Best medical treatment alone may not be adequate for all patients with asymptomatic carotid artery stenosis

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Stroke is the fifth leading cause of death in the United States, with >130,000 deaths/y.[1] Every year, about 795,000 people in the United States sustain a stroke.[1] About 610,000 of these are first strokes and 185,000 are recurrent strokes.[1] Three landmark randomized controlled trials (RCTs) demonstrated that in patients with 60% to 99% asymptomatic carotid stenosis (ACS), carotid endarterectomy (CEA) conferred a 50% relative risk reduction in the 5-year stroke risk compared with medical treatment (MT) alone (absolute risk reduction of ≈1%/y).[2-4] Based on these results, the 2011 Society for Vascular Surgery guidelines recommended that patients with 70% to 99% ACS should be considered for CEA to reduce the long-term risk of stroke, provided they have a 3- to 5-year life expectancy, and perioperative stroke and death rates are ≤3%.[5] The 2017 European Society for Vascular Surgery (ESVS) guidelines recommend that in "average surgical risk" patients with 60% to 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 (eg, silent infarction on computed tomography or magnetic resonance imaging [MRI], stenosis progression, large plaque area, large juxtaluminal black area on computerized plaque analysis, intraplaque hemorrhage on MRI, impaired cerebrovascular reserve, contralateral stroke or transient ischemic attack, plaque echolucency or spontaneous embolization on transcranial Doppler monitoring), provided documented perioperative stroke and death rates are <3% and the patient's life expectancy exceeds 5 years.[6]

Because of improvements in optimal MT (including smoking cessation, weight loss, and regular exercise besides improvements in medications themselves), it has been argued[7,8] that the stroke risk associated with MT alone is now much lower than that reported in the three RCTs[2-4] conducted 20 to 30 years ago. On this basis, some believe that currently all patients with ACS should be managed with MT alone and that CEA is not justified in any of these patients.[7,8] This article discusses the limitations of this hypothesis.

COMPARISON OF RECENT STROKE RATES WITH MT TO THOSE OF OPERATED ON PATIENTS IN RCTs DOES NOT CONSIDER IMPROVEMENTS IN SURGICAL OUTCOMES

Because of improvements in MT, it is true that the ipsilateral stroke rates in patients with ACS have decreased compared with those recorded in the mid-1980s.[7,8] At the same time, however, the periprocedural stroke rates associated with CEA for ACS have also decreased compared with the rates in the mid-1980s. There are data from Australia and Italy, for instance, whereby CEA was performed on asymptomatic patients with death and stroke as low as 0.9% and 0.5%, respectively.[9]

The reduced risk of stroke in ACS patients with MT alone (but also with CEA plus MT) has led to calls for contemporary RCTs evaluating management strategies in asymptomatic patients to include an additional medical arm for MT alone. The second Stent Protected Angioplasty vs Carotid Endarterectomy trial (SPACE-2) planning to randomize patients to CEA, carotid artery stenting (CAS), and MT was abandoned after randomizing only 513 patients because of slow recruitment.[10] The second Carotid Revascularization vs Stenting Trial (CREST-2) has started randomizing asymptomatic patients to CEA vs MT and CAS vs MT,[11] whereas the second European Carotid Surgery Trial (ECST-2) includes a medical limb for asymptomatic patients.[12] It is hoped that all surgeons and interventionists will support these ongoing RCTs, but until we get these results, a careful analysis of risk factors associated with plaque morphology, presence of silent brain infarction on MRI, spontaneous embolism on transcranial Doppler ultrasound, and others[6] is needed to evaluate which patients are at a high risk of stroke despite strict optimal MT.

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IS MT ADEQUATE FOR STROKE PREVENTION IN ALL ACS PATIENTS?

There is evidence suggesting that MT may fail to prevent carotid disease progression and the development of symptoms in some ACS patients. A study by Conrad et al[13] demonstrated that MT failed to prevent carotid disease progression in 40% of patients with ACS and the development of ipsilateral neurologic symptoms in 12% of patients with moderate (50%-69%) ACS during 5 years. In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study,[14] MT failed to prevent a first ipsilateral cerebrovascular or retinal ischemic event in 130 of the 1121 patients with 50% to 99% ACS receiving MT (11.6%) during a 4-year period.[14] These two independent studies[13,14] show that the annual stroke risk for patients with ACS receiving MT alone is not 0.5% to 1%[7,8] but much higher (2.4%[13]-2.9%[14]). However, it is true that not all patients in both studies[13,14] did receive currently optimal MT with antiplatelet therapy, lipid-lowering drugs, and antihypertensive drugs.

The detection of microemboli using transcranial Doppler is another validated method for the identification of ACS patients at high risk for future stroke. A study from Canada showed that ACS patients with more than two microemboli per hour on transcranial Doppler ultrasound had a significantly higher 1-year ipsilateral ischemic stroke risk compared with ACS patients without microemboli (15.6% vs 1.0%, respectively; $P < .0001$).[15] These results were verified in an independent multicenter international study of patients with ACS, the Asymptomatic Carotid Emboli Study (ACES).[16]

In a systematic review, Abbott supported MT alone for ACS.[7] However, many of the studies cited by Abbott[7] were small and poorly controlled, with limited follow-up and unclear duplex ultrasound criteria. Of note, in Abbott's review, many patients with ACS around 50% should not have undergone CEA. Their inclusion introduces a bias that needs to be emphasized.[17] There is currently no level 1 evidence that MT alone is good enough to prevent stroke in all patients with ACS[17]; but neither is there level 1 evidence that invasive treatment is superior to strict MT in patients with ACS.

The Asymptomatic Carotid Surgery Trial 1 (ACST-1) showed that the stroke risk with CEA plus MT was nearly half that of MT alone, irrespective of whether patients were receiving lipid-lowering, antithrombotic, and antihypertensive therapy before their stroke (0.7% vs 1.3%, respectively; hazard ratio, 0.54; 95% confidence interval, 0.34-0.86; $2P < .0001$) or not (1.7% vs 3.2%, respectively; hazard ratio, 0.55; 95% confidence interval, 0.36-0.81; $2P < .0001$).[18]

NOT ALL PATIENTS WITH ACS CARRY THE SAME RISK OF STROKE

Not all ACS patients have the same risk of stroke. The type or morphology of carotid plaque is decisive, and not all carotid plaques have the same embolic potential. Certain plaque characteristics may increase carotid plaque vulnerability, thereby supporting a prophylactic intervention. Such plaque characteristics include plaque ulceration, intraplaque hemorrhage, lipid-rich necrotic core, thin fibrous cap, increased plaque neovascularization, increased calcium burden, increased plaque volume, and carotid plaque progression.[19-24] As shown in the ACSRS study,[14] 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 a plaque progression. 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% to 69%, 70% to 89%, and 90% to 99% were 4%, 8%, and 13%, respectively.[14] In contrast, in the presence of progression, the stroke rate at 8 years was 8%, 15%, and 25%, respectively. These data clearly show that ACS patients should not be offered a "one-size-fits-all" approach. Offering CEA to every asymptomatic patient is as inappropriate as treating all ACS patients with MT alone and not offering CEA to any of these patients.

Appropriate stroke risk stratification modeling should be considered in clinical practice. The majority of ACS patients should probably be managed with MT alone. Nevertheless, current evidence suggests that a small subset of patients with ACS is at increased stroke risk and may benefit from prophylactic CEA. The 2017 ESVS guidelines identify specific ACS patient subgroups with clinical and imaging features that render them at "higher risk for stroke" on MT.[6] For such patients, the 2017 ESVS guidelines recommend that a prophylactic CEA should be considered.[6] A drawback of this recommendation is that some of the listed imaging criteria are generally not available in most North American practices.[25] Furthermore, progression of the degree of stenosis despite best MT may identify additional asymptomatic individuals for prophylactic CEA.[13,25]

Besides the fact that not all ACS patients carry the same risk of stroke, another issue to consider is that not all ACS patients are at low surgical risk. Appropriate perioperative risk stratification criteria should be established. Asymptomatic patients at high surgical risk because of cardiac, pulmonary, anatomic, or other reasons should not be considered for prophylactic CEA. This fact is also reflected in the 2017 ESVS guidelines,[6] which recommend an intervention (CEA or CAS) for ACS in patients with one or more clinical or imaging characteristics that are associated with an increased risk for late ipsilateral stroke, but only if the patient's life expectancy exceeds 5 years.

DO NOT COMPARE RATES THAT ARE NOT COMPARABLE

It is incorrect to compare the *annual* stroke rate using current MT alone with the *periprocedural* stroke rate