with recurrent TIA or stroke after maximization of medical management (aspirin or clopidogrel therapy, SBP of <140 mmHg and high-intensity statin therapy) in patients with severe stenosis (70–99%) of a major intracranial artery, the usefulness of angioplasty alone or the placement of a Wingspan stent or other stent is unknown and is considered investigational.

9. In patients with actively progressive symptoms despite starting aspirin and clopidogrel, the usefulness of angioplasty alone or the placement of a Wingspan stent or other stents is not known and considered investigational in patients with severe stenosis (70–99%) of a major intracranial artery.

10. For patients with stroke or TIA attributable to 50–99% stenosis of a major intracranial artery, EC/IC bypass surgery is not recommended.

6. Extracranial vertebral artery disease

Extracranial vertebral artery stenosis (ECVAS) is a well-recognized cause of posterior circulation stroke. Proximal vertebral (V1 segment) lesions may account for ~9% of all posterior circulation strokes [77], while vertebral artery ostial lesions may account for another third [78]. As consistent with the anterior circulation, there are two primary stroke mechanisms including (1) plaque rupture with subsequent artery to artery thromboembolism and (2) hemodynamic insufficiency. Treatment options for symptomatic ECVAS include intensive medical therapy, endovascular stenting, and in rare cases open surgical revascularization. Unfortunately, scant RCTs results exist specific to this setting. There was a small subset of 16 CAVATAS trial (see **Table 2**) participants with symptoms in the vascular territory supplied by a stenosed vertebral artery that were randomized to receive either endovascular therapy (angioplasty or stenting) or medical management alone [79]. Participants had a mean follow-up of 4.7 years. No patient in either group experienced a vertebrobasilar stroke. Among the eight patients in the endovascular group, six patients underwent percutaneous transluminal angioplasty alone while the other two had stenting, two periprocedural TIAs in the endovascular group. The investigators concluded that medical treatment should focus on global vascular risk reduction after three patients in each arm of the study died of MI or carotid territory stroke during follow-up. The Oxford Vascular Study (OXVASC) (see **Table 2**) is a population-based study of incidence and prognosis of ≥50% symptomatic vertebral or basilar artery stenosis [80]. Medical therapy

was determined by the patient's general practitioners. Of the 141 patients with posterior circulation events (26.2%) had ≥50% vertebral and basilar stenosis, compared with 41 (11.5%) patients with ≥50% ipsilateral carotid stenosis. The presence of ≥50% vertebral and basilar stenosis was unrelated to age, sex, or vascular risk factors. Carotid stenosis of ≥50% was associated with the evidence of coronary/peripheral atherosclerosis but not vertebral and basilar stenosis of ≥50%. In patients with posterior circulation events, ≥50% vertebral and basilar stenosis was associated with multiple transient ischemic attacks at presentation and with a significantly higher 90-day risk of recurrent events (OR 3.2; $p = 0.006$), reaching 22% for stroke and 46% for transient ischemic attack and stroke combined. These rates were higher than the recurrence rates of events in patients with carotid stenosis, although to re-emphasize, the medical therapy was not standardized in this study. A more recent phase 2 study performed in the Netherlands, the Vertebral Artery Stenting Trial (VAST) (see **Table 2**) identified patients with a recent transient ischemic attack or minor stroke associated with an extracranial (or intracranial) vertebral artery stenosis of at least 50% and randomized patients to stenting plus best medical treatment or best medical treatment alone [81]. All patients received 'best medical treatment' at the discretion of the treating neurologist, including antithrombotic agents, a statin, and 'rigorous control' of other vascular risk factors. The primary outcome was the composite of vascular death, myocardial infarction, or any stroke within 30 days after the start of treatment. The trial was stopped after inclusion of 115 patients because of new regulatory requirements. Fifty-seven patients were assigned to stenting and 58 were assigned to medical treatment alone. The primary outcome was observed in three patients in the stenting group within 30 days after the start of treatment (5%, 95% CI: 0–11) vs. one patient in the medical treatment group (2%, 95% CI: 0-5). During the complete period of follow-up (4 years), there were 60 serious adverse events (eight strokes) in the stenting group and 56 (seven strokes) in the medical treatment alone group. The investigators concluded that stenting of symptomatic vertebral artery stenosis was associated with a major periprocedural vascular complication in about one in 20 patients and the risk of recurrent vertebrobasilar stroke under best medical treatment alone was low, with these results leading the authors to question the need for a phase 3 study. Another study that recently completed enrollment in February 2015 is the Vertebral Artery Ischaemia Stenting Trial (VIST) [82]. This is a UK-based multiple-center RCT that will compare vertebral artery stenting/angioplasty vs. the best medical therapy alone in patients with symptomatic vertebral artery stenosis of >50%. Recruitment was stopped early due to a cessation of funding as related to a low recruitment rate. A total of 182 patients were recruited. The stated primary end points were perioperative risk and long-term efficacy, not further specified; results are forthcoming. Lastly, one can also infer from the SAMMPRIS trial [15], which evaluated the similar condition of recently symptomatic large-vessel intracranial stenosis, that aggressive medical therapy strategy including dual antiplatelet therapy for 3 months, along with statin therapy, blood pressure, and glycemic control, and risk-factor modification is highly effective for secondary prevention of stroke. It remains unclear if aggressive medical therapy would be as effective for patients with symptoms caused by hemodynamic compromise from ECVAS.

Specific to stenting in the setting of ECVAS, there has been numerous retrospective, non-randomized case series published. One review including 980 patients from 27 studies dem-

onstrated a technical success rate of 99%, with a periprocedural risk of 1.2% for stroke and 0.9% for TIA [83]. In this study, participants were followed up for an average of 21 months perioperatively, with vertebrobasilar territory stroke or TIA only occurring in 1.3 and 6.5%, respectively. A prospective database of 114 patients undergoing stenting for symptomatic vertebral ostial stenosis demonstrated a recurrence of symptoms at 1 year after stenting of just 2% [78]. In another review of 300 endovascular interventions in symptomatic vertebral artery origin stenosis, periprocedural neurologic complications occurred in 5.5% and the re-stenosis rate was 26% [84]. Nevertheless, at long-term follow-up (mean 14.2 months), the risk of death was 0.3%, and the risk for posterior stroke was 0.7%. In general, the risks of adverse events are higher with distal vertebral or basilar interventions and when interventions are performed in the setting of urgent revascularization.

Symptomatic re-stenosis rates in this setting are ECVAS stenting, which remain uncertain and a topic of study. A recent pooled analyses [85] of five studies comparing drug-eluting (DES) vs. bare-metal stents (BMS) found no significant difference in the technical success (OR 1.53; $p = 0.62$), clinical success (OR 1.92; $p = 0.27$), and periprocedural complications (OR 0.74; $p = 0.61$) between the two stent types. An OR of 0.388 for no re-stenosis in the BMS to DES arms ($p = 0.001$) indicated a significantly higher re-stenosis rate in the BMS group relative to the DES group (33.57 vs. 15.49%). When compared with the DES group, the BMS group had a significantly higher rate of recurrent symptoms (2.76 vs. 11.26%; OR 3.32; $p = 0.01$). In summary, a significantly lower rate of re-stenosis and recurrent symptoms was noted in the DES group compared with the BMS group.

Open surgical procedures for revascularization of ECVAS include vertebral artery endarterectomy and vertebral artery transposition. While such procedures are performed rarely, they can be considered in patients with persistent symptoms despite intensive medical therapy. In one older series of 27 patients, there was no perioperative stroke or death [86]. In that same series, there were two permanent neurological complications: one case of Horner syndrome and one case of vocal hoarseness. Additionally, two patients developed neurological symptoms localizable to the posterior circulation after the perioperative period [86]. In closing, larger randomized trials will be necessary to better define evidence-based recommendations for ECVAS patients and to assess whether vertebral artery stenting is of relevance as a primary treatment strategy in patients with symptomatic ECVAS.

6.1. Extracranial vertebrobasilar disease: recommendations (adapted from [10, 11])

1. Routine preventive therapy with emphasis on antithrombotic therapy, lipid lowering, BP control, and lifestyle optimization is recommended for all patients with recently symptomatic extracranial vertebral artery stenosis.

2. Endovascular stenting of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment.

3. Open surgical procedures, including vertebral endarterectomy and vertebral artery transposition, may be considered when patients are having symptoms despite optimal medical treatment.

7. Conclusion

Extracranial and intracranial large artery atherosclerosis is a common cause of ischemic stroke and TIA. Lifelong vascular risk-factor optimizations via sustained behavioral modifications and intensive medical therapy are the key elements to reduce future stroke risk in these settings. Intensive medical therapy achieves low rates of stroke and death in asymptomatic carotid stenosis. Evidence indicates that patients with moderate to severe symptomatic carotid stenosis should undergo carotid revascularization sooner rather than later and that the risk of stroke or death is lower using carotid endarterectomy than carotid stenting. Specific to stenting, the risk of stroke or death is greatest among older patients and women. When considering a revascularization procedure for carotid stenosis, patient demographics, comorbidities, as well as the periprocedural risks of stroke and death should be carefully considered.

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