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Identifying which patients with asymptomatic carotid stenosis could benefit from intervention

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Identifying Which Patients With Asymptomatic Carotid Stenosis Could Benefit From Intervention

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Carotid guidelines recommend carotid endarterectomy (CEA) for patients with 60% to 99% asymptomatic carotid stenosis (ACS) provided the perioperative stroke/death rates are <3%.[1,2] Several reports have noted that the average annual risk of ipsilateral/any territory stroke among patients with asymptomatic moderate to severe internal carotid artery stenosis receiving medical therapy (MT) alone has now fallen to ≈1%.[3–5] The decreased incidence of stroke has been attributed to modern MT and has made opinion leaders demand a revision of management strategies[4] by either refraining from CEA[6] or by identifying high-risk patients.[7] Such high-risk patients should be offered prophylactic CEA in addition to MT to reduce the risk of a future stroke. It is therefore essential to develop methods to identify these ACS patients at high enough risk to warrant prophylactic intervention.

Several methods have been proposed for the identification of ACS patients at high risk for future stroke (Table),[6,8–22] namely: (1) the detection of microemboli by transcranial Doppler (TCD), (2) identification of the unstable carotid plaque using ultrasound, (3) reduced cerebral blood flow reserve, (4) intraplaque hemorrhage using magnetic resonance imaging (MRI) scans, (5) silent embolic infarcts on brain computed tomography (CT) or MRI, and (6) progression in the severity of ACS. A discussion of the involved mechanisms and the predictive value of each of these methods is presented.

Microemboli Detection on TCD

The predictive value of microemboli detection on TCD for the identification of ACS patients at high risk for stroke has been validated by 2 independent studies and is further supported by a meta-analysis.[6,8–10,23] A small prospective, observational, cohort study failed to verify the association between TCD-detected emboli and higher stroke risk for ACS patients.[24] A possible reason is that this study accepted 1 microembolus as positive although the test was repeated at 6 monthly intervals.[24] Evidence suggests that ≥2 embolic signals detected in a recording lasting 1 hour improve the accuracy of the method.[25,26] The detection of ≥2 embolic signals in a single 1-hour recording suggests a high-risk, unstable asymptomatic plaque or a plaque with a thrombus on its surface.[26] In the most recent meta-analysis,[10] microembolic signals were detected in 195 (17%) of a total of 1144 patients. At the end of the follow-up, this high-risk group with an average annual stroke risk of 8% contained 17 (57%) of the 30 strokes that occurred during follow-up. This means that TCD recording once for 1 hour may not be enough or many plaques may rupture and produce strokes without prior microemboli. It may be argued that TCD equipment or expertise may not be available in many hospitals. However, the cost of TCD equipment is low (approximately the cost of 3 CEAs), and training and certification for TCD embolus detection is not onerous. In view of the increasing use of TCD for neurovascular disorders,[27,28] it could be argued that TCD embolus detection should be performed in all centers that perform CEA for ACS.

Identification of the Unstable Carotid Plaque Using Ultrasound

Recent reports from the largest prospective study on ACS patients undergoing medical intervention alone, the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study,[11,20,29] demonstrated clearly that not all ACS patients carry the same stroke risk. In ACSRS, 1121 patients with 50% to 99% ACS received MT and were followed up for 6 to 96 months (mean, 48 months).

As shown in ACSRS,[11,20,29] severity of stenosis, a history of contralateral transient ischemic attack (TIA) episodes and a number of plaque texture features at baseline could stratify patients into groups of varying annual stroke rate from <1% to >10%. In addition, the presence of a juxtaluminal black area of >8 mm2 in a plaque (indicating a thrombus or a thin or absent fibrous cap) identified a group of 245 patients (21% of the cohort) that had an average annual stroke rate of 4.1% and contained 42 (86%) of the strokes that occurred during follow-up.[11] These results clearly show that not all ACS patients are

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Table. Suggested Predictors of the Development of Stroke/Transient Ischemic Attack in Asymptomatic Carotid Patients

Study	Study Outcome
Microemboli detection on TCD	
Spence et al[8]	Patients with microemboli at baseline (n=32) were more likely to have a stroke during the first year of follow-up (15.6% [95% CI, 4.1–79] vs 1% [95% CI, 1.01–1.36]; $P<0.0001$)
Spence et al[6]	In the first year, a stroke was recorded in 3 of 37 patients with vs 5 of 431 patients without microemboli (10.3% vs 1.4%, respectively; $P=0.02$).
	In the second year, a stroke was recorded in 5 of 37 patients with vs 5 of 431 without microemboli (18.5% vs 1.8%, respectively; $P=0.001$)
Markus et al[10]	Patients with embolic signals on TCD had a >2.5-fold higher 2-year stroke and TIA risk compared with patients without (HR, 2.54; 95% CI, 1.20–5.36; $P=0.015$)
	For ipsilateral stroke alone, the HR was 5.57 (95% CI, 1.61–19.32; $P=0.007$)
	The absolute ipsilateral stroke or TIA annual risk was 7.13% in patients with and 3.04% in patients without embolic signal
Topakian et al[9]	Plaque echolucency (164 carotid plaques; 37.7%) was associated with an increased risk of ipsilateral stroke (HR, 6.43; 95% CI, 1.36–30.44; $P=0.019$)
	Plaque echolucency in combination with TCD emboli was associated with a >10-fold higher ipsilateral stroke risk (HR, 10.61; 95% CI, 2.98–37.82; $P=0.0003$)
Identification of unstable carotid plaques using ultrasound	
Kakkos et al[11]	The mean annual stroke rate was 0.4% in 706 patients with a JBA <4 mm^2, 1.4% in 171 patients with a JBA 4–8 mm^2, 3.2% in 46 patients with a JBA 8–10 mm^2, and 5% in 198 patients with a JBA >10 mm^2 ($P<0.001$)
	Of the 59 ipsilateral ischemic strokes, 42 (71%) occurred in the 244 patients (22% of the cohort) who had a JBA ≥8 mm^2
Reduced cerebral blood flow reserve	
Gupta et al[12]	A positive relationship was observed between baseline cerebrovascular reserve impairment and increased risk of stroke/TIA (summarized random effects OR, 3.96; 95% CI, 2.60–6.04)
Intraplaque hemorrhage using MRI	
Singh et al[13]	Of the 98 carotid arteries included, 36 had MRI-depicted intraplaque hemorrhage (36.6%)
	MRI-depicted intraplaque hemorrhage was associated with a >3.5-fold higher risk of cerebrovascular events (HR, 3.59; 95% CI, 2.48–4.71; $P<0.001$)
Hellings et al[14]	Patients with intraplaque hemorrhage had a >2-fold higher risk for the occurrence of stroke compared with patients without intraplaque hemorrhage (50 of 591 vs 9 of 227 or 8.4% vs 3.9%, respectively; HR, 2.1; 95% CI, 1.1–4.4)
van Lammeren et al[15]	The carotid plaques from ACS patients (n=182) had less frequently intraplaque hemorrhage (21 of 182 vs 25 of 82 or 11.5% vs 30.5%, respectively; $P=0.005$) compared with patients with ipsilateral events >6 mo before CEA (n=82)
Qiao et al[16]	The occurrence of cerebrovascular ischemic events was associated with the presence of intraplaque hemorrhage (OR, 10.18; 95% CI, 1.42–72.21; $P=0.02$)
Silent embolic infarcts on brain CT or MRI	
Kakkos et al[17]	In 462 patients with 60% to 99% ACS, the annual stroke rate was 3.6% vs 1.0% when embolic signals were present vs absent, respectively (HR, 3.0; 95% CI, 1.46–6.29; $P=0.002$)
	In the subgroup of 216 patients with 60% to 79% ACS, the annual TIA and stroke rate was 4.4% vs 1.3% when embolic signals were present vs absent, respectively ($P=0.005$)
Miwa et al[18]	During an average follow-up of 4.1±2.0 y (range, 1–105 mo), the presence of SCI was associated with a >8.5-fold higher risk for the development of stroke/TIA after adjustment for carotid IMT (HR, 8.56; 95% CI, 1.72–42.55; $P=0.003$)
Progression in the severity of ACS	
Balestrini et al[19]	Progression of ACS was detected in 129 patients (24.7%). Of these, 35 patients (27.1%) had an ipsilateral stroke and 22 (17.0%) had a TIA
	Progression of ACS was strongly associated with the risk of ipsilateral stroke (HR, 31.97; 95% CI, 9.83–103.91; $P<0.001$)
Kakkos et al[20]	The 8-year cumulative ipsilateral cerebral ischemic stroke rate was 0% in patients with regression, 9% of the stenosis was unchanged, and 16% if there was progression (relative risk in patients with progression, 1.92; 95% CI, 1.14–3.25; $P=0.05$).
Conrad et al[21]	Plaque progression occurred in 262 arteries and 36 (13.7%) of these developed symptoms
	The symptomatic conversion rate in patients with plaque progression was almost twice that of those without plaque progression (13.7% vs 8.5%; $P=0.02$)
Plaque ulceration on 3D ultrasound	
Madani et al[22]	Patients with >3 ulcers had a 2-year stroke risk of 18.2% vs 1.7% in patients with <3 ulcers

3D indicates 3-dimensional; ACS, asymptomatic carotid stenosis; CEA, carotid endarterectomy; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IMT, intima-media thickness; JBA, juxtaluminal black area; MRI, magnetic resonance imaging; OR, odds ratio; SCI, silent cerebral infarction; TCD, transcranial Doppler; and TIA, transient ischemic attack.

the same. It therefore seems inappropriate to offer all asymptomatic individuals the same treatment. Furthermore, these results provide proof that multiple risk stratification parameters (4 independent predictors: baseline degree of stenosis, history of contralateral stroke or TIA, size of black juxtaluminal plaque area ≥8 mm^2 without a visible echogenic cap, and the presence of discrete white areas in a hypoechoic plaque) are better than single parameters for stroke risk stratification.[11]

A limitation of this technique is that ultrasonographers require special training in equipment settings and image capture during duplex scanning and in image analysis using commercially available software (info@lifeqmedical.com) on a laptop. In the ACSRS study,[11] a 1-day course was adequate for each ultrasonographer from the 80 centers participating. Besides training, there are the issues of cost and also if these analyses could be readily and reliably performed in the community setting.

Reduced Cerebral Blood Flow Reserve

Several studies have demonstrated that impairment in cerebral blood flow reserve is associated with the development of stroke in ACS patients.[30–33] With increasing degree of carotid stenosis and an incomplete circle of Willis or contralateral occlusion, cerebral perfusion pressure is reduced. As a result of cerebrovascular autoregulation, cerebral arterioles dilate maximally to maintain a constant cerebral blood flow. However, when the arterioles are maximally dilated, further reduction in cerebral perfusion pressure (such as may occur during a hypotensive episode) is associated with a reduction in perfusion that may result in TIA or stroke.

Four studies have investigated the cerebrovascular reserve using TCD velocity measurements in response to acetazolamide or breathing 5% CO_2 in asymptomatic patients with severe stenosis or occlusion.[30–33] Average follow-up was 24 months. Raw data are not available in 1.[33] Impaired cerebrovascular reserve was present in 183 (75%) of the 244 included in the remaining three studies.[30–32] This high-risk group had an average annual event (TIA or stroke) rate of 5.7% and contained 21 (75%) of the 28 events that occurred during follow-up.

A meta-analysis summarizing the association between cerebrovascular reserve impairment with stroke risk demonstrated an ≈4-fold higher stroke risk in asymptomatic patients with impaired cerebral blood flow.[12] Reduced cerebrovascular flow reserve may therefore identify ACS patients at high risk for stroke. The cost, access, insurance coverage, and availability of trained technicians and physicians to perform and read the studies are possible limitations of this technique.

Identification of Intraplaque Hemorrhage Using MRI

Intraplaque hemorrhage is a marker of plaque instability and contributes to 2 features that synergistically increase the odds of plaque rupture, namely necrotic core size and plaque volume.[13–16] A histological study of 264 excised carotid plaques has demonstrated that intraplaque hemorrhage and a large lipid core were associated with symptomatic patients.[15] In an MRI study involving 47 patients having CEA demonstrated that intraplaque hemorrhage and adventitial enhancement indicating neovascularization were independently associated with previous events.[16]

In a study of 75 men with 50% to 70% ACS, MRI identified the presence of intraplaque hemorrhage in 36 (36.7%) of 98 carotid arteries.[13] In this high-risk group, 2 strokes and 4 TIAs occurred during a 25-month follow-up. Strokes or TIAs did not develop in the patients without intraplaque hemorrhage.[13]

The evidence to date on the value of MRI in the cerebrovascular bed is not enough and has not been validated prospectively. Moreover, this is not covered by insurance.

Silent Embolic Infarcts on Brain CT or MRI

Earlier studies demonstrated that the presence of silent embolic infarcts on brain CT or MRI scans is associated with an increased risk of stroke in the general population.[34,35] The prevalence of silent infarcts on brain CT scans in asymptomatic patients having CEA was 14% and 18% in 2 studies.[36,37] The ability of such infarcts to predict the risk of future strokes was tested in the ACSRS study.[17] Embolic infarcts were present in 61 (9.6%) of 633 patients with 60% to 99% stenosis in relation to the normal distal internal carotid. This high-risk group which had an average annual stroke rate of 3.5% contained 9 (24%) of the 38 strokes that occurred during follow-up.[17] This means that 76% of the plaques that produce a stroke will be missed probably because many plaques rupture without giving off emboli that produce silent infarcts. This report,[17] as well as an independent study,[18] seem to support that ACS patients found to have prior infarcts should be referred for intervention.

Another factor to be considered is that brain CT scans are not sensitive in demonstrating small embolic infarcts. It is well known that brain CT scans may miss ≤50% of small infarcts shown on brain MRI scans. Future longitudinal studies need to investigate the value of silent infarcts using MRI.

Progression in the Severity of ACS

Several natural history studies in medically managed patients with ACS have investigated the association between stenosis progression and risk of ipsilateral cerebrovascular events.[38–40] Most authors have concluded that progression to >80% stenosis in relation to the diameter of the distal internal carotid was associated with an increased risk of cerebrovascular events. However, these studies did not determine whether progression itself is a risk factor that is independent of the degree of stenosis and have not answered the question whether different degrees of stenosis are associated with different rates of progression.

In a recently published series involving 900 carotid arteries (794 patients) with 50% to 69% ACS, plaque progression occurred in 262 (29.1%) arteries during a mean follow-up of 3.6 years.[21] This high-risk group (average annual stroke rate, 2.1%) contained 20 (38%) of the 52 strokes that occurred during follow-up (absolute values calculated from percentages given in the article). In the absence of progression the average annual stroke rate was 1.4%.[21]

In a second study involving 523 patients with 50% to 69% ACS, plaque progression occurred in 129 (24.7%) arteries during a mean follow-up of 3.5 years.[19] This high-risk group (average annual stroke rate, 7.7%) contained 35 (92%) of the

38 strokes that occurred during follow-up. In the absence of progression the average annual stroke rate was 0.4%.[19]

In the most recently published study (ACSRS) involving 1121 patients with 50% to 99% ACS in relation to the bulb, plaque regression occurred in 43 (3.8%), no change in stenosis in 856 (76.4%), and progression in 222 (19.8%) arteries during a mean follow-up of 4.0 years.[20] This high-risk group (average annual stroke rate, 2.0%) contained 19 (32%) of the 59 strokes that occurred during follow-up. In the absence of progression the average annual stroke rate was 1.12%, whereas it was 0% in the presence of regression.[20] For patients with 80% to 99% baseline stenosis (70%–99% in relation to the distal internal carotid), the average annual ipsilateral ischemic stroke rate was 1.7% in the absence and 3.1% in the presence of progression.[20] In addition, this study demonstrated that the incidence of plaque progression is inversely proportional to the severity of baseline stenosis and that both baseline stenosis and progression were independent predictors of stroke risk.[20]

These data argue for continued screening and treatment by CEA of patients with progressive ACS even if they remain asymptomatic.

Combination of Methods

The combination of multiple risk stratification parameters, which are independent predictors (baseline degree of stenosis, history of contralateral stroke or TIA, size of black juxtaluminal plaque area ≥8 mm^2 without a visible echogenic cap and the presence of discrete white areas in a hypoechoic plaque), is better than single parameters when it comes to stroke risk stratification.[11] Another example is the combination of gray scale median score with TCD microembolic signals.[9] A low gray scale median score is an independent predictor for an increased risk of stroke during carotid intervention.[41]

Conclusions

Although intensive MT now reduces the overall risk of stroke below that of CEA in the majority of ACS patients, some patients with ACS may go on to have a stroke. It is therefore important to identify specific subgroups of ACS patients who despite MT are still at increased risk (>2%/y) and may require a carotid intervention. Identification of these high-risk ACS patients is crucial to target carotid revascularization procedures appropriately and to avoid excessive use of unnecessary interventions. Performing CEA or carotid artery stenting on those with >80% stenosis as currently practiced in many centers ignores the fact that many strokes occur in patients with moderate stenosis, which may be identified by the presence of TCD embolic signals or unstable plaques using ultrasound. Thus, the approach of selective intervention will lead to a refinement of the current indications for CEA and would also reduce costs spent on unnecessary or even harmful procedures.

Current evidence suggests that certain ACS patients (ie, those with TCD-detected microemboli,[6,8–10,23] or silent embolic infarcts on brain CT/MRI scans,[17,18,34–37] those with reduced cerebrovascular reserve,[12,30–33] ACS severity progression despite MT[19–21] or history of contralateral stroke/TIA, size of black juxtaluminal plaque area ≥8 mm^2 without a visible echogenic cap)[11] are at increased stroke risk and should be considered for prophylactic CEA or carotid artery stenting. Another modality that may be of use in the future is ulceration on 3-dimensional ultrasound.[22]

A limitation of practically all the studies reviewed above is that they have been performed during the era when MT was not optimal. Many of these studies need to be repeated in cohorts that are on what is currently considered optimal MT. Positive results from such studies are likely to make risk stratification methods accepted in routine medical practice.

Disclosures

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References

1. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Stroke Assocation; American Association of Neuroscience Nurses; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurolgocial 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; Society for Vascular Surgery; American Academy of Neurology and Society of Cardiovascular Computed Tomography. 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. *Stroke*. 2011;42:e464–e540.
2. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1–e31.
3. 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:e573–e583.
4. Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. *Nat Rev Cardiol*. 2012;9:116–124.
5. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke*. 2010;41:e11–e17.
6. Spence JD, Coates V, Li H, Tamayo A, Muñoz C, Hackam DG, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol*. 2010;67:180–186.
7. Chaturvedi S. Aggressive medical therapy alone is adequate in certain patients with severe symptomatic carotid stenosis. *Stroke*. 2013;44:2957–2958.
8. 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;36:2373–2378.
9. Topakian R, King A, Kwon SU, Schaafsma A, Shipley M, Markus HS; ACES Investigators. Ultrasonic plaque echolucency and emboli signals predict stroke in asymptomatic carotid stenosis. *Neurology*. 2011;77:751–758.
10. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol*. 2010;9:663–671.
11. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. *J Vasc Surg*. 2013;57:609–618.e1, discussion 617.
12. Gupta A, Chazen JL, Hartman M, Delgado D, Anumula N, Shao H, et al. Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke*. 2012;43:2884–2891.
13. Singh N, Moody AR, Gladstone DJ, Leung G, Ravikumar R, Zhan J, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. *Radiology*. 2009;252:502–508.

14. Hellings WE, Peeters W, Moll FL, Piers SR, van Setten J, Van der Spek PJ, et al. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. *Circulation*. 2010;121:1941–1950.
15. van Lammeren GW, den Hartog AG, Pasterkamp G, Vink A, de Vries JP, Moll FL, et al. Asymptomatic carotid artery stenosis: identification of subgroups with different underlying plaque characteristics. *Eur J Vasc Endovasc Surg*. 2012;43:632–636.
16. Qiao Y, Etesami M, Astor BC, Zeiler SR, Trout HH III, Wasserman BA. Carotid plaque neovascularization and hemorrhage detected by MR imaging are associated with recent cerebrovascular ischemic events. *AJNR Am J Neuroradiol*. 2012;33:755–760.
17. Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg*. 2009;49:902–909.
18. Miwa K, Hoshi T, Hougaku H, Tanaka M, Furukado S, Abe Y, et al. Silent cerebral infarction is associated with incident stroke and TIA independent of carotid intima-media thickness. *Intern Med*. 2010;49:817–822.
19. Balestrini S, Lupidi F, Balucani C, Altamura C, Vernieri F, Provinciali L, et al. One-year progression of moderate asymptomatic carotid stenosis predicts the risk of vascular events. *Stroke*. 2013;44:792–794.
20. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014;59:956–967.e1.
21. Conrad MF, Boulom V, Baloum V, Mukhopadhyay S, Garg A, Patel VI, et al. Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg*. 2013;58:128–35.e1.
22. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology*. 2011;77:744–750.
23. 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.
24. Abbott AL, Chambers BR, Stork JL, Levi CR, Bladin CF, Donnan GA. Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: a multicenter prospective cohort study. *Stroke*. 2005;36:1128–1133.
25. King A, Shipley M, Markus H; ACES Investigators. Optimizing protocols for risk prediction in asymptomatic carotid stenosis using embolic signal detection: the Asymptomatic Carotid Emboli Study. *Stroke*. 2011;42:2819–2824.
26. Bogiatzi C, Cocker MS, Beanlands R, Spence JD. Identifying high-risk asymptomatic carotid stenosis. *Expert Opin Med Diagn*. 2012;6:139–151.
27. Panerai BB. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auton Res*. 2009;19:197–211.
28. Rosengarten B, Deppe M, Kaps M, Klingelhöfer J. Methodological aspects of functional transcranial Doppler sonography and recommendations for simultaneous EEG recording. *Ultrasound Med Biol*. 2012;38:989–996.
29. Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*. 2010;52:1486–1496.e1.
30. Gur AY, Bova I, Bornstein NM. Is impaired cerebral vasomotor reactivity a predictive factor of stroke in asymptomatic patients? *Stroke*. 1996;27:2188–2190.
31. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283:2122–2127.
32. Yamamoto KK, Miyata T, Momose T, Nagayoshi M, Akagi D, Hosaka A, et al. Reduced vascular reserve measured by stressed single photon emission computed tomography carries a high risk for stroke in patients with carotid stenosis. *Int Angiol*. 2006;25:385–388.
33. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain*. 2001;124(pt 3):457–467.
34. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, et al; Cardiovascular Health Study Collaborative Reseach Group. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology*. 2001;57:1222–1229.
35. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34:1126–1129.
36. Martin JD, Valentine RJ, Myers SI, Rossi MB, Patterson CB, Clagett GP. Is routine CT scanning necessary in the preoperative evaluation of patients undergoing carotid endarterectomy? *J Vasc Surg*. 1991;14:267–270.
37. Cao P, Zannetti S, Giordano G, De Rango P, Parlani G, Caputo N. Cerebral tomographic findings in patients undergoing carotid endarterectomy for asymptomatic carotid stenosis: short-term and long-term implications. *J Vasc Surg*. 1999;29:995–1005.
38. Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P, et al. Progression of carotid stenosis detected by duplex ultrasonography predicts adverse outcomes in cardiovascular high-risk patients. *Stroke*. 2007;38:2887–2894.
39. Bertges DJ, Muluk V, Whittle J, Kelley M, MacPherson DS, Muluk SC. Relevance of carotid stenosis progression as a predictor of ischemic neurological outcomes. *Arch Intern Med*. 2003;163:2285–2289.
40. Muluk SC, Muluk VS, Sugimoto H, Rhee RY, Trachtenberg J, Steed DL, et al. Progression of asymptomatic carotid stenosis: a natural history study in 1004 patients. *J Vasc Surg*. 1999;29:208–214, discussion 214.
41. Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. *Circulation*. 2004;110:756–762.

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