Evaluation and Management of Atherosclerotic Carotid Stenosis

James F. Meschia, MD; James P. Klaas, MD; Robert D. Brown Jr, MD; and Thomas G. Brott, MD

From the Department of Neurology, Mayo Clinic, Jacksonville, FL (J.F.M., T.G.B.); and Department of Neurology, Mayo Clinic, Rochester, MN (J.P.K., R.D.B.).

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine and Science is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine and Science designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*.™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Credit Statement: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Objectives: On completion of this article, you should be able to (1) review current strategies and recommendations for diagnosis and management of carotid artery disease; (2) recognize the various methods for assessing carotid stenosis; (3) understand and apply various proven medical methods for reducing the risk of stroke in patients with carotid artery atherosclerosis; and (4) interpret clinical factors that influence the decision whether to choose endarterectomy or stenting for revascularization of carotid stenosis

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine and Science (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

In their editorial and administrative roles, Karl A. Nath, MBChB, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 7/1/2017

Expiration Date: 6/30/2019 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

Abstract

Medical therapies for the prevention of stroke have advanced considerably in the past several years. There can also be a role for mechanical restoration of the lumen by endarterectomy or stenting in selected patients with high-grade atherosclerotic stenosis of the extracranial carotid artery. Endarterectomy is generally recommended for patients with high-grade symptomatic carotid stenosis. Stenting is considered an option for patients at high risk of complications with endarterectomy. Whether revascularization is better than contemporary medical therapy for asymptomatic extracranial carotid stenosis is a subject of several ongoing randomized clinical trials in the United States and internationally.

© 2017 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2017;92(7):1144-1157

Atherosclerosis is not merely a by-product of the sedentary lifestyle and adverse dietary habits typical of the 21st century, because it has afflicted humanity for millennia. A whole-body computed tomographic study of mummies found that about one-third of preindustrial populations, including preagricultural hunter-gatherers, had evidence of atherosclerosis.[1] Atherosclerosis is common in the modern asymptomatic middle-aged population. In one study of asymptomatic individuals between age 40 and 54 years, nearly one-third had ultrasonographic evidence of atherosclerosis in the carotid arteries.[2] When the burden of atherosclerosis becomes severe enough to cause stenosis of the carotid artery, it may act as a source of embolism and, by extension, a cause of ischemic stroke. When cerebral infarction or reversible cerebral ischemia occurs in the perfusion zone distal to a carotid stenosis, the carotid stenosis is said to be symptomatic. The risk of future stroke increases with greater degree of stenosis in patients whose stenosis is symptomatic.[3] About 8% to 15% of ischemic strokes are attributable to carotid atherosclerosis.[4-6] In this narrative review, we summarize the data regarding the evaluation and management of asymptomatic and symptomatic carotid stenosis.

METHODS

This review and our recommendations are supported by a formal search of the medical literature updated since a prior publication on this topic in 2007 in this journal.[7] The Appendix describes the specific approach used to identify the relevant medical literature.

IDENTIFYING AND CHARACTERIZING CAROTID STENOSIS

The most common noninvasive ways of screening for carotid stenosis are duplex ultrasonongraphy, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA). In the case of carotid ultrasonography, the degree of carotid stenosis is largely determined by measuring the velocity of blood flow at various segments of the artery. Criteria have been established for translating velocity measurements into clinically useful stenosis cut points.[8,9] For example, one meta-analysis found a peak systolic velocity of 200 cm/s or greater on ultrasonography to have a sensitivity of 90% and specificity of 94% for diagnosing angiographic stenosis of 70% or more.[8] However, measurement properties vary considerably among laboratories. Factors that can affect the sensitivity of ultrasonography include heavy calcification of the artery and selected contours of the neck. Distal and proximal segments of the extracranial carotid artery cannot be visualized on ultrasonography.

Computed tomographic angiography generally correlates well with carotid ultrasonography, although unlike ultrasonography, it exposes patients to radiation and contrast media.[10] With the recent documentation of the efficacy of mechanical thrombectomy for treating acute ischemic stroke in selected patients,[11] CTA is being used with greater frequency in the initial evaluation of patients.[12] Thus, patients with nondisabling stroke who are being considered for carotid revascularization may have a CTA available for review.

Catheter angiography traditionally has been considered the criterion standard for stenosis assessment in patients with carotid disease. However, MRA fares well by comparison. A study of 103 patients undergoing endarterectomy had their plaque sectioned transversally and assessed planimetrically.[13] All patients had preoperative catheter angiography and MRA. Overall, catheter angiography underestimated histologic stenosis by 14.5%, whereas MRA underestimated histologic stenosis by only 0.7%. Among patients with catheter angiography—defined severe stenosis, MRA overestimated stenosis by 12.1%.

The risk associated with modern digital subtraction angiography is low. The rate of permanent neurologic complications is about 0.5%.[14] Rates of transient neurologic complications range from 0% to 2.4%, and rates of major nonneurologic complications range from 0.26% to 4.3%.[15] Nonetheless, there is little justification to expose asymptomatic patients to the risk of catheter-based angiography before treatment decisions.

The cost of carotid imaging should be considered. A prospective study of 167 patients found that the most cost-effective approach to carotid imaging for evaluating patients before endarterectomy was carotid ultrasonography and contrast-enhanced MRA, proceeding to digital subtraction angiography only in cases of discrepancy in which the MRA is positive for high-grade stenosis and the ultrasonography is negative.[16]

A challenge regarding the use of revascularization for preventing stroke in patients with asymptomatic carotid stenosis is the generally low risk of stroke in untreated patients. Various imaging techniques are being used and developed to stratify risk of stroke in asymptomatic stenosis. Magnetic resonance imaging (MRI) techniques can be used to characterize plaque beyond degree of stenosis. Intraplaque hemorrhage, a lipid-rich necrotic core, and thinning and rupture of the fibrous cap predict risk of stroke.[17] Statistical modeling suggests that detection of intraplaque hemorrhage by MRI may be cost-effective for identifying asymptomatic patients most likely to benefit from carotid endarterectomy.[18] Transcranial Doppler can also stratify risk.[19,20] The Asymptomatic Carotid Emboli Study (ACES) involving 482 patients across 26 centers found that transcranial Doppler—detected microembolic signals are associated with ipsilateral ischemic stroke in patients with asymptomatic carotid stenosis (hazard ratio, 6.37).[21]

SCREENING FOR ASYMPTOMATIC CAROTID STENOSIS

Clinically important carotid stenosis is not rare. Ultrasound studies have found the prevalence of moderate to severe atherosclerotic stenosis to range from 2% to 8% among adults in North America, Europe, and East Asia (Table 1[22-35]). The US Preventive Services Task Force issued an updated recommendation against screening for asymptomatic carotid stenosis in the general population.[36] The Task Force raised concerns that no randomized trial has specifically documented the value of screening for carotid disease as a first step in the prevention of ischemic stroke. Further concerns were raised about false-positive detection of stenosis and of potential complications in patients undergoing revascularization. In clinical populations, carotid ultrasonography is done for diverse indications. A review of Veterans Health Administration patients who had a revascularization procedure for asymptomatic carotid stenosis found that about half had initial ultrasonography for carotid bruit or follow-up of carotid disease.[37]

Several clinical features point to populations with a high pretest probability for detecting carotid stenosis on ultrasonography. Patients with peripheral artery disease (PAD) are at increased risk of having coexisting carotid stenosis. A review of Life Line Screening data from 3.67 million US adults found that the presence of PAD, defined as an ankle-brachial index of less than 0.9, had a 3.28 odds ratio for detection of carotid stenosis.[38] Further, increasing severity of PAD increased the odds of carotid stenosis. Patients with ophthalmoscopic evidence of a cholesterol embolus within a retinal artery (Hollenhorst plaque) have a 13% prevalence of high-grade extracranial carotid stenosis, and patients with both Hollenhorst plaque and carotid bruit have a 37% prevalence of high-grade carotid stenosis.[39] Patients undergoing coronary artery bypass grafting at one referral center had a 38% prevalence of carotid stenosis on ultrasonography.[40] A multisociety evidence-based guideline recommended that screening for carotid stenosis could be considered for asymptomatic patients with either (1) symptomatic PAD, coronary artery disease, or atherosclerotic aortic aneurysm or (2) 2 or more of the following risk factors:

TABLE 1. Prevalence of Atherosclerotic Carotid Stenosis of 50% or Greater Detected by Ultrasonography

Reference, year	No. of patients examined	Age (y)	Prevalence rate (%)	Country
Colgan et al,[22] 1988	348	24-91	4	United States
Ricci et al,[23] 1991	328	>49	5	Italy
O'Leary et al,[24] 1992	5201	≥65	6	United States
Pujia et al,[25] 1992	239	>65	5	United States
Fine-Edelstein et al,[26] 1994	1116	66-93	8	United States
Kiechl et al,[27] 1994	909	40-79	8	Italy
Harer and Gusev,[28] 1996	529	36-84	4.2	Russia
Mannami et al,[29] 1997	1694	50-79	4.4	Japan
Meissner et al,[30] 1999	567	≥45	8	United States
Mineva et al,[31] 2002	500	50-79	6.4	Bulgaria
Mathiesen et al,[32] 2001	6727	25-84	2.2	Norway
Suri et al,[33] 2008	5449	≥65	4.2	United States
Huang et al,[34] 2016	5349	>40	6.7	China
Yan et al,[35] 2016	1375	>60	7.0	China

hypertension, hyperlipidemia, tobacco smoking, a family history of early-onset (less than 60 years of age) atherosclerotic disease in a first-degree relative, or a family history of ischemic stroke.[41]

MEDICAL MANAGEMENT

Although there have been numerous successful clinical trials of various medical strategies for primary and secondary stroke prevention,[42,43] surprisingly few trials have specifically focused on the prevention of stroke by medical means in patients with carotid stenosis. Nonetheless, several evidence-based recommendations can be made.

Antiplatelet and Antithrombotic Therapy

Aspirin, the combination of aspirin and extended-release dipyridamole, and clopidogrel all have efficacy for secondary prevention of ischemic stroke in patients with noncardioembolic stroke.[43] Although long-term aspirin monotherapy is not indicated for primary stroke prevention in low-risk individuals,[42] a multisociety guideline recommends that patients with obstructive or nonobstructive extracranial carotid disease take aspirin at a daily dose of 75 to 325 mg.[44] Aspirin clearly reduces the risk of stroke in patients who have had prior ischemic stroke or transient ischemic attack (TIA).[45] However, aspirin has not been clearly proven to prevent stroke in asymptomatic patients with carotid bruit and stenosis.[46] Aspirin is recommended in asymptomatic patients with carotid stenosis to prevent coronary events. Long-term dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is not generally indicated for secondary stroke prevention because of increased risk of hemorrhage[43] and is not typically used for primary stroke prevention.

For patients undergoing revascularization, antiplatelet therapy is routinely used before and after the procedure, although the practice varies considerably depending on the nature of the revascularization procedure. In the Asymptomatic Carotid Surgery Trial (ACST)-2, survey data indicate that for patients undergoing stenting, 82% of centers used DAPT preprocedure and 86% of centers used DAPT postprocedure, with a mean postprocedure duration of 3 months.[47] For patients undergoing endarterectomy, only 31% of centers used DAPT preoperatively and 24% used DAPT postoperatively, with a mean postoperative duration of 3 months.[47] In the Vascular Quality Initiative using propensity score matching, DAPT was associated with a lower risk of stroke and a higher risk of reoperation for bleeding in patients undergoing endarterectomy.[48] When perioperative aspirin therapy is considered, more is not always better. The randomized double-blind ASA and Carotid Endarterectomy (ACE) Trial involving 2849 patients found that the rate of stroke, myocardial infarction, and death at 1 and 3 months was lower in patients taking low-dose aspirin (81 mg or 325 mg/d) compared with patients taking high-dose aspirin (650 mg to 1300 mg/d).[49]

Antihypertensive Therapy

Blood pressure control is essential for preventing stroke, coronary heart disease, and heart failure.[50] Trials of antihypertensive therapy at the time of an acute stroke have not reported significant effects on short- or long-term outcomes.[51,52] Nonetheless, there remains concern that rapid lowering of blood pressure immediately following stroke in a patient with symptomatic carotid disease might increase infarct volume and worsen neurologic deficit. For asymptomatic patients, the American Heart Association strongly recommends maintaining blood pressure below 140/90 mm Hg.[44] Beyond the several hours to days following a stroke or TIA, patients with symptomatic stenosis should be treated to a target similar to that for patients with asymptomatic stenosis.[44]

Lipid-Lowering Therapy

Most patients with carotid stenosis will benefit from statin therapy for cholesterol lowering. Current guidelines regarding the use of statins for primary prevention focus on adjusting the intensity of therapy based on projected risk of cardiovascular disease. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial randomized patients with a low-density lipoprotein cholesterol (LDL-C) level of 100 to 190 mg/dL (to convert to mmol/L, multiply by 0.0259) within 1 to 6 months following a stroke or TIA to placebo or atorvastatin at 80 mg/d. The subgroup of patients with known carotid stenosis in the trial had a 33% reduction in all strokes and a 43% reduction in major coronary events with atorvastatin.[53] Moderate evidence supports lipid lowering with a statin to a target LDL-C level below 100 mg/dL in all patients with extracranial atherosclerotic stenosis and for those who have had symptoms, lowering to a more aggressive target LDL-C level below 70 mg/dL.[44]

Cigarette Smoking

Smoking increases the risk of stroke in a dose-dependent manner, and quitting smoking decreases the risk.[54] Smoking is also associated with the prevalence of carotid plaque.[55] Smokers should be encouraged to quit, and if necessary, drugs to assist in quitting should be prescribed. Higher pack-years increases inflammatory markers such as highly sensitive C-reactive protein in active smokers, and time from quitting in former smokers reduces inflammatory markers as well as subclinical vascular disease, including carotid disease.[56]

Interventions for Other Risk Factors

Increasing regular physical activity should be encouraged in patients with carotid atherosclerosis. In a study involving more than 3 million carotid ultrasound tests, the intensity of self-reported physical activity was associated with lower odds of carotid atherosclerotic stenosis.[57] Obesity is another modifiable risk factor. As proof of principle, bariatric surgical procedures have been found to reduce the risk of stroke by 50%.[58] Intensive glucose control is generally recommended in patients with diabetes mellitus, although the benefits regarding stroke prevention are not clear.[59]

CAROTID ENDARTERECTOMY

Carotid endarterectomy, a procedure with over a half-century history,[60] is one of the most studied surgical procedures in clinical practice. As a technique that can both cause and prevent stroke, it became clear that only properly powered trials with long-duration follow-up could provide reliable evidence as to the net benefits of the procedure. Historically, randomized clinical trials have focused on treating either symptomatic or asymptomatic patients (Table 2[61-69]).

Symptomatic Patients

There is little controversy regarding the net benefit of carotid endarterectomy in patients with symptomatic moderate- to high-grade stenosis. A key finding was that the benefits are greater for patients with higher degrees of stenosis. A meta-analysis of the 3 major clinical trials pooled individual patient data on 6092 patients and 35,000 patient-years.[70] The analysis revealed that endarterectomy was marginally beneficial for patients with 50% to 69% stenosis, with an annual absolute risk reduction of ipsilateral ischemic stroke of 4.6%. The procedure was substantially more beneficial for patients with 70% to 99% stenosis, with an annual absolute risk reduction of ipsilateral ischemic stroke of 16%. Subgroup analysis revealed the greatest benefits for men, patients 75 years of age or older, and patients randomized within 2 weeks after their last ischemic event. A separate pooled analysis of trial data from the ECST (European Carotid Surgery Trial) and the NASCET (North American Symptomatic Carotid Endarterectomy Trial) concluded that the greatest benefit from endarterectomy comes from early surgical intervention, preferably within 2 weeks.[71] Early revascularization has become commonplace, such that by 2013, 73% of patients in Florida, California, and New York had their procedure (either endarterectomy or stenting) within 14 days of stroke.[72] It should be noted, however, that early revascularization in an unstable patient with either stroke in evolution or crescendo TIA carries a high risk of stroke and death.[73]

Asymptomatic Patients

Although the effectiveness of timely endarterectomy for symptomatic high-grade carotid stenosis is well established, the benefits of endarterectomy in patients with asymptomatic carotid stenosis are less certain. Two pivotal randomized trials support endarterectomy for asymptomatic stenosis: the Asymptomatic Carotid Atherosclerosis Study (ACAS)[67] and the ACST.[69] Both trials enrolled patients with at least 60% stenosis. The ACAS monitored

Mayo Clin Proc. ■ July 2017;92(7):1144-1157 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.020
www.mayoclinicproceedings.org

TABLE 2. Major Randomized Trials of Carotid Endarterectomy[a]

Study, year	Stenosis (%)	No. of randomized patients	Average follow-up (y)	Randomization to surgery (d), median	End point	Medical therapy (%)	Surgical therapy (%)	RRR (%)	ARR (%)	*P* value	NNT
Symptomatic CEA											
NASCET,[61] 1991	70-99	659	1.5	3	Ipsilateral stroke	26	9	65	17	<.001	6[b]
NASCET,[62] 1998	50-69	858	5	3	Ipsilateral stroke	22.2	15.7	29	6.5	.045	15[c]
VACSP,[63] 1991[d]	50-99	189	1	2	Stroke/TIA	19.4	7.7	60	11.7	.011	9[e]
ECST,[64] 2003	≥70[f]	429	6.1	14	Ipsilateral stroke, surgical stroke, or death	NA	NA	NA	21.2	<.0001	5[c]
	50-69	646	6.1	14	Ipsilateral stroke, surgical stroke, or death	NA	NA	NA	5.7	.05	18[c]
CETC,[65] 2003[g]	70-99	1095	5.4	6	Ipsilateral stroke	NA	NA	NA	16	<.001	6[c]
	50-69	1549	5.4	6	Ipsilateral stroke	NA	NA	NA	4.6	.04	22[c]
Asymptomatic CEA											
VACSP,[66] 1993[d]	50-99	444	4	10	Stroke/TIA	24.5	12.8	48	11.7	<.002	9[h]
ACAS,[67] 1995	≥60	1662	2.7	11	Ipsilateral stroke, surgical stroke, or death	11	5.1	53	5.9	.004	17[c]
ACST,[68] 2004	≥60	3120	3.4	30	Any stroke or surgical death	11.8	6.4	46	5.4	<.0001	19[c]
ACST,[69] 2010	≥60	3120	9	30	Any stroke or surgical death	17.9	13.4	25	4.5	.009	22[i]

[a]ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ARR = absolute risk reduction; CEA = carotid endarterectomy; CETC= Carotid Endarterectomy Trialists' Collaboration; ECST = European Carotid Surgery Trial; NA = not available; NASCET = North American Symptomatic Carotid Endarterectomy Trial; NNT = number needed to treat; RRR = relative risk reduction; TIA = transient ischemic attack; VACSP = Veterans Affairs Cooperative Studies Program.

[b]At 2 years.

[c]At 5 years.

[d]Only males included.

[e]At 1 year.

[f]Without near occlusion.

[g]Pooled analysis of NASCET, ECST, and VACSP trials.

[h]At 4 years.

[i]At 10 years.

patients for an average of 2.7 years and found that surgical intervention resulted in an absolute reduction in the risk of ipsilateral stroke, surgical stroke, or death of 5.9%. The ACST monitored patients for an average of 9 years and found that surgical treatment resulted in an absolute reduction in the risk of any stroke or surgical death of 4.5%.

Those who argue against endarterectomy in this patient population today point to the steady decline in risk of stroke in medically treated patients from the 1980s to 2010, with recent studies reporting ipsilateral stroke rates of less than 1% per year.[74] Trials are under way to clarify the role of endarterectomy compared with intensive medical therapy in patients with asymptomatic carotid stenosis. The Stent-protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy (SPACE)-2 trial, with centers in Germany, Austria, and Switzerland, is comparing best medical therapy to revascularization by either endarterectomy or stenting. Slow recruitment into the SPACE-2 trial led to halting of recruitment after randomization of 513 patients; however, patients continue to be followed up for end points.[75] The National Institute of Neurological Disorders and Stroke Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2) is also comparing best medical therapy with revascularization by either endarterectomy or stenting. A total of 574 patients have been recruited as of April 13, 2017, and recruitment and follow-up are ongoing.

CAROTID ANGIOPLASTY AND STENTING

Carotid angioplasty and stenting evolved as a potentially safer alternative to endarterectomy. A series of randomized trials ensued, mostly in patients with symptomatic stenosis[7,76-91] (Table 3).

Patients at High Risk for Endarterectomy

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial tested whether stenting was noninferior to endarterectomy for patients at high risk for complications following endarterectomy.[83] Patients were considered at high risk for complications with endarterectomy for a number of reasons, including history of contralateral carotid occlusion or laryngeal nerve palsy, severe coronary artery disease, and radical dissection or radiation therapy to the neck. In this noninferiority trial, carotid stenting was found to be noninferior to endarterectomy for the primary end point (the composite primary end point of death, stroke, or myocardial infarction within 30 days after the intervention or ipsilateral stroke between 31 days and 1 year).[80] The 3-year rates for the secondary composite outcome of death, stroke, or myocardial infarction within 30 days or ipsilateral stroke thereafter were 26.2% for stenting and 30.3% for endarterectomy, a difference that was not significant.[83]

Symptomatic Patients

Using data from 3 randomized trials, the Carotid Stenting Trialists' Collaboration found that any stroke or death occurred significantly more often in the stenting group than the endarterectomy group (risk ratio, 1.53).[92] Using data from 4 trials, the Collaboration found that endarterectomy was clearly superior to stenting in symptomatic patients over age 70 to 74 years because of the increased risk of stroke with age for stenting but not for endarterectomy.[93] The long-term results of the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), which extended follow-up to 10 years, did not document a significant difference between endarterectomy and stenting when including perioperative myocardial infarction in the primary outcome.[90]

Carotid stenting generally has higher procedural stroke rates than endarterectomy in randomized trials. However, the picture is slightly more complex than implied by simple counts of stroke. In the International Carotid Stenting Study (ICSS)-Magnetic Resonance Imaging Substudy, patients were scanned using 1.5-T or 3.0-T MRI at 1 to 7 days before treatment, 1 to 3 days after treatment, and 27 to 33 days after treatment. Patients who had stenting had higher lesion counts than patients who had endarterectomy, but the lesions tended to be smaller and were more likely to involve the cortex and subjacent white matter.[94] Furthermore,

TABLE 3. Randomized Trials of Carotid Endarterectomy Compared With Carotid Angioplasty[a,b]

Study, year	No. of randomized patients	Stenosis (%)	Patient status	Embolic protection	Findings
Naylor et al,[76] 1998[c]	17	70-99	Symptomatic	No	Stopped early: 0/10 strokes CEA, 5/7 strokes CAS
CAVATAS,[77] 2001	504	50-99	Symptomatic	Optional	No significant difference in 30-d rate of stroke or death
Brooks et al,[78] 2001[c]	104	70-99	Symptomatic	No	No stroke in either treatment group
Brooks et al,[79] 2004[c]	85	80-99	Asymptomatic	No	No stroke or death in either treatment group
SAPPHIRE,[80] 2004	334	50-99	Both, high risk	Yes	Primary end point: 12.2% CAS, 20.1% CEA (*P*=.004 for noninferiority, *P*=.053 for superiority)
SAPPHIRE,[83] 2008	334	50-99	Both, high risk	Yes	No significant difference in long-term outcomes between CAS and CEA
EVA-3S,[82] 2006	527	60-99	Symptomatic	Yes	30-Day incidence of disabling stroke or death: 1.5% CEA, 3.4% CAS
SPACE,[81] 2006	1200	50-99	Symptomatic	Optional	Failed to prove noninferiority. 30-Day rate of death or ipsilateral stroke: 6.84% CAS, 6.34% CEA
CREST,[85] 2010	2502	50-99	Both	Yes	No significant difference in 4-y rates of primary end point between CAS (7.2%) and CEA (6.8%)
CREST,[90] 2016	2502	50-99	Both	Yes	No significant difference in 10-y rates of primary end point between CAS (11.8%) and CEA (9.9)
ICSS (CAVATAS-2),[86] 2010	1713	50-99	Symptomatic	Optional	CAS has a 3.3% higher risk of stroke, death, or procedural myocardial infarction vs CEA in the short term (120 d)
ICSS (CAVATAS-2),[89] 2015	1713	50-99	Symptomatic	Optional	No significant difference in 5-y risk of fatal or disabling stroke between CAS (6.4%) and CEA (6.5%)
ACT I,[91] 2016	1453	70-99	Asymptomatic	Yes	CAS was noninferior to CEA for primary composite end point (event rate 3.8% and 3.4%, respectively)
Ongoing trials					**Study Design**
SPACE-2	Goal: 3640	70-99	Asymptomatic	Optional	2 Parallel trials: CEA + OMT vs OMT alone and CAS + OMT vs OMT alone
ACST-2	Goal: 5000	70-99	Asymptomatic	Optional	CEA compared to CAS
ECST-2	Goal: 2000	50-99	Both	Optional	Revascularization (CEA or CAS) compared with OMT alone
CREST-2	Goal: 2480	70-99	Asymptomatic	Yes	2 Parallel trials: CEA + OMT vs OMT alone; CAS + OMT vs OMT alone

[a]ACST = Asymptomatic Carotid Surgery Trial; ACT = Asymptomatic Carotid Trial; BMT = best medical therapy; CAS = carotid artery stenting; CAVATAS = Carotid and Vertebral Artery Transluminal Angioplasty Study; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy Versus Stenting Trial; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis; ICSS = International Carotid Stenting Study; OMT = optimal medical treatment; SAPPHIRE = Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy; SPACE = Stent-Protected Percutaneous Angioplasty of the Carotid Versus Endarterectomy.

[b]Angioplasty may or may not have been done with stenting.

[c]Single-center study.

the total lesion volume was not significantly different between treatment groups. The functional implications of these topographic differences are unknown.

Asymptomatic Patients

About half of the patients in CREST were asymptomatic at randomization. An analysis stratified by symptomatic status revealed no significant difference for the primary end point in CREST for asymptomatic patients.[95] The Asymptomatic Carotid Trial (ACT)-1 randomized 1453 patients at standard risk of complications with endarterectomy to either endarterectomy or protected stenting.[91] There was noninferiority for the primary end point of perioperative stroke, death, or myocardial infarction or ipsilateral infarction within 1 year.

Factors Influencing the Approach to Revascularization

Many patients with carotid stenosis can undergo revascularization safely and effectively by either endarterectomy or stenting. However, some anatomic and clinical considerations should influence which approach is preferred (Table 4). It has been argued that carotid artery stenting is less invasive, and thus one might suspect that stenting would be less expensive. However, formal cost-effectiveness studies have not confirmed this to be the case. In the ICSS, there was no significant difference in adjusted costs between endarterectomy and stenting.[96] Stenting had slightly higher costs in the CREST trial than endarterectomy.[97]

TABLE 4. Factors to Consider in Choice of Carotid Revascularization Method

Factor	Favors
Age >70 y	CEA
Recently symptomatic patient (<2 wk)	CEA
Tortuous and/or heavily calcified vessels	CEA
Contralateral carotid occlusion	CAS
Restenosis after prior CEA	CAS
Previous neck operation and/or radiation	CAS
Laryngeal nerve palsy	CAS
Periprocedural risk of:	
Myocardial infarction	CAS
Cranial nerve injury	CAS
Stroke	CEA
Death	CEA
Long-term risk of:	
Myocardial infarction	No difference
Stroke	No difference
Death	No difference

CAS = carotid artery stenting; CEA = carotid endarterectomy.

EFFECT OF EXPERIENCE ON OUTCOMES

With a caveat to be discussed subsequently, experience matters both for endarterectomy and stenting. A Canadian hospital registry found that low hospital and surgeon case volumes are risk factors for complications following endarterectomy.[98] A 10-year Maryland statewide audit found surgeon volume to inversely correlate with risk of death following endarterectomy.[99] Operator experience, as measured by average time interval between carotid stenting cases, was an independent predictor of death, stroke, or myocardial infarction in the Carotid Stenting for High Surgical-Risk Patients; Evaluating Outcomes Through the Collection of Clinical Evidence (CHOICE) registry.[100] The Nationwide Inpatient Sample found that case volume rather than operator training specialty predicted stenting outcomes.[101] The Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE) 2 prospective, independently adjudicated registry reported an inverse relationship between perioperative event rates and hospital and operator volumes.[102] The Carotid Stenting Trialists' Collaboration found that the 30-day risk of stroke or death was inversely related to in-trial operator volumes.[103] The caveat to operator experience being the cause of good outcomes, rather than a marker, is the given operator's threshold for operation or stent placement. For example, busy surgeons or interventionists could be busier than their colleagues in part, or in large part, because of a lower threshold to intervene. Hence, their patients would be less often symptomatic and so less often at high risk. The operative or stenting outcomes would be expected to be more favorable because of the lower threshold to intervene and not because of experience. In addition, symptomatic patients may be more likely to be referred to neurologically trained surgeons and interventionists than vascular surgeons or interventionists trained in vascular surgery or cardiology. The pool of symptomatic patients is much lower than the pool of asymptomatic patients. The ratio of the prevalence of high-grade asymptomatic carotid stenosis to recent (within 6 months) symptomatic carotid stenosis may be as high as 38:1 (estimated using a 3% prevalence of carotid stenosis in the general population over age 65 years, an estimate of 345,825 prevalent recent ischemic strokes,[104] an 8% rate of carotid stenosis among patients with ischemic stroke,[6] an estimate of 120,000 prevalent recent TIAs,[105] and a 13% rate of carotid stenosis among patients with TIA[106]). Of course, not every patient with asymptomatic carotid stenosis will be detected, and not every patient with recent ischemic stroke will be suitable for carotid intervention because of acquired disability.

Neurosurgeons or neurointerventionists could have both a lower frequency of procedures performed overall and a higher proportion of procedures performed on a more at-risk cohort of patients. This circumstance, which is consistent with practice patterns, would be a confounder of cause and effect for experience and improved outcomes.

CONCLUSION

Patients with recent nondisabling ischemic stroke or TIA need prompt evaluation for possible high-grade carotid stenosis and if detected, referral for revascularization. Patients with asymptomatic stenosis may also be candidates for revascularization, but the net benefit is likely to be low even under the best of circumstances because unselected asymptomatic patients are at low long-term risk of stroke without revascularization. Techniques like transcranial ultrasonographic assessment for microemboli and MRI for plaque may help to stratify risk in asymptomatic patients and thereby identify patients most likely to benefit from endarterectomy or stenting, but further research is needed. Patients who are at high risk for complications with endarterectomy may be at lower risk for complications with stenting, as reported in the SAPPHIRE study. However, in these high-risk patients, neither procedure may be the preferred course of action because of an unacceptably high absolute risk of complications with either one. Making decisions regarding whether and how to revascularize patients is only part of the management of carotid stenosis and should not distract from the importance of control of medical risk factors, including hypertension, hyperlipidemia, and smoking cessation.

APPENDIX

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> **Search Strategy:**
1 exp *Carotid Stenosis/(10685)
2 exp Angioplasty/(57482)
3 exp Endarterectomy, Carotid/(7586)
4 (carotid adj2 stent$).mp. [mp= Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word] (3460)
5 1 and 2 (2030)
6 1 and 4 (2124)
7 3 or 5 or 6 (9414)
8 limit 7 to (English language and humans and yr="2007-2016" and "all adult (19 plus years)") (2496)
9 8 and (symptomatic$ or asymptomatic$).mp. [mp= Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word] (1097)
10 limit 9 to (clinical trial, all or controlled clinical trial or evaluation studies or meta-analysis or multicenter study or randomized controlled trial or validation studies) (288)
11 from 10 keep 1-288 (288)
Search run on August 23, 2016, by Tara J. Brigham, MLIS.

Abbreviations and Acronyms: **ACST** = Asymptomatic Carotid Surgery Trial; **CREST** = Carotid Revascularization Endarterectomy Versus Stenting Trial; **CTA** = computed tomographic angiography; **DAPT** = dual antiplatelet therapy; **LDL-C** = low-density lipoprotein cholesterol; **MRA** = magnetic resonance angiography; **MRI** = magnetic resonance imaging; **PAD** = peripheral artery disease; **TIA** = transient ischemic attack

Correspondence: Address to James F. Meschia, MD, Department of Neurology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224 (Meschia.james@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Neurosciences will be available for purchase from our website www.mayoclinicproceedings.org.

The Symposium on Neurosciences will continue in an upcoming issue.

REFERENCES

1. Thompson RC, Allam AH, Lombardi GP, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. *Lancet*. 2013; 381(9873):1211-1222.
2. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution, and multiterritorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. *Circulation*. 2015;131(24):2104-2113.

3. Sheehan OC, Kyne L, Kelly LA, et al. Population-based study of ABCD2 score, carotid stenosis, and atrial fibrillation for early stroke prediction after transient ischemic attack: the North Dublin TIA study. *Stroke*. 2010;41(5):844-850.
4. Hajat C, Heuschmann PU, Coshall C, et al. Incidence of aetiological subtypes of stroke in a multi-ethnic population based study: the South London Stroke Register. *J Neurol Neurosurg Psychiatry*. 2011;82(5):527-533.
5. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes; a population-based study. *Stroke*. 2001;32(12):2735-2740.
6. Flaherty ML, Kissela B, Khoury JC, et al. Carotid artery stenosis as a cause of stroke. *Neuroepidemiology*. 2013;40(1):36-41.
7. Meschia JF, Brott TG, Hobson RW II. Diagnosis and invasive management of carotid atherosclerotic stenosis. *Mayo Clin Proc*. 2007;82(7):851-858.
8. Jahromi AS, Cinà CS, Liu Y, Clase CM. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. *J Vasc Surg*. 2005;41(6):962-972.
9. Shaalan WE, Wahlgren CM, Desai T, Piano G, Skelly C, Bassiouny HS. Reappraisal of velocity criteria for carotid bulb/internal carotid artery stenosis utilizing high-resolution B-mode ultrasound validated with computed tomography angiography. *J Vasc Surg*. 2008;48(1):104-112.
10. Matz O, Nikoubashman O, Rajkumar P, et al. Grading of proximal internal carotid artery (ICA) stenosis by Doppler/duplex ultrasound (DUS) and computed tomographic angiography (CTA): correlation and interrater reliability in real-life practice. *Acta Neurol Belg*. 2017;117(1):183-188.
11. Powers WJ, Derdeyn CP, Biller J, et al; American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020-3035.
12. Ehrlich ME, Turner HL, Currie LJ, Wintermark M, Worrall BB, Southerland AM. Safety of computed tomographic angiography in the evaluation of patients with acute stroke: a single-center experience. *Stroke*. 2016;47(8):2045-2050.
13. Netuka D, Ostrý S, Belsán T, et al. Magnetic resonance angiography, digital subtraction angiography and Doppler ultrasonography in detection of carotid artery stenosis: a comparison with findings from histological specimens. *Acta Neurochir (Wien)*. 2010;152(7):1215-1221.
14. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. *Radiology*. 2003;227(2):522-528.
15. Al-Ameri H, Thomas ML, Yoon A, et al. Complication rate of diagnostic carotid angiography performed by interventional cardiologists. *Catheter Cardiovasc Interv*. 2009;73(5):661-665.
16. U-King-Im JM, Hollingworth W, Trivedi RA, et al. Cost-effectiveness of diagnostic strategies prior to carotid endarterectomy. *Ann Neurol*. 2005;58(4):506-515.
17. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke*. 2013;44(11):3071-3077.
18. Gupta A, Mushlin AI, Kamel H, Navi BB, Pandya A. Cost-effectiveness of carotid plaque MR imaging as a stroke risk stratification tool in asymptomatic carotid artery stenosis [published correction appears in *Radiology*. 2015;277(3):927]. *Radiology*. 2015;277(3):763-772.
19. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. *Stroke*. 2005;36(11):2373-2378.
20. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology*. 2011;77(8):744-750.
21. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol*. 2010;9(7):663-671.
22. Colgan MP, Strode GR, Sommer JD, Gibbs JL, Sumner DS. Prevalence of asymptomatic carotid disease: results of duplex scanning in 348 unselected volunteers. *J Vasc Surg*. 1988;8(6):674-678.
23. Ricci S, Flamini FO, Marini M, et al. The prevalence of stenosis of the internal carotid in subjects over 49: a population study [in Italian]. *Epidemiol Prev*. 1991;13(48-49):173-176.
24. O'Leary DH, Polak JF, Kronmal RA, et al; CHS Collaborative Research Group. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. *Stroke*. 1992;23(12):1752-1760.
25. Pujia A, Rubba P, Spencer MP. Prevalence of extracranial carotid artery disease detectable by echo-Doppler in an elderly population. *Stroke*. 1992;23(6):818-822.
26. Fine-Edelstein JS, Wolf PA, O'Leary DH, et al. Precursors of extracranial carotid atherosclerosis in the Framingham Study. *Neurology*. 1994;44(6):1046-1050.
27. Kiechl S, Willeit J, Rungger G, Egger G, Oberhollenzer F. Quantitative assessment of carotid atherosclerosis in a healthy population. *Neuroepidemiology*. 1994;13(6):314-317.
28. Harer C, Gusev EI. Asymptomatic cervical artery stenoses in Moscow. *Acta Neurol Scand*. 1996;93(4):286-290.
29. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. *Stroke*. 1997;28(3):518-525.
30. Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. *Mayo Clin Proc*. 1999;74(9):862-869.
31. Mineva PP, Manchev IC, Hadjiev DI. Prevalence and outcome of asymptomatic carotid stenosis: a population-based ultrasonographic study. *Eur J Neurol*. 2002;9(4):383-388.
32. Mathiesen EB, Joakimsen O, Bønaa KH. Prevalence of and risk factors associated with carotid artery stenosis: the Tromso Study. *Cerebrovasc Dis*. 2001;12(1):44-51.
33. Suri MF, Ezzeddine MA, Lakshminarayan K, Divani AA, Qureshi AI. Validation of two different grading schemes to identify patients with asymptomatic carotid artery stenosis in general population. *J Neuroimaging*. 2008;18(2):142-147.
34. Huang X, Wang A, Liu X, et al. Association between high sensitivity C-reactive protein and prevalence of asymptomatic carotid artery stenosis. *Atherosclerosis*. 2016;246:44-49.
35. Yan Z, Liang Y, Shi J, et al. Carotid stenosis and cognitive impairment amongst older Chinese adults living in a rural area: a population-based study. *Eur J Neurol*. 2016;23(1):201-204.
36. LeFevre ML; U.S. Preventive Services Task Force. Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement [published correction appears in *Ann Intern Med*. 2015;162(4):323]. *Ann Intern Med*. 2014;161(5):356-362.
37. Keyhani S, Cheng EM, Naseri A, et al. Common reasons that asymptomatic patients who are 65 years and older receive carotid imaging. *JAMA Intern Med*. 2016;176(5):626-633.
38. Razzouk L, Rockman CB, Patel MR, et al. Co-existence of vascular disease in different arterial beds: peripheral artery disease and carotid artery stenosis—data from Life Line Screening®. *Atherosclerosis*. 2015;241(2):687-691.

39. Bakri SJ, Luqman A, Pathik B, Chandrasekaran K. Is carotid ultrasound necessary in the clinical evaluation of the asymptomatic Hollenhorst plaque? (An American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc*. 2013;111:17-23.
40. Taneja S, Chauhan S, Kapoor PM, Jagia P, Bisoi AK. Prevalence of carotid artery stenosis in neurologically asymptomatic patients undergoing coronary artery bypass grafting for coronary artery disease: role of anesthesiologist in preoperative assessment and intraoperative management. *Ann Card Anaesth*. 2016;19(1):76-83.
41. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery [published corrections appear in *Circulation*. 2012;126(2):e26 and *Circulation*. 2011;124(4):e146]. *Circulation*. 2011;124(4):e54-e130.
42. Meschia JF, Bushnell C, Boden-Albala B, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(12):3754-3832.
43. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2015;46(2):e54]. *Stroke*. 2014;45(7):2160-2236.
44. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary; a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery [published correction appears in *Circulation*. 2011;124(4):e145]. *Circulation*. 2011;124(4):489-532.
45. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324(7330):141]. *BMJ*. 2002;324(7329):71-86.
46. Côté R, Battista RN, Abrahamowicz M, Langlois Y, Bourque F, Mackey A; Asymptomatic Cervical Bruit Study Group. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. *Ann Intern Med*. 1995;123(9):649-655.
47. Huibers A, Halliday A, Bulbulia R, Coppi G, de Borst GJ; ACST-2 Collaborative Group. Antiplatelet therapy in carotid artery stenting and carotid endarterectomy in the Asymptomatic Carotid Surgery Trial-2. *Eur J Vasc Endovasc Surg*. 2016;51(3):336-342.
48. Jones DW, Goodney PP, Conrad MF, et al. Dual antiplatelet therapy reduces stroke but increases bleeding at the time of carotid endarterectomy. *J Vasc Surg*. 2016;63(5):1262-1270e3.
49. Taylor DW, Barnett HJ, Haynes RB, et al; ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet*. 1999;353(9171):2179-2184.
50. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967.
51. Zhao R, Liu FD, Wang S, et al. Blood pressure reduction in the acute phase of an ischemic stroke does not improve short- or long-term dependency or mortality: a meta-analysis of current literature. *Medicine (Baltimore)*. 2015;94(23):e896.
52. Lee M, Ovbiagele B, Hong KS, et al. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. *Stroke*. 2015;46(7):1883-1889.
53. Sillesen H, Amarenco P, Hennerici MG, et al; SPARCL Investigators. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke*. 2008;39(12):3297-3302.
54. Mons U, Müezzinler A, Gellert C, et al; CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ*. 2015;350:h1551.
55. Högberg D, Kragsterman B, Björck M, Tjärnström J, Wanhainen A. Carotid artery atherosclerosis among 65-year-old Swedish men—a population-based screening study. *Eur J Vasc Endovasc Surg*. 2014;48(1):5-10.
56. McEvoy JW, Nasir K, DeFilippis AP, et al. Relationship of cigarette smoking with inflammation and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35(4):1002-1010.
57. Stein RA, Rockman CB, Guo Y, et al. Association between physical activity and peripheral artery disease and carotid artery stenosis in a self-referred population of 3 million adults. *Arterioscler Thromb Vasc Biol*. 2015;35(1):206-212.
58. Kwok CS, Pradhan A, Khan MA, et al. Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. *Int J Cardiol*. 2014;173(1):20-28.
59. Mattila TK, de Boer A. Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs*. 2010;70(17):2229-2245.
60. De Bakey ME, Crawford ES, Morris GC Jr, Cooley DA. Arterial reconstructive operations for cerebrovascular insufficiency due to extracranial arterial occlusive disease. *J Cardiovasc Surg (Torino)*. 1962;3:12-25.
61. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325(7):445-453.
62. Barnett HJ, Taylor DW, Eliasziw M, et al; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med*. 1998;339(20):1415-1425.

63. Mayberg MR, Wilson SE, Yatsu F, et al; Veterans Affairs Cooperative Studies Program 309 Trialist Group. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *JAMA*. 1991;266(23):3289-3294.

64. Rothwell PM, Gutnikov SA, Warlow CP; European Carotid Surgery Trialist's Collaboration. Reanalysis of the final results of the European Carotid Surgery Trial. *Stroke*. 2003;34(2):514-523.

65. Rothwell PM, Eliasziw M, Gutnikov SA, et al; Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361(9352):107-116.

66. Hobson RW II, Weiss DG, Fields WS, et al; Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med*. 1993;328(4):221-227.

67. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273(18):1421-1428.

68. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial [published correction appears in *Lancet*. 2004;364(9432):416]. *Lancet*. 2004;363(9420):1491-1502.

69. Halliday A, Harrison M, Hayter E, et al; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-Year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet*. 2010;376(9746):1074-1084.

70. Rerkasem K, Rothwell PM. Carotid endarterectomy for symptomatic carotid stenosis. *Cochrane Database Syst Rev*. 2011;(4):CD001081.

71. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363(9413):915-924.

72. Reznik M, Kamel H, Gialdini G, Pandya A, Navi BB, Gupta A. Timing of carotid revascularization procedures after ischemic stroke. *Stroke*. 2017;48(1):225-228.

73. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke*. 2009;40(10):e564-e572.

74. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. *Nat Rev Cardiol*. 2011;9(2):116-124.

75. Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W; SPACE 2 Investigators. SPACE-2: a missed opportunity to compare carotid endarterectomy, carotid stenting, and best medical treatment in patients with asymptomatic carotid stenoses. *Eur J Vasc Endovasc Surg*. 2016;51(6):761-765.

76. Naylor AR, Bolia A, Abbott RJ, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg*. 1998;28(2):326-334.

77. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357(9270):1729-1737.

78. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol*. 2001;38(6):1589-1595.

79. Brooks WH, McClure RR, Jones MR, Coleman TL, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery*. 2004;54(2):318-324.

80. Yadav JS, Wholey MH, Kuntz RE, et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351(15):1493-1501.

81. SPACE Collaborative Group. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial [published correction appears in *Lancet*. 2006;368(9543):1238]. *Lancet*. 2006;368(9543):1239-1247.

82. Mas JL, Chatellier G, Beyssen B, et al; EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355(16):1660-1671.

83. Gurm HS, Yadav JS, Fayad P, et al; SAPPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358(15):1572-1579.

84. Rudarakanchana N, Dialynas M, Halliday A. Asymptomatic Carotid Surgery Trial-2 (ACST-2): rationale for a randomised clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. *Eur J Vasc Endovasc Surg*. 2009;38(2):239-242.

85. Brott TG, Hobson RW 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363(1):11-23.

86. International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet*. 2010;375(9719):985-997.

87. Perkins WJ, Lanzino G, Brott TG. Carotid stenting vs endarterectomy: new results in perspective. *Mayo Clin Proc*. 2010;85(12):1101-1108.

88. Reiff T, Eckstein HH, Amiri H, Hacke W, Ringleb PA; SPACE-2 Study Group. Modification of SPACE-2 study design. *Int J Stroke*. 2014;9(3):E12-E13.

89. Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet*. 2015;385(9967):529-538.

90. Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med*. 2016;374(11):1021-1031.

91. Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med*. 2016;374(11):1011-1020.

92. Carotid Stenting Trialists' Collaboration. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*. 2010;376(9746):1062-1073.

93. Howard G, Roubin GS, Jansen O, et al; Carotid Stenting Trialists' Collaboration. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials [published correction appears in *Lancet*. 2016;387(10025):1276]. *Lancet*. 2016;387(10025):1305-1311.

94. Gensicke H, Zumbrunn T, Jongen LM, et al; ICSS-MRI Substudy Investigators. Characteristics of ischemic brain lesions after stenting or endarterectomy for symptomatic carotid artery stenosis: results from the International Carotid Stenting Study-Magnetic Resonance Imaging Substudy. *Stroke*. 2013;44(1):80-86.

95. Silver FL, Mackey A, Clark WM, et al; CREST Investigators. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke*. 2011;42(3):675-680.

96. Morris S, Patel NV, Dobson J, et al; International Carotid Stenting Study Investigators. Cost-utility analysis of stenting versus endarterectomy in the International Carotid Stenting Study. *Int J Stroke*. 2016;11(4):446-453.

97. Vilain KR, Magnuson EA, Li H, et al. Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Stroke*. 2012;43(9):2408-2416.

98. Feasby TE, Quan H, Ghali WA. Hospital and surgeon determinants of carotid endarterectomy outcomes. *Arch Neurol*. 2002;59(12):1877-1881.

99. Nazarian SM, Yenokyan G, Thompson RE, Griswold ME, Chang DC, Perler BA. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. *J Vasc Surg*. 2008;48(2):343-350.

100. Shishehbor MH, Venkatachalam S, Gray WA, et al. Experience and outcomes with carotid artery stenting: an analysis of the CHOICE study (Carotid Stenting for High Surgical-Risk Patients; Evaluating Outcomes Through the Collection of Clinical Evidence). *J Am Coll Cardiol Interv*. 2014;7(11): 1307-1317.

101. Sgroi MD, Darby GC, Kabutey NK, Barleben AR, Lane JS III, Fujitani RM. Experience matters more than specialty for carotid stenting outcomes. *J Vasc Surg*. 2015;61(4):933-938.

102. Gray WA, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P; CAPTURE 2 Investigators and Executive Committee. Influence of site and operator characteristics on carotid artery stent outcomes: analysis of the CAPTURE 2 (Carotid ACCU-LINK/ACCUNET Post Approval Trial to Uncover Rare Events) clinical study. *J Am Coll Cardiol Interv*. 2011;4(2): 235-246.

103. Calvet D, Mas JL, Algra A, et al. Carotid stenting: is there an operator effect? a pooled analysis from the Carotid Stenting Trialists' Collaboration. *Stroke*. 2014;45(2): 527-532.

104. Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):447-454.

105. Kleindorfer D, Panagos P, Pancioli A, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005;36(4):720-723.

106. Walker J, Isherwood J, Eveson D, Naylor AR. Triaging TIA/minor stroke patients using the ABCD2 score does not predict those with significant carotid disease. *Eur J Vasc Endovasc Surg*. 2012;43(5):495-498.