Stroke prevention in asymptomatic carotid artery disease: revascularization of carotid stenosis is not the solution

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ABSTRACT
Asymptomatic carotid stenosis (ACS) exceeding 50% is present in about 2% of 60-year-old patients and an even higher fraction of older individuals. The major independent risk factors include advancing age, male sex, tobacco smoking, and a history of vascular disease. The best available evidence does not support either population screening for ACS or routine carotid revascularization when ACS is discovered. There is an urgent need to identify patients with ACS and a sufficiently high risk of ipsilateral stroke (despite contemporary medical management) to warrant invasive treatment. The mainstays of medical management are antiplatelet therapy (usually low-dose aspirin), high-dose statins, blood pressure control, and smoking cessation. Patients with ACS should be periodically educated about symptoms of transient ischemic attack and stroke that require emergent medical attention. Current guidelines vary widely in recommendations regarding revascularization (ie, endarterectomy or carotid stenting). The benefits of revascularization strategies remain uncertain for patients with ACS who receive contemporary medical management.

KEY WORDS
asymptomatic carotid stenosis, carotid artery atherosclerosis, carotid artery revascularization, carotid endarterectomy

Introduction
Cervical carotid artery atherosclerosis as a cause of stroke was initially emphasized 65 years ago, and the search for effective and safe preventive strategies has vexed clinicians ever since. About 15% of ischemic strokes occurring among patients in Europe and North America are associated with cervical carotid artery atherosclerotic stenosis (figure). Consistent results of large randomized trials conducted in the 1980s and 1990s demonstrated that carotid endarterectomy roughly halves the risk of ipsilateral stroke in patients with asymptomatic carotid stenosis (ACS), and population screening for ACS followed by revascularization would at first thought seem a reasonable approach to reducing the burden of stroke associated with ACS. However, it has proven not to be so straightforward.

A vast number of publications continue to be published yearly concerning management of ACS, testifying to ongoing uncertainties and controversies. In this commentary, we review recent studies and current concepts and guidelines concerning the management of ACS. We conclude that revascularization of ACS is not the solution to substantially reducing the burden of stroke from cervical carotid artery atherosclerosis and that decisions regarding revascularization of ACS based solely on the degree of stenosis are poorly informed.

Frequency of asymptomatic carotid stenosis
A recent pooled analysis of 4 population-based studies from Europe and North America involving 23,706 people screened with ultrasonography yielded a frequency of ACS exceeding 50% in 2% and of ACS exceeding 70% in 0.5% of the combined cohort at a mean age of 61 years. ACS exceeding 70% was present in 0.3% of this cohort in the absence of a history of vascular disease and in 1.9% of those with clinical coronary artery disease. Age, male sex, current tobacco smoking, and a history of vascular disease were the strongest independent predictors of severe ACS. Considering 29 published studies (not restricted to population-based cohorts), the prevalence of ACS of 50% or higher was 5% among men vs. 2% for women.

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The most likely explanation for the decline in stroke rates is an interval improvement in medical management, particularly the use of "statin" medications that have been proved to remarkably reduce stroke risk in patients with carotid artery atherosclerosis. Consequently, the modest absolute benefit conferred by carotid endarterectomy documented by randomized trials conducted 20 years ago is likely to be even smaller for contemporary patients with ACS managed aggressively with blood pressure control, lipid lowering using statins, and antiplatelet therapy. In short, because of low ipsilateral stroke rates in contemporary patients with ACS, many have questioned the relevance of these earlier trials to current practice.

On the other hand, the complication rates associated with revascularization of ACS may also be declining. ACS is a risk factor for covert/silent brain infarcts detected by computed tomography in under the age of 70 years. Among a cohort of patients with manifest arterial disease or diabetes mellitus with a mean age of 58 years, the frequency of ACS of 50% or higher was 8%. However, in many of these studies, screening with carotid artery ultrasonography was not confirmed by other imaging modalities, and false-positive results are likely to have inflated prevalence estimates for ACS (see "Population screening for asymptomatic carotid stenosis" below).

**Risk of stroke and other vascular events associated with asymptomatic carotid stenosis** Based on consistent evidence, the absolute rate of ipsilateral stroke is low in contemporary patients with ACS, averaging 1% per year or lower among unselected patients and those with vascular disease. Current stroke rates associated with ACS are consistently lower than those reported in the 1980s and 1990s (which averaged 2%-4% per year) and are lower than stroke rates reported in the medically-treated arms of randomized trials testing carotid endarterectomy. The most likely explanation for the decline in stroke rates is an interval improvement in medical management, particularly the use of "statin" medications that have been proved to remarkably reduce stroke risk in patients with carotid artery atherosclerosis. Consequently, the modest absolute benefit conferred by carotid endarterectomy documented by randomized trials conducted 20 years ago is likely to be even smaller for contemporary patients with ACS managed aggressively with blood pressure control, lipid lowering using statins, and antiplatelet therapy. In short, because of low ipsilateral stroke rates in contemporary patients with ACS, many have questioned the relevance of these earlier trials to current practice. On the other hand, the complication rates associated with revascularization of ACS may also be declining. ACS is a risk factor for covert/silent brain infarcts detected by computed tomography in
patients without a history of stroke; however, covert/silent infarcts are equally distributed ipsilaterally and contralaterally to the side of the ACS. Patients with ACS also have a substantial frequency of coronary artery atherosclerosis: myocardial infarction is about half as frequent as stroke, while the risk of cardiovascular death exceeds that of stroke. Aggressive medical management of ACS offers the additional benefit of prevention of coronary events. There are too few high-quality studies to determine whether ACS is an independent risk factor for cognitive dysfunction, and the effect of revascularization on measures of cognition have been mixed.

Can patients with asymptomatic carotid stenosis at high risk for stroke be identified? The degree of stenosis alone is a relatively weak predictor of ipsilateral stroke and does not identify medically treated patients with carotid artery atherosclerosis who have sufficient absolute rates of ipsilateral stroke to justify revascularization. It has been estimated that with contemporary medical management only about 10% of unselected patients with ACS could benefit from additional revascularization. Can high-risk subgroups be identified? This critical issue has recently received considerable attention. ACS patients with other clinical manifestations of atherosclerosis (ie, coronary artery disease, peripheral vascular disease) or previous stroke have higher stroke risks, but the absolute rates have not been well characterized. High-resolution magnetic resonance imaging has been promising for identification of “vulnerable plaques” associated with higher risk of stroke. However, many experts believe that there are as yet no externally validated, reliable indicators that can identify ACS patients at an increased risk of stroke.

Revascularization for asymptomatic carotid stenosis: current guidelines Despite the concern that carotid revascularization is of no substantial benefit for the majority of ACS patients who are treated with contemporary medical management, current guideline endorsements favor revascularization for many patients with ACS (Table 2). Although guidelines attempt to synthesize the best available management recommendations, they are not without limitations. Guideline recommendations favoring revascularization of ACS have been criticized on the basis that revascularization does not make sense for ACS patients with an annual risk of ipsilateral stroke of 1% to 2% because of the inherent upfront risk of opening the carotid arteries. The most recent European Stroke Organisation guideline is perhaps the most cautious regarding revascularization: “There is uncertainty about the benefit of revascularization for asymptomatic carotid stenosis ... there is not enough data to recommend [stenting] as an alternative to [carotid endarterectomy].”

Population screening for asymptomatic carotid stenosis There is a general agreement in the recent literature that population screening for ACS is not warranted. Using optimistic estimates for the sensitivity (95%) and specificity (92%) of carotid ultrasonography, screening of 100,000 adults assuming a true prevalence of ACS of 1% would yield 940 true-positive results and 7920 false-positive results, or a positive predictive value of about 10%. Of note, the positive predictive value of ultrasonography is much higher in patients presenting to clinicians with asymptomatic bruises or other clinical manifestations of atherosclerosis (eg, peripheral vascular disease, contralateral ischemic stroke). The U.S. Preventive Services Task Force has recently reaffirmed its recommendation against screening for ACS in the general adult population based on

### Table 1: Predictors of stroke in asymptomatic cervical carotid stenosis (adapted from Paraskevas et al.)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>degree of maximal stenosis</td>
<td>statistically significant, but relatively weak predictor of ipsilateral stroke</td>
</tr>
<tr>
<td>progression of stenosis by serial ultrasound imaging</td>
<td>incidence of progression 10%–25% (varying by method of assessment and criteria) over 2–4 years and associated with double, but still relatively low (2% per year), ipsilateral stroke risk</td>
</tr>
<tr>
<td>history of stroke or TIA</td>
<td>hazard ratio for stroke, ~3</td>
</tr>
<tr>
<td>microembolic signals detected by transcranial Doppler ultrasound</td>
<td>abnormal signals detected distal to carotid stenosis independently associated with subsequent ipsilateral stroke</td>
</tr>
<tr>
<td>carotid plaque characteristics defined by ultrasonography</td>
<td>plaque echolucency or ulceration; new techniques include 3-dimensional contrast-enhanced ultrasound</td>
</tr>
<tr>
<td>carotid plaque characteristics (including intraplaque hemorrhage) detected by high-resolution MRI with special sequences</td>
<td>intraplaque hemorrhage, plaque rupture, and luminal thrombus associated with higher risks of stroke in nonstenotic carotid plaques</td>
</tr>
<tr>
<td>silent ipsilateral brain infarcts on CT or MRI</td>
<td>prevalence 10%–20% by CT, associated with about double the stroke risk</td>
</tr>
<tr>
<td>18FDG-PET-CT features of plaque</td>
<td>assessed by transcranial Doppler with acetazolamide challenge/carbon dioxide challenge or positron emission tomography; “isolated hemisphere” due to incomplete Circle of Willis</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; 18FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; TIA, transient ischemic attack.
### TABLE 2 Selected guideline recommendations for management of asymptomatic carotid artery stenosis

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Summary of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Stroke Organisation (ESO) (2008)15</td>
<td>low-dose aspirin for &gt;50% stenosis; CEA not recommended for 60%–99% stenosis “except in those at high risk of stroke”2; angioplasty/stenting not recommended</td>
</tr>
<tr>
<td>ESO Karolinska Stroke Update: Consensus Statements 201216</td>
<td>“There is uncertainty about the benefit of revascularization for asymptomatic carotid stenosis … not enough data to recommend [stenting] as an alternative to CEA.”</td>
</tr>
<tr>
<td>European Society of Cardiology (2011)17</td>
<td>antiplatelet therapy and statin; “CEA should be considered” if life expectancy &gt;5 years and perioperative stroke/death rate &lt;3%; stenting may be considered at centers with documented stroke/death rate &lt;3%</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (2011)18</td>
<td>medical control of cardiovascular risk factors; if severe, “sometimes treated by CEA”; caution against routine use of stenting (“well-documented risks … evidence on efficacy is inadequate”)</td>
</tr>
<tr>
<td>American Heart Association / American Stroke Association (2014)21</td>
<td>aspirin and statin; CEA “reasonable” for &gt;70% stenosis if perioperative risk is &lt;3%; angioplasty/stenting “might be considered in highly selected patients … but effectiveness compared with medical therapy alone not well established”; it is reasonable to repeat duplex ultrasonography annually to assess progression in CAS &gt;50%</td>
</tr>
<tr>
<td>Canadian Best Practice Recommendations (2014)19</td>
<td>antiplatelet therapy and statin; CEA for selected patients with 60%–99% stenosis if life expectancy &gt;5 years and &lt;3% perioperative risk; stenting may be considered for nonoperative candidates</td>
</tr>
<tr>
<td>Society for Vascular Surgery (2011)22</td>
<td>antiplatelet therapy; consider CEA for ≥60% diameter stenosis if ≥3 year life expectancy and perioperative stroke/death rate &lt;3%</td>
</tr>
</tbody>
</table>

a high risk of stroke not defined

Abbreviations: CAS, coronary artery stenosis; CEA, carotid endarterectomy

### TABLE 3 Management of patients with asymptomatic carotid artery stenosis

- antiplatelet therapy (usually low-dose aspirin)
- high-dose statin therapy
- control of hypertension (target blood pressure <140/90 mmHg)
- smoking cessation (if applicable)
- lifestyle modification for cardiovascular health (physical activity, diet)
- patient education:
  - recognition of symptoms of transient ischemic atta warranting urgent reevaluation
  - importance of seeking emergent care for symptoms of stroke
- revascularization (carotid endarterectomy or carotid artery stenting):
  - recommended as an option for >70% stenosis or ill-defined “high-risk” or “selected” patients by many guidelines
  - about 10% of patients with acute coronary syndrome estimated to benefit from revascularization
  - no generally accepted criteria to define those at high-risk
  - occasionally justified by strong patient preferences

the uncertain absolute benefits of revascularization with either endarterectomy or stenting if added to current medical management.42

Ongoing randomized trials involving patients with asymptomatic carotid stenosis The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)(NCT02 089 217) is comparing medical management with carotid revascularization (endarterectomy and stenting separately) added to medical management in 2480 patients with asymptomatic carotid artery stenosis of 70% or higher. The Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs. Endarterectomy (SPACE2)(ISRCTN 78 592 017) is enrolling patients with asymptomatic (within the previous 6 months) carotid artery stenosis of 50% or higher, comparing two revascularization options with medical management alone. The Aggressive Medical Treatment Evaluation for Asymptomatic Carotid Artery Stenosis (AMTEC) trial (NCT00 805 311) compared carotid endarterectomy with medical therapy in 400 patients and was recently terminated, but results have not been published.57 The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS)(NCT01 776 424) is anticipated to include about 1200 patients with ACS randomized to receive aspirin, rivaroxaban, or their combination and followed for about 4 years, but it will likely be underpowered to meaningfully assess relative effects of the antithrombotic agents on prevention of ipsilateral stroke.

At least 3 additional randomized trials are comparing carotid endarterectomy with stenting in ACS patients: (Asymptomatic Carotid Surgery Trial-2 (ACST-2)(NCT00 883 402)38; Randomized Evaluation of Short Term and Long Term Outcome After Endovascular Repair by Stenting of Carotid Artery Stenosis in Patients with Severe (70% and Higher) Asymptomatic Carotid Stenosis (NCT00 772 278); Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease (ACT 1)(NCT001 069 938) (terminated, but as yet unpublished).

It appears unlikely that addition of revascularization to medical management will show worthwhile absolute benefits for ACS patients chosen for inclusion based only on the degree of stenosis. In our view, restricting inclusion to ACS patients who have additional stroke risk factors will be required for randomized trials to have “positive”, clinically meaningful results. For example, atrial fibrillation is a more powerful risk factor for stroke than ACS, and recent large randomized...
Management of asymptomatic carotid stenosis in 2015

Carotid artery stenosis of any degree is a relatively weak predictor of ipsilateral stroke, and it is time to move beyond ACS to focus research on defining high-risk carotid plaques (with stenosis as only one component). It is clear that nonstenotic carotid artery plaques can be a source of brain ischemia. Medical management of ACS should include smoking cessation, antplatelet therapy, high-dose “statin” therapy, and optimizing blood pressure (Table 3). Educating and periodically reeducating of ACS patients about symptoms of transient ischemic attack and stroke is important. We occasionally obtain ultrasonography in patients with asymptomatic cervical bruits to demonstrate ACS to further motivate patients to stick with prevention strategies (especially the difficult challenge of cessation of tobacco smoking).

Enthusiasm for revascularization is driven in part by the worst nightmare of rescuers that their patient with known ACS who is being treated medically experiences disabling stroke and that they “should have done more.” This faulty reasoning is rarely in the best interest of their patient, exposing the overwhelming majority (95%) of ACS patients to unnecessary procedures that are not without risk. Revascularization is not the right thing to do for most ACS patients, and restraint is warranted (although not everyone agrees). Until high-risk subgroups of ACS patients receiving contemporary medical therapy who could benefit substantially from revascularization are reliably identified (or the much larger low-risk subgroups who cannot), and revascularization is shown to be beneficial in contemporary randomized trials in high-risk ACS patients, the management controversies surrounding ACS will continue. Alas, there is no end in sight.

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Zapobieganie udarom mózgu u chorych z bezobjawową miażdżycą tętnic szyjnych: rewaskularyzacja nie jest rozwiązaniem

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bezobjawowe zwężenie tętnic szyjnych, endarterektomia tętnic szyjnych, miażdżycą tętnic szyjnych, rewaskularyzacja tętnic szyjnych

STRESZCZENIE
Bezobjawowe zwężenie tętnic szyjnych (asymptomatic carotid stenosis – ACS) >50% występuje u ok. 2% osób w wieku 60 lat i u jeszcze większego odsetka starszych chorych. Głównymi niezależnymi czynnikami ryzyka rozwoju choroby są zaawansowany wiek, płeć męska, palenie papierosów oraz choroby układu naczyńnego w wywiadzie. Najlepsze dostępne dowody nie przemawiają za wykonywaniem populacyjnych badań przesiewowych w kierunku ACS ani za rutynową rewaskularyzację w przypadku rozpoznania ACS. Istnieje pilna potrzeba wyselekcjonowania chorych z ACS oraz wysokim ryzykiem ipsilateralnego udaru mózgu (pomimo nowoczesnego leczenia zachowawczego), uzasadniającym wdrożenie leczenia zabiegowego. Podstawą leczenia zachowawczego ACS są leki przeciwplastrykowe (najczęściej kwas acetylosalicylowy w niewielkiej dawce), statyny w wysokich dawkach, kontrola ciśnienia tętniczego oraz zaprzestanie palenia papierosów. Chorzy z ACS powinni być regularnie informowani o wymagającym kontaktu z lekarzem objawach przemijającego ataku niedokrwieniowego oraz udaru mózgu. Aktualne wytyczne różnią się od siebie w zakresie rekomendacji dotyczących wykonywania rewaskularyzacji (tj. endarterektomii lub angioplastyki wewnątrznaczyniowej z wszczepieniem stentu). U chorych z ACS dotychczas leczonych zachowawczo korzyści z rewaskularyzacji pozostają niepewne.