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Review Article

Evaluation and Management of Symptomatic Carotid Stenosis

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Abstract

Carotid artery disease is a significant cause of stroke. Risk stratification with regard to suitability for intervention is still largely based on the results of studies performed 20 years ago comparing medical treatment with carotid endarterectomy. Importantly, improvements in medical management have reduced stroke risk since this time. We here review the evidence in support of intervention, along with recent outcome comparisons between carotid endarterectomy and stenting. We also discuss some newer approaches to the evaluation of symptomatic carotid disease.

Keywords: Carotid Endarterectomy; Carotid Artery Stenting; Symptomatic Carotid Artery Disease; Stroke; Magnetic Resonance Imaging Plaque Haemorrhage; Microembolic Signals

Abbreviations

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MRI: Magnetic Resonance Imaging; TCD: Transcranial Doppler Ultrasonography; MES: Microembolic Signals; MRIPH: Magnetic Resonance Imaging Plaque Haemorrhage; TIA: Transient Ischaemic Attack; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study; PROGRESS: Perindopril Protection Against Recurrent Stroke Study; SAMMPRIS: Stenting Versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; EVA-3S: Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis; ICSS: International Carotid Stenting Study; CREST: Carotid Revascularization Endarterectomy Versus Stenting Trial

Introduction

Carotid artery disease accounts for approximately 10-20% of stroke [1,2], although estimates vary widely depending on the population examined [3]. Identifying which patients should be referred for carotid intervention is a common dilemma in clinical practice. International guidelines tend to focus on degree of stenosis when recommending cut-offs for intervention [4-8]. However, Magnetic Resonance Imaging (MRI) techniques delineating plaque morphology and detection of microembolic signals (MES) using Transcranial Doppler Ultrasonography (TCD) are emerging as tools that may assist with risk stratification in patients with carotid disease [9-15]. Current recommendations regarding benefit in symptomatic patients are based on data from the only adequately powered trials to date examining outcomes in patients randomized to medical therapy versus carotid endarterectomy (the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [16] and the European Carotid Surgery Trial (ECST) [17]), performed between 1981 and 1996.However, improvements in medical therapy since this time demonstrably reduce recurrent stroke risk [18-23], making it difficult to know the absolute benefit to intervention in 2015.

We here discuss the evidence to date regarding thresholds for intervention as well as recent outcome comparisons between carotid endarterectomy and stenting. We further review other factors that might assist with risk stratification in symptomatic patients with carotid disease.

Background

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) [16,17] and the European Carotid Surgery Trial (ECST) [24,25] were the pivotal trials proving secondary gains of Carotid Endarterectomy (CEA) in moderate and high grade stenosis more than two decades ago. These trials examined rates of stroke and death following CEA compared with medical treatment among patients with varying degrees of symptomatic carotid stenosis following a qualifying event of transient ischaemic attack, non-disabling ischaemic stroke, or retinal infarction with stenosis of the ipsilateral carotid artery preceding enrolment up to six months. Both trials used catheter angiography to rate the stenosis and together included over 5500 patients with an average follow up of 5 and 6.1 years, respectively. While different methods were used to quantify stenosis in these trials leading to significant variation of stenosis grading and outcome between these two trials, data from ECST have since been re-analyzed according to NASCET angiographic criteria [26] (the angiographic method now in common-use for quantifying carotid stenosis in terms of low moderate (less than 50%), high moderate (50-69%), or severe (70-99%) stenosis). In the remainder of this manuscript all stenosis grading is based on NASCET criteria.

An additional trial, the Veterans Affairs Cooperative Study (VA309) [27], was halted when the results of NASCET and ECST became available.

Since then, Duplex Ultrasound and Time Of Flight (TOF) MR angiography have emerged as the most commonly used methods to rate carotid artery stenosis. Direct equivalence with regard to degree of stenosis as reported using angiographic criteria and other imaging modalities is lacking. A universally accepted criteria by which to measure degree of stenosis by ultrasonography does not exist,

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although a NASCET sonographic index has been devised [28,29]. Haemodynamic criteria and the presence or absence of collateral flow can assist estimates of severity and ultrasound can provide useful information regarding plaque morphology [30]. Transcranial Doppler sonography further enables detection of microembolic signals predicting neurovascular events [12-15]. It is generally accepted that MR angiography may over-estimate degree of stenosis compared to CT angiography but high resolution MR imaging with contrast-enhanced MR angiography has shown promise in terms of reliability and reproducibility for evaluation of carotid plaque morphology, thus identifying plaque characteristics that herald recurrent neurovascular events [12,31,32]. Newer MR techniques can identify features associated with risk such as the presence of a lipid-rich necrotic core and, possibly, intra-plaque haemorrhage and fibrous cap rupture [9-12,31,33-37], which is discussed further below.

Severe (>70%) Symptomatic Stenosis

Consistent results were noted among the NASCET and ECST trials despite some differences in their inclusion criteria with a clear benefit to carotid endarterectomy demonstrated among patients with severe (70-99%) symptomatic carotid stenosis. In the NASCET trial of 659 patients with severe stenosis, the reported risk of any stroke or surgical death in this group of patients fell from 32.3% in the medically-treated group to 15.8% in the surgically-treated group at two years (a 16.5% absolute risk reduction at 2 years) [16]. ECST demonstrated a 5 year absolute risk reduction of stroke or surgical death of 21.2% in 429 patients with severe symptomatic carotid stenosis of 70-99% according to NASCET criteria. Excluded were patients with "near occlusion", in whom no benefit was observed despite a reduction in recurrent transient ischaemic attacks over 5 years) [26]. Benefits were maintained at 8 and 10 years of follow up, respectively [17,26].

Although stopped prematurely, the VA309 study (n=193) also showed a stenosis-dependent effect that supported the benefit of CEA in patients with high grade stenosis (>70%) with an absolute risk reduction of 17.7% at 11.9 months in men randomized to treatment within 120 days [27].

Combined analysis of individual patient data from these trials found that six patients needed to be treated to prevent one ipsilateral carotid territory stroke or operative stroke or death at five years, and 14 to prevent one disabling or fatal ipsilateral stroke or operative stroke or death at five years [38].

It should be noted that patients were randomized out to four months from their symptomatic event in NASCET and six months in VA309 and ESCT [39]. Antiplatelet regimes also differed.

Moderate (50-69%) Symptomatic Stenosis

Examining the complete NASCET dataset for this subgroup of patients (n=857), a modest benefit was seen for carotid endarterectomy in patients with symptomatic 50-69% carotid stenosis with a 5 year ipsilateral stroke rate of 15.7 % in surgically-treated patients versus 22.2% in medically-treated patients, resulting in an absolute risk reduction of 6.5%. Fifteen patients needed to be treated to prevent one ipsilateral stroke during the five year period. Confidence intervals of event-free survival curves overlapped, unlike those in patients with greater than 70% stenosis (reflecting less significant results in this group of patients with 50-69% stenosis) [17]. The authors comment that a surgical risk of greater than 2% for disabling stroke or death would negate the small benefit seen looking at the NASCET dataset for this group of patients. Importantly, benefit was not observed for women who had a lower 5 year stroke risk than men on medical treatment (15% in women versus 25% in men) [17]. This was attributed to higher operative risk and lower stroke risk without surgery [40].

Examining the ESCT data, a borderline statistically significant reduction in risk of any stroke or surgical death (the primary outcome) was observed in patients with 50-69% stenosis (NASCET angiographic criteria). No reduction in risk of ipsilateral carotid territory stroke or surgical stroke or death (or risk of disabling or fatal ipsilateral territory stroke or disabling stroke or death) was observed [26]. At the level of operative risk quoted in this study for any stroke or death (7.5% at 30 days), convincing benefit of carotid endarterectomy in patients with 50-69% stenosis was not established.

The role for intervention in carefully selected patients with moderate stenosis has since been examined using pooled individual data from the NASCET and ECST trials [41]. At an operative stroke or death rate of 7%, benefit from CEA in patients with 50-69% stenosis was not clearly observed in women. CEA led to a 5 year absolute risk reduction of 8% in men with 50-69% stenosis. Clinically important benefit was only seen in patients randomized within two weeks of a symptomatic event (median time from randomization to trial surgery was 3 days in NASCET, and 14 days in ECST [39]). Delayed surgical treatment diminished the treatment benefit. Meta-analysis of all three early trials (NASCET, ECST and VA309) suggested some benefit in patients aged 75 years or older [39,41].

It is worth pointing out that, while women may face a slightly greater peri-operative risk than men, more recent studies do not demonstrate the same sex-related increase in stroke/death as seen in some of the earlier studies [42-47]. A recent meta-analysis suggests that an association is not observed when gender-related outcomes are examined as a primary aim (despite an observed increase in risk in women when this is examined as a secondary outcome), such that any increase in peri-operative risk (stroke and death) in women is of questionable clinical significance [47]. The authors point to an ongoing need for sex-specific trials and examination of registry data since women tend to be under-represented in clinical trials and since it can be difficult to translate trial data into the real-world setting where intervention is not limited to patients fulfilling the trial inclusion criteria [47].

While many current trials comparing CAS with CEA include patients with 50-69% carotid stenosis, studies directly comparing optimal medical management with revascularization therapy in the present day setting are lacking.

Mild (<50%) Symptomatic Stenosis

A significant reduction in risk has not been observed in symptomatic patients with less than 50% stenosis. No benefit was seen in those with 30-49% stenosis and surgery was harmful in patients with less than 30% stenosis on re-analysis of ESCT data according to NASCET angiographic criteria [26]. A recent meta-analysis of

individual patient data from ECST, NASCET and VA304 confirm these findings [39].

Quantifying Risk

A caveat to blankly applying a "degree of stenosis" to assessment of risk versus benefit in individual patients is that medical management has progressed since the NASCET and ECST trial data was published more than 20 years ago [23,48]. Best medical treatment in the 1980's consisted of aspirin in varying dosages and antihypertensive treatment. Although the first HMG Co A reductase inhibitor Lovan was approved in 1987 in North America, uptake was very low in both trials. Newer antiplatelet therapies were not yet available in the medical arms. Clopidogrel and dipyridamole as well as more potent statins and stringent blood pressure targets have undoubtedly reduced the risk of recurrent stroke from that observed in the medical arms of NASCET and ECST.

The Perindopril Protection against Recurrent Stroke Study (PROGRESS), the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, as well as the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, illustrate the potential of medical intervention to reduce stroke risk.

Intervention in the PROGRESS trial with combination antihypertensive therapy reduced risk of recurrent stroke by 30-40% (it is unknown how many of these patients had carotid disease) [18].

In patients with carotid artery stenosis not requiring intervention at baseline in the SPARCL trial, treatment with high dose atorvastatin was associated with a 33% reduction in the risk of any stroke and a reduced risk of subsequent carotid revascularization [20]. Reduction in early stroke risk following transient ischaemic attack in patients with carotid stenosis commenced on stat in therapy has been shown [21].

The SAMMPRIS trial (a comparison of maximal medical management versus stenting for intracranial stenosis) illustrated how aggressive medical treatments can half the natural risk of stroke in a group of patients at high risk of stroke [22,49].

In light of this decline in risk on medical therapy, surgical risk is paramount when evaluating potential surgical benefit, which is operator-dependent with a clear volume effect [50-52]. More recent trials and consecutive case series suggest that an achievable risk of peri-operative stroke or death for CEA is less than 4%, with lower rates still for disabling stroke or death in symptomatic patients [42,46,53]. Surgical risk is greater in small volume centres and must be known when weighing up treatment decisions.

Moving away from degree of stenosis, imaging may further assist with risk stratification. MRI- defined plaque haemorrhage (MRIPH) has been identified as a strong predictor of recurrent ischaemic events in patients with symptomatic carotid disease [12,31,32]. In a recent study of 134 patients with symptomatic carotid disease, the association between MR plaque haemorrhage and recurrent cerebrovascular events was confirmed (HR 8.68; $p<0.001$), along with detection of microembolic signals (MES) on transcranial sonography (HR 3.23; $p=0.001$). Combining these further improved the observed association [12], which is not surprising since a number of other studies have shown an association between detection of microembolic signals (MES) in the cerebral circulation and stroke in patients with carotid disease [13,15].

Histopathological studies have further identified presence of a lipid-rich necrotic core, thrombus, inflammation [10], and possibly intra-plaque haemorrhage and thinning/rupture of the fibrous cap [54], as features that might be associated with elevated risk. Increased risk in the setting of a lipid-rich necrotic core, cap rupture and intra-plaque haemorrhage in particular is supported by the results of multi-contrast weighted MRI studies examining plaque morphology with regard to risk of future events [11,31,54].

It is therefore hoped that future large-scale studies will solidify the role of various imaging biomarkers in risk stratification in patients with carotid disease.

Carotid Endarterectomy Versus Endovascular Intervention

Many of the early trials comparing endovascular treatment and carotid endarterectomy were poorly designed, underpowered, and sometimes terminated early when increased complication rates were observed in the stenting arms [55-59]. Others stopped when recruitment for larger trials commenced [60,61]. More recent studies have produced closer comparisons between endovascular intervention and endarterectomy in terms of middle- to long-term outcomes with follow up extending out to 10 years [46,62]. Inclusion of short-term outcomes, however, still favors endarterectomy, particularly in older patients [38,62]. The two largest trials to date examining CAS versus CEA are the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST; n= 2522) and the International Carotid Stenting Study (ICSS; n=1713) [45,63].

Endovascular intervention has evolved from balloon angioplasty to stenting with or without the use of embolic protection devices, the potential benefit of which has not been established in terms of peri-procedural stroke prevention [38]. Proponents of carotid artery stenting point to the potential for faster recovery and avoidance of surgical complications, which may also be achieved with regional anaesthesia during CEA in some cases [53]. Whether or not CAS is associated with a reduced risk of myocardial infarction in the short-term has been debated, in part due to controversy surrounding the definition of myocardial infarction used in CREST [53,64], which examined perioperative myocardial infarction, stroke or death with subsequent ipsilateral stroke as its primary endpoint [45]. Inconsistent findings were noted among CREST and ICSS with regard to the risk of myocardial infarction following CAS and CEA [46,53,63]. Furthermore, myocardial infarction was not associated with death and was not found to influence quality of life to the extent that minor stroke did in CREST [46].

Data from 16 trials involving 7572 patients, including some of the first-ever trials, were the subject of a 2012 Cochrane review [38]. A later publication examined carotid endarterectomy versus carotid stenting alone (as opposed to angioplasty and stenting as examined in the Cochrane review) [62]. Both are discussed below.

Outcomes in Symptomatic Patients

The primary safety outcome of the 2012 Cochrane review was

death or stroke of any severity from randomization until 30 days after the procedure. A significant excess was observed in the endovascular treatment group (OR 1.72; p=0.0003) [38], as was peri-procedural stroke risk of any severity (OR 1.81; p<0.0001) [38], although peri-procedural rates of death or major or disabling stroke did not differ (OR 1.28; p=0.13) [38]. This was particularly the case for symptomatic patients 70 years of age or older who had significantly greater risk of peri-procedural death or stroke of any severity with endovascular treatment (OR 2.20 versus 1.16 for patients under 70 years of age; p=0.02) [38].

When short-term peri-procedural risk was combined with number of ipsilateral strokes at last follow-up, the combined outcome was also significantly more frequent after endovascular treatment (OR 1.39; p=0.005), as were death or any stroke (OR 1.41; p=0.01) [38].

Despite a lower risk of fatal or non-fatal myocardial infarction up to 30 days after treatment in patients assigned endovascular treatment (OR 0.44; p=0.02), myocardial infarction combined with peri-procedural death or stroke favored endarterectomy (OR 1.44 for endovascular treatment; p=0.002).

Treatment effects did not differ significantly in men and women (p=0.52) [38].

With regard to procedural complications, cranial nerve palsy was significantly less common with endovascular treatment compared to endarterectomy (OR 0.08; p<0.00001) [38]. Furthermore, access site haematoma (requiring surgery, blood transfusion or prolonging hospital stay) was significantly less common with endovascular treatment (OR 0.37; p=0.008) [38].

Higher rates of re-stenosis were observed following endovascular intervention among six trials (OR 2.41; p=0.007) [38]. More patients were treated with balloon angioplasty in at least one of these trials [65]. Heterogeneity of the data and possible measurement error in some cases make it difficult to know what significance to attribute to these findings. Follow up data from ICSS (which constitute roughly one third of the available data) suggest that rates might not differ significantly at 10 years [62]. The relationship between re-stenosis and subsequent stroke risk also remains unclear.

CEA versus CAS and Functional Outcomes

The authors of ICSS performed an analysis of primary carotid stenting versus endarterectomy in symptomatic patients [62], which incorporated additional long-term data from the Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S) [66] and ICSS [62]. Again, the combined outcome of peri-procedural stroke or death or subsequent ipsilateral stroke was significantly more frequent in patients randomized to stenting compared to endarterectomy (OR 1.47; p=0.001) [62].

Given that a similar distribution of modified Rankin scores was noted at the end of follow up among the two treatment groups, the authors of ICSS point to an excess in non-disabling procedural stroke as contributing to the less favourable risk profile of carotid stenting [62], and possibly to an excess of non-ipsilateral strokes for reasons that are unclear [62]. They did not; however, control for other variables which may have influenced the scores. As mentioned previously, CREST researchers identified an impact of minor stroke on quality of life. A possible neurocognitive impact of minor stroke (or clinically silent ischaemic lesions, as observed more frequently following CAS [67,68]), cannot be excluded [53].

Anatomical/Surgical Considerations

Certainly, anatomical considerations may preclude endarterectomy in some circumstances (radical neck dissection, radiotherapy or surgically inaccessible lesions for example). Likewise, a patient with extensive atherosclerotic disease of the aortic arch may face higher risks of embolization with stenting and patients may have otherwise unfavourable vascular or arch anatomy for stenting [53].

Conclusion

Improvements in medical intervention have undoubtedly reduced the risk of stroke recurrence in the setting of symptomatic carotid disease over the past 20 years. Results of current trials examining the natural history of carotid stenosis on maximal medical management with or without carotid endarterectomy or carotid stenting will help further identify which patients may benefit from intervention. Updated risk models based on current risk in the setting of aggressive medical therapy, ideally incorporating validated measures of plaque stability, are required.

Uncertainty regarding the absolute benefit of intervention makes it all the more important to appreciate risk when recommending carotid intervention. Whether or not risks of stenting are increased by operators with less experience or in less experienced centres has not been definitively shown [38] (generally, comfort lies with operators who have performed at least 30-50 procedures). Risks of CEA, however, are demonstrably inversely related to surgical volume and CEA should therefore only be performed in high volume centres with published registry data. Finally, it should be emphasized that the potential benefit of endarterectomy is most pronounced within two weeks of a symptomatic event, after which risk of recurrent stroke notably declines. The optimal timing of CAS has not been established.

While an important consideration, the possibility that milder strokes resulting in less functional impairment are driving the current disparity between stenting and endarterectomy does not diminish the fact that current evidence favors endarterectomy, particularly in older patients. In younger patients, this may be slightly offset by an increased risk of cranial nerve palsy and problems secondary to access site haematoma formation. Debate surrounding the definition of myocardial infarction in the various studies makes it difficult to know how much weight to permit observations regarding incidence of myocardial infarction following CEA or CAS [64].

The results of upcoming trials such as ECST-2 (http://www.ecst-2.com) designed to examine carotid revascularization versus optimal medical treatment in low-to-intermediate risk symptomatic patients, are eagerly anticipated. In the interim, patients need to be informed that there exists some uncertainty regarding the absolute benefit of carotid intervention in the setting of symptomatic carotid disease, but that clear benefit to aggressive medical treatment (regardless of intervention) has been established.

References

1. Writing Group Members, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon

M, Dai S. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010; 121: e46-46e215.

2. Leyden JM, Kleinig TJ, Newbury J, Castle S, Cranefield J, Anderson CS, et al. Adelaide stroke incidence study: declining stroke rates but many preventable cardioembolic strokes. Stroke. 2013; 44: 1226-1231.

3. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003; 2: 43-53.

4. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. 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. Stroke. 2014; 45: 2160-2236.

5. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, 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. Developed in collaboration with the American Academy of Neurology and Society of Cardiovascular Computed Tomography. Catheter Cardiovasc Interv, 2013; 81: E76-123.

6. Coutts SB, Wein TH, Lindsay MP, Buck B, Cote R, Ellis P, et al. Canadian Stroke Best Practice Recommendations: secondary prevention of stroke guidelines, update 2014. Int J Stroke. 2015; 10: 282-291.

7. Wright L, Hill KM, Bernhardt J, Lindley R, Ada L, Bajorek BV, et al. Stroke management: updated recommendations for treatment along the care continuum. Intern Med J. 2012; 42: 562-569.

8. In Stroke: National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA). 2008: London.

9. den Hartog AG, Bovens SM, Koning W, Hendrikse J, Luijten PR, Moll FL, et al. Current status of clinical magnetic resonance imaging for plaque characterisation in patients with carotid artery stenosis. Eur J Vasc Endovasc Surg. 2013; 45: 7-21.

10. Howard DP, van Lammeren GW, Rothwell PM, Redgrave JN, Moll FL, de Vries JP, et al. Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk. Stroke. 2015; 46: 182-189.

11. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke. 2013; 44: 3071-3077.

12. Altaf N, Kandiyil N, Hosseini A, Mehta R, MacSweeney S, Auer D. Risk factors associated with cerebrovascular recurrence in symptomatic carotid disease: a comparative study of carotid plaque morphology, microemboli assessment and the European Carotid Surgery Trial risk model. J Am Heart Assoc. 2014; 3: e000173.

13. King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke. 2009; 40: 3711-3717.

14. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. Stroke. 2005; 36: 971-975.

15. Vuković-Cvetković V. Microembolus detection by transcranial Doppler sonography: review of the literature. Stroke Res Treat. 2012; 2012: 382361.

16. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke Stroke and Trauma Division. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. Stroke. 1991; 22: 816-817.

17. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, 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: 1415-1425.

18. Progress Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358: 1033-1041.

19. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006; 355: 549-559.

20. Sillesen H, Amarenco P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, et al. 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: 3297-3302.

21. Merwick Á, Albers GW, Arsava EM, Ay H, Calvet D, Coutts SB, et al. Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment. Stroke. 2013; 44: 2814-2820.

22. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014; 383: 333-341.

23. Brown MM. Aggressive medical therapy alone is not adequate in certain patients with severe symptomatic carotid stenosis. Stroke. 2013; 44: 2955-2956.

24. [No authors listed]. Endarterectomy for moderate symptomatic carotid stenosis: interim results from the MRC European Carotid Surgery Trial. Lancet. 1996; 347: 1591-1593.

25. [No authors listed]. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST) Lancet. 1998; 351: 1379-1387.

26. 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: 514-523.

27. Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. JAMA. 1991; 266: 3289-3294.

28. Hathout GM, Fink JR, El-Saden SM, Grant EG. Sonographic NASCET index: a new doppler parameter for assessment of internal carotid artery stenosis. AJNR Am J Neuroradiol. 2005; 26: 68-75.

29. Hathout G, Nayak N, Abdulla A, Huang J. The Revised Sonographic NASCET Index: A New Hemodynamic Parameter for the Assessment of Internal Carotid Artery Stenosis. Ultraschall Med. 2015; 36: 362-368.

30. von Reutern GM, Goertler MW, Bornstein NM, Del Sette M, Evans DH, Hetzel A, et al. Grading carotid stenosis using ultrasonic methods. Stroke. 2012; 43: 916-921.

31. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI--initial results. Stroke. 2006; 37: 818-823.

32. Hosseini AA, Kandiyil N, Macsweeney ST, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging strongly predicts recurrent ischemia and stroke. Ann Neurol. 2013; 73: 774-784.

33. Underhill HR, Hatsukami TS, Fayad ZA, Fuster V, Yuan C. MRI of carotid atherosclerosis: clinical implications and future directions. Nat Rev Cardiol. 2010; 7: 165-173.

34. Watanabe Y, Nagayama M. MR plaque imaging of the carotid artery. Neuroradiology. 2010; 52: 253-274.

35. Turc G, Oppenheim C, Naggara O, Eker OF, Calvet D, Lacour JC, et al. Relationships between recent intraplaque hemorrhage and stroke risk factors in patients with carotid stenosis: the HIRISC study. Arterioscler Thromb Vasc Biol. 2012; 32: 492-499.

36. Ahmed RM, Harris JP, Anderson CS, Makeham V, Halmagyi GM. Carotid endarterectomy for symptomatic, but "haemodynamically insignificant" carotid stenosis. Eur J Vasc Endovasc Surg. 2010; 40: 475-482.

37. Wang J, Yarnykh VL, Hatsukami T, Chu B, Balu N, Yuan C. Improved suppression of plaque-mimicking artifacts in black-blood carotid atherosclerosis imaging using a multislice motion-sensitized driven-equilibrium (MSDE) turbo spin-echo (TSE) sequence. Magn Reson Med. 2007; 58: 973-981.

38. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2012; 9: CD000515.

39. Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003; 361: 107-116.

40. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? Lancet. 2004; 364: 1122-1123; author reply 1125-1126.

41. 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: 915-924.

42. De Rango P, Brown MM, Leys D, Howard VJ, Moore WS, Paciaroni M, et al. Management of carotid stenosis in women: consensus document. Neurology. 2013; 80: 2258-2268.

43. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. Cerebrovasc Dis. 2005; 20: 69-77.

44. Kapral MK, Wang H, Austin PC, Fang J, Kucey D, Bowyer B, et al. Sex differences in carotid endarterectomy outcomes: results from the Ontario Carotid Endarterectomy Registry. Stroke. 2003; 34: 1120-1125.

45. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010; 363: 11-23.

46. Silver FL, Mackey A, Clark WM, Brooks W, Timaran CH, Chiu D, et al. Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke. 2011; 42: 675-680.

47. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD 2nd, Gonzales NR, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol. 2011; 10: 530-537.

48. Doig D, Brown MM. Carotid stenting versus endarterectomy. Annu Rev Med. 2012; 63: 259-276.

49. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011; 365: 993-1003.

50. AbuRahma AF, Stone PA, Srivastava M, Hass SM, Mousa AY, Dean LS, et al. The effect of surgeon's specialty and volume on the perioperative outcome of carotid endarterectomy. J Vasc Surg. 2013; 58: 666-672.

51. Cowan JA Jr, Dimick JB, Thompson BG, Stanley JC, Upchurch GR Jr. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. J Am Coll Surg. 2002; 195: 814-821.

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

53. Harbaugh RE, Patel A. Surgical advances for extracranial carotid stenosis. Neurosurgery. 2014; 74: S83-91.

54. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation. 2006; 113: 2320-2328.

55. Naylor AR, Bolia A, Abbott RJ, Pye IF, Smith J, Lennard N, et al. Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. J Vasc Surg. 1998; 28: 326-334.

56. Alberts MJ. Results of a multicentre prospective randomized trial of carotid artery stenting vs carotid endarterectomy. Stroke. 2001; 32: 325.

57. Mas JL, Chatellier G, Beyssen B; EVA-3S Investigators. Carotid angioplasty and stenting with and without cerebral protection: clinical alert from the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial. Stroke. 2004; 35: e18-20.

58. Group SC, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet. 2006; 368: 1239-1247.

59. 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: 1589-1595.

60. Hoffman A, Engelterb S, Taschner C, Mendelowitsch A, Merlo A, Radue EW, et al. Carotid artery stenting versus carotid endarterectomy - a prospective randomised controlled single-centre trial with long-term follow up (BACASS). Schweizer Archiv fur Neurologie und Psychiatrie. 2008; 159: 84-89.

61. Link J, Manke C, Rosin L, Borisch I, Töpel I, Horn M, et al. [Carotid endarterectomy and carotid stenting. A pilot study of a prospective, randomized and controlled comparison]. Radiologe. 2000; 40: 813-820.

62. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, 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: 529-538.

63. International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, 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: 985-997.

64. Paraskevas KI, Mikhailidis DP, Liapis CD, Veith FJ. Critique of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST): flaws in CREST and its interpretation. Eur J Vasc Endovasc Surg. 2013; 45: 539-545.

65. [No authors listed]. 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: 1729-1737.

66. Mas JL, Arquizan C, Calvet D, Viguier A, Albucher JF, Piquet P, et al. Long-term follow-up study of endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis trial. Stroke. 2014; 45: 2750-2756.

67. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol. 2010; 9: 353-362.

68. Schnaudigel S, Gröschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. Stroke. 2008; 39: 1911-1919.

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