REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Management of Atherosclerotic Carotid Artery Disease: A Brief Overview and Update

Sara Hassani, MD, Marc Fisher, MD

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass.

ABSTRACT

Extracranial carotid atherosclerotic disease has been associated with approximately 15%-20% of ischemic stroke cases and is a leading cause of mortality and disability worldwide. Medical, surgical, and endovascular therapies for the prevention of stroke from carotid disease have advanced considerably over the past quarter century. The objective of this review is to outline the clinical presentation of symptomatic carotid artery stenosis and the risk factors associated with development of carotid artery stenosis and then summarize the current evidence-based medical treatment modalities, along with available surgical and endovascular therapies.

 • The American Journal of Medicine (2022) 135:430–434

KEYWORDS: Carotid artery atherosclerotic disease; Carotid artery stenting; Carotid endarterectomy; Ischemic stroke prevention; Transcarotid revascularization

Population-based studies have estimated that extracranial carotid artery stenosis from atherosclerotic disease is associated with 15%-20% of ischemic strokes[1-3] and leads to subsequent substantial disability. With the aging of the general population and the wide availability of noninvasive imaging modalities, physicians in general clinical practice frequently encounter patients with carotid artery stenosis. Identification of the subset of these patients at high risk of stroke, and treatment of this population, has become a vigorous and fruitful area of research and therapeutic endeavor, generating spirited debate and a myriad of new treatment regimens. This article will briefly outline the clinical presentation of symptomatic carotid artery stenosis and the risk factors associated with development of carotid artery stenosis,and then review the current evidence-based medical treatment modalities, along with the surgical and endovascular therapies available.

Overall, the prevalence of severe atherosclerotic carotid artery stenosis, which is defined as ≥70%, in the general population is estimated to be 0.1% to 3%, with an increased prevalence noted in men, **Caucasians**, American Indians, those with coronary artery disease, and the elderly (older than 65 years of age).[4] Modifiable risk factors associated with carotid artery stenosis include smoking, hypertension, hyperlipidemia, and diabetes mellitus.[1]

Clearly defining and distinguishing between symptomatic and asymptomatic carotid artery stenosis is important because the natural history, and subsequent extrapolations on the benefit of medical treatment or surgical or endovascular procedures, differs markedly between them. A patient with carotid artery stenosis is considered symptomatic if the patient has transient or permanent loss of vision in the ipsilateral eye or focal neurologic symptoms in the contralateral cerebral hemisphere. Symptoms of carotid artery stenosis include ipsilateral transient visual obscuration (amaurosis fugax) from retinal ischemia, contralateral weakness or numbness of an arm, a leg, or the face, or of a combination of these locations, a visual field defect, dysarthria, and in the case of dominant (usually left) hemisphere involvement, aphasia. In daily medical practice, carotid artery stenosis is identified in many patients during the workup of vaguely defined episodes of "dizziness," generalized weakness, syncope or near-syncope episodes, "blurry vision," or transient positive visual phenomena (eg, "floaters"). Such nonspecific symptoms in patients with carotid artery stenosis do not qualify as symptomatic

Funding: None.

Conflicts of Interest: None.

Authorship: Both authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Sara Hassani, MD, Beth Israel Deaconess Medical Center, Stroke Division, 330 Brookline Ave, Palmer 127, Boston, MA, 02215.

E-mail address: sara.hassani@gmail.com

0002-9343/
https://doi.org/10.1016/j.amjmed.2021.09.027

vascular events; these patients are considered asymptomatic, even in the presence of high-grade (over 70%) or severe carotid artery stenosis.

Initial management of symptomatic carotid artery stenosis should always attend to modifying cardiovascular risk by starting antiplatelet therapy with aspirin, as well as aggressive control of vascular risk factors (Table). All patients presenting with carotid artery stenosis should be started on aspirin.[5] Class I evidence suggests that perioperative single antiplatelet therapy with low-dose aspirin (81 mg) reduces the risk of stroke perioperatively for up to 6 months.[5] Beyond the routine implementation of aspirin therapy, current recommendations regarding medical treatments for carotid artery stenosis have evolved from a series of clinical trials over the past 50 years that progressively expanded the pharmacologic toolbox available to clinicians.[6] Based on some early studies, many providers have begun aggressively treating carotid artery stenosis by adding novel antiplatelet agents to aspirin for short periods of time[7] and high-intensity statins. Clopidogrel or ticagrelor[8] are both efficacious options that can be added to aspirin for secondary prevention of ischemic stroke in patients with symptomatic carotid artery stenosis. Long-term dual antiplatelet therapy (DAPT) with aspirin, together with clopidogrel or ticagrelor, is not generally indicated for secondary stroke prevention because of increased risk of hemorrhage over time.[8,9] However, in the early phase of symptomatic carotid stenosis where the risk of recurrence is particularly high, dual antiplatelet therapy has been shown to reduce the risk of recurrent asymptomatic cerebral embolization and stroke,[10] though the optimal duration is unknown.

CLINICAL SIGNIFICANCE

- Studies estimate that extracranial carotid artery stenosis from atherosclerotic disease is associated with 15%-20% of ischemic strokes and leads to subsequent substantial disability.
- Providers should refer patients with symptomatic carotid artery stenosis of 70%-99% for revascularization. Prompt revascularization in the hands of experienced operators produces a dramatic reduction in future stroke risk.
- Intensive medical therapy may be equal to carotid revascularization in stroke risk reduction for asymptomatic stenosis.

The introduction of statins, in particular, has dramatically altered the landscape of therapy for vascular disease. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial cemented the place of statins as standard medical therapy for transient ischemic attack (TIA) or stroke.[11] In this study, among a subgroup of 1007 patients with a mean rate of carotid artery stenosis of 51%, the patients receiving high-intensity statin had an impressive 33% reduction in any stroke.[11]

The strategy for antithrombotic treatment in cases of asymptomatic carotid artery stenosis remains controversial because aspirin has not been clearly shown to prevent stroke in this population,[12] and similarly the benefits of a surgical or stenting procedure in these patients are less certain. A challenge regarding the use of revascularization for preventing stroke in patients with asymptomatic carotid artery stenosis is the generally low risk of stroke in untreated carotid artery stenosis.[13] Furthermore, data reviewing patients with asymptomatic carotid artery stenosis have suggested that combinations of the newer antiplatelet medications (ie, clopidogrel, ticagrelor) and high-intensity statins may provide stroke risk reduction approaching that of surgical treatment with carotid endarterectomy. The 3 major randomized trials that evaluated the benefit of endarterectomy in the asymptomatic population, Veterans Affairs Cooperative Study Group (VA trial),[14] Asymptomatic Carotid Atherosclerosis Study (ACAS),[15] and the Asymptomatic Carotid Surgery Trial (ACST),[16] were published more than 10 years ago, in an era of less effective and less intensive medical management. A meta-analysis of these 3 trials found that endarterectomy for asymptomatic carotid artery stenosis is associated with a small absolute risk reduction for the outcome of any stroke, varying from 1% in the VA trial over a 4-year period to 3.1% in ACST over a 3.4-year period.[17] Data from more recent systematic reviews intimate that annual stroke rates among only medically managed asymptomatic carotid artery stenosis declined from greater than 2% before the year 2000 to roughly 1% by 2010.[18,19] In studies from the UK,[20] the Netherlands,[21] and Canada,[22] performed after 2010, stroke rates were 1% or less annually in medically managed asymptomatic carotid artery stenosis with a stenosis of 50% or greater; risks were no higher in patients with carotid artery stenosis of 70% or higher than in those with carotid artery stenosis of 50% to 69%. Though these studies were relatively small, the low stroke rates are consistent, despite the considerable burden of risk factors

Table Aggressive Medical Management of Symptomatic Carotid Artery Stenosis

Risk Factor	Medical Intervention
—	Start aspirin; can consider dual antiplatelet therapy by adding clopidogrel or ticagrelor for 90 days or less
Smoking	Encouragement of smoking cessation
Hypertension	Initiation or adjustment of antihypertensive regimen to attain blood pressure goal <130/80 mm Hg
Diabetes mellitus	Target HbA1c less than 7
Hyperlipidemia	Initiation of high-intensity statin, target serum LDL of <70 mg/dL; consider adding ezetimibe for patients with high LDL despite statin usage
Lifestyle	Encouragement of exercise, weight loss, and modifications to diet

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

among the studied patients. The net benefit of surgical treatment of asymptomatic carotid artery stenosis, which is associated with periprocedural stroke, is thus marginal at best.

The advances in intensive medical management of asymptomatic carotid artery stenosis leading to lower stroke rates raise the most important question: whether carotid revascularization is still indicated. The value of revascularization in asymptomatic patients is being assessed in the ongoing Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis II (CREST-2) trial.[23]

There is little controversy regarding the benefit of endarterectomy in symptomatic moderate- to high-grade carotid artery stenosis. Two major trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[24] and the European Carotid Surgery Trial (ECST),[25] consistently found an increased risk of stroke, especially with higher degrees of stenosis, and established that symptomatic carotid artery stenosis patients benefit from surgical treatment with endarterectomy. In NASCET,[24,,26] patients were divided into 3 groups: low-moderate (<50%), moderate (50%-69%), and severe/high-grade (≥70%) symptomatic stenosis. Those with symptomatic 50%-69% stenosis had a 29% relative reduction in the 5-year risk of ipsilateral stroke, while those with <50% stenosis had no such benefit.[24] Those with ≥70% stenosis had such a dramatic benefit (65% relative risk reduction) that this study arm was prematurely stopped, and all patients with severe stenosis were subsequently referred for endarterectomy.[26] Thus, current guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend endarterectomy for patients with recent (within the past 6 months) ipsilateral 70% to 99% carotid artery stenosis, so long as the perioperative risk of stroke and death for the surgeon or center is <6%.[6]

Prompt evaluation and triage of patients with symptomatic carotid artery stenosis is essential to diminish the risk of early recurrent stroke. Prospective studies have shown that the risk of ipsilateral stroke is highest within the first 90 days, and especially within the first month, after a TIA.[27] Urgent revascularization can lower this risk by up to 80%.[27]

When carotid endarterectomy is indicated for patients with TIA or stroke, the AHA/ASA guidelines state that it is reasonable to perform the intervention within 2 weeks of symptom onset, rather than delaying surgery, if there are no contraindications to early revascularization.[6] No high-quality prospective, randomized trials have specifically evaluated outcomes related to the timing of endarterectomy after a recent stroke or TIA, and data for outcomes related to the optimal timing of carotid artery stenosis revascularization in general is scarce.

One important consideration is that in patients with total or near total occlusion (100%) of a symptomatic ipsilateral internal carotid artery, intervention is not recommended by multiple specialty society guidelines.[28] Internal carotid artery occlusion at the carotid bifurcation leads to dissemination of thrombus distally into the intracranial portion of the vessel, which precludes restoration of blood flow by intervention.[28] Medical management (Table), rather than revascularization, is recommended for these patients.[28]

The lingering uncertainty about the benefit of carotid endarterectomy in women should also be noted. A combined review of Asymptomatic Carotid Atherosclerotic Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST) identified that men with asymptomatic carotid artery stenosis had a 51% relative risk reduction.[29] No significant reduction in the stroke rate was observed in women;[29] however, these studies may have been underpowered to detect a risk reduction in women.

In the generation since the trials on carotid endarterectomy were performed, a newer technology in the form of endovascular transfemoral carotid artery stenting emerged as a potential alternative treatment for carotid artery stenosis. Compared with endarterectomy, transfemoral carotid artery stenting has several advantages: It can be done with mild sedation, requires no incision and is minimally invasive, carries no risk of cranial nerve palsy, and has fewer cardiovascular complications.[30] Patients undergoing transfemoral carotid artery stenting are usually treated with a dual antiplatelet regimen prior to the procedure and continued for 30 days or longer after the procedure.

There have been more than 10 randomized trials comparing endarterectomy and transfemoral carotid artery stenting (the largest of these to date being CREST[30]) with the results consistently suggesting that the 2 modalities, when performed by expert operators, achieve equivalent long-term benefits. However, the procedures have differing safety profiles, with transfemoral carotid artery stenting patients incurring more peri-procedural minor strokes, while endarterectomy patients have more peri-procedural myocardial infarctions and develop higher rates of postprocedural cranial nerve palsy.[30] Older adult patients have worse outcomes with transfemoral carotid artery stenting compared with endarterectomy,[31] even though older age was originally proposed to be associated with high risk for surgery and, therefore, a potential indication for carotid stenting rather than endarterectomy. This point is illustrated by the findings of a 2016 meta-analysis[31] that evaluated pooled patient-level data from subjects with symptomatic carotid artery stenosis from multiple randomized trials. The peri-procedural risk of stroke and death was significantly increased with transfemoral carotid artery stenting compared with endarterectomy for patients aged 70 to 74 years, 75 to 79 years, and ≥80 years.[31] In clinical practice, the 2 interventions are best viewed as complementary approaches rather than exclusive of the other. There are many patients who have comorbid conditions (significant cardiac, pulmonary, or other disease that greatly increases the risk of anesthesia), anatomic characteristics (a carotid lesion that is not suitable for surgical access or unfavorable neck anatomy such as contralateral vocal cord paralysis), or are of advanced age that clearly benefit from 1 approach over the other. The current AHA/ASA guidelines recommend transfemoral carotid artery stenting for recently symptomatic

and severe carotid artery stenosis, when performed by an operator with a 30-day stroke and mortality rate of <6%, and also state that it is reasonable to consider patient age in choosing between transfemoral carotid artery stenting and endarterectomy.[6]

Regardless of the type of carotid revascularization performed, whether transfemoral carotid artery stenting or endarterectomy, in several studies, experience of the operator has been shown to influence patient outcomes.[13] In the randomized trials that evaluated efficacy of transfemoral carotid artery stenting or endarterectomy, such as CREST,[30] proceduralists at high-volume academic centers underwent rigorous vetting with case review and participation in a lead-in phase, prior to patient enrollment, to alleviate any potential effect of operator experience. However, there is evidence that outcomes in the community, where operator volume is lower, may not be as good. In a large observational study of elderly Medicare beneficiaries in the US undergoing transfemoral carotid artery stenting, lower annual operator volume and early experience were associated with increased 30-day mortality.[32] A Canadian hospital registry found that low hospital and surgeon case volumes are risk factors for complications following endarterectomy.[33] Outside large volume, academic centers with experienced operators, therefore, the applicability of the randomized trial results to individual community hospitals and community operators, and the subsequent benefit of revascularization, remains unclear. If at all possible, clinicians involved in the management of carotid artery stenosis should be aware of the complication rate of the operator to whom they are referring for revascularization; the perioperative risk of stroke and death for the surgeon or center should be <6%.[6]

Transcarotid revascularization is a novel technique that has evolved over the past decade and represents a hybrid of endarterectomy and transfemoral carotid artery stenting.[34] Transcarotid revascularization uses a transcarotid approach to stenting and, additionally, incorporates a protection mechanism deployed to prevent cerebral embolization.[34] The major Achilles heel of traditional transfemoral carotid artery stenting, known from prior studies,[30,,35] is the higher peri-procedural risk of stroke in comparison with endarterectomy. Transcarotid revascularization differs importantly from transfemoral carotid artery stenting in that the operator avoids navigating the aortic arch, a known key source of embolization and subsequent stroke, particularly in elderly patients. The mechanism of neuroprotection with transcarotid revascularization is with the use of an extracorporeal reversal flow system and also clamping of the carotid artery below the sheath insertion, which leads to obligate reversal flow in the carotid system during the case.[34]

The reported results from the recent Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure II study (ROADSTER II)[36] on transcarotid revascularization are compelling and represent the lowest perioperative stroke rate ever reported in a prospective carotid revascularization study. There were strokes in only 0.6% at 30 days. In comparison, the 30-day stroke rate from the CREST study,[30] which compared transfemoral carotid artery stenting with endarterectomy, was notably higher at 4.1% for transfemoral carotid artery stenting and 2.3% for endarterectomy. Although the reported results from the ROADSTER II study[36] are promising, longer-term follow-up data to confirm these early transcarotid revascularization stroke outcomes and directly compare them to endarterectomy and transfemoral carotid artery stenting in a randomized clinical trial are lacking at this point. The most recent AHA/ASA guidelines report that the utility of transcarotid revascularization for the prevention of recurrent stroke and TIA remains uncertain[6] at the present time.

In summary, patients with symptomatic carotid artery stenosis with 70%-100% stenosis (by North American Symptomatic Carotid Endarterectomy Trial [NASCET]-defined criteria) have an increased risk of stroke, in comparison with patients with asymptomatic carotid artery stenosis, where the natural history is more favorable. Revascularization, whether with transfemoral carotid stenting or endarterectomy, should be considered in patients with symptomatic carotid artery stenosis of 70%-99% and performed as soon as possible. Prompt revascularization in the hands of an experienced operator produces a dramatic reduction in recurrent stroke risk. Intensive medical therapy may be equal to carotid revascularization in stroke risk reduction, and randomized studies with forthcoming results to answer this question are ongoing.

References

1. Woo SY, Joh JH, Han SA, et al. Prevalence and risk factors for atherosclerotic carotid stenosis and plaque: a population-based screening study. *Medicine (Baltimore)* 2017;96(4):e5999. https://doi.org/10.1097/MD.0000000000005999.
2. Fung AY, Saw J. Epidemiology and significance of carotid artery stenosis. In: Saw J, Exaire JE, Lee DS, et al, eds. *Handbook of Complex Percutaneous Carotid Intervention Contemporary Cardiology*. Totowa, NJ: Humana Press; 2007:3-10.
3. Petty GW, Brown RD Jr, Whisnant JP, et al. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke* 2000;31(5):1062–8. https://doi.org/10.1161/01.str.31.5.1062.
4. de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. *Stroke* 2010;41(6):1294–7. https://doi.org/10.1161/STROKEAHA.110.581058.
5. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 1999;353(9171):2179–84. https://doi.org/10.1016/s0140-6736(99)05388-x.
6. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;52(7):e364–467. https://doi.org/10.1161/STR.0000000000000375.
7. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)

trial. *Circulation* 2005;111(17):2233–40. https://doi.org/10.1161/01.CIR.0000163561.90680.1C.
8. Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med* 2020;383(3):207–17. https://doi.org/10.1056/NEJMoa1916870.
9. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018;379(3):215–25. https://doi.org/10.1056/NEJMoa1800410.
10. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol* 2010;9(5):489–97. https://doi.org/10.1016/S1474-4422(10)70060-0.
11. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;355(6):549–59. https://doi.org/10.1056/NEJMoa061894.
12. Cote R, Battista RN, Abrahamowicz M, et al. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. *Ann Intern Med* 1995;123(9):649–55. https://doi.org/10.7326/0003-4819-123-9-199511010-00002.
13. Meschia JF, Klaas JP, Brown RD Jr, et al. Evaluation and management of atherosclerotic carotid stenosis. *Mayo Clin Proc* 2017;92(7):1144–57. https://doi.org/10.1016/j.mayocp.2017.02.020.
14. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med* 1993;328(4):221–7. https://doi.org/10.1056/NEJM199301283280401.
15. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273(18):1421–8.
16. Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;376(9746):1074–84. https://doi.org/10.1016/S0140-6736(10)61197-X.
17. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database Syst Rev* 2005(4):CD001923. https://doi.org/10.1002/14651858.CD001923.pub2.
18. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke* 2009;40(10):e573–83. https://doi.org/10.1161/STROKEAHA.109.556068.
19. Raman G, Moorthy D, Hadar N, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. *Ann Intern Med* 2013;158(9):676–85. https://doi.org/10.7326/0003-4819-158-9-201305070-00007.
20. Marquardt L, Geraghty OC, Mehta Z, et al. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke* 2010;41(1):e11–7. https://doi.org/10.1161/STROKEAHA.109.561837.
21. den Hartog AG, Achterberg S, Moll FL, et al. Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. *Stroke* 2013;44(4):1002–7. https://doi.org/10.1161/STROKEAHA.111.669267.
22. Madani A, Beletsky V, Tamayo A, et al. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology* 2011;77(8):744–50. https://doi.org/10.1212/WNL.0b013e31822b0090.
23. Mott M, Koroshetz W, Wright CB. CREST-2: identifying the best method of stroke prevention for carotid artery stenosis: National Institute of Neurological Disorders and Stroke Organizational Update. *Stroke* 2017;48(5):e130–1. https://doi.org/10.1161/STROKEAHA.117.016051.
24. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;339(20):1415–25. https://doi.org/10.1056/NEJM199811123392002.
25. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351(9113):1379–87.
26. North American Symptomatic Carotid Endarterectomy Trial C, Barnett HJM, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325(7):445–53. https://doi.org/10.1056/NEJM199108153250701.
27. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007;370(9596):1432–42. https://doi.org/10.1016/S0140-6736(07)61448-2.
28. 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. *Stroke* 2011;42(8):e420–63. https://doi.org/10.1161/STR.0b013e3182112d08.
29. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke* 2004;35(10):2425–7. https://doi.org/10.1161/01.STR.0000141706.50170.a7.
30. 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. https://doi.org/10.1056/NEJMoa0912321.
31. Howard G, Roubin GS, Jansen O, et al. 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. *Lancet* 2016;387(10025):1305–11. https://doi.org/10.1016/S0140-6736(15)01309-4.
32. Nallamothu BK, Gurm HS, Ting HH, et al. Operator experience and carotid stenting outcomes in Medicare beneficiaries. *JAMA* 2011;306(12):1338–43. https://doi.org/10.1001/jama.2011.1357.
33. Feasby TE, Quan H, Ghali WA. Hospital and surgeon determinants of carotid endarterectomy outcomes. *Arch Neurol* 2002;59(12):1877–81. https://doi.org/10.1001/archneur.59.12.1877.
34. Kwolek CJ, Jaff MR, Leal JI, et al. Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. *J Vasc Surg* 2015;62(5):1227–34. https://doi.org/10.1016/j.jvs.2015.04.460.
35. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;7(10):893–902. https://doi.org/10.1016/S1474-4422(08)70196-0.
36. Kashyap VS, Schneider PA, Foteh M, et al. Early Outcomes in the ROADSTER 2 study of transcarotid artery revascularization in patients with significant carotid artery disease. *Stroke* 2020;51(9):2620–9. https://doi.org/10.1161/STROKEAHA.120.030550.