

# Selection of Patients With Asymptomatic CAS for Carotid Revascularization

The case for risk stratification.

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It is intuitive that primary prevention is the best option for reducing the burden of stroke in individual patients and society. Most strokes that occur in patients with asymptomatic carotid artery stenosis (CAS) are not preceded by warning transient ischemic attacks (TIAs),<sup>1</sup> and even when TIAs occur, many patients do not seek timely medical attention.<sup>2</sup> Therefore, the argument that carotid revascularization should be withheld in these patients waiting for a warning clinical sign is unacceptable because the first presenting symptom in the majority of patients will be a complete stroke. For each patient, clinicians should balance the net benefits of a given preventive therapy (medical, endovascular, or surgical) against its associated risks and costs. In the case of patients with asymptomatic CAS, prospective randomized clinical trials comparing medical therapy alone to medical therapy and carotid endarterectomy (CEA) have shown that CEA is superior in preventing stroke.<sup>3,4</sup> The largest and most contemporary of these trials is the Asymptomatic Carotid Surgery Trial (ACST),<sup>4</sup> which supports and extends the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS).<sup>3</sup> ACST showed a statistically significant reduction in 5-year risk of stroke (5.3%; 95% confidence interval [CI], 3%–7.8%) and a small but definite reduction in the risk of disabling or fatal stroke with surgery (2.5%; 95% CI, 0.8%–4.3%) compared to medical therapy alone.

Despite this evidence, recommendations regarding the treatment of patients with asymptomatic CAS vary from endorsement of carotid revascularization for selected patients with moderate to severe stenosis (60%–99% or 80%–99%) in whom the procedure can be performed with a low (ie, <3%) complication rate to advising that this procedure not be performed in patients without ipsilateral neurological symptoms.

## WHY THE SKEPTICISM REGARDING CAROTID REVASCLARIZATION IN ASYMPTOMATIC PATIENTS?

Critics use two arguments against the routine use of carotid revascularization to treat moderate to severe asymptomatic CAS.

First, the assertion that the number of patients with asymptomatic CAS who need to be treated with CEA (number needed to treat [NNT]) to prevent one stroke is too high (Table 1). Proponents of this view also insist, despite the absence of evidence, that stand-alone medical therapy is sufficient for stroke reduction. Although medical therapy should always be the cornerstone of any treatment strategy for patients with asymptomatic CAS, declaring stand-alone medical therapy as the optimal therapeutic strategy is speculative at best until it is proven in clinical trials. Also, although medical therapy undoubtedly reduces the incidence of stroke, the number of neurologically asymptomatic patients who need

**TABLE 1. PATIENTS WITH ASYMPTOMATIC CAS WHO NEED TO BE TREATED WITH CEA TO PREVENT ONE STROKE**

NNT to Prevent One Stroke	
At 2 years <sup>5</sup>	67 patients
At 3 years <sup>6</sup>	53 patients
At 5 years <sup>5</sup>	16–20 patients
	40 patients (for disabling or fatal stroke)

to be treated to prevent one stroke is exceedingly high. Table 2 lists the number of neurologically asymptomatic patients who need to be treated with statins or aspirin to prevent one stroke at 5 years. It is clear from these data that although primary prevention with medical therapy is efficacious, a significantly larger number of patients will need to be treated to prevent a single event.

Second, there is lack of confidence in the generalizability of the CEA trials because the complication rate after CEA in clinical trials has not been reproduced in the community. Rothwell et al<sup>7</sup> compared the operative risks in ACAS with the results of a meta-analysis of 46 surgical case series that published operative risks for asymptomatic CAS during ACAS and the 5 years after publication.<sup>8</sup> The operative mortality rate was eight times higher than in ACAS (1.11% vs 0.14%;  $P < .01$ ), and the risk of stroke and death was approximately three times higher among comparable studies in which outcome was assessed by a neurologist (4.3% vs 1.5%;  $P < .001$ ). The higher perioperative complication rate after CEA in the community can significantly diminish the long-term efficacy of this operation (Table 3).

This issue is certainly of real clinical significance, and it also extends to carotid artery stenting. Although carotid artery stenting in patients with asymptomatic CAS can be performed by experienced operators with an acceptably low complication rate, the procedure can be associated with a high complication rate if performed by inexperienced operators, particularly in older patients with complex anatomy.<sup>9</sup> In any case, institution-specific assessment of the risk of carotid intervention, endarterectomy, or stenting should be a prime consideration in clinical decision making regarding carotid revascularization in patients with asymptomatic CAS.

## RISK STRATIFICATION OF PATIENTS WITH ASYMPTOMATIC CAS

Most experts agree that there are patients with asymptomatic CAS who are at high risk for stroke and who may derive significant benefit from carotid revas-

cularization. Identifying those patients, however, has been elusive in clinical trials. Risk stratification of patients with asymptomatic CAS is particularly important among patients with 60% to 79% stenosis, in whom the appropriate management is more uncertain. Identifying high-risk patients will certainly lead to better resource utilization for both medical and revascularization therapies for patients with asymptomatic CAS.

In current clinical practice and clinical trials, deciding who should be revascularized is often based solely on stenosis severity at the time of patient encounter (>70% for low-surgical-risk patients and >80% for high-surgical-risk patients). Simplification of clinical decision making certainly has its advantages, but the available data clearly indicate that stenosis severity is only one of many other parameters that determine future stroke risk in these patients.

## DEMOGRAPHIC AND CLINICAL PARAMETERS

### Age

Patients older than 80 years are at higher risk of stroke from carotid disease, as well as from other causes.<sup>10</sup> These patients are also at higher risk of complications after carotid revascularization.<sup>9,11</sup> The decision to proceed with carotid revascularization in octogenarians should be made on a case-by-case basis by implementing a strict risk stratification process to select those at highest risk for ischemic stroke, those at lowest risk for overall mortality, and those at manageable risk for the carotid revascularization procedure under consideration (CAS vs CEA). Other factors, such as mental health, functional capacity, and the extent of other comorbidities, should also be considered. Age alone should not exclude otherwise-qualified candidates from consideration for carotid revascularization.

### Gender

The natural history of conservatively treated asymptomatic CAS is more favorable in women than men.<sup>12</sup> Until further evidence is available, selected women with asymptomatic CAS should be considered for carotid revascularization, however, with two caveats: (1) the threshold for carotid revascularization should be higher in women than that in men and (2) proper patient counseling should emphasize the differential in net benefit between men and women undergoing CEA (men benefit more than women),<sup>4</sup> a differential that is not apparent with carotid artery stenting.

### Comorbid Conditions

Among patients with severe asymptomatic CAS, the presence of renal insufficiency and a history of con-

**TABLE 2. PATIENTS WITH ASYMPTOMATIC CAS WHO NEED TO BE TREATED WITH CEA, STATINS, OR ASPIRIN TO PREVENT ONE STROKE AT 5 YEARS**

Treatment	Study	NNT to Prevent One Stroke at 5 Years
CEA + usual medical care	ACST <sup>4</sup>	16–20 patients
Statins	Primary prevention trials <sup>14</sup>	200 patients
Aspirin*	Primary prevention trials <sup>15</sup>	500 patients

\*Follow-up 6.4 years, no stroke reduction in men.

tralateral neurological symptoms significantly increase the risk of future stroke. These patients should be strongly considered for carotid revascularization.<sup>13</sup>

## CAROTID STENOSIS PARAMETERS

### Carotid Stenosis Severity

The higher the degree of carotid stenosis in neurologically asymptomatic individuals, the higher the risk of stroke and TIA.<sup>13,16</sup> Most experts agree that a critical threshold of >80% stenosis is associated with a rise of ipsilateral ischemic neurological events and should trigger an evaluation for carotid revascularization. Nonetheless, it should be clear that lesion severity is only one of many variables that have an impact on future stroke risk.

### Carotid Stenosis Progression

Among patients with asymptomatic CAS, the risk of stroke and TIA is three times greater in those with carotid stenosis progression to 80% stenosis or more compared to those without such progression.<sup>16,17</sup>

### Carotid Stenosis Morphology

Data on the prognostic significance of carotid plaque qualitative parameters in neurologically asymptomatic patients are either lacking (plaque ulceration) or conflicting (plaque echogenicity). Some studies have shown that echolucent carotid plaques are associated with a two- to fivefold increased risk for stroke; however, the clinical utility of these observations for triaging patients to carotid revascularization awaits prospective confirmation.<sup>18</sup>

## END-ORGAN (BRAIN) PARAMETERS

### Silent Brain Infarcts

The prognostic value of silent cerebral infarcts in patients with asymptomatic CAS has been suggested by various studies. Tegos and colleagues<sup>19</sup> demonstrated that the presence of discrete cortical or subcortical silent cerebral infarcts on brain CT in patients with carotid disease increases their risk of future stroke by approximately fourfold. These findings have also been

corroborated by magnetic resonance diffusion-weighted imaging.<sup>20</sup> Therefore, despite the lack of consensus on this issue, the presence of ipsilateral silent cerebral infarcts in patients with asymptomatic CAS, particularly when discrete and cortical, may be indicative of higher risk for future stroke.

### Cerebral Microembolic Signals

Cerebral microembolic signals are detected by transcranial Doppler in 1% to 23% of patients with asymptomatic CAS.<sup>21–23</sup> The variability in the prevalence of cerebral microembolic signals in patients with asymptomatic CAS depends on the severity of the carotid stenosis and the morphology of the carotid plaque, and the frequency and duration of transcranial Doppler monitoring. The presence of cerebral microembolic signals in patients with asymptomatic CAS is associated with a four- to fivefold increased risk of stroke.<sup>23</sup> However, the clinical utility of this technique to discriminate among patients who will benefit from carotid revascularization versus those who would not awaits confirmation in prospective trials.

### Cerebral Vascular Reserve

Cerebral vascular reserve is the capacity of the brain to maintain a constant cerebral blood flow during a wide range of changes of mean arterial blood pressure. Cerebral vascular reserve can be tested by increasing passive CO<sub>2</sub> or by altering mean arterial blood pressure. That can be accomplished by breath holding (passive CO<sub>2</sub> accumulation), acetazolamide challenge, inhaled CO<sub>2</sub>, Valsalva maneuver, and other methods.<sup>25–27</sup> Changes in cerebral blood flow during the cerebral vascular reserve testing may be measured by transcranial Doppler, positive emission tomography, magnetic resonance imaging-based techniques, single photon emission computed tomography, and xenon CT.<sup>28,29</sup> Patients with asymptomatic CAS and impaired cerebral vasoreactivity are at higher risk of ischemic neurological events, and they should be strongly considered for carotid revascularization.<sup>30</sup>

**TABLE 3. PROJECTED IMPACT OF OPERATIVE RISK ON 5-YEAR EFFICACY OF CEA IN PATIENTS WITH ASYMPTOMATIC CAROTID ARTERY DISEASE<sup>3</sup>**

Operative Risk (%)	ACAS 60% to 99%	
	ARR at 5 years	NNT at 5 years
0	8.2%	12
2	6.2%	16
4	4.2%	24
6	2.2%	45
8	0.2%	500
10	NA	NA

ARR, absolute risk reduction.

Adapted from JAMA. 1995;273:1421-1428.<sup>3</sup>

## CONCLUSION

Atherosclerotic carotid stenosis elevates the risk of ischemic stroke among asymptomatic individuals. However, because the risk is dependent on many other factors, including demographics, medical comorbidities, intrinsic plaque characteristics, and cerebral vascular reserve, the optimal management of asymptomatic carotid stenosis requires individualized care that integrates these considerations in calculating risks and benefits of treatments. A comprehensive evaluation of the patient with asymptomatic carotid stenosis and assessment of global vascular risk may allow clinicians to better select patients for medical, interventional, and combined strategies. The scientific advances in the development of subclinical biomarkers and imaging correlates of plaque instability may also be of great utility in identifying high-risk patients, allowing for more precise risk stratification, selecting patients for earlier treatments, encouraging the development of novel medications, and ultimately preventing the potential devastating consequences of ischemic stroke. ■

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