Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement

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International Angiology 2022 April;41(2):158-69
DOI: 10.23736/S0392-9590.21.04825-2

REVIEW

CAROTID DISEASE

EDITOR'S CHOICE

Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement

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ABSTRACT

The recommendations of international guidelines for the management of asymptomatic carotid stenosis (ACS) often vary considerably and extend from a conservative approach with risk factor modification and best medical treatment (BMT) alone, to a more aggressive approach with a carotid intervention plus BMT. The aim of the current multispecialty position statement was to reconcile the conflicting views on the topic. A literature review was performed with a focus on data from recent studies. Several clinical and imaging high-risk features have been identified that are associated with an increased long-term ipsilateral ischemic stroke risk in patients with ACS. Such high-risk clinical/imaging features include intraplaque hemorrhage, impaired cerebrovascular reserve, carotid plaque echolucency/ulceration/ neovascularization, a lipid-rich necrotic core, a thin or ruptured fibrous cap, silent brain infarction, a contralateral transient ischemic attack/stroke episode, male patients <75 years and microembolic signals on transcranial Doppler. There is growing evidence that 80-99% ACS indicate a higher stroke risk than 50-79% stenoses. Although aggressive risk factor control and BMT should be implemented in all ACS patients, several high-risk features that may increase the risk of a future cerebrovascular event are now documented. Consequently, some guidelines recommend a prophylactic carotid intervention in high-risk patients to prevent future cerebrovascular events. Until the results of the much-anticipated randomized controlled trials emerge, the jury is still out regarding the optimal management of ACS patients.

(*Cite this article as:* Paraskevas KI, Mikhailidis DP, Antignani PL, Baradaran H, Bokkers RP, Cambria RP, *et al.* Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement. Int Angiol 2022;41:158-69. DOI: 10.23736/S0392-9590.21.04825-2)

Key words: Carotid stenosis; Stroke; Endarterectomy, carotid.

The incidence of recurrent stroke after a first transient ischemic attack (TIA) or minor stroke episode in patients with symptomatic carotid stenosis is up to 22% at 7 days and up to 25% at 14 days.[1-3] Carotid endarterectomy (CEA) is currently strongly recommended for patients with a 70-99% carotid stenosis within 14 days of a TIA/minor ischemic stroke episode in order to remove the "unstable" atherosclerotic carotid plaque (which is the source of the thromboemboli) and, consequently, to reduce the risk of recurrent stroke/death (Class I; Level of Evidence: A).[4, 5]

In contrast to symptomatic carotid stenosis, the optimal management of asymptomatic carotid stenosis (ACS) is enduringly controversial. Each year there are about 800,000 strokes in the United States[6] and approximately 1,400,000 strokes in Europe.[4] Overall, about 10-15% of all ischemic strokes follow thromboembolism from a previously asymptomatic >50% carotid stenosis.[4] Although several international Societies/Associations have published guidelines and recommendations for the management of patients with ACS over the last 25 years (Table I),[4, 5, 7-18] there is still substantial controversy regarding the optimal therapeutic approach for these patients. The current position statement will address several key issues and will attempt to reconcile the different views on the topic.

TABLE I.—*Recommendations and guidelines provided by different Societies/Associations for the management of patients with asymptomatic carotid stenosis.*[4, 5, 7-18]

Guideline (Year)	Recommendation
Stroke Council of the AHA[7] (1998)	• CEA is acceptable for patients with ≥60% ACS, if the surgical risk is <3% and a life-expectancy of >5 years [Grade A recommendation]
National Stroke Association[8] (1999)	• CEA is recommended for patients with ≥60% ACS with a surgical morbidity and mortality of <3% [Grade A recommendation]
Stroke Council of the AHA[9] (2001)	• CEA may be considered in patients with high-grade ACS if morbidity/mortality rates are <3% [Level of Evidence I, Grade A]
AHA/ASA Guidelines[10] (2006)	• CEA is recommended in highly selected patients with ≥60% ACS, if morbidity/mortality rates are <3% [Class I; Level of Evidence: A]
SVS Guidelines[11] (2008)	• In patients with ≥60% ACS, CEA plus medical management is recommended as long as perioperative risk is low [Grade 1 recommendation, high quality evidence]
ESVS Guidelines[12] (2009)	• CEA can be recommended for men <75 years with 70-99% ACS if the risk associated with surgery is <3% [Grade A recommendation] • The benefit from CEA in women with ACS is significantly less than in men; CEA should therefore be considered only in younger, fit women [Grade A recommendation]. Meanwhile, it is advisable to offer CAS in asymptomatic patients only in high-volume centers with documented low peri-procedural stroke and death rates or within well-conducted clinical trials [Grade C recommendation] • For ACS patients at 'extremely' high risk (several medical comorbidities at the same time), BMT might be the best option instead of invasive intervention [Grade C recommendation]
AHA/ASA Guidelines[13] (2011)	• Prophylactic CEA performed with <3% morbidity and mortality can be useful in highly selected patients with ACS (≥60% by angiography, ≥70% by validated Doppler ultrasound) [Class IIa; Level of Evidence: A] • Prophylactic CAS might be considered in highly selected patients with ACS (≥60% by angiography, ≥70% by validated Doppler ultrasound, ≥80% on computed tomographic or magnetic resonance angiography [Class IIb; Level of Evidence: B]
SVS Guidelines[14] (2011)	• Patients with ≥60% ACS should be considered for CEA for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates can be <3% [Grade I; Level of Evidence: A] • There are insufficient data to recommend CAS as primary therapy for patients with 70-99% ACS. In properly selected patients with ACS, CAS is equivalent to CEA in the hands of experienced interventionalists with a combined stroke/death rate <3% [Grade II; Level of Evidence: B]
ESC Guidelines[15] (2011)	• In patients with ≥60% ACS, CEA should be considered as long as the perioperative stroke/death rates is <3% and the patient's life expectancy exceeds 5 years [Class IIa; Level of Evidence: A] • In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate <3% [Class IIb; Level of Evidence: B]
AHA/ASA Guidelines[16] (2014)	• It is reasonable to consider performing CEA in patients with >70% ACS if the risk of perioperative stroke, MI, and death is <3%. However, its effectiveness compared with contemporary BMT alone is not well established [Class IIa; Level of Evidence: A]. • Prophylactic CAS might be considered in highly selected patients with ACS (≥60% by angiography, ≥70% by validated Doppler ultrasound), but its effectiveness compared with BMT alone in this situation is not well established [Class IIb; Level of Evidence: B]. • In ACS patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization *versus* BMT alone is not well established [Class IIb; Level of Evidence: B].
ESVS Guidelines[4] (2017)	• In "average surgical risk" patients with a 60-99% ACS, CEA should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years [Class IIa; Level of Evidence: B] • In "average surgical risk" patients with a 60-99% ACS in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years [Class IIb; Level of Evidence: B]
German-Austrian Guidelines[17] (2020)	• In the presence of a 60-99% ACS, CEA should be considered, provided there is no increased surgical risk and ≥1 clinical or imaging findings are available that are associated with an increased risk of carotid-related stroke in follow-up (Level of Evidence: 1) • In the presence of a 60-99% ACS, CAS may be considered, provided there is no increased treatment-associated risk and ≥1 clinical or imaging findings are available that are presumably associated with an increased risk of carotid-related stroke in follow-up (Level of Evidence: 2a) • The periprocedural stroke/death rate should be as low as possible for CEA or CAS for ACS. The in-hospital stroke/death rate should be monitored by expert neurologists and should not exceed 2% [Strong recommendation; Level of Evidence: 2a]
SVS Guidelines[5] (2021)	• In low surgical risk patients with >70% ACS (documented by validated duplex ultrasound or computed tomography angiography) CEA plus BMT is recommended over BMT alone for the long-term prevention of stroke and death [Grade I; Quality of Evidence: B]
ESO Guideline[18] (2021)	• In patients with ≥60% ACS considered to be at increased risk of stroke on BMT alone, CEA is recommended (Quality of evidence: Moderate +++, Strength of recommendation: Strong for CEA) • In patients with ACS, CAS is not recommended as an alternative to BMT alone (Quality of evidence: Very low +; Strength of recommendation: Weak against CAS)

AHA: American Heart Association; CEA: carotid endarterectomy; ACS: asymptomatic carotid stenosis; ASA: American Stroke Association; SVS: Society for Vascular Surgery; ESVS: European Society for Vascular Surgery; BMT: best medical treatment; CAS: carotid artery stenting; ESC: European Society for Cardiology; ESO: European Stroke Organization.

Debating the usefulness of CEA for ACS

Three randomized controlled trials (RCTs), the Veterans Affairs Cooperative Study (VACS),[19] the Asymptomatic Carotid Atherosclerosis Study (ACAS)[20] and the Asymptomatic Carotid Surgery Trial (ACST),[21] compared CEA plus best medical treatment (BMT) *vs.* BMT alone in patients with significant ACS. In VACS, the incidence of ipsilateral and contralateral neurologic events was 12.8% in the CEA plus BMT group *vs.* 24.5% in the BMT alone group (absolute risk reduction: 11.6%; relative risk with CEA: 0.51; 95% confidence interval [CI]: 0.32-0.81; P<0.002).[19] In ACAS, the risk of 5-year ipsilateral stroke plus any perioperative stroke/death was halved in patients with >60% ACS treated surgically compared with those receiving BMT alone (5.1 *vs.* 11.0%, respectively; risk reduction: 53%; 95% CI: 22-72%; P=0.004).[20] Similarly, in ACST, the 5-year all-stroke risk (perioperative events and non-perioperative strokes) was nearly 50% less with CEA plus BMT *vs.* BMT alone (6.4 *vs.* 11.8%, respectively; net gain: 5.4%; 95% CI: 3.0-7.8%; P<0.0001).[21] Based on these results,[19-21] the 2008 Society for Vascular Surgery (SVS) guidelines[11] and the 2009 European Society for Vascular Surgery (ESVS) guidelines[12] recommended CEA plus BMT for patients with ≥60%[11] or ≥70%[12] ACS, respectively, provided perioperative stroke/death rates are <3%. These recommendations were similar with those of earlier guidelines, *i.e.* the 1998,[7] 2001[9] and 2006[10] guidelines of the American Heart Association/American Stroke Association (AHA/ASA) and the 1999 recommendations of the National Stroke Association.[8] All these guidelines recommended CEA for patients with ≥60% ACS, provided perioperative stroke/death rates were <3%.[7-10]

Due to advances in BMT since the landmark RCTs,[19-21] it was argued that the stroke rates in ACS patients with BMT alone have decreased to such an extent that prophylactic CEA may not provide any additional benefit.[22, 23] Indeed, the 1-year stroke rates of 0.9% with BMT alone in the Stent Protected Angioplasty *versus* Carotid Endarterectomy (SPACE)-2[24] trial provide evidence that outcomes with BMT alone have improved compared with those of ACAS[20] and ACST.[21] It was thus supported that ACS patients should no longer be offered a prophylactic CEA, but instead should only be managed with BMT alone.[22, 23] Along these lines, the 2011 AHA/ASA guidelines noted that the advantage of revascularization over modern BMT alone is not well established and explicitly mentioned that "*the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3% threshold for complication rates may be high because of interim advances in medical therapy*."[13]

The definition of BMT has evolved considerably since the landmark RCTs[19-21] and now also includes counseling on diet, lifestyle changes (*e.g.* regular moderate exercise), advanced smoking cessation techniques (including nicotine replacement therapy) and high dose statins±ezetimibe, a fibrate and, more recently, a proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor (Table II).[19-21, 25] Intensive risk factor modification and high-dose statin treatment was not pursued rigorously in the early RCTs.[19-21] In the Treating to New Targets (TNT) study,[28] 10,001 patients with documented coronary heart disease were randomized to atorvastatin 10 *vs.* 80 mg/day and were followed-up for a median of 4.9 years. Patients on high-dose statin treatment demonstrated a 23% reduction in cerebrovascular events (hazard ratio [HR]: 0.77; 95% CI: 0.64-0.93; P=0.007) and a 25% reduction in stroke (HR: 0.75; 95% CI: 0.59-0.96; P=0.02) compared with patients on 10 mg atorvastatin.[28] A meta-analysis including over 90,000 individuals participating in statin trials demonstrated that each 10% reduction in low-density lipoprotein cholesterol reduced the risk of all strokes by 15.6% (95% CI: 6.7-23.6%; P<0.0001).[29] In addition, a 2013 meta-analysis of RCTs (N.=14 studies; 9012 patients) evaluating the efficacy and safety of dual *vs.* single antiplatelet therapy initiated within 3 days of an acute non-cardioembolic ischemic stroke or TIA demonstrated that dual antiplatelet therapy significantly reduced the risk of stroke recurrence (risk ratio [RR]: 0.69; 95% CI: 0.60-0.80; P<0.001) and the composite outcome of stroke, TIA, acute coronary syndrome and all-death (RR: 0.71; 95% CI: 0.63-0.81; P<0.001) compared with single antiplatelet treatment.[30] More recent evidence from the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)[31] RCT showed that dual antiplatelet treatment initiated within 12 hours after a TIA/minor ischemic stroke provides short-term (but not long-term) benefits. A pooled analysis of POINT[31] and another RCT comparing dual *vs.* single antiplatelet therapy in patients with TIA or minor ischemic stroke, the Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE)[32] trial, showed that the benefit of dual antiplatelet therapy is seen within the first 21 days after minor ischemic stroke or TIA, but not later.[33]

Consequently, the value of "modern" BMT for patients with ACS is currently indisputable.[34] All patients with atherosclerotic carotid artery stenosis (whether symptomatic or asymptomatic) should receive optimal risk factor control and BMT not only for the reduction of the risk of stroke, but also to lower the risk of myocardial infarction (MI) and cardiovascular events.[34] Nevertheless, the

TABLE II.—*Lifestyle and medical measures that comprised Best Medical Treatment in the landmark randomized controlled trials and at present.*[19-21, 25]

BMT in RCTs[19-21]	Modern BMT
VACS[19]	Lifestyle measures*
• 650 mg aspirin twice daily for all patients, which was reduced to 325 mg/day for patients who could not tolerate the high dose.	Smoking cessation • Counseling • Nicotine replacement therapy • Bupropion • Varenicline
ACAS[20]	Obesity
• 325 mg/day aspirin for all patients	• Counseling on caloric restriction
• Discussion of diastolic and systolic hypertension, diabetes mellitus, abnormal lipid levels, smoking and excessive alcohol use	• Referral to dietician • Bariatric surgery in patients with refractory, severe obesity
ACST[21]	Mediterranean diet[25]
• Antiplatelet therapy	• Counseling
• Antihypertensive therapy	• Provision of a booklet with dietary recommendations/recipes
• Lipid-lowering therapy (not routinely)	• Reduce sodium intake by at least 1g/day sodium (2.5 g/day salt)[25]
	Exercise
	At least 150 to 300 minutes of moderate-intensity aerobic physical activity a week, or 75 to 150 minutes of vigorous-intensity activity, or an equivalent combination of moderate- and vigorous-intensity activity[26]
	Medical therapy
	Blood pressure control
	• Aim at blood pressure values of 130/80 mmHg in all patients[25, 27]
	Lipid lowering
	• Highest tolerated statin dose (40-80 mg atorvastatin or 20-40 mg rosuvastatin) for LDL-C values <1.8 mmol/l (70 mg/dl)[4, 25]
	• Addition of ezetimibe and fibrates/PCSK-9 inhibitor (as needed for low high-density lipoprotein cholesterol/ high triglycerides)
	Antiplatelet agents
	• Low-dose aspirin with possible addition of clopidogrel
	Diabetes mellitus
	• Reinforcement of lifestyle changes ± antidiabetic agents
	• Aim to achieve a goal of HBA1c ≤ 7%[25]

BMT: Best medical treatment; RCTs: randomized controlled trials; VACS: Veterans Affair Cooperative Study; ACAS: Asymptomatic Carotid Atherosclerosis Study; ACST: Asymptomatic Carotid Surgery Trial; PCSK-9: Proprotein Convertase Subtilisin/Kexin type 9
* For a detailed description of lifestyle measures and medical therapy, authors are encouraged to read the 2021 American Heart Association/ American Stroke Association Guidelines for the Secondary Prevention of Stroke.[25]

question of whether modern BMT alone is equivalent or superior to CEA/carotid artery stenting (CAS) plus BMT has not yet been answered in well-designed, prospective, multicenter RCTs. As a result, there is currently no Level I evidence that BMT alone is adequate for the management of all ACS patients, and that no ACS patient should be offered a prophylactic carotid revascularization procedure. SPACE-2 had to be abandoned prematurely due to patient unwillingness to participate in a 3-arm RCT (CEA plus BMT *vs.* CAS plus BMT *vs.* BMT alone).[35] Many individuals were reluctant to be randomized to the "BMT alone" arm, especially when patients in all 3 study arms received BMT anyway.[35]

In the recently published ACST-2,[36] 3625 patients were randomly allocated to CAS (N.=1811) or CEA (N.=1814) between January 15, 2008 and December 31, 2020. A disabling stroke or death occurred in about 1% of the procedures (15 patients allocated to CAS and 18 to CEA), while another 2% of the patients suffered a non-disabling periprocedural stroke (48 CAS and 29 CEA patients).[36] Kaplan-Meier estimates of 5-year outcomes were 2.5% in each group for fatal or disabling stroke. Although ACST-2 did not address the question of whether or not a carotid intervention is appropriate for ACS patients, it demonstrated that stroke or death is similarly uncommon after both CAS and CEA, while the long-term effects of the two carotid revascularization procedures on fatal or disabling stroke are comparable.[36] The results of the Carotid Revascularization Endarterectomy *versus* Stenting Trial (CREST)-2[37] are eagerly expected to provide additional evidence on the topic.

Stroke risk of ACS patients

The view that not all ACS patients should be considered candidates for a prophylactic CEA was already expressed in VACS in the early 1990s.[19] It was explicitly mentioned that despite their higher TIA and stroke risk compared with individuals without ACS, most ACS patients will die as a result of coronary heart disease, not stroke (for the medical group: 20.2% *vs.* 1.7% for fatal cardiac *vs.* fatal strokes, respectively; for the surgical group: 20.9% *vs.* 0.5% for fatal

cardiac *vs.* fatal strokes, respectively).[19] It was therefore advised that patient selection was essential to select those ACS individuals more likely to benefit from surgery.[19] The AHA/ASA guidelines similarly indicated that only "highly selected" ACS patients should be offered a carotid intervention,[13, 16] but did not define these ACS patient subgroups.

The 2017 ESVS guidelines[4] recognized this discrepancy in the previous guidelines and provided specific imaging/clinical characteristics that may be associated with an increased risk of late ipsilateral stroke (Table III). These imaging/clinical characteristics included silent embolic infarcts on brain computed tomography/magnetic resonance imaging (MRI), progression in the severity of ACS, a history of contralateral TIA/stroke, microemboli detection on transcranial Doppler, the presence of intraplaque hemorrhage, a lipid-rich necrotic core or a thin/ruptured fibrous cap on carotid MRI, plaque ulceration, reduced cerebrovascular reserve, a large plaque area (>40 mm^2) on carotid ultrasound longitudinal images and plaque echolucency as shown by a low gray scale median (GSM<30) and presence of a large (>8 mm^2) juxtaluminal hypoechoic area after image normalization of Duplex ultrasound images.[4] In "average surgical risk" patients with 60-99% ACS and one or more of the above imaging characteristics, the ESVS guidelines recommended that CEA should be considered (Class IIa; Level of Evidence: B) and CAS may be considered (Class IIb; Level of Evidence: B), provided perioperative stroke/death rates with CEA/CAS are <3% and patient life expectancy exceeds 5 years.[4]

A disadvantage of some of these imaging characteristics is the variation in inter-rater and intra-rater reliability, while other imaging parameters are very reproducible. The accuracy of duplex ultrasound, for instance, largely depends on the expertise of the examiner and its results vary considerably (especially in inexperienced hands). Furthermore, some characteristics (*e.g.* spontaneous embolization on transcranial Doppler) are associated with a higher risk of future stroke risk compared with others (Table III).

A recent systematic review and meta-analysis (N.=64 studies; 20,751 participants) provided proof that high-risk carotid plaques are relatively frequent in ACS individuals, with a pooled prevalence of 26.5%.[38] The most prevalent

Table III.—*Clinical/imaging features associated with an increased risk of late stroke in patients with 50-99% asymptomatic carotid stenosis treated medically.*[4]

Imaging/clinical parameter (stenosis severity)	Annual rate of ipsilateral stroke	OR/HR (95% CI); P
Silent infarction on CT (60-99% stenoses)	Yes=3.6% No=1.0%	3.0 (1.46-6.29); P=0.002
Stenosis progression (50-99% stenoses)	Regression=0% Unchanged=1.1% Progression=2.0%	1.92 (1.14-3.25); P=0.05
Stenosis progression (70-99% stenoses)	Regression No change Progression by 1 stenosis grade Progression by 2 stenosis grades	0.7 (0.4-1.3) Comparator 1.6 (1.1-2.4) 4.7 (2.3-9.6)
Plaque area on computerized plaque analysis (70-99% stenoses)	<40 mm^2=1.0% 40-80 mm^2=1.4% >80 mm^2=4.6%	1.0 2.08 (1.05-4.12) 5.81 (2.67-12.67)
Juxtaluminal black area on computerized plaque analysis (50-99% stenoses)	<4 mm^2=0.4% 4-8 mm^2=1.4% 8-10 mm^2=3.2% >10 mm^2=5.0%	Trend P<0.001
Intraplaque hemorrhage on MRI (50-99%)	Yes *vs.* No	3.66 (2.77-4.95); P<0.01
Impaired CVR 70-99% stenoses	Yes *vs.* No	6.14 (1.27-29.5); P=0.02
Plaque lucency on Duplex ultrasound (50-99% stenoses)	Predominantly echolucent: 4.2% Predominantly echogenic: 1.6%	2.61 (1.47-4.63); P=0.001
Spontaneous embolization on TCD (50-99% stenoses)	Yes *vs.* No	7.46 (2.24-24.89); P=0.001
Spontaneous embolization on TCD plus uniformly or predominantly echolucent plaque (70-99% stenoses)	Yes=8.9% No=0.8%	10.61 (2.98-37.82); P=0.0003
Contralateral TIA/stroke (50-99% stenoses)	Yes=3.4% No=1.2%	3.0 (1.9-4.73); P=0.0001

OR: odds ratio; HR: hazard ratio; CI: confidence interval; CVR: cerebrovascular reserve; TCD: transcranial Doppler TIA: transient ischemic attack.

high-risk plaque features were neovascularization, echolucency and lipid-rich necrotic core.[38] Other high-risk plaque features were also frequently observed, including impaired cerebrovascular reserve, a thin or ruptured fibrous cap, silent brain infarction, intraplaque hemorrhage, microembolic signals and plaque ulceration (Table IV).[38] Importantly, the prevalence of high-risk plaques was not directly associated with the grade of carotid stenosis.[38] A limitation of this study is the considerable heterogeneity and substantial variations often seen in some of the outcomes reported in the contributing studies.[38]

The risk of ipsilateral ischemic cerebrovascular events associated with high-risk plaque features was analyzed in a meta-analysis of 22 studies (N.=10,381 patients).[38] After a mean follow-up of 2.8 years (range: 0.7-6.5 years), the incidence of ipsilateral ischemic cerebrovascular events in the overall population of ACS patients was 3.2 events/100 person-years (95% CI: 2.2-4.3). The incidence of ipsilateral ischemic events in patients with high-risk features was 3-fold higher compared with those without high-risk features (4.3 [95% CI: 2.5-6.5] *vs.* 1.2 [0.6-1.8] events/100 person-years; odds ratio [OR]: 3.0; 95% CI: 2.1-4.3; P<0.001; I^2=48.8%).[38] In the subgroup of studies focusing only on ACS patients with ≥70% stenosis (9 cohorts; 2128 individuals), the incidence of ipsilateral ischemic cerebrovascular events was 3.7 (95% CI: 1.9-6.0) events/100 person-years. The incidence of ipsilateral ischemic cerebrovascular events was >3-fold higher in high-risk ACS patients *vs.* those without high-risk features (7.3 [95% CI: 2.0-15.0] *vs.* 1.7 [95% CI: 0.6-3.3] events/100 person-years; OR: 3.2; 95% CI: 1.7-5.9; P<0.001; I^2=39.6%). Importantly, the incidence of ipsilateral ischemic events in patients with high-risk plaques was not modified by the use of statin or antiplatelet therapy.[38] These results indicate that the risk of ipsilateral ischemic events among the overall population of ACS patients (3.2%) and among the subgroups of patients with high-risk plaque features (4.3%) is considerably higher than the commonly quoted annual stroke incidence of 1%,[22, 23] which was calculated using the 10-year results of ACST-1.[39]

Another meta-analysis of individual patient data from 7 cohort studies showed a prevalence of intraplaque hemorrhage on MRI of 29.4% in patients with ACS and of 51.6% in patients with symptomatic carotid stenosis.[40] In patients with ACS, the presence of intraplaque hemorrhage at baseline increased the risk of ipsilateral stroke by nearly 8-fold (unadjusted HR: 7.9; 95: CI: 1.3-47.6), with an annual ipsilateral stroke rate of 5.4% *vs.* 0.8%, in patients with *vs.* without intraplaque hemorrhage, respectively.[40] These results suggest that intraplaque hemorrhage is a marker of increased stroke risk in patients with ACS.

An independent, recent population-based cohort study, systematic review and meta-analysis demonstrated that the risk of stroke increases significantly with the degree of stenosis in patients with ACS.[41] The Oxford Vascular Study (OxVasc) enrolled patients from April 1, 2002, to April 1, 2017, who were referred for carotid imaging and were found to have ACS (N.=2178).[41] Of these, 207 had 50-99% ACS. After a median follow-up of 5.9 years, there were 16 ischemic events (8 strokes and 8 TIAs) in the territory of the 50-99% stenosis. The 5-year risk of ipsilateral ischemic stroke was significantly greater in patients with 70-99% than in patients with 50-69% stenosis (14.6% [95% CI: 3.5-25.7] *vs.* 0%; P<0.0001) and greater in patients with 80-99% than in those with 50-79% stenosis (18.3% [95% CI: 7.7-29.9] *vs.* 1.0% [95% CI: 0.0-2.9]; P<0.0001).[41] A meta-analysis of 23 studies (N.=8419 patients) reporting ipsilateral stroke risk in patients with moderate and severe

Table IV.—*Prevalence of high-risk plaque features in patients with asymptomatic carotid stenosis.*[38]

High-risk feature	Number of studies	Cases/participants	Prevalence (95% CI); P
Neovascularization	8	360/785	43.4% (31.4-55.8%); P<0.001
Echolucency	16	4223/12364	42.3% (32.2-52.8%); P<0.001
Lipid-rich necrotic core	11	1514/3728	36.3% (27.7-45.2%); P<0.001
Plaque irregularity	1	15/44	34.1% (21.9-48.9); P=NE
AHA type 4, 5 or 6	3	57/168	30.8% (15.6-48.4%); P<0.001
Impaired CVR	5	109/348	29.2% (15.1-45.7%); P<0.001
Thin or ruptured fibrous cap	8	177/670	24.1% (12.0-38.7); P<0.001
Ipsilateral silent brain infarct	7	428/2226	21.9% (15.6-28.8%); P<0.001
Intraplaque hemorrhage	16	934/3245	19.1% (13.8-25.0%); P<0.001
Microembolic signals	14	245/1648	14.3% (10.0-19.2%); P<0.001
Ulceration	8	197/2086	13.1% (3.5-27.1%); P<0.001
Mural thrombus	1	3/41	7.3% (2.5-19.4%); P=NE
Any feature	64	20751	26.5% (22.9-30.3%); P<0.001

AHA: American Heart Association; CVR: cerebrovascular reserve; NE: Not possible to estimate because of small number of studies (N.<3).

stenosis revealed a linear association of stroke risk with degree of stenosis (P<0.0001), with a >2-fold higher risk for patients with 70-99% *vs.* 50-69% stenosis (OR: 2.1; 95% CI: 1.7-2.5; P<0.0001) and a 2.5-fold risk for patients with 80-99% *vs.* 50-79% stenosis (OR: 2.5; 95% CI: 1.8-3.5; P<0.0001).[41] It was concluded that although the reported rates of ipsilateral stroke have fallen over time, the stroke risk is still high for patients with high-grade stenosis on contemporary BMT, "*suggesting that the benefits of surgical intervention might be underestimated*."[41] Therefore, both the OxVasc Study[41] and the two 2020 meta-analyses[38, 40] concurred that the stroke risk is not the same for all ACS patients, but varies significantly depending on plaque type[38, 40] and/or degree of carotid stenosis.[41]

Progression of ACS despite BMT may be another indication for considering a prophylactic carotid intervention. A study from Boston, USA, demonstrated that BMT failed to prevent carotid disease progression in 40% of patients with ACS (N.=794 patients; 900 carotid arteries) and the development of ipsilateral neurologic symptoms in 12% of patients with moderate (50-69%) ACS over 5 years.[42] Similarly, in the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study,[43] BMT failed to prevent a first ipsilateral cerebrovascular or retinal ischemic event in 130 of the 1121 patients (11.6%) with 50-99% ACS receiving BMT over a 4-year period.[43] The 8-year cumulative ipsilateral ischemic stroke rate was 0% in patients with carotid plaque regression, 9% if plaque was unchanged and 16% if there was plaque progression.[43] In the subgroup of patients with unchanged carotid stenosis, the 8-year cumulative ipsilateral cerebral ischemic stroke rates for patients with baseline stenosis of 50-69%, 70-89% and 90-99% were 4%, 8% and 13%, respectively.[43] In contrast, in the presence of progression, the stroke rate at 8 years was 8%, 15% and 25%, respectively.[43] The results from these two independent studies[42, 43] suggest that not only the degree of ACS, but also ACS progression should play an important role in the decision to offer patients a prophylactic carotid intervention.

Current guideline recommendations

The SVS recently released its updated guidelines on the management of patients with asymptomatic and symptomatic carotid stenosis.[5] The 2021 SVS Guidelines provided a strong recommendation for CEA plus BMT over BMT alone for "low surgical risk patients" with >70% ACS provided perioperative stroke/death rates are <3% and the patient has a life expectancy of >5 years (Level of recommendation: Grade 1 [Strong]; Quality of Evidence: B [Moderate]).[5]

The 2021 European Stroke Organization (ESO) guidelines reported that there is moderate quality evidence that CEA reduces the long-term risk of ipsilateral stroke, including periprocedural stroke in any territory or periprocedural death compared with BMT alone (RR: 0.73, 95% CI: 0.59-0.90; equivalent to 19 fewer events with CEA per 1000).[18] Consequently, these guidelines recommended CEA in patients with >60% ACS considered to be at increased risk of stroke on BMT alone (Quality of evidence: moderate; strength of recommendation: strong for CEA).[18]

Finally, the 2020 updated German-Austrian clinical practice guidelines stated that in the presence of a 60-99% ACS, CEA should be considered provided there is no increased surgical risk and one or more clinical or imaging findings are available that are associated with an increased risk of carotid-related stroke on follow-up (Level of Evidence: 1).[17] CAS may be considered only for these patient groups (Level of Evidence: 2a).[17] Based on data from ACST-1,[21] which demonstrated a 6.5% absolute risk reduction after 5 years, the German-Austrian guidelines acknowledged that men <75 years belong to the group of patients with an increased remote stroke risk.[17] In addition, these guidelines specifically recommended that periprocedural stroke/death rates should be as low as possible for CEA/CAS and should not exceed 2%.[17] This lower threshold for complications (<2%[17] instead of the previously quoted <3%)[4, 5, 11, 12] is a recognition of the lower current perioperative stroke/death rates following CEA/CAS compared with those of the landmark RCTs.[19-21]

The Controversial Issue of Screening for ACS

Each year in the United States about 795,000 patients suffer a stroke.[44] Stroke is the fifth leading cause of death in the U.S.A., killing almost 140,000 American/year.[44] In Europe there are around 1,400,000 strokes/year causing 1100,000 deaths.[4] About 15% of all first-ever strokes occur due to atheroembolism from a previously untreated 50-99% ACS.[4] Therefore, the identification of patients with ACS and the implementation of measures to prevent them from becoming symptomatic could reduce the number of strokes. Despite that, the U.S. Preventive Services Task Force [USPSTF] recently reaffirmed its recommendation against screening for ACS in the general adult population.[45] The arguments for not recommending screening for ACS include: a) the harm associated with screening, b) the questionable clinical benefit conferred by CEA or CAS, c) the lack of proven reduction in the risk of stroke, d) the large number of possible false positive/false negative tests, and, e) the question of cost-effectiveness of such screening programs.[45]

In contrast to ACS, a one-time ultrasound screening is strongly recommended for men 65-75 years of age with a history of tobacco use for the detection of abdominal aortic aneurysms (AAAs; Level of recommendation: 1 [Strong]; Quality of Evidence: A [High]).[46] Screening for asymptomatic AAAs is strongly recommended to reduce the AAA-related mortality.[46]

Although routine screening for ACS in the general adult population should not be recommended,[45] it may be reasonable to consider selective screening for specific population subgroups.[47] Screening for (and detection of) ACS should not be viewed as an indication for surgery, but rather as an opportunity for risk factor management (*e.g.* smoking cessation and weight loss) and timely initiation of BMT.[47] ACS is not only a risk factor for stroke, but also a marker of increased risk for MI and cardiovascular death.[47] By not detecting ACS and by not initiating risk factor management and BMT, these individuals remain at high risk not only for stroke, but also for MI and cardiovascular mortality.[47] It may therefore be reasonable to consider screening for ACS in selected population subgroups (*e.g.* for males 65-75 years of age with a history of tobacco use, as in the case of AAAs[46]).

Future directions

A number of controversial issues and shortfalls concerning ACS have been identified in this review. Others, not addressed here, include the questionable benefit of CEA/CAS *vs.* BMT alone for female ACS patients, the debatable advantage of CEA plus BMT over BMT alone with increasing age, the sex differences in the evaluation, carotid imaging and treatment of acute stroke, the role of transcarotid artery revascularization (TCAR) procedures in the management of ACS patients and the need to centralize carotid interventions in highly specialized centers.[48-53] Improvements in ranking of evidence, research reporting and standard of care are additional topics that require attention.[48, 49]

An under-recognized topic that deserves more research in the future is the progressive cognitive deterioration in patients with severe ACS.[54, 55] There is evidence that patients with ACS have a >4-fold probability of developing cognitive decline compared with individuals without ACS (OR: 4.16; 95% CI: 1.89-9.11; P<0.001).[56] The presence of an associated hemodynamic impairment ipsilateral to the side of ACS significantly increases the risk of cognitive dysfunction (OR: 14.66; 95% CI: 7.51-28.59; P<0.001).[56] Cognitive performance should therefore be included among the outcomes investigated when evaluating the results of BMT *vs.* CEA/CAS plus BMT in ACS patients. A secondary study of CREST-2 (CREST-Hemodynamics) is under way and aims to determine treatment differences with regards to cognitive function.[57] There is also evidence that non-stenosing, complicated carotid artery plaques (AHA-lesion type IV) are an under-recognized cause of stroke.[58]

An important novel finding reported in the recent systematic review and meta-analysis on the prevalence of high-risk plaques and stroke risk in ACS patients is worth mentioning.[38] The authors demonstrated that the prevalence of high-risk plaques was not directly associated with the grade of ACS.[38] This finding has important implications, since it suggests that the presence or absence of high-risk plaques may play a more pivotal role in the selection of conservative or invasive management of ACS patients than the degree of ACS. This issue should be addressed in future studies.

Finally, the role/effect of race/ethnicity in decision-making with regards to the conservative or invasive approach of ACS patients is largely unknown. The risk of having a first stroke is nearly twice as high for black compared with white individuals.[44] In addition, blacks have the highest rate of death due to stroke.[44] Finally, although stroke rates have declined among all race/ethnicities, Hispanics have seen an increase in death rates since 2013.[44] Consequently, the management of ACS patients may need to be individualized depending on race/ethnicity.[59] These issues should be addressed in appropriately designed clinical trials to resolve the uncertainties surrounding the optimal management of ACS patients.

Conclusions

The optimal management of patients with severe ACS remains controversial and is still the subject of extensive debates. Although progress has been made in certain areas, controversy in other areas will persist. The most recent guidelines, namely the 2021 SVS,[5] the 2021 European Stroke Organisation[18] and the 2020 German-Austrian guidelines[17] still recommend CEA plus BMT instead of BMT alone in patients with ≥60%[17, 18] or >70% ACS[5] at low surgical risk and a reasonable life-expectancy for the long-term prevention of stroke/death. It is now clear that all ACS patients do not have the same stroke risk[38, 40, 41] and therefore the management of patients with ACS may need to be individualized based on specific imaging/clinical criteria,[4,17] as well as individual patient preferences/needs.[59] Perioperative stroke/death rates should be as low as possible to ensure the maximal benefit for ACS patients from prophylactic CEA. The 2020 German-Austrian guidelines have proposed a new, lower threshold for

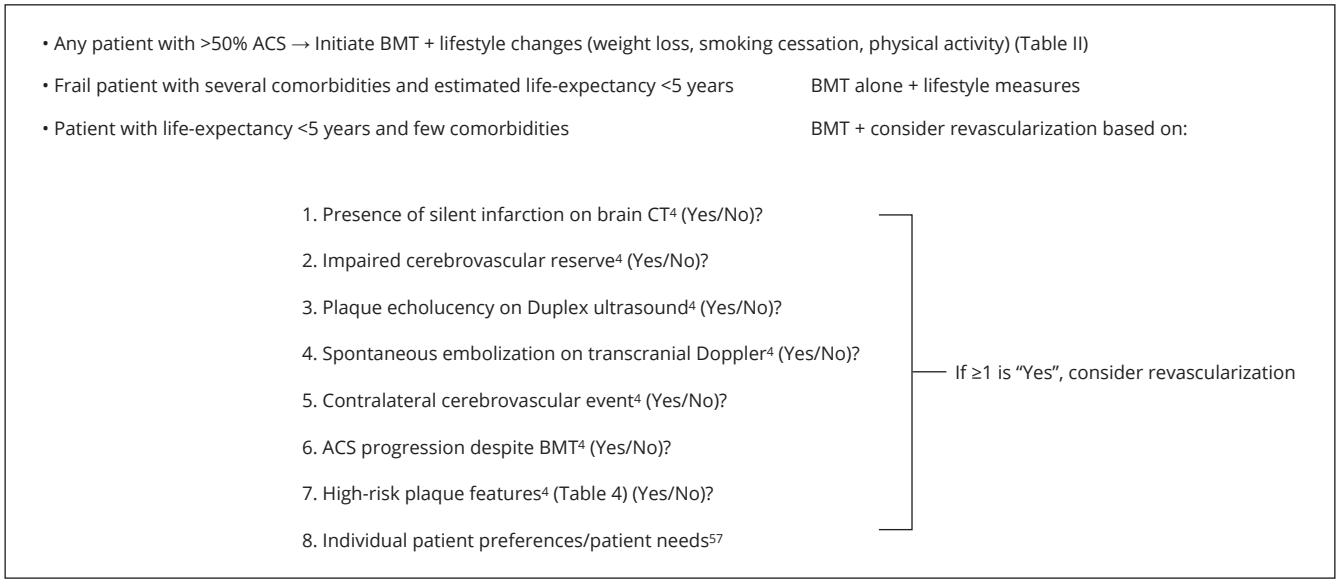

Figure 1.—Algorithm for the management of patients with asymptomatic carotid stenosis.

perioperative stroke/death of <2%[17] instead of the so-far quoted <3%.[4, 5, 7-16]

Although it is essential that all ACS patients should receive BMT to reduce all-cause and cardiac mortality,[60] it has been proposed that specific ACS patient subgroups should be considered for a prophylactic carotid procedure (Figure 1).[4, 59] Nevertheless, the evidence in favor of an intervention in some patient subgroups is weaker than in others. Therefore, until the results of the much-anticipated RCTs emerge, the jury is still out regarding the optimal management of ACS patients. Physicians should use the currently available evidence in combination with the recommendations of international guidelines, the individual patient needs/characteristics (*e.g.* age, comorbidities, patient preference, etc.) and their own clinical judgment to optimize the management of ACS patients.[59]

References

1. Ois A, Cuadrado-Godia E, Rodríguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. Stroke 2009;40:2727–31.

2. Fairhead JF, Mehta Z, Rothwell PM. Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. Neurology 2005;65:371–5.

3. Marnane M, Prendeville S, McDonnell C, Noone I, Barry M, Crowe M, *et al.* Plaque inflammation and unstable morphology are associated with early stroke recurrence in symptomatic carotid stenosis. Stroke 2014;45:801–6.

4. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, *et al.*; Esvs Guidelines Committee; Esvs Guideline Reviewers. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3–81.

5. AbuRahma AF, Avgerinos EM, Chang RW, Darling RC 3rd, Duncan AA, Forbes TL, *et al.* Society for Vascular Surgery Clinical Practice Guidelines for Management of Extracranial Cerebrovascular Disease. J Vasc Surg 2022;75:45–225.

6. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, *et al.*; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation 2021;143:e254–743.

7. Biller J, Feinberg WM, Castaldo JE, Whittemore AD, Harbaugh RE, Dempsey RJ, *et al.* Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 1998;29:554–62.

8. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, *et al.* Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. JAMA 1999;281:1112–20.

9. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, *et al.* Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280–99.

10. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, *et al.*; American Heart Association; American Stroke Association Stroke Council. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2006;113:e873–923.

11. Hobson RW 2nd, Mackey WC, Ascher E, Murad MH, Calligaro KD, Comerota AJ, *et al.*; Society for Vascular Surgery. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. J Vasc Surg 2008;48:480–6.

12. Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fer-

nandes e Fernandes J, *et al.*; ESVS Guidelines Collaborators. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009;37(Suppl):1–19.

13. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, *et al.*; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517–84.

14. 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:e1–31.

15. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, *et al.*; European Stroke Organisation; ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851–906.

16. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, *et al.*; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754–832.

17. Eckstein HH, Kühnl A, Berkefeld J, Lawall H, Storck M, Sander D. Diagnosis, Treatment and Follow-up in Extracranial Carotid Stenosis. Dtsch Arztebl Int 2020;117:801–7.

18. Bonati LH, Kakkos S, Berkefeld J, de Borst GJ, Bulbulia R, Halliday A, *et al.* European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J 2021;6:I.

19. Hobson RW 2nd, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, *et al.*; The Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. N Engl J Med 1993;328:221–7.

20. [No authors listed]. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421–8.

21. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, *et al.*; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–502.

22. 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:e573–83.

23. Abbott A. Asymptomatic carotid artery stenosis—it's time to stop operating. Nat Clin Pract Neurol 2008;4:4–5.

24. Reiff T, Eckstein HH, Mansmann U, Jansen O, Fraedrich G, Mudra H, *et al.* Angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy compared to best medical treatment: one-year interim results of SPACE-2. Int J Stroke 2019;15:1747493019833017.

25. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, *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:e364–467.

26. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, *et al.* The Physical Activity Guidelines for Americans. JAMA 2018;320:2020–8.

27. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13–115.

28. Waters DD, LaRosa JC, Barter P, Fruchart JC, Gotto AM Jr, Carter R, *et al.* Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. J Am Coll Cardiol 2006;48:1793–9.

29. Amarenco P, Labreuche J, Lavallée P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke 2004;35:2902–9.

30. Wong KS, Wang Y, Leng X, Mao C, Tang J, Bath PM, *et al.* Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. Circulation 2013;128:1656–66.

31. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, *et al.*; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med 2018;379:215–25.

32. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, *et al.*; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11–9.

33. Pan Y, Elm JJ, Li H, Easton JD, Wang Y, Farrant M, *et al.* Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack: A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials. JAMA Neurol 2019;76:1466–73.

34. Paraskevas KI, Mikhailidis DP, Veith FJ, Spence JD. Definition of Best Medical Treatment in Asymptomatic and Symptomatic Carotid Artery Stenosis. Angiology 2016;67:411–9.

35. Eckstein HH, Reiff T, Ringleb P, Jansen O, Mansmann U, Hacke W; SPACE 2 Investigators. SPACE-2: A Missed Opportunity to Compare Carotid Endarterectomy, Carotid Stenting, and Best Medical Treatment in Patients with Asymptomatic Carotid Stenoses. Eur J Vasc Endovasc Surg 2016;51:761–5.

36. Halliday A, Bulbulia R, Bonati LH, Chester J, Cradduck-Bamford A, Peto R, *et al.*; ACST-2 Collaborative Group. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. Lancet 2021;398:1065–73.

37. Howard VJ, Meschia JF, Lal BK, Turan TN, Roubin GS, Brown RD Jr, *et al.*; CREST-2 study investigators. Carotid revascularization and medical management for asymptomatic carotid stenosis: protocol of the CREST-2 clinical trials. Int J Stroke 2017;12:770–8.

38. Kamtchum-Tatuene J, Noubiap JJ, Wilman AH, Saqqur M, Shuaib A, Jickling GC. Prevalence of High-risk Plaques and Risk of Stroke in Patients With Asymptomatic Carotid Stenosis: A Meta-analysis. JAMA Neurol 2020;77:1524–35.

39. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, *et al.*; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;376:1074–84.

40. Schindler A, Schinner R, Altaf N, Hosseini AA, Simpson RJ, Esposito-Bauer L, *et al.* Prediction of Stroke Risk by Detection of Hemorrhage in Carotid Plaques: Meta-Analysis of Individual Patient Data. JACC Cardiovasc Imaging 2020;13:395–406.

41. Howard DP, Gaziano L, Rothwell PM; Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. Lancet Neurol 2021;20:193–202.

42. Conrad MF, Boulom V, Mukhopadhyay S, Garg A, Patel VI, Cambria

RP. Progression of asymptomatic carotid stenosis despite optimal medical therapy. J Vasc Surg 2013;58:128–35.e1.

43. 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.

44. Stroke Fact Sheet. Centers for Disease Control and Prevention [Internet]. Available from: https://www.cdc.gov/stroke/facts.htm [cited 2021, Sep 18].

45. Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, *et al.*; US Preventive Services Task Force. Screening for Asymptomatic Carotid Artery Stenosis: US Preventive Services Task Force Recommendation Statement. JAMA 2021;325:476–81.

46. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, *et al.*; US Preventive Services Task Force. Screening for Abdominal Aortic Aneurysm: US Preventive Services Task Force Recommendation Statement. JAMA 2019;322:2211–8.

47. Paraskevas KI, Eckstein HH, Mikhailidis DP, Veith FJ, Spence JD. Rationale for screening selected patients for asymptomatic carotid artery stenosis. Curr Med Res Opin 2020;36:361–5.

48. Abbott AL, Brunser AM, Giannoukas A, Harbaugh RE, Kleinig T, Lattanzi S, *et al.* Misconceptions regarding the adequacy of best medical intervention alone for asymptomatic carotid stenosis. J Vasc Surg 2020;71:257–69.

49. Abbott A. Critical Issues That Need to Be Addressed to Improve Outcomes for Patients With Carotid Stenosis. Angiology 2016;67:420–6.

50. Saba L, Yuan C, Hatsukami TS, Balu N, Qiao Y, DeMarco JK, *et al.*; Vessel Wall Imaging Study Group of the American Society of Neuroradiology. Carotid Artery Wall Imaging: Perspective and Guidelines from the ASNR Vessel Wall Imaging Study Group and Expert Consensus Recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 2018;39:E9–31.

51. Bushnell C, Howard VJ, Lisabeth L, Caso V, Gall S, Kleindorfer D, *et al.* Sex differences in the evaluation and treatment of acute ischaemic stroke. Lancet Neurol 2018;17:641–50.

52. Schermerhorn ML, Liang P, Eldrup-Jorgensen J, Cronenwett JL, Nolan BW, Kashyap VS, *et al.* Association of Transcarotid Artery Revascularization vs Transfemoral Carotid Artery Stenting With Stroke or Death Among Patients With Carotid Artery Stenosis. JAMA 2019;322:2313–22.

53. Schermerhorn ML, Liang P, Dakour-Aridi H, Kashyap VS, Wang GJ, Nolan BW, *et al.* In-hospital outcomes of transcarotid artery revascularization and carotid endarterectomy in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2020;71:87–95.

54. Silvestrini M, Paolino I, Vernieri F, Pedone C, Baruffaldi R, Gobbi B, *et al.* Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. Neurology 2009;72:1062–8.

55. Buratti L, Balucani C, Viticchi G, Falsetti L, Altamura C, Avitabile E, *et al.* Cognitive deterioration in bilateral asymptomatic severe carotid stenosis. Stroke 2014;45:2072–7.

56. Balestrini S, Perozzi C, Altamura C, Vernieri F, Luzzi S, Bartolini M, *et al.* Severe carotid stenosis and impaired cerebral hemodynamics can influence cognitive deterioration. Neurology 2013;80:2145–50.

57. Marshall RS, Lazar RM, Liebeskind DS, Connolly ES, Howard G, Lal BK, *et al.* Carotid revascularization and medical management for asymptomatic carotid stenosis - Hemodynamics (CREST-H): study design and rationale. Int J Stroke 2018;13:985–91.

58. Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, *et al.* Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke. J Am Coll Cardiol 2020;76:2212–22.

59. Paraskevas KI, Mikhailidis DP, Baradaran H, Davies AH, Eckstein HH, Faggioli G, *et al.* Management of Patients with Asymptomatic Carotid Stenosis May Need to Be Individualized: A Multidisciplinary Call for Action. J Stroke 2021;23:202–12.

60. Giannopoulos A, Kakkos S, Abbott A, Naylor AR, Richards T, Mikhailidis DP, *et al.* Long-term Mortality in Patients with Asymptomatic Carotid Stenosis: Implications for Statin Therapy. Eur J Vasc Endovasc Surg 2015;50:573–82.

Conflicts of interest.— Ajay Gupta reports non-financial support from GE Healthcare and Siemens Medical Solutions USA, Inc.; Dimitri P. Mikhailidis has given talks, acted as a consultant or attended conferences sponsored by Amgen, Novo Nordisk and Libytec; Niki Katsiki has given talks, attended conferences and participated in trials sponsored by Angelini, Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Mylan, Novo Nordisk, Sanofi and Servier; Seemant Chaturvedi is an Associate Editor of *Stroke* and is on the executive committee of the Carotid Revascularization Endarterectomy *versus* Stenting Trial (CREST) 2 and the Asymptomatic Carotid Trial (ACT) I. The other authors have no conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Kosmas I. Paraskevas had the conception and design of the article, gathered and analyzed the data and wrote the first draft of the manuscript; Dimitri P. Mikhailidis critically revised and edited the first draft for intellectual concept; Pier L. Antignani, Hediyeh Baradaran, Reinoud P. Bokkers, Richard P. Cambria, Alun H. Davies, Hans-Henning Eckstein, Gianluca Faggioli and Jose Fernandes e Fernandes reviewed the manuscript for scientific content and critically revised the first draft; Alan Dardik, Ajay Gupta, Mateja K. Jezovnik, Stavros K. Kakkos, Niki Katsiki, M. Eline Kooi, Gustav Fraedrich, George Geroulakos and Gaetano Lanza performed the second round of revisions of the manuscript; Christos D. Liapis, Ian M. Loftus, Antoine Millon, Andrew N. Nicolaides, Pavel Poredos and Rodolfo Pini verified the scientific content and information reported and revised the manuscript. Peter Gloviczki, Jonathan Golledge, Michael Knoflach and Armando Mansilha prepared the 4 Tables; Thomas S. Riles and Peter Arthur Ringleb prepared Figure 1; Felix Schlachetzki, Mauro Silvestrini and Jasjit S. Suri verified the information included in the Tables and Figure 1; Jean-Baptiste Ricco, Tatjana Rundek, Luca Saba, Francesco Spinelli, Francesco Stilo, Sherif Sultan, Clark J. Zeebregts performed the final check of the revised manuscript and made additional revisions. Seemant Chaturvedi revised the initial manuscript and had the overview of the work. All authors read and approved the final version of the manuscript.

Acknowledgements.—All authors are members of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATS; available at www.FACTCATS.org) with the shared goal of optimizing stroke prevention. The views of particular FACTCATS do not necessarily reflect the views of other FACTCATS.

This article was first published in *The Journal of Stroke and Cerebrovascular Diseases*, namely: Paraskevas KI, Mikhailidis DP, Antignani PL, Baradaran H, Bokkers RPH, Cambria RP, *et al.* Optimal Management of Patients with Asymptomatic Carotid Stenosis in 2021: The Jury is Still Out. An International, Multispecialty, Expert Review, and Position Statement. J Stroke Cerebrovasc Dis 2021 Nov 1;31(1):106182 doi: 10.1016/j.jstrokecerebrovasdis.2021.106182.

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History.—Article first published online: December 16, 2021. - Manuscript accepted: December 9, 2021. - Manuscript received: November 21, 2021.