CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will weigh the pros and cons of medical therapy compared with percutaneous or surgical revascularization for asymptomatic carotid artery stenosis

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Asymptomatic carotid artery disease: A personalized approach to management

ABSTRACT

Asymptomatic carotid artery disease is relatively common and poses a challenge for internists as well as vascular specialists when deciding whether to pursue surgical endarterectomy, percutaneous stenting, or medical therapy alone. The authors review the management of asymptomatic carotid disease, reflecting the most current data.

KEY POINTS

Current guidelines are based on outdated data that may not represent the best evidence regarding the management of asymptomatic carotid disease.

Stroke is a devastating outcome of carotid disease, and most patients and physicians are wary of deferring revascularization until a stroke occurs.

Given the inherent risk associated with revascularization (endarterectomy or stenting) and the paucity of data, the approach should be personalized on the basis of life expectancy, sex, risk factors for stroke, and clinical acumen.

Future research should focus on noninvasive tools to determine which patients are at high risk of stroke and may benefit from revascularization.

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Carotid artery disease that is asymptomatic poses a dilemma: Should the patient undergo revascularization (surgical carotid endarterectomy or percutaneous stenting) or receive medical therapy alone?

On one hand, because one consequence of carotid atherosclerosis—ischemic stroke—can be devastating or deadly, many physicians and patients would rather "do something," ie, proceed with surgery. Furthermore, several randomized trials[1–4] found carotid endarterectomy superior to medical therapy.

On the other hand, these trials were conducted in the 1990s. Surgery has improved since then, but so has medical therapy. And if we re-examine the data from the trials in terms of the absolute risk reduction and number needed to treat, as opposed to the relative risk reduction, surgery may appear less beneficial.

Needed is a way to identify patients who would benefit from surgery and those who would more likely be harmed. Research in that direction is ongoing.

Here, we present a simple algorithmic approach to managing asymptomatic carotid artery stenosis based on the patient's age, sex, and life expectancy. Our approach is based on a review of the best available evidence.

UP TO 8% OF ADULTS HAVE STENOSIS

Stroke is the third largest cause of death in the United States and the leading cause of disability.[5] From 10% to 15% of strokes are associated with carotid artery stenosis.[6,7]

The prevalence of asymptomatic carotid disease, defined as stenosis greater than 50%, ranges from 4% to 8% in adults.[8]

However, major societies recommend against screening for carotid stenosis in the general

TABLE 1

Recommendations for screening for asymptomatic carotid artery stenosis

US Preventive Services Task Force[13]

No screening for asymptomatic carotid stenosis in the general population

There is no evidence that screening by auscultation of the neck to detect carotid bruits is accurate or provides benefit

Auscultation of a cervical bruit correlates more closely with systemic atherosclerosis than with hemodynamically significant carotid stenosis

American College of Cardiology[9]

Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis

Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurologic or psychiatric disorders unrelated to focal cerebral ischemia

American Society of Neuroimaging[11]

No screening of unselected population

Screen adults over age 65 who have three or more cardiovascular risk factors

American Heart Association/American Stroke Association[10]

No screening in the general asymptomatic population

Clinical Expert Consensus Panel on Carotid Stenting[12]

Screen asymptomatic patients with carotid bruits who are potential candidates for carotid revascularization

Screen patients in whom coronary artery bypass surgery is planned

population.[9–12] Similarly, the US Preventive Services Task Force also discourages the use of carotid auscultation as screening in the general population (**Table 1**).[13] Generally, cases of asymptomatic carotid stenosis are diagnosed by ultrasonography after the patient's physician happens to hear a bruit during a routine examination, during a preoperative assessment, or after the patient suffers a transient ischemic attack or stroke on the contralateral side.

CLASS II RECOMMENDATIONS FOR SURGERY OR STENTING

There are well-established guidelines for managing symptomatic carotid disease,[14] based on evidence from the North American Symptomatic Carotid Endarterectomy Trial[15] and the European Carotid Surgery Trial,[16] both from 1998. But how to manage asymptomatic carotid disease remains uncertain.

If stenosis of the internal carotid artery is greater than 70% on ultrasonography, computed tomography, or magnetic resonance imaging, and if the risk of perioperative stroke and death is low (< 3%), current guidelines[14] give carotid endarterectomy a class IIa recommendation (ie, evidence is conflicting, but the weight of evidence is in favor), and they give prophylactic carotid artery stenting with optimal medical treatment a class IIb recommendation (efficacy is less well established).[5]

But medical management has improved, and new data suggest that this improvement may override the minimal net benefit of intervention in some patients.[17] Some authors suggest that it is best to use patient characteristics and imaging features to guide treatment.[18]

EVIDENCE TO SUPPORT CAROTID REVASCULARIZATION

Three major trials (**Table 2**) published nearly 20 years ago provide the foundation of the current guidelines:

- the Endarterectomy for Asymptomatic Carotid Atherosclerosis Study (ACAS)[1]
- the Asymptomatic Carotid Surgery Trial (ACST)[2,3]
- the Veterans Affairs (VA) Cooperative Study.[4]

A Cochrane review of these trials,[19] where medical therapy consisted only of aspirin and little use of statin therapy, found that carotid endarterectomy reduced the rate of perioperative stroke or death or any subsequent stroke in the next 3 years by 31% (relative risk 69%, 95% confidence interval [CI] 0.57–0.83). "Perioperative" was defined as the period from randomization until 30 days after surgery in the surgical group and an equivalent period in the medical group.

Moreover, carotid endarterectomy reduced

TABLE 2

Landmark trials in asymptomatic carotid stenosis

	ACAS[1]	ACST[2,3]	VA[4]
Patients	1,662 patients with asymptomatic carotid stenosis > 60%	3,120 patients with asymptomatic carotid stenosis > 60%	444 male veterans with asymptomatic carotid stenosis > 50%
Exclusions	Stroke in the distribution of the carotid artery under study or in that of the vertebrobasilar arterial system Symptoms in the contralateral cerebral hemisphere within the previous 45 days Contraindication to aspirin A disorder that could seriously complicate surgery A condition that could prevent continuing participation or was likely to produce disability or death within 5 years	No stroke or any other relevant neurologic symptoms in the past 6 months No circumstances or condition precluding long-term follow-up	Previous cerebral infarction Previous endarterectomy with restenosis Previous extracranial to intracranial bypass High surgical risk due to associated medical illness Long-term anticoagulant therapy Intolerance of aspirin or long-term aspirin therapy at a high dose Life expectancy < 5 years Surgically inaccessible lesion Noncompliance or refusal to participate in the protocol
Intervention	Carotid revascularization plus medical management vs medical management alone	Immediate endarterectomy plus medical treatment, vs medical treatment alone until revascularization became necessary	Medical treatment alone or combined with carotid endarterectomy
Follow-up	5 years	10 years	40.9 months
Outcomes of interest[a]	5-year risk of ipsilateral stroke, perioperative stroke, or death 5.1% vs 12.4% ($P = .004$)	5-year risk of any stroke or perioperative death 6.9% vs 10.9%; 10-year risk 13.4% vs 17.9%	Risk of transient ischemic attack, stroke, or death 8.0% vs 20.6% ($P < .001$)

[a] Carotid endarterectomy vs medical therapy.

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; VA = Veterans Affairs Cooperative Study

the rate of disabling or fatal nonperioperative stroke by 50% compared with medical management alone.[1,2,19] Patients who had contralateral symptomatic disease or who had undergone contralateral carotid endarterectomy seemed to benefit more from the procedure than those who had not.[19]

Also, the ACST investigators found that revascularization was associated with a reduction in contralateral strokes (which occurred in 39 vs 64 patients, $P = .01$) independent of contralateral symptoms or contralateral carotid endarterectomy.[2,3] The exact mechanism is unknown but could be related to better blood

pressure control and risk factor modification after carotid endarterectomy.

Another factor supporting revascularization is that the outcomes of revascularization have improved over time. In 2010, the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)[20] reported a 30-day periprocedural incidence of death or stroke of only 1.4%, compared with 2.9% in the earlier landmark trials.

Stenting is a noninferior alternative

For patients who have asymptomatic stenosis greater than 80% on color duplex ultrasonography and a risk of stroke or death during carotid endarterectomy that is prohibitively high (> 3%), carotid stenting has proved to be a noninferior alternative.[21,22]

The Stenting and Angioplasty With Protection of Patients With High Risk for Endarterectomy (SAPPHIRE) trial[21] reported a risk of death, stroke, or myocardial infarction of about 5% at 30 days and 10% at 1 year after stenting. A recent observational study revealed lower perioperative complication rates, with a risk of death or stroke of about 3%, which satisfy current guideline requirements.[23]

A Cochrane review found a 31% relative risk reduction in perioperative stroke or death or 3-year stroke incidence with surgery

To be deemed at high surgical risk and therefore eligible for the SAPPHIRE trial,[21] patients had to have clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal-nerve palsy, recurrent stenosis after carotid endarterectomy, previous radical neck surgery or radiation therapy to the neck, or age greater than 80.

EVIDENCE AGAINST CAROTID REVASCULARIZATION

Although carotid revascularization has evidence to support it, further interpretation of the data may lessen its apparent benefits.

Small absolute benefit, high number needed to treat

If we compare the *relative* risk reduction for the outcome of perioperative death or any stroke over 5 years (30% to 50%) vs the *absolute* risk reduction (4% to 5.9%), revascularization seems less attractive.[19]

The benefit may be further diminished if we consider only strokes related to large vessels, since up to 45% of strokes in patients with carotid disease are lacunar or cardioembolic.[24] Assessing for prevention of large-vessel stroke using the ACAS data, the benefit of carotid endarterectomy for prevention of stroke is further decreased to a 3.5% absolute risk reduction, and the number needed to treat for 2 years increases from 62 to 111.[24,25] Nevertheless, revascularization is necessary in appropriately selected patients, as a cerebrovascular event can cause life-altering changes to a patient's cognitive, emotional, and physical condition.[26]

Medical therapy—and surgery—are evolving

The optimal medical management used in the landmark studies was significantly different from what is currently recommended. The ACAS trial[18] used only aspirin as optimal medical management, with no mention of statins. In the ACST trial,[2,3] the use of statins increased over time, from 7% to 11% at the beginning of the trial to 80% to 82% at the end.

On the other hand, the ACAS[1] surgeons were required to have an excellent safety record to participate. This might have compromised the trial's validity or our ability to generalize its conclusions.

Recent data from Abbott[17] suggested a loss of a statistically significant surgical advantage in prevention of ipsilateral stroke and transient ischemic attack from the early 1990s. This is most likely explained by improved medical therapy, since there was a 22% increase in baseline proportion of patients receiving antiplatelet therapy from 1985 to 2007, with 60% of patients taking antihypertensive drugs and 30% of patients taking lipid-lowering drugs. Moreover, since 2001, the annual rates of ipsilateral stroke in patients receiving medical management alone fell below those of patients who underwent carotid endarterectomy in the ACAS trial.

The analysis by Abbott[17] has major limitations: inclusion of small studies, many crossover patients, and heterogeneity. In support of this allegation, a small trial (33 patients) reported a risk of stroke ipsilateral to an asymptomatic carotid stenosis as low as 0.34% per year.[25] Even when contrasting the outcomes of medical therapy against those of current carotid endarterectomy, in which the rate of

TABLE 3

Optimal medical therapy for carotid artery stenosis

Treatment	Recommendations
Antiplatelet therapy	Aspirin is recommended for prevention of myocardial infarction and other ischemic events, though benefit has not been established for prevention of stroke in asymptomatic patients
	No added benefit exists when combining antiplatelet agents unless the patient has concomitant symptomatic coronary artery disease
Antihypertensive treatment	Lower blood pressure to < 140/90 mm Hg
Statins	Lower the low-density lipoprotein cholesterol level to < 100 mg/dL, or < 70 mg/dL in patients with diabetes
Antidiabetes therapy	Diet, exercise, and glucose-lowering drugs can be useful for patients with diabetes mellitus, but there is no benefit from tight glucose control (hemoglobin A_{1c} < 7%)
Smoking cessation	Mandatory

Based on information in reference 9.

perioperative stroke and death have fallen to 0.88% to 1.7%,[17,27,28] there is concern that the risk associated with surgery may outweigh the long-term benefit.

Flaws in the landmark trials

Beyond the debate of the questionable benefit of revascularization, well-defined flaws in the landmark trials weaken or limit their influence on current treatment guidelines and protocols for deciding whether to revascularize.

No significant benefit was found for patients over age 75.[2,3] This was thought to be due to decreased life expectancy, since the benefit from revascularization becomes significant after 3 years from intervention.[1–3] Also, studies have shown that increasing age is associated with a higher risk of perioperative stroke and death.[20,21]

Women showed no benefit at 5 years and only a trend toward benefit at 10 years (P = .05),[2] likely from a higher rate of periprocedural strokes.

Blacks and Hispanics were underrepresented in the landmark studies,[19] while one observational study reported a higher incidence of in-hospital stroke after carotid endarterectomy in black patients (6.6%) than in white patients (2%).[29]

When associated with contralateral carotid occlusion, carotid endarterectomy carries a higher risk of perioperative stroke or death.[23,30,31]

Carotid revascularization failed to reduce the risk of death—the total number of deaths within 10 years was not significantly reduced by immediate carotid endarterectomy compared with deferring the procedure.[2]

EVIDENCE SUPPORTING OPTIMAL MEDICAL MANAGEMENT

Optimal medical therapy mainly consists of antiplatelet therapy, blood pressure management, diabetic glycemic control, and statin therapy along with lifestyle changes including smoking cessation, exercise, and weight loss (**Table 3**).[9] Detailed recommendations are provided in the American Heart Association/American Stroke Association guidelines for primary prevention of stroke.[32]

Relative risk reduction in death or stroke with carotid surgery is 30%–50%; absolute risk reduction is 4%–5.9%

Antiplatelet therapy has been shown to reduce the incidence of stroke by 25%. There is no added benefit in combining antiplatelet agents unless the patient has concomitant symptomatic coronary artery disease, recent coronary stenting, or severe peripheral artery disease.[33,34]

Blood pressure control can reduce the incidence of stroke by 30% to 40%, and recent data suggest that drugs working on the renin-angiotensin system offer more benefit than

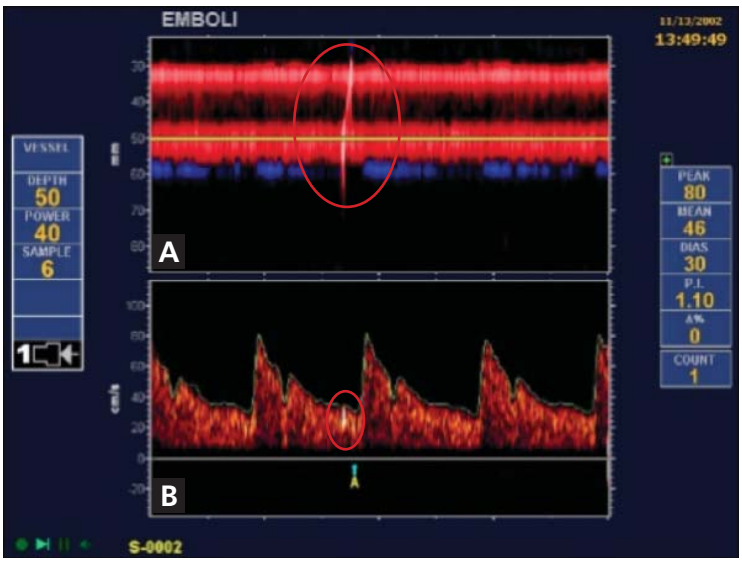

FIGURE 1. Embolic signal on transcranial Doppler ultrasonography. **A,** micro-emboli signal (circle) on M-mode. **B,** Doppler high-amplitude, unidirectional, transient signals showing sound reflection from the embolus (circle).

Statins shrink carotid plaques and reduce the risk of stroke by 15% for each 10% reduction in LDL-C

beta-blockers for the same reduction in blood pressure.[34,35]

Diabetic glycemic control is supported, as higher hemoglobin A_{1c} and fasting glucose values are associated with higher relative risk of stroke.[32,36,37] However, the stroke rate does not differ significantly between patients receiving intensive therapy and those receiving standard therapy.[34]

Statins actually shrink carotid plaques and reduce the risk of stroke by 15% for each 10% reduction in low-density lipoprotein cholesterol. It is estimated that statin therapy confers a 30% relative risk reduction of stroke over 20 years.[34,38–41]

Smoking increases the overall risk of stroke by 150%, making its cessation mandatory.[42]

HIGH-RISK FEATURES FOR STROKE IN ASYMPTOMATIC CAROTID STENOSIS

Studies have tried to identify risk factors for stroke, so that patients at high risk could undergo revascularization and benefit from it. However, no well-defined high-risk features have yet been described that would identify patients who would benefit from early surgery.

For instance, no correlation has been found between age, sex, diabetes mellitus, lipid levels, or smoking and progression of disease.[43] In contrast, having either contralateral symptomatic carotid disease or contralateral total occlusion translated into a higher ipsilateral stroke risk.[18] And in several studies, the 5-year risk of ipsilateral stroke was as high as 16.2% for those with 60% to 99% stenosis.[1,2,18,24,43]

Features of the plaque itself

More recently, there has been a focus on plaque evaluation to predict outcomes.

Percent stenosis. An increased risk of death or stroke has been reported with higher degrees of stenosis or plaque progression.[44,45] The gross annual risk of ipsilateral stroke increases from 1.5% with stenosis of 60% to 70%, to 4.2% with stenosis of 71% to 90%, and to 7% with stenosis of 91% to 99%. Nevertheless, current data are insufficient to determine whether there is increasing benefit from surgery with increasing degree of stenosis in asymptomatic carotid disease.[1,3,24,44]

Plaque progression translates to a 7.2% absolute increase in the incidence of stroke (1.1% if the plaque is stable vs 8.3% if the plaque is progressing). Interestingly, plaque progression to greater than 80% stenosis results in worse outcomes (relative risk 3.4, 95% CI 1.5–7.8) compared with the same level of stenosis without recent progression.[33]

Intimal wall thickening of more than 1.15 mm confers a hazard ratio for stroke of 3 (95% CI 1.48–6.11).[46]

Increased echolucency also confers a hazard ratio for stroke of 3 (95% CI 1.4–8.0).[46]

A low gray-scale median (a surrogate of plaque composition) and plaque area have been identified as independent predictors of ipsilateral events.[44]

Embolic signals on transcranial Doppler ultrasonography (Figure 1) have been associated with a hazard ratio for stroke of 2.54 over 2 years.[47]

Carotid plaques predominantly composed of lipid-rich necrotic cores carry a higher risk of stroke (hazard ratio 7.2, 95% CI 1.12–46.20).[48]

High tensile stress (circumferential wall tension divided by the intima-media thickness), and fibrous cap thickening (< 500 µm) predict plaque rupture.[49]

Plaque ulceration. The risk of stroke increases with worsening degree of plaque ulceration: 0.4% per year for type A ulcerated

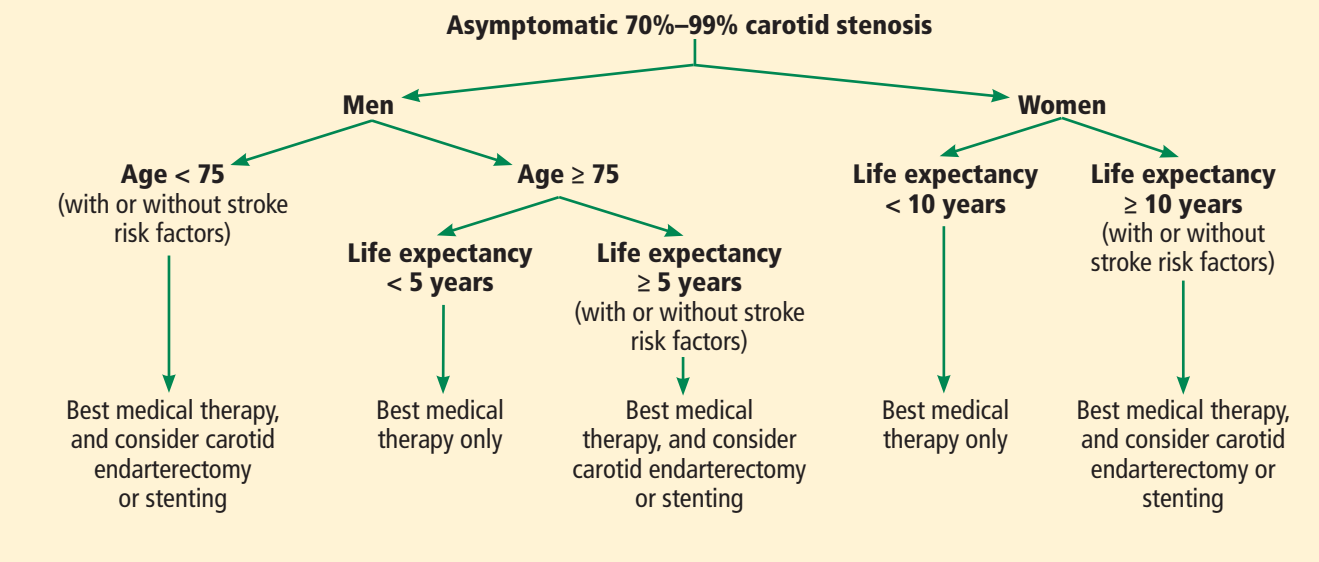

FIGURE 2. Algorithm for management of severe asymptomatic carotid artery stenosis.

plaques (small minimal excavations) compared with 12.5% for type B (large obvious excavations) and type C (multiple cavities or cavernous).[50]

Low cerebrovascular reactivity. Perfusion studies such as cerebrovascular reactivity evaluate changes in cerebral blood flow in response to a stimulus such as inhaled carbon dioxide, breath-holding, or acetazolamide. This may provide a useful index of cerebral vascular function. For instance, low reactivity has been associated with ipsilateral ischemic events (odds ratio 14.4, 95% CI 2.63–78.74, $P = .0021$).[51,52] Silvestrini et al[53] reported that the incidence of ipsilateral cerebrovascular ischemic events was 4.1% per year in patients who had normal cerebral vasoreactivity during breath-holding, vs 13.9% in those with low cerebral reactivity.

BEST MEDICAL THERAPY, ALONE OR COMBINED WITH REVASCULARIZATION

For carotid revascularization to be a viable option for asymptomatic carotid stenosis, the morbidity and mortality rates associated with the operation must be less than the incidence of neurologic events in patients who do not undergo the operation.[54] An important caveat is that the longer a patient survives after carotid endarterectomy, the greater the potential benefit, since the adverse consequences of surgery are generally limited to the perioperative period.[19]

The current evidence regarding medical management of asymptomatic carotid stenosis suggests that the rate of ipsilateral stroke is now lower than it was in the control groups in the landmark trials.[2,3,17,45,47,55,56] Ultimately, adherence to current best medical management takes priority over the decision to revascularize. The best current medical therapy includes, but is not limited to, antithrombotic therapy, statin therapy, blood pressure control, diabetes management, smoking cessation, and lifestyle changes (**Table 3**).

Smoking increases the risk of stroke by 150%

As noted above, stroke risk seems variable in the asymptomatic population according to the presence or absence of risk factors. Yet no well-defined "high-risk stroke profile" has been identified. Therefore, a patient-by-patient decision based on best available evidence should identify patients who may benefit from carotid revascularization. If asymptomatic carotid stenosis of 70% to 99% is found, factors that favor revascularization are male sex, younger age, and longer life expectancy (**Figure 2**).

For those with intermediate or high-risk surgical features, uncertainty exists in management since no studies have compared revascularization against medical management only in this group of patients.[1] However, data from high-risk cohorts had high enough complication rates in both intervention arms to

question the benefit of revascularization over medical therapy.[20,21] Therefore, the individual perioperative risk of stroke, myocardial infarction, and death must be weighed against the potential benefit of revascularization for each patient.

If revascularization is pursued, studies have demonstrated that carotid artery stenting is not inferior to endarterectomy[15,16] in high-surgical-risk patients. However, the revascularization approach must be tailored to the patient profile, since stenting demonstrated a lower risk of periprocedural myocardial infarction but a higher risk of stroke compared with endarteretomy.[20]

Finally, the current acceptable risks of perioperative stroke and death must be revised if revascularization is elected. Current data suggest that a lower threshold—around 1.4%—can be used.[20] Moreover, further guidelines must determine the impact of adding myocardial infarction to the tolerable perioperative risks, since it has been excluded from main trials and guidelines.[20]

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