The urgent need for contemporary clinical trials in patients with asymptomatic carotid stenosis

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ABSTRACT

Asymptomatic extracranial internal carotid artery atherosclerotic stenosis increases with age and is more common in men. Studies performed more than 2 decades ago showed that carotid endarterectomy reduced the rate of stroke in carefully selected patients with asymptomatic carotid stenosis compared with medical therapy in the long term. Those trials were completed more than 20 years ago and with advances in the treatment of atherosclerotic disease, the question has been raised to as to whether endarterectomy is still of value for patients with asymptomatic narrowing. Perioperative risk of carotid revascularization procedures has also declined. Due to improvements in both medical and surgical treatments for carotid artery stenosis, it is timely to reevaluate the efficacy of carotid intervention relative to medical treatment for patients with asymptomatic stenosis. ***Neurology*® 2016;87:2271–2278**

GLOSSARY

ACAS = Asymptomatic Carotid Atherosclerosis Study; **ACST** = Asymptomatic Carotid Surgery Trial; **AMM** = aggressive medical management; **CAS** = carotid artery stenting; **CEA** = carotid endarterectomy; **CREST** = Carotid Revascularization Endarterectomy versus Stenting Trial; **CREST 2** = Carotid Revascularization and Aggressive Medical Management Trial; **ECST 2** = European Carotid Surgery Trial 2; **ICA** = internal carotid artery; **MMSE** = Mini-Mental State Examination; **PAD** = peripheral artery disease; **SAMMPRIS** = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; **SPARCL** = Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

Results of the first major randomized clinical trial comparing carotid endarterectomy (CEA) to medical therapy for patients with asymptomatic internal carotid artery (ICA) stenosis were published 21 years ago.[1] In the Asymptomatic Carotid Atherosclerosis Study (ACAS), there was a 5.9% absolute benefit over 5 years favoring CEA relative to medical therapy. Since that time, there have been dramatic changes in the treatment modalities available to clinicians, including advances in medical therapy, refined surgical techniques, and the availability of carotid artery stenting (CAS).[2,3] These advances in the management of carotid stenosis, especially the decline in risk with intensified medical management, raise the question of whether carotid revascularization is still indicated.[2,4,5]

In this update, we review the evolution in strategies for managing ICA stenosis over the last 2 decades. We also review the potential relationship between carotid stenosis and impaired cognition.[6] Finally, we discuss the pressing need for results from new multicenter trials in the field of ICA stenosis.

EPIDEMIOLOGY AND PROGNOSIS In the Framingham Heart study, common atherosclerosis risk factors including older age, cigarette smoking, systolic blood pressure, and total cholesterol were associated with the degree of carotid stenosis.[7] Whether the ICA stenosis is associated with a recent ipsilateral stroke or TIA is a major determinant of future stroke risk. Patients with an asymptomatic ICA stenosis exceeding 75%, with 1990s medical therapy, had a stroke risk of 2%–2.5% per year.[8] In contrast, patients with symptomatic carotid stenosis of 70%–99% carried a 2-year stroke risk of 26% with 1990s medical therapy.[8] During the course of these trials, neither statins nor angiotensin-converting enzyme inhibitors were in widespread use.

Age, sex, and atherosclerosis risk factors affect the prevalence of moderate (>50%) or severe (>70%) ICA stenosis in the general population. A systematic review of 40 studies found that in patients <70 years of age, the prevalence of moderate (>50%) stenosis was 4.8% in men and 2.2% in women.[9] In patients >70 years of

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age, the prevalence of moderate stenosis was 12.5% in men and 6.9% in women.[9] In a meta-analysis of 4 longitudinal studies, the prevalence of severe stenosis ranged from 0% to 3.1% according to age and sex groups.[10] These investigators identified several factors that were linked with an increased likelihood of ICA stenosis. The most potent predictors were current tobacco smoking, increasing age, male sex, and history of vascular disease. In patients with established systemic arterial disease, such as coronary artery occlusive disease or peripheral arterial disease, the frequency of severe (>70%) carotid stenosis ranges from 10% to 15%.[11,12]

What constitutes severe stenosis varies in the literature. Although many epidemiologic studies use >70% stenosis by ultrasound as the cutoff value for severe stenosis, some clinical trials (such as ACAS) have included 60%–99% stenosis as an inclusion criterion. In addition, while trials of asymptomatic stenosis have not shown a definite difference in terms of the benefit of CEA in 60%–79% stenosis compared to 80%–99% stenosis, several longitudinal, ultrasound-based studies have shown an increased risk of stroke with higher degrees of stenosis in asymptomatic patients.[13]

PRIOR LANDMARK STUDIES IN PATIENTS WITH ASYMPTOMATIC CAROTID STENOSIS In the late 1980s, ACAS was initiated to compare medical therapy alone compared to medical therapy combined with CEA in patients between the ages of 40 and 79 years. Patients were enrolled with 60%–99% stenosis, with patients in the surgical arm having angiography. The trial was conducted in North America and was terminated early after a significant benefit from CEA was observed. The projected 5-year stroke rates for ipsilateral stroke were 5.1% in the CEA group and 11.0% in the medical therapy alone group.[1] These results meant there was a 55% relative risk reduction and 1.2% absolute risk reduction per year with the addition of CEA. There was an overall 2.3% combined stroke and death rate within 30 days for patients in the surgical arm, with about half of the events associated with angiography. From this trial, it is estimated that 17 patients would need to have CEA to prevent one stroke over 5 years. The decrease in stroke was seen only in men, and there was no reduction in disabling strokes, although ACAS did not have robust statistical power to test outcomes according to sex or stroke severity. The publication of the ACAS results led to a marked increase in the number of CEA operations performed in the United States.[14,15]

A second study, the Asymptomatic Carotid Surgery Trial (ACST), was primarily conducted in Europe and featured a pragmatic study design. Patients with asymptomatic stenosis could be enrolled if the medical team was uncertain with regard to the benefit of CEA. Angiography was not mandated. Inclusion required 60%–99% stenosis by duplex ultrasound.[16] As with ACAS, ACST also showed a statistically significant reduction in stroke with CEA, but at 10 years, the absolute benefit was <1% per year (10.8% vs 16.9% in the CEA+ medical therapy and medical therapy groups, respectively).[17] Reduction in stroke was noted for both men and women. It is also important to note that ACST included strokes in any territory as part of the primary endpoint, whereas ACAS only included ipsilateral stroke as part of the primary endpoint. During the course of ACST, there was an increase in utilization of statins and antihypertensives. Stroke risk in medically treated patients fell in the later years of the study coincident with increased utilization of statins and antihypertensives. Over the course of 10 years, the stroke risk in any territory was 24.9% in patients not receiving lipid-lowering treatment, compared to 14.5% in patients receiving lipid-lowering medication. The benefit of CEA was greater in patients not treated with lipid-lowering therapy.

After ACAS and ACST, there has been lingering uncertainty regarding the benefit of CEA in 2 important patient subgroups, women and the elderly. Regarding women, a combined review of ACAS and ACST identified that men with asymptomatic carotid stenosis had a 51% relative risk reduction.[18] No reduction in the stroke rate was observed in women. A possible explanation for the lower stroke risk in women is that women have reduced macrophage staining in carotid plaques and higher amounts of smooth muscle, providing for an overall "more stable" plaque phenotype relative to men.[19] Since women have typically constituted only a small minority of the patients in previous carotid trials (25%–35%), there have been calls for a future clinical study focused on women with carotid stenosis.[20]

Patients >79 years old were excluded from ACAS, but there was no age restriction in the ACST, which did not show a clear benefit with CEA in patients over age 75 years. However, ACST was inadequately powered to evaluate this subgroup. Nevertheless, since elderly patients are expected to have a lower life expectancy and since clinical guidelines recommend at least a 5-year life expectancy for asymptomatic patients,[8] it is crucial to meticulously evaluate the projected long-term survival in older patients being considered for carotid operations. Some studies have begun to address how best to predict life expectancy in older adults.[21] Previous cardiac disease, renal dysfunction, and diabetes have been linked with lower long-term survival.[22] Due to the uncertainties regarding benefit of carotid revascularization in these 2 subgroups, it is important that current clinical trials enroll an adequate number of women and elderly patients.

EFFECT OF IMPROVED MEDICAL THERAPY All patients with either symptomatic or asymptomatic ICA stenosis should receive medical therapy and revascularization (CEA or CAS) can be offered to select patients.[23–26] With respect to medical therapy, patients should receive the essential components of atherosclerosis treatment. This includes the following:

1. Antithrombotic therapy
2. Aggressive treatment of hyperlipidemia
3. Control of hypertension
4. Control of diabetes to achieve A1C levels <7%
5. Tobacco smoking cessation
6. Lifestyle modification, including dietary modification and exercise

The introduction of statins has dramatically altered the therapy for vascular disease. Statins have become an essential component of therapy for patients with TIA or ischemic stroke since being evaluated in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.[27] A subgroup of 1,007 patients in SPARCL had a mean carotid artery stenosis of 51%. Patients receiving atorvastatin had a 33% reduction in any stroke, 43% decrease in coronary events, and 56% lowering in the rate of carotid revascularization procedures.[28] In the ACST, there was an increasing utilization of lipid-lowering treatment in the second half of the trial. As described above, for patients not on lipid-lowering therapy who were assigned to the deferred CEA portion of the study, the 10-year rate of stroke was 24.9%.[17] This figure was lowered to 14.5% for patients who received cholesterol-lowering medications. As a consequence of these observations, therapy with statins has become an important component of treatment of patients with carotid stenosis and has been universally incorporated into recent guidelines.[25]

Data in patients with intracranial atherosclerotic large artery stenosis also strongly support the role of aggressive multimodal medical therapy for lowering the risk of stroke. In the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, patients with recently symptomatic 70%–99% stenosis of a major intracranial artery (intracranial carotid, middle cerebral, basilar, or vertebral) were assigned to aggressive medical management (AMM) alone or in combination with intracranial stenting. The AMM-alone group had a significantly lower rate of stroke during follow-up. Although there was not a control group in SAMMPRIS treated with less intensive usual medical management, the 1-year stroke rate in the AMM-alone group in SAMMPRIS was half the 1-year stroke rate in patients with the same entrance criteria in the immediately preceding Warfarin Aspirin Symptomatic Intracranial Disease trial who were treated with less intensive medical management.[29]

The question naturally arises as to what effect the SAMMPRIS regimen (table 1) would have on the outcome of patients with extracranial carotid stenosis. It would seem that the core elements of the SAMMPRIS regimen (antiplatelet therapy, aggressive statin use, blood pressure treatment, and lifestyle modification) are highly relevant to extracranial carotid stenosis and deserve to be tested for both asymptomatic and symptomatic stenosis patients.[30]

The studies cited above (SPARCL and SAMMPRIS) were secondary prevention studies. Although there could be uncertainty as to whether these therapies will be efficacious for asymptomatic carotid stenosis, recent observational studies also support the concept that contemporary medical therapy is having an important effect on lowering the stroke rates for patients with asymptomatic carotid stenosis (table 2). In the Oxford Vascular Study, 101 patients with 50%–99% asymptomatic stenosis were enrolled in a longitudinal study and the annual ipsilateral stroke rate was only 0.3%.[31] In the Netherlands, the Second Manifestations of Arterial Disease study found that the stroke rate for patients with asymptomatic stenosis was 0.5% per year.[32] These results do not represent randomized clinical trial data, and the studies include patients with lower degrees of stenosis than those that are generally offered revascularization, but they suggest that advances in medical therapy may have substantially lowered the rate of stroke in patients with asymptomatic carotid stenosis.

Additional evidence regarding the effect of improved medical therapy comes from analyzing the year of enrollment in ACAS and ACST and the stroke rates observed in medically treated patients. Among ACAS patients, the medically treated cohort had an annual stroke rate of 2.2%.[1] In years 1–5 of the ACST, medically treated patients had a 1.1% annual risk of stroke. In years 6–10 of the ACST, medically treated patients had a 0.7% risk of stroke per year.[33] The decline in stroke rates from 1995 to 2010 corresponded with increased utilization of statins and antihypertensive medications. As an example, fewer than 10% of patients randomized to medical therapy alone were on lipid-lowering treatment in the first year of the study and this increased to 82% in the later years of ACST. In addition, diastolic blood pressure improved from 84 mm Hg in 1995 to 77.5 mm Hg in 2005.

IMPROVED RESULTS WITH CAROTID REVASCULARIZATION In tandem with the improvements in medical therapy, operative results of CEA and of CAS are also improving. In an earlier trial of asymptomatic patients conducted in the 1980s, the rate of stroke/death within 30 days of CEA was 4.7%.[34] In the Carotid Revascularization Endarterectomy

Table 1 Components of aggressive medical therapy in the SAMMPRIS study

Treatment	Details
Antiplatelet therapy	Aspirin + clopidogrel for first 90 days followed by aspirin alone
Statin	Goal LDL <70 mg/dL
Systolic BP lowering	Goal <140 mm Hg for nondiabetic participants, <130 mm Hg for diabetic participants
Hemoglobin A1c lowering in diabetic participants	Target <7%
INTERVENT coaching	Lifestyle risk factor control (tobacco avoidance, physical activity, dietary change, weight loss)

Abbreviations: BP = blood pressure; LDL = low-density lipoprotein; SAMMPRIS = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.

versus Stenting Trial (CREST), the rate of periprocedural stroke or death and postprocedure ipsilateral stroke was 3.2% for symptomatic patients and 1.4% for asymptomatic patients[3] (table 3). These rates were far below the recommended upper limit of periprocedural complications of <6% for symptomatic and <3% for asymptomatic patients. Among vascular surgeons in CREST, the periprocedural stroke or death rate (1.1%) was the lowest ever observed in a clinical trial.[35] A systematic review of over 200,000 CEA operations for asymptomatic stenosis (in either trials or registries) found an average 6% relative reduction in the rate of postoperative stroke or death between 1991 and 2010.[36] These authors propose that a postoperative stroke/death rate of 1.2% should become a new benchmark when operating on asymptomatic patients. When large registries and clinical trials are reviewed, periprocedural results with CAS also appear to be improving.[37,38]

The reasons for the improved surgical results are likely multifactorial. First, there has been an increased appreciation for protecting cerebral perfusion during surgical clamping of the carotid artery, increased utilization of a patch to close surgical arteriotomies, improved methods of preventing and capturing emboli during stenting, and additional improvements in perioperative anesthetic care. Second, increased periprocedural use of statins has been associated with a decrease in complications among patients undergoing noncardiac vascular surgery. In one meta-analysis, the rate of periprocedural stroke was 46% less in statin users compared to nonusers.[39] Increased use of vessel patching during CEA has been associated with a reduced rate of restenosis.[40] Finally, there have been refinements in strategies for periprocedural antiplatelet and statin treatment, especially for patients undergoing CAS.[41]

PHENOTYPE OF THE ASYMPTOMATIC PATIENT In routine practice, what are the potential avenues that lead to awareness of asymptomatic carotid stenosis? First, some patients may have had neurologic symptoms in other cerebrovascular distributions. Second, routine physical examinations may disclose a carotid bruit on auscultation of the neck. In addition, patients may have a carotid ultrasound performed as a screening test due to the existence of atherosclerotic heart disease or peripheral artery disease (PAD). This practice is controversial[42] but, based on the increased prevalence of carotid atherosclerosis in patients with PAD, the Society for Vascular Surgery recommends screening in such high-risk groups of patients.[26]

Although the first-generation CEA trials focused on prevention of stroke as the primary endpoint, there has been a resurgence of interest in recent decades on vascular contributions to cognitive impairment and dementia.[43] Specifically, can carotid stenosis contribute to cognitive deterioration, even in the otherwise asymptomatic patient?

Animal models with a permanent carotid occlusion model have shown that carotid occlusion can be associated with ipsilateral white matter rarefaction, oligodendrocyte loss, and reduced myelin density.[44] Another model in mice utilized gradual constriction of the common carotid artery.[45] After 28 days of gradual constriction, there was 79.3% area stenosis. This was associated with a 52% and 55% reduction

Table 2 Annual risk of stroke in patients with asymptomatic carotid stenosis

Study	No. patients in medical arm	Stenosis range of patients enrolled	Stroke risk per year (follow-up duration)	Year published	Reference
ACAS	834	60%–99%	2.2% (mean 2.7 y)	1995	1
ACST	1,560	60%–99%	2.4% (mean 3.4 y)	1995	16
London, Ontario (without ME)	199 (pre-2003); 269 (after 2003)	60%–99%	4.4% pre-2003; 0.5% after 2003 (at least one 1 y)	2010	2
Oxford	101	50%–99%	0.34% (mean 3 y)	2010	31
SMART	193	70%–99%	0.5% (mean 6 y)	2013	32

Abbreviations: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ME = microemboli; SMART = Second Manifestations of Arterial Disease.

Table 3 Periprocedural complication rates in previous asymptomatic carotid trials

Trial	Year published	Perioperative stroke/death, %	Reference
VA asymptomatic	1993	4.7	34
ACAS	1995	2.3	1
ACST	2004	3.1	16
CREST	2010	1.4	3

Abbreviations: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CREST = Carotid Revascularization Endarterectomy versus Stenting Trial; VA = Veterans Administration.

in subcortical and cortical cerebral blood flow. On examination of the white matter, it was noted that there was oligodendrocyte loss, and activation of astrocytes and microglia. The mice in this model also exhibited deficits in motor function and on working memory tasks.

Human studies have shown variable results. In a longitudinal study of 538 people free of neurologic disease at the outset, increasing carotid intima media thickness was associated with a greater rate of cognitive decline during a follow-up period of up to 11 years.[46] Deficits were particularly noted in verbal and nonverbal memory and executive function. Another study of 66 patients with Alzheimer disease noted greater reductions in the Mini-Mental State Examination (MMSE) score with increasing scores on a carotid plaque index.[47]

On the other hand, in the ACAS study, there was no difference in the MMSE score during 5 years of follow-up in the medical and surgical treatment arms.[48] In addition, a systematic review did not find lateralized differences in leukoaraiosis in the presence of carotid stenosis.[49] Finally, a meta-analysis of studies evaluating the effect of CEA on cognitive function found that the data were insufficient to conclude that CEA improved cognition.[50]

Table 4 Current carotid stenosis trials with a medical treatment arm

Study acronym	Design	Status (as of July 2016)
ECST 2	OMT vs OMT + carotid revascularization	Enrolling
	Asymptomatic or symptomatic low risk	
CREST 2	2 Parallel trials	Enrolling
	Asymptomatic average surgical risk	
	CEA + intensive medical management vs intensive medical management alone	
	CAS + intensive medical management vs intensive medical management alone	

Abbreviations: CAS = carotid artery stenting; CEA = carotid endarterectomy; CREST 2 = Carotid Revascularization and Aggressive Medical Management Trial; ECST = European Carotid Surgery Trial; OMT = optimal medical therapy.

PATHOPHYSIOLOGIC CONSIDERATIONS The mechanism of stroke distal to an asymptomatic carotid stenosis is likely to be multifactorial. With noncritical (<70%) levels of stenosis, embolic phenomena may lead to cerebral infarction and factors unrelated to the carotid stenosis (small vessel disease, cardioembolism) must be considered.

With severe degrees of stenosis, there are likely to be heterogeneous causes. Hemodynamic failure typically occurs when both severe stenosis and inadequate collateral circulation are present. A variety of risk stratification tools can be used for patients with asymptomatic carotid stenosis. These include plaque characterization, transcranial Doppler, analysis for silent brain infarcts, and investigation of intraplaque hemorrhage on MRI. These methods are beyond the scope of our article but have been summarized elsewhere.[51]

CURRENT AND FUTURE CAROTID STENOSIS TRIALS Improvements in medical management and carotid revascularization have led to the perfect storm scenario to compare once again the relative benefits of aggressive medical therapy vs CEA or CAS (table 4). Are the improvements in medical therapy sufficient to meaningfully alter the risk/benefit ratio of CEA or CAS in patients with asymptomatic carotid stenosis?

In North America, the Carotid Revascularization and Aggressive Medical Management Trial (CREST 2) has started.[52] As of April 15, 2016, there are 91 centers in the United States and Canada open to randomizing patients. CREST 2 is recruiting patients with asymptomatic carotid stenosis of 70%–99% by duplex ultrasound. Patients are evaluated by treating clinicians to make sure they are not at excessively high risk for carotid revascularization. All patients receive intensive medical management as utilized in the SAMMPRIS study, with slight modifications. Depending on patient suitability for CEA and for CAS, the site physician considers whether to enroll the patient in one of the study's 2 arms. These are comparing intensive medical management alone vs intensive medical management + CEA or intensive medical management alone vs intensive medical management + CAS. CREST 2 advises that treating clinicians consider factors including age in deciding on CEA or CAS portion of the study. For example, patients older than 75 years should be preferentially enrolled in the CEA portion of the study due to the elevated rate of periprocedural stroke/death with CAS in the elderly.[3] The planned sample size of CREST 2 is 2,480 patients.

The only current study evaluating medical therapy vs a revascularization strategy that includes symptomatic patients is the European Carotid Surgery Trial 2 (ECST 2).[53] Patients with recent stroke or TIA are evaluated with a carotid risk score (http://www.stroke.ox.ac.uk/model/form1.html) and if the projected stroke

risk is <4%/year, then the patient may be considered for ECST 2. The trial will compare intensive medical management alone vs intensive medical management + carotid revascularization. Patients may be enrolled with >50% stenosis and it is anticipated that the majority of patients in the revascularization group will receive CEA, although CAS is an option. The primary endpoint is any stroke at any time plus nonstroke deaths within 30 days of revascularization. The planned sample size is 2,000 patients.

In the currently ongoing studies, it is highly desirable to enroll a substantial number of elderly patients, especially above age 80 years. Earlier trials, such as ACAS, excluded patients 80 years or older. This has made it difficult for existing guidelines to provide evidence-based treatment advice for patients >80 years.[54] Since the segment of the population over age 80 years is rapidly increasing, inclusion of these patients is important in current carotid stenosis trials.

DISCUSSION Therapy for extracranial carotid stenosis continues to change and the best treatment for an individual patient remains a moving target. The combination of improvements in medical management, carotid surgery, and carotid stenting has led to the need for contemporary carotid stenosis trials comparing revascularization with optimal medical therapy. Some experts have called for a moratorium on CEA and CAS for asymptomatic stenosis, unless the patients are identified as high risk using risk stratification tools.[51,55] Clinicians have an ethical responsibility to enroll patients in these trials so that we can provide patients with a true reflection of the risk/benefit ratio for modern carotid revascularization when compared with contemporary medical management.

AUTHOR CONTRIBUTIONS

S. Chaturvedi: study concept and design, wrote first draft, interpretation of data. M. Chimowitz: study concept and design, critical revisions. R. Brown: study concept and design, critical revisions. B. Lal: analysis and interpretation of data, critical revisions. J. Meschia: analysis and interpretation of data, critical revisions.

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