Circulation Research Compendium on Stroke

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Marc Fisher, Costantino Iadecola, and Ralph Sacco, Editors

Stroke Caused by Extracranial Disease

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Abstract: **Extracranial internal carotid artery atherosclerotic occlusive disease is a common ischemic stroke mechanism. Vascular risk factor control remains the cornerstone of stroke prevention in patients with both asymptomatic and symptomatic carotid occlusive diseases. Intensive medical therapy refers to the contemporary approach of antiplatelet therapy, blood pressure control, low-density lipoprotein reduction, and lifestyle modification to reduce stroke risk. Carotid revascularization with endarterectomy or angioplasty and stenting are established treatments for patients with symptomatic carotid stenosis ≥70%. Previously accepted ischemic stroke preventative strategies, such as carotid revascularization for asymptomatic carotid stenosis, require reassessment given advances in both medical therapy and surgical techniques. The purpose of this review is to describe contemporary approaches to the management of extracranial carotid atherosclerotic occlusive disease and the basis of these recommendations. Results from recently published clinical trials will be highlighted in addition to updated information from clinical trials addressing knowledge gaps in prevention of stroke caused by extracranial disease. (*Circ Res*. 2017;120:496-501. DOI: 10.1161/CIRCRESAHA.117.310138.)**

Key Words: angioplasty ■ carotid artery diseases ■ carotid stenosis ■ endarterectomy ■ stroke

Worldwide, stroke carries a significant public health burden with an estimated 16 million new strokes each year and a prevalence exceeding 60 million.[1] In the United States, ≈800 000 new and recurrent strokes occur each year. Stroke is the fifth leading cause of death and the leading cause of adult disability in the United States. Extracranial internal carotid artery atherosclerotic occlusive disease is a common stroke mechanism. Estimates of first-time ischemic stroke attributable to carotid artery disease range from 7% to 18% of all incident stroke.[2,3] Carotid revascularization with endarterectomy or angioplasty and stenting are established treatments for patients with symptomatic carotid stenosis ≥70%. The magnitude of benefit associated with revascularization of symptomatic carotid stenosis may not be the same as was demonstrated in early randomized clinical trials comparing revascularization to medical therapy given advances in risk factor management and antithrombotic therapy. Previously accepted ischemic stroke preventative strategies, such as carotid revascularization for asymptomatic carotid stenosis, require reassessment given advances in both medical therapy and surgical techniques. The purpose of this review is to describe contemporary approaches to the management of extracranial

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Nonstandard Abbreviations and Acronyms	
CAS	carotid artery stenting
CEA	carotid endarterectomy
CI	confidence interval
CREST	Carotid Revascularization Endarterectomy Versus Stenting Trial
CREST-2	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis
CT	computed tomography
HR	hazard ratio
MI	myocardial infarction
MRA	magnetic resonance angiography
SPACE-2	Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis Versus Endarterectomy

carotid atherosclerotic occlusive disease. Results from recently published clinical trials will be highlighted along with ongoing clinical trials addressing key questions in prevention of stroke caused by extracranial disease.

Stroke Caused by Extracranial Disease—General Concepts

Identification of carotid atherosclerotic occlusive disease often occurs as the result of cervical vascular imaging performed during the evaluation of bruits or after ischemic stroke/transient ischemic attack. In some instances, carotid stenosis may be identified incidentally when cervicocephalic vascular imaging is performed for a nonstroke-related indication. The most common noninvasive imaging modalities used to detect carotid stenosis are duplex ultrasonography, magnetic resonance angiography (MRA), or computed tomographic (CT) angiography. These techniques are able to provide an estimate of the degree of stenosis and are often used in a complementary fashion to estimate severity. Each modality has relative strengths and limitations that should be considered when interpreting results. Duplex ultrasonography is low cost, widely available, but does not reliably discriminate between occlusion and very high-grade stenosis (>95%), where Doppler frequencies and velocities may fall off and be undetectable. MRA visualizes the entirety of the carotid system in the neck and intracranial segments but may overestimate degree of stenosis when narrowing is high grade. CT angiography is less susceptible to the overestimation of degree of stenosis but requires radiation exposure and contrast which may be limited in patients with renal insufficiency.

Historical information on transient symptoms is important because optimal management of carotid stenosis will be determined by the symptomatic status of the artery. Neuroimaging evidence of cerebral ischemia in the vascular distribution of the diseased artery confirms symptomatic status. Hemispheric or retinal symptoms ipsilateral to carotid stenosis are because of artery-to-artery embolism or hypoperfusion. Symptomatic status and degree of stenosis of extracranial carotid occlusive disease are important factors in guiding evidence-based management. In general, vascular risk factor modification serves as the primary treatment for stroke prevention in all patients with extracranial carotid disease. Carefully selected patients, as discussed below, may benefit from carotid revascularization in addition to vascular risk factor modification.

Extracranial Atherosclerotic Carotid Occlusive Disease—Risk Factor Management

Vascular risk factor control remains the cornerstone of stroke prevention in patients with both asymptomatic and symptomatic carotid occlusive diseases. Treatments focused on use of antiplatelet agents, control of blood pressure, lipid-lowering agents, and lifestyle modification have been termed Intensive Medical Therapy. Recent guidelines include comprehensive and evidence-based recommendations for primary and secondary stroke prevention though physical activity, diet and nutrition, and tobacco cessation.[4,5] The goal of intensive medical therapy is to reduce cardiovascular outcomes through a variety of mechanisms, including atherosclerotic plaque regression.[6] The contemporary concept of intensive medical therapy is the synergistic benefit of multiple, continuous, and lifelong approaches to stroke risk factor reduction and behavioral modification.

Antiplatelet agents commonly used for stroke prevention in carotid occlusive disease include aspirin, clopidogrel, and combination of aspirin and dipyridamole. On the basis of the results of comparative clinical trials, no significant differential efficacy between these antiplatelet agents has been identified for stroke prevention. However, the study cohorts were not restricted to patients with carotid occlusive disease. In clinical practice, aspirin is the most commonly used antiplatelet agent given its favorable cost/benefit ratio and accessibility to patients. Aspirin for primary prevention of stroke is supported by evidence when estimated 10-year cardiovascular risk is sufficiently high. Dual antiplatelet therapy is not commonly used as a long-term preventative strategy in carotid occlusive disease because comparative trials of antiplatelet monotherapy versus dual antiplatelet therapy with aspirin and clopidogrel have demonstrated an excess risk of hemorrhage without incremental reduction in cardiovascular outcomes.[7] Dual antiplatelet therapy has been shown to significantly reduce microembolic signals detected by transcranial Doppler compared with aspirin monotherapy in extracranial arterial stenosis, but the clinical significance of this remains uncertain with respect to outcomes of stroke or death.[8]

Hypertension is a strong and independent risk factor for stroke and is modifiable through lifestyle and pharmacological interventions. Lowering blood pressure is associated with stroke risk reduction; therefore, treatment of hypertension represents one of the most effective and impactful interventions for stroke prevention. In general, reduction of blood pressure to a systolic goal of <140 mm Hg is associated with decreased risk of stroke caused by extracranial disease. Several classes of antihypertensive medications exist without comparative efficacy trials to guide selection of a specific agent. Angiotensin-converting enzyme inhibitors, thiazide diuretics, and calcium channel blockers are the most commonly used agents. Antihypertensive medications that cause increased variability of systolic blood pressure measurements are associated with increased risk of stroke.[9] Among those agents studied, amlodipine was associated with reduced variability

over time, and atenolol was associated with the highest variability in systolic blood pressure measurements. Blood pressure medications should be chosen based on the ability to reduce the mean blood pressure and reduce variability of measurements over time.

Diabetes mellitus is an independent risk factor for stroke and increases risk of recurrent stroke in the elderly by 60%.[10] Diabetes mellitus is also associated with progression of carotid intima-medial thickness as measured by duplex ultrasonography.[11] Carotid intima-media thickness has been associated with cardiovascular risk in epidemiological studies and may serve as an informative biomarker for risk stratification. The optimal treatment and target for glucose control has not been clearly established, but a reasonable target for patient with diabetes mellitus is a glycosylated hemoglobin <7%.[12]

Hyperlipidemia is an important risk factor for atherosclerosis and serves as a high-priority target for risk factor modification within an intensive medical therapy regimen. Statins are the preferred class of lipid-lowering medications in extracranial occlusive disease because other classes of lipid-modifying therapy have not been shown to significantly reduce stroke risk.[13] Recent guidelines introduced a paradigm shift in the management of hyperlipidemia—movement away from a specific low-density lipoprotein cholesterol target and toward a focus on treatment with statins that can lower cholesterol by 50% or more (high intensity) or lower cholesterol 30% to 50% (moderate intensity).[14] High-intensity statin therapy should be initiated in patients with stroke caused by extracranial atherosclerotic disease or in those with a low-density lipoprotein cholesterol of >100 mg/dL as part of intensive medical therapy.

Primary Stroke Prevention in Asymptomatic Carotid Stenosis

Multicenter randomized clinical trials of carotid endarterectomy (CEA) for stroke prevention in asymptomatic carotid stenosis demonstrated significant benefit of surgery plus medical therapy compared with medical therapy alone.[15–17] However, the absolute risk reduction favoring surgery was small. In ACST (Asymptomatic Carotid Surgery Trial) at a median follow-up of 9 years, the 5- and 10-year risk of any stroke was 6.4% and 13.9% for the CEA group and 10.9% and 17.9% for the medical group, respectively, for an absolute risk reduction of 4.1% at 5 years and 4.6% at 10 years. These trials did not emphasize medical therapy. In ACAS, the percentage of patients on lipid-lowering drugs was not reported, and control of hypertension and other risk factors for stroke was not monitored. In ACST, from the early 1990s to 2007, the proportion of patients taking lipid-lowering drugs increased from 10% to 81%.[18] The proportion of patients receiving antihypertensive therapy increased from 53% to 88%. These increases were associated with a 5 mm Hg reduction in mean diastolic blood pressure and a roughly two-thirds reduction in the benefit of CEA. Evidence has emerged that the effectiveness of medical therapy has advanced since the completion of these trials.[19] Recent data suggest that the stroke rate in medically treated patients with asymptomatic carotid artery stenosis has decreased to ≤1% per year.[20] In ACST, the rate of absolute benefit from CEA per year was lower in patients on lipid-lowering therapy (0.6% per year) compared with patients not on therapy (1.5% per year).[18] Carotid revascularization has improved substantially since the completion of these trials in the 1990s. In ACAS, the rate for perioperative stroke and death in patients <80 years was 2.3%.[16] In CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial), rates of stroke and death for patients <80 years old were 1.5% for CEA and 2.4% for carotid artery stenting (CAS).[21] Current guidelines recommend the consideration of CEA in asymptomatic patients with >70% stenosis if the risk of perioperative stroke, myocardial infarction (MI), and death is <3%.[4] The guidelines acknowledge that the effectiveness of CEA in this population compared with best medical management is not well established.

The advent of CAS as an option for carotid revascularization has further complicated therapeutic decision-making for asymptomatic carotid stenosis. CAS was originally evaluated in patients with factors associated with increased procedural risk during CEA. SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy Investigators) included asymptomatic patients with >80% stenosis and found that CAS was associated with a lower risk of the composite outcome of stroke, MI, or death at 1 year than CEA (9.9% versus 21.5%).[22] These generalizabilities of the results are limited by the lack of a medical control arm and the high complication rates in both treatment arms that may exceed risk associated with medical therapy alone. Randomized trials of CAS compared with CEA have been performed, but the studies included both symptomatic and asymptomatic patients and did not include a control arm receiving medical therapy alone.[23,24] CREST enrolled both symptomatic and asymptomatic patients with carotid stenosis who were eligible to undergo either CEA or CAS.[24] Asymptomatic patients could be included if they had a stenosis of ≥60% on angiography, ≥70% on ultrasonography, or ≥80% on CT angiography or MRA if the stenosis on ultrasonography was 50% to 69%. In the periprocedural period, the risk of any stroke or death among asymptomatic patients was low (2.5% in CAS versus 1.4% for CEA; hazard ratio [HR], 1.88; 95% confidence interval [CI], 0.79–4.42; P=0.15). The overall estimated 4-year rate of any periprocedural stroke or death or postprocedural ipsilateral stroke, however, was higher with stenting compared with endarterectomy (HR, 1.50; 95% CI, 1.05–2.15; P=0.03). Although the trial was not powered to evaluate symptomatic and asymptomatic patients separately, there was a trend favoring CEA over CAS in asymptomatic (HR, 1.86; 95% CI, 0.95–3.66; P=0.07) patients. In addition to the advances made in contemporary intensive medical therapy described above, advances in interventional techniques with improved device technology and operator experience have occurred since the completion of these trials. Current guidelines recommend that CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound) but acknowledge that efficacy compared with medical therapy alone is not well established.

Comparative studies of intensive medical therapy and carotid revascularization for stroke prevention in asymptomatic carotid stenosis have been designed to resolve the existing knowledge gap.[25] The CREST-2 trial (Carotid Revascularization

and Medical Management for Asymptomatic Carotid Stenosis)[26] is designed as 2 parallel randomized trials. The surgical trial will measure treatment differences between CEA plus intensive medical therapy versus intensive medical therapy alone. The stenting trial will measure treatment differences between CAS plus intensive medical therapy versus intensive medical therapy alone. CREST-2 includes adult patients (≥35 years old) with ≥70% carotid stenosis as measured by duplex ultrasound defined by a peak systolic velocity of ≥230 cm/s plus and an end-diastolic velocity ≥100 cm/s. If the end-diastolic velocity is not ≥100 cm/s, patients may also be eligible for the trial if the internal carotid/common carotid artery peak systolic velocity ratio is ≥4.0, or CT angiography shows ≥70% stenosis, or MRA shows ≥70% stenosis. Patients with ≥70% stenosis by NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria on conventional angiography are also eligible. No stroke or transient ischemic attack can have occurred ipsilateral to the target artery within 180 days of enrollment. Intensive medical therapy is centrally directed and protocol driven to maximize achievement of evidence-based targets for blood pressure and low-density lipoprotein cholesterol. An individualized lifestyle intervention program will be implemented to promote tobacco cessation, weight loss, and physical activity. The primary efficacy end point is a composite of periprocedural stroke or death at 44 days and any ipsilateral stroke thereafter out to 4 years of follow-up. An important secondary outcome measures treatment differences between carotid revascularization and medical therapy on cognitive outcomes. Target recruitment is 2480 patients (1240 in each study) and as of January 6, 2017, a total of 447 patients have been randomized (202 CEA trial, 245 CAS trial), and 122 centers have been approved to randomize (116 of the 122 are actively enrolling). The Site Selection Committee has approved 150 centers to proceed with Institutional Review Board submission. Credentialing is ongoing, with 324 approved surgeons and 135 approved interventionists; 126 additional conditionally approved interventionists will be able to submit additional cases for review under the CREST-2 Registry. The Centers for Medicare and Medicaid will offer CAS reimbursement for Registry enrollees. CREST-2 will leverage the CREST network of providers and research infrastructure developed over the last decade to recruit with similar efficiency (eg, nearly 1200 asymptomatic patients recruited into CREST within 3 years).

The SPACE-2 trial (Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis Versus Endarterectomy)[26] was a randomized clinical trial comparing best medical treatment alone with best medical therapy plus CEA or CAS in patients with high-grade asymptomatic extracranial carotid stenosis. The original design, which began recruitment in 2008, was a 3-arm intervention: best medical therapy alone versus CAS plus best medical therapy versus CEA plus best medical therapy. A fundamental revision to the design of the trial because of slow recruitment occurred in 2013 and transitioned to 2 parallel superiority trials of CEA (SPACE-2a) versus medical therapy and CAS versus medical therapy (SPACE-2b). The redesign of the trial was done to promote recruitment at centers that only performed CEA or CAS and to also reduce the complexity of the trial from the patient perspective. The change in study design did not result in improved recruitment, and the study was stopped after recruiting 513 patients over 5 years.[27] The 30-day rate of stroke and death was 1.97% for CEA and 2.54% for CAS; there were no events in patients randomized to best medical therapy in the first 30 days. Follow-up of all recruited patients is planned, and the data will be made available for any future meta-analyses prepared by the Carotid Stenosis Trialists Collaboration.

Symptomatic Extracranial Carotid Occlusive Disease

Three randomized trials have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with a >70% extracranial carotid stenosis. Symptomatic patients included those who had both >70% ipsilateral carotid stenosis and transient ischemic attacks, transient monocular blindness, or nondisabling strokes. A pooled analysis of these 3 largest randomized trials involving >3000 symptomatic patients (ECST [European Carotid Surgery Trial], NASCET, and VACS [Veteran's Affairs Cooperative Study]) found a 30-day stroke and death rate of 7.1% in surgically treated patients.[28] In addition, each of the 3 major trials showed that for patients with stenoses <50%, surgical intervention did not offer benefit in terms of stroke risk reduction. The role of CEA was less clear among patients with symptomatic stenosis in the 50% to 69% range. Among 858 symptomatic NASCET patients with a stenosis of 50% to 69%, the 5-year rate of any ipsilateral stroke was 15.7% in patients treated surgically compared with 22.2% in those treated medically (P=0.045). Thus, to prevent 1 ipsilateral stroke during the 5-year follow-up period, 15 patients would have to undergo CEA. The conclusions justify CEA only given appropriate case selection and when the risk/benefit ratio is favorable for the patient when evaluating surgical and anesthetic risks. In NASCET, the rate of perioperative stroke or death was 6.7%, and given that medical management has improved since NASCET, current guidelines advise proceeding with CEA in the setting of symptomatic stenosis only if the risk of perioperative stroke or death is <6%.[4,5]

The CREST was a multicenter trial designed to compare the outcomes of CAS with CEA among patients with extracranial carotid stenosis. Eligible patients were randomly assigned to CAS (n=1262) or endarterectomy (n=1240). In contrast to preceding randomized trials of carotid intervention in conventional-risk patients, CREST enrolled both symptomatic patients (≥50% stenosis by angiography, ≥70% by carotid ultrasound, or ≥70% on CT angiography or MRA if the stenosis on ultrasound was 50% to 69%; n=1321) and asymptomatic patients (≥60% stenosis by angiography, ≥70% by ultrasound, or ≥80% on CT angiography or MRA if the stenosis on ultrasound was 50% to 69%; n=1181). The primary end point was the composite of any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization.

The estimated 4-year rates for the primary end point—7.2% for CAS and 6.8% for CEA—were not significantly different (HR for stenting, 1.11; 95% CI, 0.81–1.51; P=0.51). During the periprocedural period, the incidence of the primary end point—5.2% for CAS and 4.5% for CEA—did not differ significantly (HR for stenting, 1.18; 95% CI, 0.82–1.68; P=0.38).

No differences in treatment effect with respect to the primary end point were observed according to the symptomatic status or sex. After the periprocedural period, the incidence of ipsilateral stroke was 2.0% for CAS and 2.4% for CEA (*P*=0.85).

Comparisons of individual end points between treatment groups were significantly different. The 4-year rate of stroke or death was 6.4% for stenting and 4.7% for endarterectomy (HR for stenting, 1.50; 95% CI, 1.05–2.15; *P*=0.03). During the periprocedural period, the incidence of stroke was 4.1% for stenting and 2.3% for endarterectomy (HR for stenting, 1.79; 95% CI, 1.14–2.82; *P*=0.01). The incidence of any periprocedural stroke or death or postprocedural ipsilateral stroke was 4.4% for stenting and 2.3% for endarterectomy (HR for stenting, 1.90; 95% CI, 1.21–2.98; *P*=0.005). The incidence of MI was 1.1% for stenting and 2.3% for endarterectomy (HR for stenting, 0.50; 95% CI, 0.26–0.94; *P*=0.03). The incidence of cranial nerve palsies was 0.3% for stenting and 4.7% for endarterectomy (HR for stenting, 0.07; 95% CI, 0.02–0.18).

The treatment effect was significantly modified by age at the time of treatment. CAS showed greater efficacy for patients younger than 70 years, and endarterectomy demonstrated greater benefit for those older than 70 years. A similar association between age and adverse events was observed during the CREST lead-in phase.[8] During the lead-in, the incidence of stroke and death at 30 days for symptomatic subjects older than 75 years (9.1%) was significantly higher than the incidence for such patients who were aged 75 or younger (4.5%). A significant difference was also found for asymptomatic patients older than 75 years (7.5%) compared with asymptomatic patients aged 75 years or less (2.4%). The higher complication rates observed with advancing age persisted despite adjustment for potential confounding factors. Catheter-based techniques may pose higher risk in older patients because of vascular tortuosity and calcifications, which are more prevalent in elderly populations.[9]

Given the state of current evidence, guidelines recommend CEA for patients with symptomatic severe (70%–99%) stenosis if the perioperative risk is <6%. For symptomatic patients with moderate (50%–69%) stenosis, CEA is recommended depending on patient-specific factors such as age and sex if the perioperative risk is <6%. CAS can be considered as an alternative to CEA in symptomatic patients with severe (>70%) carotid stenosis and average or low risk of complications. It is reasonable to consider patient age in choosing between CAS and CEA. For patients >70 years, CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke.[5]

Conclusions

Extracranial atherosclerotic carotid occlusive disease is a common cause of stroke. The primary treatment modality regardless of degree of stenosis or symptomatic status is intensive medical therapy of modifiable vascular risk factors. Carotid revascularization has an established, evidence-based role in addition to intensive medical therapy in carefully selected patients with symptomatic carotid stenosis >50%. There is uncertainty on the optimal management strategy for stroke prevention in high-grade asymptomatic carotid stenosis—ongoing randomized trials have been designed to close this knowledge gap.

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Disclosures

None.

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