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Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease

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ABSTRACT

Management of carotid bifurcation stenosis in stroke prevention has been the subject of extensive investigations, including multiple randomized controlled trials. The proper treatment of patients with carotid bifurcation disease is of major interest to vascular surgeons and other vascular specialists. In 2011, the Society for Vascular Surgery published guidelines for the treatment of carotid artery disease. At the time, several randomized trials, comparing carotid endarterectomy (CEA) and carotid artery stenting (CAS), were reported. Since the 2011 guidelines, several studies and a few systematic reviews comparing CEA and CAS have been reported, and the role of medical management has been reemphasized. In the present publication, we have updated and expanded on the 2011 guidelines with specific emphasis on five areas: (1) is CEA recommended over maximal medical therapy for low-risk patients; (2) is CEA recommended over transfemoral CAS for low surgical risk patients with symptomatic carotid artery stenosis of >50%; (3) the timing of carotid intervention for patients presenting with acute stroke; (4) screening for carotid artery stenosis in asymptomatic patients; and (5) the optimal sequence of intervention for patients with combined carotid and coronary artery disease.

A separate implementation document will address other important clinical issues in extracranial cerebrovascular disease. Recommendations are made using the GRADE (grades of recommendation assessment, development, and evaluation) approach, as was used for other Society for Vascular Surgery guidelines. The committee recommends CEA as the first-line treatment for symptomatic low-risk surgical patients with stenosis of 50% to 99% and asymptomatic patients with stenosis of 70% to 99%. The perioperative risk of stroke and death in asymptomatic patients must be <3% to ensure benefit for the patient. In patients with recent stable stroke (modified Rankin scale score, 0-2), carotid revascularization is considered appropriate for symptomatic patients with >50% stenosis and should be performed as soon as the patient is neurologically stable after 48 hours but definitely <14 days after symptom onset. In the general population, screening for clinically asymptomatic carotid artery stenosis in patients without cerebrovascular symptoms or significant risk factors for carotid artery disease is not recommended. In selected asymptomatic patients with an increased risk of carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis as long as the patients would potentially be fit for and willing to consider carotid intervention if significant stenosis is discovered. For patients with symptomatic carotid stenosis of 50% to 99%, who require both CEA and coronary artery bypass grafting, we suggest CEA before, or concomitant with, coronary artery bypass grafting to potentially reduce the risk of stroke and stroke/death. The sequencing of the intervention depends on the clinical presentation and institutional experience. (J Vasc Surg 2022;75:4S-22S.)

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SUMMARY OF RECOMMENDATIONS

1. **Is CEA recommended over maximal medical therapy for asymptomatic carotid stenosis in low surgical risk patients?**

1.1. For low surgical risk patients with asymptomatic carotid bifurcation atherosclerosis and stenosis of >70% **(documented by validated duplex ultrasound or CTA/angiography)**, we recommend CEA with best medical therapy instead of maximal medical therapy alone for the long-term prevention of stroke and death. **Level of recommendation: grade 1 (strong); quality of evidence: B (moderate)**.

2. **Is CEA recommended over TF-CAS for low surgical risk patients with symptomatic carotid artery stenosis of >50%?**

2.1. We recommend CEA over TF-CAS in low- and standard-risk patients with >50% symptomatic carotid artery stenosis. Level of recommendation: **grade 1 (strong); quality of evidence: A (high)**.

3. **What is the optimal timing of carotid intervention for patients presenting with acute stroke? Management of acute neurologic syndrome:**

3.1. In patients with recent stable stroke (modified Rankin scale score 0-2), we recommend carotid revascularization for symptomatic patients with >50% stenosis to be performed as soon as the patient is neurologically stable after 48 hours but definitely before 14 days after the onset of symptoms. **Level of recommendation: grade 1 (strong); quality of evidence: B (moderate)**.

3.2. In patients undergoing revascularization within the first 14 days after the onset of symptoms, we recommend CEA rather than carotid stenting. Level of recommendation: **grade 1 (strong); quality of evidence: B (moderate)**.

3.3. We recommend against revascularization, regardless of the extent of stenosis for patients who experienced a disabling stroke, have a modified Rankin scale score of ≥3, whose area of infarction is >30% of the ipsilateral middle cerebral artery territory, or who have altered consciousness to minimize the risk of postoperative parenchymal hemorrhage. **These patients can be reevaluated for revascularization later if their neurologic recovery is satisfactory. Level of recommendation: grade 1 (strong); quality of evidence: C (low)**.

4. **Screening for carotid artery stenosis in asymptomatic patients**

4A. **Is screening for asymptomatic carotid stenosis recommended for the general population?**

4.1. We recommend against routine screening for clinically asymptomatic carotid artery stenosis in individuals without cerebrovascular symptoms or significant risk factors for carotid artery disease. **Level of recommendation: grade 1 (strong); quality of evidence: B (moderate)**.

4B. **Is screening for carotid stenosis recommended for high-risk asymptomatic patients?**

4.2. In selected asymptomatic patients who are at an increased risk of carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis, especially if patients are willing to consider carotid intervention if significant stenosis is discovered. **Level of recommendation: grade 2 (weak); quality of evidence: B (moderate)**.

4C. **What imaging test is best for screening for carotid stenosis in asymptomatic patients?**

4.3. In asymptomatic patients who are undergoing screening for carotid artery stenosis, we recommend duplex ultrasound performed in an accredited vascular laboratory as the imaging modality of choice instead of CTA, MRA, or other imaging modalities. **Level of recommendation: grade 1 (strong); quality of evidence: B (moderate)**.

5. What is the optimal sequence for intervention in patients with combined carotid artery stenosis and CAD?

5.1. For patients with symptomatic carotid stenosis of 50% to 99%, who require both CEA and CABG, we suggest CEA before, or concomitant with, CABG to potentially reduce the risk of stroke and stroke/death. The sequencing of the intervention depends on the clinical presentation and institutional experience. **Level of recommendation: grade 2 (weak); quality of evidence: C (low)**.

5.2. In patients with severe (70%-99%) bilateral asymptomatic carotid stenosis or severe asymptomatic stenosis and contralateral occlusion, we suggest CEA before, or concomitant with, CABG. **Level of recommendation: grade 2 (weak); quality of evidence: C (low)**.

5.3. In patients requiring carotid intervention, staged or synchronous with coronary intervention, we suggest that the decision between CEA and CAS be determined by the timing of procedure, the need for anticoagulation or antiplatelet therapy, patient anatomy, and patient characteristics. **Level of recommendation: grade 2 (weak); quality of evidence: B (moderate)**.

Management of extracranial cerebrovascular disease has been the focus of intense investigation and debate by multiple vascular specialists since the introduction of carotid endarterectomy (CEA) as a therapeutic modality for the prevention and treatment of stroke more than several decades earlier. The initial hopes that CEA could reverse the clinical course of stroke were proved false, and the role of surgical treatment of extracranial carotid and vertebral artery disease was defined by the results of the multicenter randomized clinical trial, the Joint Study on the Extracranial Circulation.[1] That study of 5000 patients established the role of CEA in the treatment of minor stroke, transient ischemic attack (TIA), and amaurosis fugax and confirmed that surgery has a role in the treatment of established stroke, with a limited role for vertebral reconstruction in the treatment of cerebrovascular insufficiency. However, during the subsequent decades, with surgical refinements to CEA and the increasing detection of asymptomatic carotid stenosis identified using noninvasive vascular studies, CEA assumed a primarily prophylactic role for prevention of major stroke in asymptomatic patients and those with evidence of transient cerebral or ocular ischemia. Large prospective, randomized trials have established the role and efficacy of CEA in stroke prevention.[2-6]

During the past two decades, carotid artery stenting (CAS) has also evolved as a catheter-based alternative to CEA and medical therapy for stroke prevention and treatment. Approximately 135,000 interventions on lesions in the carotid bifurcation are performed annually in the United States. It has been reported that 90% are performed for patients without neurologic symptoms and that 11% are catheter-based procedures performed by a variety of specialists, including vascular surgeons, general surgeons, neurosurgeons, cardiologists, thoracic surgeons, interventional radiologists, and interventional neurologists.[7] However, others believe that the best data we have regarding symptom status come from the Vascular Quality Initiative (VQI) and National Surgical Quality Improvement Program, with the proportion closer to 60% to 70%.[8] Also, although these data might not be generalizable to the entire U.S. population, they are far better than the Nationwide Inpatient Sample data.[8]

Because multiple options can be available for the treatment of a single disease entity, defining the optimal therapy can be challenging, especially, when multiple specialties, often with nonoverlapping expertise, are involved in these treatment options. Thus, extensive and often conflicting literature has developed around the current standard for the diagnosis and management of extracranial carotid disease. Four large, prospective, randomized trials have been reported comparing the efficacy of CEA and CAS in the management of extracranial carotid stenosis.[9-12] A meta-analysis comparing CAS and CEA, which included some of these trials, was published in the *Journal of Vascular Surgery*.[13] Another recent meta-analysis conducted by the Mayo Clinic Evidence Practice Center and comparing CAS and CEA for symptomatic standard surgical risk patients also will be reported in the *Journal of Vascular Surgery*.[14]

In 2011, the Society for Vascular Surgery (SVS) published clinical practice guidelines for the management of extracranial carotid artery disease in the *Journal of Vascular Surgery*.[15] A multispecialty document also was published on the "Management of Patients with Extracranial Carotid and Vertebral Artery Disease."[16] More recently, the European Society for Vascular Surgery published their guidelines "Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)."[17] Because of these publications, the Society for Vascular Surgery elected to update their 2011 guidelines, because vascular surgeons play a major, if not predominant, role in the treatment of patients with carotid bifurcation disease.

METHODS

Guideline framework

The writing committee met several times, both in person and via several conference calls, to select the most important issues and questions of major interest to the clinician to be addressed in the clinical practice guidelines. A systematic review and meta-analysis was conducted by the Mayo Clinic Evidence Practice Center to address these questions, which will be reported separately in the *Journal of Vascular Surgery*. These five issues and questions were as follows:

1. Is CEA recommended over maximal medical therapy for asymptomatic carotid stenosis in low surgical risk patients?

2. Is CEA recommended over transfemoral (TF)-CAS for low surgical risk patients with symptomatic carotid artery stenosis of >50%?
3. What is the optimal timing of carotid intervention in patients presenting with acute stroke?
4. Screening for carotid artery stenosis in asymptomatic patients
5. What is the optimal sequence for intervention in patients with combined carotid and coronary artery disease (CAD)?

However, because several other important topics could not be covered in the clinical practice guidelines (eg, optimal modern medical therapy and risk factor modification, transcarotid artery reconstruction [TCAR]), these topics were addressed in separate comprehensive implementation document, which will be used as a reference for further details regarding the treatment of patients with extracranial cerebrovascular disease.

Each member of the committee was assigned responsibility for compiling information pertinent to a specific area of the document. These data were distributed to all members for review, and each area was subsequently discussed via conference calls. A consensus of the recommendation and level of evidence to support it was reached. Each recommendation in this document represents the unanimous opinion of the writing group.

The committee used the GRADE (grades of recommendation assessment, development, and evaluation) approach to rate the certainty of evidence (confidence in the estimates) and to grade the strength of the recommendations.[18] This system, adopted by >100 other organizations, has been adapted by the SVS to express the level of certainty as A, B, and C, consistent with high, moderate, and low certainty; respectively. The GRADE system categorizes recommendations as strong (grade 1) or weak, also called conditional (grade 2) according to the certainty of the evidence, the balance between desirable and undesirable effects, patient values and preferences, and other decisional factors. Grade 1 recommendations are meant to identify practices for which the benefit clearly outweighs the risk and can be adopted as a standard of care. Grade 2 recommendations are made when the benefits and risks are more closely matched or less certain; a situation in which shared decision-making is critical. A detailed explanation of the GRADE approach has been previously presented to the vascular surgery community.[19,20] The committee reached consensus for all the recommendations and the level of supporting evidence.

Evidence synthesis

The committee commissioned several systematic reviews, which will be reported separately in a document titled "Society for Vascular Surgery Technical Review Supporting Guidelines on the Management of Carotid Artery Disease."[14] The protocols and inclusion criteria for the reviews were determined a priori through collaboration between the committee and the Mayo Clinic Evidence-Based Practice Center. The questions selected for the present guidelines were specified using the PICO (population, intervention, comparison, outcomes) framework and chosen based on the daily clinical dilemmas encountered by patients and surgeons in practice. Patient-important outcomes were chosen for decision-making.[21] Meta-analyses were conducted when appropriate.

To make the guidelines more practical and helpful to clinicians, the committee drafted a second document to provide the implementation details and facilitate adoption and operationalization of the recommendations.[22] The implementation document is not an SVS guideline and should be considered as best practice identified by the committee based on their knowledge of the reported data and their clinical expertise.

Evidence to decision framework

The guideline committee considered patient values and preferences and the feasibility and acceptability of the recommended interventions. The availability of surgical expertise and institutional experience were also factors that were considered when making the recommendations. Stroke prevention was considered the most critical outcome across all guideline questions, and the overall certainty of the evidence was dependent on the certainty for this outcome. The guideline committee made strong recommendations for the third question (timing of revascularization) despite the variable certainty of the direct evidence, based on additional indirect evidence and by placing greater value on avoiding the possibility of any worsening of neurologic deficits. The strong recommendation against routine screening for average risk patients was determined by the lack of comparative studies showing improvement in outcomes with screening.

Question 1: Is CEA recommended over maximal medical therapy for low surgical risk patients?

Patients	Intervention	Comparison	Outcomes	Study design
Asymptomatic low-risk patients with >70% internal carotid artery stenosis	CEA	Maximal medical therapy	Stroke and death at 1 and 5 years	Randomized controlled trial

Evidence and rationale

Several randomized controlled trials (RCTs) compared CEA and best medical therapy. The results of the ACAS (asymptomatic carotid atherosclerosis study)[2] and ACST (asymptomatic carotid surgery trial)[5] favored CEA in the treatment of low surgical risk patients with severe asymptomatic carotid artery stenosis. The ACAS, which randomized 1662 patients to immediate CEA vs medical therapy demonstrated the superiority of CEA over antiplatelet therapy alone for asymptomatic patients with carotid stenosis of >60% (5.1% for surgical patients and 11.0% for patients treated medically; aggregate risk reduction, 53%; 95% confidence interval [CI], 22%-72%).[2] The ACAS recommended CEA for patients aged <80 years as long as the expected combined stroke and mortality rate for the individual surgeon was not >3%. The conclusions from the ACAS were supported by a subsequent larger RCT that had randomized 3120 patients to immediate CEA vs medical therapy.[5] That trial also showed an advantage in limiting stroke and death at 5 years for CEA compared with maximal medical therapy (4.1% vs 10.0%; 95% CI, 4.0%-7.8%). The long-term effectiveness of CEA for asymptomatic patients was confirmed by the long-term results of the ACST, as reported by Halliday et al.[23] That trial had compared CEA and a medical arm, in which patients had primarily received antithrombotic and antihypertensive therapy. The results showed that the CEA arm (patients aged <75 years) experienced significantly lower perioperative and 10-year stroke rates (13.3% vs 17.9%).[23] The strength of these conclusions has been questioned owing to the relatively modest absolute benefits of CEA and the contention that the medical therapy arm did not reflect contemporary medical management.[24,25] The question of whether modern medical therapy (including statins) is equivalent or superior to CEA or CAS has not yet been addressed by well-designed, appropriately funded, prospective, multicenter, and randomized trials. However, when the stroke rate of the patients receiving lipid-lowering medication in the ACST trial was analyzed, the patients who had undergone CEA with lipid-lowering medication had a lower stroke incidence compared with the medical therapy arm. However, the effect of CEA was not as great (0.7% vs 1.3% annually; $P < .0001$) for those receiving lipid-lowering therapy compared with 1.8% vs 3.3% annually ($P < .0001$) for those not receiving lipid-lowering therapy.[23]

More recently, Howard et al[26] conducted a prospective population-based cohort study (Oxford vascular study) and systematic review and meta-analysis to analyze the correlation between ipsilateral stroke and the degree of asymptomatic carotid stenosis in patients treated with contemporary best medical therapy. They enrolled 2354 consecutive patients (2178 patients with carotid imaging studies), including 207 with 50% to 99% asymptomatic carotid stenosis. The ipsilateral stroke rate at 5 years for the patients with 70% to 99% carotid stenosis was 14.6% (6 of 53) compared with 0% for the 154 patients with 50% to <70% stenosis ($P < .0001$). For patients with 80% to 99% carotid stenosis, the ipsilateral stroke rate was significantly greater than that for those with 50% to <80% stenosis: 5 of 34 (18.3%) vs 1 of 173 (1%; $P < .0001$). In their systematic review of 56 reports and 13,717 patients, 23 studies provided data on ipsilateral stroke and the degree of asymptomatic carotid stenosis in 8419 patients. Ipsilateral stroke was also linearly associated with the degree of ipsilateral carotid stenosis ($P < .0001$). Patients with 70% to 99% carotid stenosis (386 of 3778 patients) had a greater risk of ipsilateral stroke than those with 50% to <70% stenosis (181 of 3806 patients; odds ratio [OR] 2.1; $P < .0001$). They concluded that the benefit of CEA might have been underestimated for patients with severe stenosis (>70%). In addition, the 5-year stroke risk was relatively low in those patients with <70% stenosis receiving contemporary best medical therapy.[26]

Concerns have also been raised regarding whether the results of the previously described controlled trials could be attained in vascular surgical practice outside of clinical trials. Critics pointed out that these trials had been performed at centers of excellence and that the patients had been highly selected. However, subsequent reports of patients who would have been excluded from these trials suggested that the exclusion criteria did not falsely lower the complication rates. The combined stroke and death rates after CEA for patients defined as high risk or eligible for high-risk carotid registries varied from 1.4% to 3.6%, well within the American Heart Association guidelines.[27-29] Similarly, studies of large National Surgical Quality Improvement Program, state, and Medicare databases of 4000 to 35,000 patients demonstrated stroke and death rates as low as 2.2%, with a maximum of 6.9% (symptomatic patients only), suggesting that the results that conform to national guidelines are achievable across large patient populations.[7,30,31] The role of TF-CAS or transcervical carotid artery revascularization (TCAR) is even less clear because no completed studies have compared these treatments for patients with asymptomatic carotid stenosis against best medical therapy.

Several upcoming, multicenter randomized trials have been designed to answer the role of modern pharmacologic therapy in the management of asymptomatic carotid stenosis. These trials include the SPACE-II (stent-protected angioplasty in asymptomatic carotid artery stenosis) study[25] and CREST-2.[32]

Recommendation 1.1: In low surgical risk patients with asymptomatic carotid bifurcation atherosclerosis and stenosis of >70% (documented by validated duplex ultrasound or computed tomography angiography [CTA]/angiography), we recommend CEA with best medical therapy over maximal medical therapy alone for the long-term prevention of stroke and death (grade IB).

Question 2. Is CEA recommended over TF-CAS for low surgical risk patients with symptomatic carotid artery stenosis of >50%?

Patients	Intervention	Comparison	Outcomes	Study design	Subgroups
Symptomatic low-risk patients with >50% internal carotid artery stenosis	CEA	TF-CAS	Stroke, death, and myocardial infarction	RCT	30 days, >30 days, ≥5 years

Evidence and rationale

Once a patient with clinically significant symptomatic carotid stenosis has been identified, appropriate treatment must be selected. Treatment is primarily directed at the reduction of stroke risk. In general, the rates of stroke, myocardial infarction (MI), and death have been used when comparing CAS against CEA. In most clinical trials comparing CAS with CEA, stroke, MI, and death have been given equal weight in determining a composite endpoint to test overall efficacy. Data from the CREST (carotid revascularization endarterectomy vs stenting trial),[9] however, indicated that stroke has a more significant effect on patients' quality of life at 1 year than does nonfatal MI. Because the primary goal of intervention for carotid stenosis is stroke prevention, in developing the recommendations, the committee placed more emphasis on the prevention of stroke and procedurally related death than on the occurrence of periprocedural MI. This could have resulted in committee recommendations that differed from the reported results from some trials in which these three endpoints were given equal weight in the analysis.

The threat of stroke in symptomatic patients with <50% stenosis has generally been considered to be small and typically will not warrant intervention. The ECST (European Carotid Surgery Trial) and NASCET (North American Symptomatic Carotid Endarterectomy Trial) demonstrated that CEA was unable to reduce the subsequent neurologic event rates in patients with symptoms of cerebral ischemia and bifurcation stenosis of <50% diameter reduction and was actually associated with increased morbidity compared with medical management.[33-35]

NASCET and ECST both demonstrated the benefit of CEA compared with maximal medical treatment for neurologically symptomatic patients with carotid stenosis with a reduced diameter of >50%.[6,33-35] NASCET demonstrated a relative risk (RR) reduction of 65% and an absolute risk reduction in stroke of 17% at 2 years (26% in the medical arm vs 9% in the surgical arm) for patients with >70% carotid stenosis. ECST demonstrated a similar reduction in stroke risk after 3 years. The medical arm had a 26.5% stroke risk compared with 14.9% in the surgical group, an absolute risk reduction of 11.6%. In both studies, the risk of stroke in the medical arm and, therefore, the benefit of CEA, increased with an increasing degree of stenosis. The results of these trials established CEA as the treatment of choice for patients with severe carotid stenosis and have been widely accepted throughout the medical community. The benefit of CEA for those with stenosis of 50% to 69% was more moderate—15.7% rate of stroke after CEA vs 22.2% rate of stroke with medical therapy at 5 years—but the difference was still statistically significant.[4]

CEA vs TF-CAS in symptomatic stenosis

A number of trials have examined the role of TF-CAS in the management of neurologically symptomatic patients with >50% diameter stenosis. Several early trials such as SAPPHIRE (stenting and angioplasty with protection in patients at high risk for endarterectomy) of high surgical risk patients demonstrated overall equivalence of CAS and CEA in the management of carotid stenosis, although the number of symptomatic patients was too small for a subgroup analysis.[36] Two large prospective randomized European trials, EVA-3S (endarterectomy vs angioplasty in patients with symptomatic severe carotid stenosis)[11] and SPACE1 (stent-supported percutaneous angioplasty of the carotid artery vs endarterectomy),[12] examined the role of CAS vs CEA in neurologically symptomatic patients. EVA-3S showed statistically inferior 30-day outcomes for CAS compared with CEA. The 30-day incidence of any stroke or death was 3.9% after CEA (95% CI, 2.0-7.2) and 9.6% after TF-CAS (95% CI, 6.4-14.0). The RR of any stroke or death after CAS compared with CEA was 2.5 (95% CI, 1.2-5.1). The 30-day incidence of disabling stroke or death was 1.5% after CEA (95% CI, 0.5-4.2) and 3.4% after CAS (95% CI, 1.7-6.7); the RR was 2.2 (95% CI, 0.7-7.2). However, EVA-3S study was criticized because of the relatively low level of experience (minimum of 12 CAS cases or 35 supra-aortic trunk cases, of which 5 were CAS procedures) required in the CAS arm. The SPACE trial was designed to test the "equivalence" between CEA and CAS for patients with neurologic symptoms. However, the trial was stopped after the recruitment of 1200 patients owing to the futility of proving equivalence between the two treatments. The rate of death or ipsilateral stroke at 30 days was 6.84% for CAS and 6.34% for CEA in for randomized patients. However, the study was not powered appropriately and failed to show the noninferiority of CAS compared with CEA ($P < .09$).[12] More recently, two large randomized trials comparing CEA and TF-CAS for symptomatic patients were completed. The ICST (international carotid stenting study trial) enrolled 1713 patients and demonstrated an increased periprocedural stroke risk with CAS (7.7%) compared with CEA (4.1%) in neurologically symptomatic patients.[10] The observed difference was statistically significant ($P < .002$). The rate of any stroke or death within 30 days after treatment in the CAS group was more than twice the rate recorded for the CEA group (7.4% vs 3.4%; $P < .0004$). In addition, the composite endpoint of stroke, death, and MI significantly favored CEA (5.2%) vs CAS (8.5%; $P < .006$). These findings were similar to those for the symptomatic patients enrolled in the CREST (carotid revascularization endarterectomy vs stenting trial).[9] In the CREST, the periprocedural rate of stroke and death was significantly greater after TF-CAS than after CEA for symptomatic patients (6.0% ± 0.9% vs 3.2% ± 0.7%; hazard ratio [HR], 1.89; 95% CI, 1.11-3.21; $P < .02$). The rate of MI was lower after CAS than after CEA for symptomatic patients (1.0% ± 0.4% vs 2.3% ± 0.6%; HR, 0.45; 95% CI, 0.18-1.11; $P < .08$); however, the differences were not significant. The CSTC (Carotid Stenosis Trialists' Collaboration) performed a meta-analysis of 4754 patients from the four randomized trials comparing CEA and TF-CAS. These investigators demonstrated a CEA vs TF-CAS periprocedural HR of 1.61 (95% CI, 0.90-2.88), in favor of CEA for patients aged 65 to 69 years and an HR of 2.09 (95% CI, 1.32-3.32) for patients aged 70 to 74 years.[37] If octogenarians (>80 years) were removed from the data to allow the CREST findings to be compared with those from other trials in which such patients were not enrolled, the results demonstrated that the 30-day stroke and death rate was significantly lower for patients undergoing CEA (2.6% ± 0.7% for CEA and 5.6% ± 1.0% for CAS; $P = .006$).[37] The pooled analysis of 30-day outcomes of stroke and death were lower for symptomatic patients treated with CEA vs TF-CAS[14] (Fig 1).

The long-term outcomes of CAS vs CEA for symptomatic patients were examined using a preplanned pooled analysis of individual patient data from the EVA-3S, SPACE, ICSS, and CREST studies.[38] These four trials randomized a total of 4754 symptomatic patients with >50% internal carotid artery stenosis. The median length of follow-up was 2 to 6.9 years. The risk of stroke or death within 120 days of the index procedure was 5.5% for CEA and 8.7% for CAS (risk difference, 3.2%; 95% CI, 1.7-4.7). After the periprocedural period of 120 days, no differences were found in the annual rate of late ipsilateral stroke (annual event rate, 0.60% for CEA vs 0.64% for CAS). These findings lend support that both procedures have similar durability, although the long-term outcomes have continued to favor CEA owing to the lower periprocedural stroke and death rate (Figs 2 and 3).

Concern might exist regarding whether the data from RCTs of CEA and CAS can be extrapolated to real world experience. In general, those performing CAS in these trials were highly experienced and rigorously adjudicated before being allowed to enroll patients. In a review of physicians treating Medicare beneficiaries with

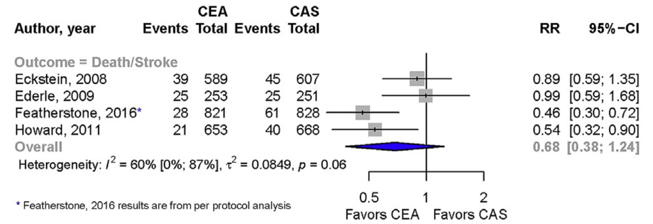

Fig 1. Thirty-day death and stroke. *CAS,* Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *RR,* relative risk.

CAS, <10% of physicians would have met the criteria to participate in the CREST owing to a lack of volume or a high complication rate.[39] It is unclear whether results similar to those from RCTs will be obtained for CAS by operators who might be less experienced or for patients who would not be eligible for clinical trials. Nolan et al[40] reviewed data from the Vascular Study Group of New England and showed a higher rate of stroke and death for symptomatic patients treated with CAS compared with those treated with CEA (5.1% with CAS vs 1.6% with CEA; $P = .001$). Similarly, Hicks et al[41] studied almost 52,000 carotid procedures in the VQI and found that for symptomatic high-risk patients (determined using Medicare criteria), the risk of stroke and death after CEA was 2.3% compared with 3.6% after CAS ($P < .001$). The difference in the stroke rate was twofold greater for CAS in both the general population and the propensity-matched patient cohorts (HR, 2.23; 95% CI, 1.58-3.15; $P < .001$).[41] The lower stroke and death rates observed in registries includes only in-hospital events and, as such, could be lower than those observed in clinical trials that use 30-day event rates and mandatory postprocedure evaluations by an independent neurologist.

Timing of CEA. Increasing evidence has shown that CEA provides maximum benefit if performed in <14 days for patients presenting with TIA or amaurosis fugax.[17] Natural history studies reported that the incidence of recurrent symptoms after the index TIA ranges from 5% to 8% at 48 hours, 4% to 17% at 72 hours, 8% to 22% at 7 days, and 11% to 25% at 14 days.[17]

Transcarotid artery revascularization

Early data suggested that TCAR might have a role in the treatment of patients with symptomatic carotid occlusive disease. Studies have shown that TCAR results in a similar rate of infarcts using diffusion-weighted imaging (DWI) on postprocedure magnetic resonance imaging compared with CEA and that TF-CAS is associated with a two-to threefold greater rate of DWI.[42] Up to 50% of the infarcts on DWI and strokes that occur after TF-CAS were contralateral, suggesting arch pathology as the etiology.[43] Two recent trials, ROADSTER-1 (safety and efficacy study for reverse flow used during carotid artery stenting procedure) and ROADSTER-2 (post-approval

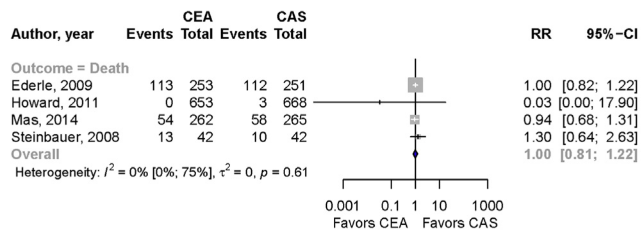

Fig 2. Five-year risk of death. *CAS,* Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *RR,* relative risk.

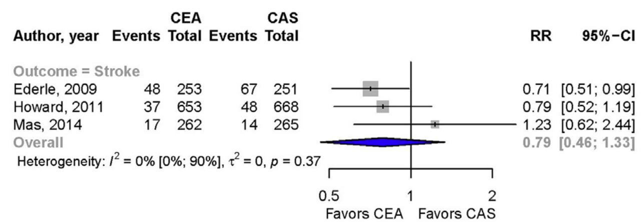

Fig 3. Five-year risk of any stroke. *CAS,* Carotid artery stenting; *CEA,* carotid endarterectomy; *CI,* confidence interval; *RR,* relative risk.

cranial nerve injury and shorter hospital stays. The effect of developing a TCAR program on overall carotid revascularization outcomes was examined by Columbo et al.[49] They compared the risk of major adverse cardiovascular events (MACE), defined as stroke, death, and MI, in centers that performed only CEA vs the risk of MACE in centers that performed both CEA and TCAR. At 1 year, the incidence of MACE was 10% lower at the centers that performed both TCAR and CEA vs CEA alone (OR, 0.9; 95% CI, 0.81-0.99; $P = .04$).[49] Although these studies appear promising and have been supported by a clinical competency statement from the SVS,[50] it is important to remember that to date the vast majority of TCAR procedures have been performed in patients at high anatomic or medical risk for CEA and the data at present are inadequate to make a recommendation on the role of TCAR for low surgical risk patients with symptomatic carotid stenosis. In summary, TCAR is superior or preferable to TF-CAS or CEA for patients with high anatomic and/or physiologic surgical risk (more detail provided in the Implementation Document).

Recommendation 2.1.: We recommend CEA over TF-CAS for low- and standard-risk patients with >50% symptomatic carotid artery stenosis (grade IA).

Question 3. What is the optimal timing of carotid intervention in patients presenting with acute stroke?

Patients	Intervention	Comparison	Outcomes	Study design	Subgroups
Patients presenting with stroke with >50% ipsilateral carotid stenosis	Urgent CEA or CAS	Early vs delayed intervention	Patients with Rankin scale score of ≤2 will benefit from early intervention	Retrospective	CEA ≤48 hours, 1 week, 2 weeks, and 6 weeks after index event

study of transcarotid artery revascularization in patients with significant carotid artery disease) have been completed.[44-46] The incidence of 30-day stroke in the symptomatic per protocol patients in both trials was 0.6% in each trial. No deaths occurred in the per protocol symptomatic patients in ROADSTER-2 for a combined 30-day stroke and death rate of 0.6%.[44,45] A more recent study examined 3286 propensity-matched patients from the VQI and demonstrated a significantly lower incidence of in-hospital stroke and death for the patients treated with TCAR vs TF-CAS (1.6% vs 3.1%; RR, 0.51; 95% CI, 0.37-.72).[47] No difference was found in MI between the groups. Finally, Malas et al[48] examined a more recent cohort of patients from the VQI Transcarotid Revascularization Project. These investigators propensity score matched 6384 pairs of patients who had undergone either TCAR or CEA. In this cohort, 3333 symptomatic patients were compared.[48] No differences were found in the in-hospital stroke and death rates between the symptomatic patients undergoing TCAR vs CEA (2.2% vs 2.6%; $P = .46$), and TCAR was associated with a lower incidence of

Evidence and rationale

Acute stroke is often associated with intracranial thrombosis or embolization. Thus, a major management goal is to identify those patients with intracranial occlusions and to reperfuse the ischemic brain as rapidly as possible. Primarily, therapy should be directed at the intracranial occlusion that affects a significant amount of the vasculature and resultant brain at risk. Only ~15% of patients with acute stroke will present within the 6-hour window for acute intervention. However, as techniques and diagnosis have improved, neurointerventionalists have expanded this therapeutic window.

Many patients present outside this 6-hour therapeutic window. Intervention for these patients is directed at the carotid bifurcation rather than the intracranial circulation, with the goal of preventing recurrent events rather than re-establishing intracranial flow in the occluded arteries.

However, for patients with acute stroke who present obtunded or severely neurologically debilitated, it is often necessary to delay CEA because they could have a greater risk of hemorrhagic transformation of an infarct or intracerebral hemorrhage. Patients with a significant neurologic deficit (modified Rankin scale score >2), with an area of infarction >30% of the middle cerebral artery territory and those with altered consciousness should not undergo CEA until significant neurologic improvement has occurred. Factors that have been found to influence outcomes include the extent of hemispheric involvement, the time to the initiation of therapy, time to perfusion, patient age, blood glucose, and female sex. The most important of these appears to be the degree of hemispheric involvement (<30% of middle cerebral artery by volume), time to reperfusion, and age.[51-53]

Patients with an acute fixed deficit of >6 hours' duration and a mild to moderate deficit can be considered for carotid intervention after a period of medical stabilization. Waiting >14 days could increase the risk of recurrent neurologic events by 10% to 20%.[54]

Numerous series have documented the safety of early CEA (0-14 days after the index event). In a single-center series, Sharpe et al[55] reported a 30-day death and stroke rate of 2.4% when patients had undergone CEA within 48 hours of symptom onset. Other registry data from Germany, Sweden, the United States, and single-series reports from the United States have shown equally good results for CEA performed within the first week but not within the first 48 hours.[56-59] In an analysis of the VQI of 8408 patients, the results were comparable among the patients who had undergone surgery after 48 hours but <14 days after stroke and those who had undergone surgery >14 days after the index event.[59] When the cohorts were stratified by 3 to 8 days and 8 to 14 days, the multivariate analysis demonstrated that performing CEA at 3 to 7 days after stroke was protective for postoperative stroke/death ($P = .003$) and any postoperative complication ($P = .028$). The investigators concluded that surgery should be delayed for ≥48 hours after acute stroke and should be performed within 14 days after the stroke.[59] Avgerinos et al[60] corroborated these data, suggesting CEAs performed 2 to 5 days after the index neurologic event will have outcomes similar to the outcomes of CEAs performed later.

These findings confirmed the results of an analysis of the Swedish Vascular Registry, including 2596 patients who had undergone CEA for symptomatic carotid stenosis, including stroke. The combined stroke/death rate was 11.5% among those who had undergone surgery within the first 2 days of the neurologic event compared with 3.6%, 4.0%, and 5.4% among those who had undergone CEA at 3 to 7, 8 to 14, and 15 to 180 days after the acute neurologic event, respectively. A multivariate analysis demonstrated that patients who underwent CEA within the first 2 days after an acute neurologic event experienced a relative OR of 4.24 (95% CI, 2.07-8.70; $P < .001$) for perioperative complications compared with those undergoing surgery within 3 to 7 days.[58] These data were corroborated by Hasan et al[14] in their meta-analysis concerning the timing of the intervention after index stroke. Avgerinos et al[60] demonstrated an increased risk of complications if CEA were performed within 48 hours of the index event (RR, 2.3053) for stroke but no difference between 2 and 14 days. This short delay could allow for a more complete patient evaluation and to allow the symptoms to stabilize and plateau.

The preponderance of evidence indicates that CEA performed early (<2 weeks) after an acute stroke is preferable to a delay of 4 to 6 weeks to CEA.[61-67] The data on CAS in the setting of acute stroke are scant, even in the recent meta-analysis by Hasan et al.[14] Most reports were based on anecdotal studies; thus, we could not draw any significant conclusions regarding the benefits of CAS for acute strokes with carotid-based lesions. At present, CEA is the procedure of choice for patients with stable strokes and >50% carotid bifurcation stenosis.

Recommendations for management of acute neurologic syndrome

3.1: For patients with a recent stable stroke (modified Rankin scale score, 0-2), we recommend carotid revascularization for symptomatic patients with >50% stenosis to be performed as soon as the patient is neurologically stable after 48 hours but definitely before 14 days after the onset of symptoms (grade IB).

3.2: For patients undergoing revascularization within the first 14 days after the onset of symptoms, we recommend CEA rather than CAS (grade IB).

3.3: We recommend against revascularization, regardless of the extent of stenosis, for patients who have experienced a disabling stroke, have a modified Rankin scale score of ≥3, whose area of infarction is >30% of the ipsilateral middle cerebral artery territory, or who have altered consciousness to minimize the risk of postoperative parenchymal hemorrhage. These patients can be reevaluated for revascularization later if their neurologic recovery is satisfactory (grade IC).

Question 4A. Is screening for asymptomatic carotid stenosis recommended in the general population?

Patients	Intervention	Comparison	Outcomes	Study design
General population with no symptoms of cerebrovascular disease	Screening for carotid artery disease with Duplex ultrasound	No screening	Prevalence of ≥50% carotid stenosis and incidence of stroke or death related to carotid disease	Any

Evidence and rationale

No consensus has been reached on which patient populations should undergo carotid screening for the detection of asymptomatic carotid disease, and no direct evidence is available on the benefits of screening regarding the actual outcomes of future stroke. The rationale behind screening for asymptomatic disease has been determined by the assumptions that unheralded stroke is often the first symptom of significant carotid atherosclerosis and that the medical, surgical, or endovascular treatment of identified severe carotid artery stenosis can prevent future cerebral infarction. The efficacy of screening is directly related to the prevalence of disease in the designated population. Screening has been found to reduce the risk of stroke in a cost-effective manner when the prevalence of significant stenosis is ≥20%.[68] However, with a prevalence of <5% in the general population,[68,69] screening does not appear to reduce the stroke risk and might, in fact, be harmful if it leads to inappropriately performed invasive procedures. In addition, the rate of false-positive carotid Duplex ultrasound findings could be increased in a population with such a low prevalence of disease.[70] Because of the relatively low prevalence of disease, widespread screening of the general population, therefore, is clearly not indicated. This position is supported by multiple professional organizations, including the National Stroke Association, Canadian Stroke Consortium,[71,72] and the U.S. Preventive Services Task Force.[70]

Recommendation 4.1: We recommend against the routine screening for clinically asymptomatic carotid artery stenosis for individuals without cerebrovascular symptoms or significant risk factors for carotid artery disease (grade IB).

Therefore, specific high-risk asymptomatic populations have been proposed as appropriate for carotid screening. The American Stroke Association/American Heart Association Stroke Council concluded that screening of highly selected populations might be of benefit.[73] Multiple societies, including the American College of Cardiology Foundation and others, have recommended screening for asymptomatic patients with a carotid bruit found on physical examination and for those for whom coronary artery bypass grafting (CABG) is planned.[74] The SVS has advocated for consideration of carotid artery screening of high-risk patients aged ≥55 years with cardiovascular risk factors.[75]

Several groups have attempted to further refine and identify the population subsets for whom the prevalence of carotid stenosis is ≥20%, which would possibly justify screening of asymptomatic patients. In a report of a single-institution screening program, a model identifying patients at high risk of ≥50% asymptomatic stenosis was proposed. The patients screened were >60 years old and had had one or more of the following risk factors: hypertension, CAD, current cigarette smoking, and/or a first-degree family member with a history of stroke. The prevalence of significant stenosis was only 2% if none of these risk factors were present but increased dramatically with the coexisting presence of additional risk factors. The prevalence of carotid stenosis was 14% with two risk factors, 16% with three risk factors, and 67% with four risk factors.[76] In another analysis from the same institution, patients with both hypertension and known cardiac disease of any type had a prevalence of carotid stenosis of ≥50% of 22.1%.[77]

Similarly, a report from the Western New York stroke screening program identified the following variables to

Question 4B. Is screening for carotid stenosis recommended for high-risk asymptomatic patients?

Patients	Intervention	Comparison	Outcomes	Study design	Subgroups
Patients with significant risk factors for carotid atherosclerosis but no symptoms of cerebrovascular disease	Screening for carotid artery disease with Duplex ultrasound	No screening	Prevalence of ≥50% carotid stenosis and incidence of stroke or death related to carotid disease	Any	Patients with atherosclerotic risk factors, peripheral arterial disease, AAA, CAD, audible neck bruit, previous radiotherapy to the neck, findings of cerebral infarction on brain imaging studies

Evidence and rationale

Atherosclerotic risk factors and medical comorbidities predisposing toward an increased prevalence of carotid artery stenosis. Screening has been found to reduce the risk of stroke in a cost-effective manner when the prevalence of significant stenosis is ≥20%.[68]

be associated with ≥60% carotid stenosis: age ≥65 years (OR, 4.1), current smoking (OR, 2), CAD (OR, 2.4), and hypercholesterolemia (OR, 1.9).[78] Patients undergoing coronary artery bypass surgery were noted to have a prevalence of significant carotid stenosis of 8%. The American College of Cardiology/American Heart

Association guidelines noted that screening before CABG is probably indicated for the following subset of patients: age ≥65 years; the presence of left main coronary artery stenosis; a history of smoking, a history of TIA, stroke, or carotid bruit; and known peripheral arterial disease (PAD).[78] Based on these and other reports, the SVS does advocate carotid artery screening for high-risk patients aged ≥55 years with appropriate cardiovascular risk factors.[75,79]

Other investigators have noted that the prevalence of occult carotid stenosis is increased in those with diabetes compared with those without diabetes (8.7% vs 2.8%; $P <$ .01)[80] and in patients requiring hemodialysis and undergoing tunneled catheter placement (9.8%).[81] In a study of 1500 subjects specifically recruited for carotid screening, the overall prevalence of significant stenosis was 5.2%. The independent predictors of an increased prevalence of carotid stenosis included hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, and a family history of stroke.[82] One investigator reported that screening of asymptomatic patients is appropriate if they were aged ≥60 years and had three or more traditional atherosclerotic risk factors.[83]

However, few direct comparative studies have evaluated the efficacy of screening with respect to the actual clinical outcomes of stroke or death. Most reported studies have used the prevalence of significant carotid stenosis in the studied populations as the actual outcome measure. In a report by Berens et al,[84] >1000 patients aged ≥65 years who were undergoing cardiac surgery were screened with carotid duplex ultrasound scans before surgery. The prevalence of disease was 17% for those with ≥50% stenosis and 5.9% those with ≥80% stenosis. Using multivariate analysis, five variables were found to be significant independent predictors of ≥80% stenosis: female sex, peripheral vascular disease, a history of TIA or stroke, a positive smoking history, and the presence of left main coronary disease. If all patients with at least one of those risk factors were screened, the mathematical model predicted that 95% of the patients with ≥80% stenosis would be identified before their cardiac operation.[84]

Lin et al[85] reported the outcomes of 3233 patients who had undergone cardiac surgery. They performed comparisons between those who had undergone preoperative carotid duplex ultrasound scanning (n = 515) and those who had not (n = 2718). No difference was found in the risk factors or a history of previous TIA between the two cohorts. Among the patients who had undergone screening with ultrasound before isolated CABG (n = 306), the incidence of significant disease was relatively low: 25 (8.2%) had had unilateral moderate (50%-69%) stenosis, 10 (3.3%) bilateral moderate stenosis, 9 (2.9%) unilateral severe (70%-99%) stenosis, 2 (0.7%) bilateral severe stenosis, 5 (1.6%) unilateral total occlusion, and 1 (0.3%) bilateral total occlusion. The outcomes regarding perioperative mortality and stroke did not differ between those who had and those who had not undergone duplex ultrasound. Operative intervention of severe carotid stenosis before CABG was performed in 2 of 17 patients identified (11.8%).[85]

When the results of these two studies were combined in a systematic review and meta-analysis, screening in these defined populations did reveal a benefit with regard to the mortality outcome and less so for the stroke outcome (Fig 4). Additionally, the systematic review revealed that certain patient cohort populations might be expected to have an approximate prevalence of ≥20% of significant carotid artery stenosis even if asymptomatic, making them appropriate to consider for screening (Fig 5)[14]:

- Patients with current cigarette smoking
- Patients with hypertension and CAD
- Patients with renal failure and diabetes, hypertension, or CAD
- Patients with hypertension, hypercholesterolemia, and CAD

Subgroups

Patients with PAD. Patients with lower extremity PAD have an increased prevalence of carotid artery stenosis and might benefit from screening.[86,87] The prevalence of ≥60% carotid artery stenosis in patients with symptomatic lower extremity PAD is likely ≥20% and was nearly 25% in one epidemiologic study.[87]

Multiple studies have confirmed the high prevalence of carotid artery stenosis in patients with lower extremity PAD.[86,88-97] In one study of >400 patients with PAD undergoing surgery, patients with occult carotid stenosis were also noted to have an increased risk of stroke in the postoperative period.[96] In that study, the risk of stroke in patients with symptomatic high-grade stenosis was ameliorated by performing CEA either before or simultaneously with the designated arterial bypass surgery.[96] However, it has generally been accepted that if carotid stenosis is asymptomatic, intervention for critical limb ischemia can proceed before consideration of carotid revascularization. Nevertheless, carotid screening for patients with lower extremity PAD is clearly appropriate, considering the markedly increased risk of occult disease.

Patients undergoing coronary artery bypass surgery. Multiple reports have documented a markedly increased prevalence of occult carotid artery stenosis in patients with CAD, especially in those undergoing coronary artery bypass surgery.[84,85,98-107] Two direct comparative studies regarding screening of CABG patients using the actual outcomes of stroke and death have been previously discussed in detail.[84,85,98-107] An increased prevalence of carotid stenosis has also been documented in patients undergoing coronary angioplasty.[108] Among patients

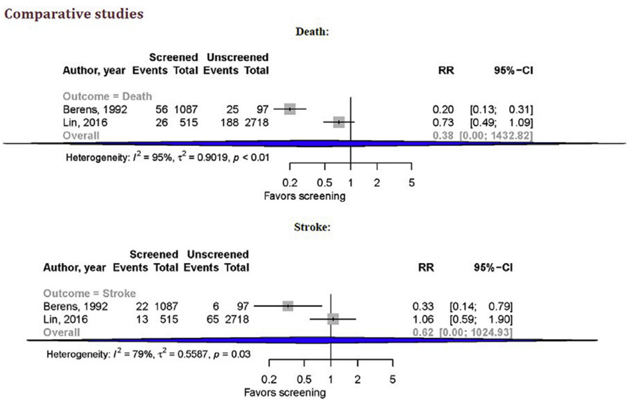

Fig 4. Comparative studies. *CI,* Confidence interval; *RR,* relative risk.

undergoing coronary artery bypass, the presence of a carotid bruit and diabetes mellitus increased the predictive value.[104] Additionally, carotid stenosis in coronary bypass patients has been noted to be a risk factor for perioperative stroke.[104] Considering the prevalence of occult carotid disease, carotid screening for patients undergoing coronary artery bypass is believed to be appropriate. However, the evidence in favor of screening for patients with documented CAD without plans for coronary artery bypass procedures is less robust.

Asymptomatic patients with an audible carotid bruit. The finding of an audible bruit in the neck is believed to be a sign of turbulent blood flow at the bifurcation and of carotid artery atherosclerosis. However, this physical finding is not particularly specific or sensitive for clinically significant carotid artery stenosis. In a reported meta-analysis of studies describing the relationship between carotid bruit and carotid stenosis, 28 prospective cohort studies involving >17,000 patients were analyzed.[109] The stroke rate was 1.6 per 100 patient-years for those with bruits compared with 1.3 per 100 patient-years for those without carotid bruits. Thus, the presence of a carotid bruit likely increases the risk of cerebrovascular disease and, therefore, might justify screening of otherwise asymptomatic patients.

In the Northern Manhattan study, the presence of ≥60% carotid stenosis was 2.2%, and the presence of a carotid bruit was 4.1% among 686 asymptomatic subjects.[110] The positive predictive value of an ipsilateral carotid bruit was 25%, and the negative predictive value was 99%. The sensitivity, specificity, and overall accuracy was 56%, 98%, and 97.5%, respectively. However, in another observational study of >1500 patients who had undergone carotid ultrasound specifically because of the presence of an audible bruit, 31% had had significant (≥50%) stenosis.[111] However, for the patients with 50% to 99% carotid stenosis, the presence of a carotid bruit had an accuracy of 75%, sensitivity of 71%, specificity of 81%, and positive likelihood ratio of 3.65. Therefore, although carotid bruits are not necessarily accurate enough to confirm or exclude the presence of significant carotid stenoses, these signs are thought to be an appropriate indication for further directed screening with carotid duplex ultrasound, especially if the carotid bruit is noted in a patient with other atherosclerotic risk factors.

Asymptomatic patients with previous neck irradiation. With the increased use and success of radiotherapy to treat head and neck malignancies, the survival of patients with these diseases has achieved remarkable progress.[112] Vascular injury and carotid stenosis have received increased attention. Patients who have undergone neck irradiation >5 years earlier have an eight times greater risk of developing carotid stenosis compared with those with a postradiotherapy interval of <5 years. Severe postradiotherapy carotid stenosis is also associated with older age, smoking, and heart disease. Patients who have undergone radiotherapy of the head and neck might have a prevalence of significant carotid stenosis that would justify screening in asymptomatic patients.[113] The greatest incidence of carotid stenosis was noted ~15 years after radiation exposure, with ipsilateral rates of stenosis as high as 21.3%.[15,113,114] Unlike typical atherosclerotic disease, which often involves only the carotid bifurcation, the distribution of radiation-induced carotid disease can also involve the proximal common carotid arteries. The presence of extensive proximal disease would have obvious implications for surgical or endovascular treatment of such lesions, if indicated.

It has been proposed by some that patients with previous radiotherapy should undergo screening duplex evaluations even in the absence of clinical cerebrovascular symptoms.[114] However, the optimal timing and frequency of such screening are undefined, and this concept has not been universally accepted. The evidence does not appear to be sufficient to recommend routine screening for asymptomatic patients with previous neck radiotherapy in the absence of other defined risk factors.

Patients with abdominal aortic aneurysms. Although patients with PAD and severe CAD are clearly at greatly increased risk of having occult carotid artery stenosis, the correlation in patients with abdominal aortic aneurysms (AAAs) is not as robust. The prevalence of carotid stenosis of ≥70% was 8.8% in a population of patients with AAAs compared with 12.5% in a cohort of PAD patients.[115] In a prospective study of patients with AAAs, the prevalence of asymptomatic carotid stenosis of ≥70% was 10.8%.[116] No correlation was noted between the size of the AAA and the degree or presence of carotid

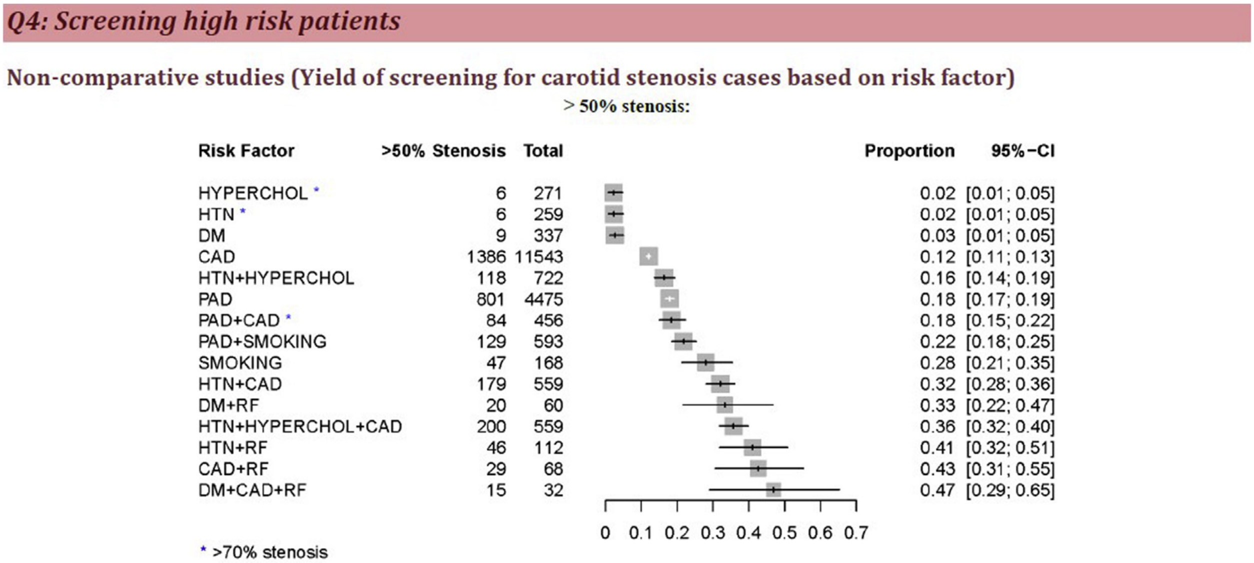

Fig 5. Noncomparative studies (yield of screening for carotid stenosis cases based on risk factor). *CAD,* Coronary artery disease; *CI,* confidence interval; *DM,* diabetes mellitus; *HTN,* hypertension; *Hyperchol,* hypercholesterolemia, *PAD,* peripheral artery disease; *RF,* renal failure.

stenosis. In an additional report of 332 patients with AAA who had undergone carotid duplex ultrasound scans, a greater prevalence of carotid stenosis was noted, with 30.4% found to have ≥50% stenosis in one or both carotid arteries.[117] However, several additional studies have revealed the prevalence of carotid stenosis in patients with AAAs to be <20%.[118] Clearly, the correlation of carotid atherosclerosis with isolated abdominal aneurysmal disease is not thought to be as significant as the relationship with coronary and lower extremity atherosclerotic occlusive disease. Therefore, routine screening for carotid stenosis in asymptomatic patients with AAAs but without other defined high-risk factors is not recommended.[119]

Patients with clinically occult cerebral infarction or high-risk factors on brain imaging. Finally, asymptomatic patients in whom brain imaging has identified cerebral infarction despite the absence of any corresponding history of neurologic symptoms represent a population that might benefit from imaging of the carotid artery. An increased subsequent stroke rate of 4.4% in patients with 60% to 79% initially asymptomatic stenosis has been reported if a silent infarct was identified on brain imaging studies.[120] Therefore, screening is generally recommended for patients with asymptomatic cerebral infarctions.[120] The detection of cerebral emboli using transcranial Doppler (TCD) studies also had a high positive predictive value to identify asymptomatic patients at high risk of stroke. The patients with two or more microemboli per hour on TCD studies had a markedly increased risk of 1-year ipsilateral ischemic stroke compared with patients with asymptomatic carotid stenosis without TCD-detected microemboli (15.6% vs 1.0%, respectively; $P < .0001$).[121] However, at present, it is unclear how this technology might be practically applied to all asymptomatic patients with known carotid stenosis.

Recommendation 4.2 In selected asymptomatic patients who are at an increased risk of carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis, especially if patients are willing to consider carotid intervention if significant stenosis is discovered (grade 2B). These high-risk groups include

- Patients with lower extremity PAD
- Patients undergoing coronary artery bypass surgery
- Patients aged ≥55 years with at least two traditional atherosclerotic risk factors
- Patients aged ≥55 years and active cigarette smoking
- Patients with diabetes, hypertension, or CAD
- Patients with clinically occult cerebral infarction noted on brain imaging studies

Additional remarks.

1. In these patient cohorts, the presence of a carotid bruit increases the likelihood of detecting significant stenosis
2. Asymptomatic individuals with an AAA or previous radiotherapy to the neck who do not meet the criteria for any of the high-risk groups noted above do not require screening

Question 4C. What imaging test is best for screening for carotid stenosis in asymptomatic patients?

Patients	Intervention	Comparison	Outcomes	Study design
Asymptomatic patients undergoing screening for carotid stenosis	Imaging study	Duplex ultrasound or other imaging study (CTA, magnetic resonance angiography)	Sensitivity and specificity in identification of ≥50% and ≥70% carotid stenosis	Any

Evidence and rationale

The most important features of imaging of carotid bifurcation disease are the degree of stenosis and the character of the plaque.[2,6,15,33,122] A greater degree of stenosis is generally thought to represent a progressively increased risk of future stroke.[6,33] However, plaque morphology also clearly plays a significant role.[122] The morphologic features of the plaque likely related to the risk of future stroke include heterogeneity, measurement of plaque area and juxtaluminal black area, gray-scale median, and echogenicity.

Duplex ultrasound is safe, accurate, and reliable. Because it is heavily dependent on technique, it should be performed in an accredited ultrasound laboratory.[15] Duplex ultrasound is the first-line imaging modality for carotid artery imaging, screening, and the identification of patients with 70% to 99% stenosis of the internal carotid artery.[75,123] The rationale for the widespread use of Duplex ultrasound include its low cost, ease of performance, and robust sensitivity (85%-92%) and specificity (84%).[123,124] Consensus ultrasound criteria for diagnosing the varying degrees of carotid artery stenosis have been extensively developed, widely used, and validated.[125] Duplex ultrasound also has the ability to evaluate features of plaque morphology that might indicate patients with a high risk of stroke.[122]

Determination of the degree of carotid stenosis is determined by an analysis of the hemodynamic parameters obtained from Doppler ultrasound analysis, including the peak systolic and end-diastolic velocities. The ultrasound criteria for the degree of carotid stenosis should be defined by the angiographic and imaging correlation in each vascular laboratory. The most commonly recognized consensus criteria include a cutoff peak systolic velocity of the internal carotid artery of ≥125 cm/s to denote angiographic stenosis of ≥50%. A combination of peak systolic velocity of 230 cm/s and an end-diastolic velocity of ≥100 cm/s or a peak systolic velocity ratio between the internal and common carotid artery of ≥4 can be used to predict a stenosis of ≥70%.[126] Using these criteria, the reported sensitivity, specificity, and accuracy of duplex ultrasound in predicting 50% to 69% or ≥70% stenosis were 93%, 68%, and 85% and 99%, 86%, and 95%, respectively.[125] The major limitations of duplex ultrasound include its dependence on a skilled operator and its inability to completely image the proximal and intracranial vasculature. Certain anatomic features can also reduce the accuracy of duplex ultrasound imaging, including severe vascular calcification and arterial tortuosity.[15]

At present, contrast-enhanced magnetic resonance angiography (MRA) can provide three-dimensional images that can rival those of formal arteriography.[75] Its main advantages include the absence of radiation and the avoidance of iodinated-based contrast materials. Additionally, MRA can be combined with magnetic resonance imaging of the brain, delineating clinically silent cerebral infarction. It can also evaluate plaque morphology, in particular, the presence of intraplaque hemorrhage.[127] Contraindications include the presence of metallic implants, including some pacemakers and defibrillators. MRA has no role, however, in screening for carotid artery disease, owing to its considerable expense.

Multidimensional CTA can be used to rapidly and accurately evaluate soft tissue, bone, and vascular structures simultaneously. It is also able to evaluate the extent of vessel calcification, especially in the aortic arch. CTA is less likely to overestimate the severity of carotid stenosis compared with MRA.[15,75] The requirement for radiation and the use of contrast remain its most significant limitations. CTA is not appropriate for screening purposes, because of its significant cost and the degree of radiation exposure.[75]

Catheter arteriography was previously considered the reference standard in the evaluation of carotid artery stenosis, especially preoperatively before CEA.[75] Because of its invasive nature and small, but present, risk of complications, it has no role in screening for extracranial cerebrovascular disease.

Recommendation 4.3: For asymptomatic patients who are undergoing screening for carotid artery stenosis, we recommend duplex ultrasound performed in an accredited vascular laboratory as the imaging modality of choice instead of CTA, MRA, or other imaging modalities (grade 1B).

Question 5. what is the optimal sequence for intervention in patients with combined carotid and coronary disease?

Patients	Intervention	Comparison	Outcomes	Study design	Subgroups
Patients with both carotid stenosis >70% and CAD requiring CABG	CEA or CAS and CABG	Combined CEA and CABG or CABG first or CEA first	Stroke, death, MI, combined stroke/death	RCT, observational	Asymptomatic, carotid stent

Evidence and rationale

The recommendation for staged or synchronous carotid interventions in patients with 50% to 99% stenosis and a history of stroke or TIA in the preceding 6 months who require CABG is supported by the reported data.[128-133] However, the optimal timing for these interventions is unclear. In patients with severe (>70%) stenosis and symptomatic disease, minimal studies have addressed the timing of the interventions.[134] In an analysis of multiple observational studies, patients undergoing combined CABG and CEA compared with CABG first had a similar risk of death (RR, 0.58; 95% CI, 0.32-1.05), stroke (RR, 0.87; 95% CI, 0.34-2.22), and MI (RR, 0.64; 95% CI, 0.09-4.34).[14] When comparing CABG first vs CEA first, the groups had a similar risk of death (RR, 0.94; 95% CI, 0.44-2.01), stroke (RR, 1.4; 95% CI, 0.64-3.06), and MI (RR, 0.51; 95% CI, 0.22-1.18). Finally, if the CABG first group were compared with the CEA first group, the risks of death, stroke, and MI were also similar. As expected, a small trend was found toward a greater risk of MI if CEA were performed first and an increased trend toward a risk of stroke if CABG were performed first; however, these differences were not significant.

One of the most controversial issues is the role of prophylactic CEA and/or CAS in CABG patients with unilateral 70% to 99% asymptomatic stenosis, for whom the stroke risk might be <2%.[135,136] Two RCTs and several observational series compared combined CEA and CABG with a strategy of CABG first and delayed CEA in patients with unilateral asymptomatic carotid stenosis.[137,138] In the series by Illuminati et al,[137] the risk of stroke with CABG first was greater than that in the combined series; however, in the series by Weimar et al,[138] the contrary was true. Owing to small numbers in both series, these differences were not significant; therefore, one must assess larger series to obtain meaningful interpretations.

For patients undergoing CAS, a trend was found for decreased mortality with CAS first; however, the number of patients assessed was small.[14] If the option of carotid intervention is considered as either CEA or CAS, when comparing combined carotid intervention vs carotid intervention first for asymptomatic patients, the endpoints of stroke and stroke/death are slightly favored in the carotid intervention group.[14] Because these data are based primarily on observational data, the certainty of the conclusions remains low.

Patients' values and preferences

Patients undergoing CABG already have an increased risk of stroke and, therefore, many would prefer combined treatment to potentially decrease their risk with one procedure. However, if patients are severely symptomatic from either coronary disease or carotid disease, they might be more likely to wish for symptomatic relief rather than overall risk reduction. If anatomically suitable, CAS seems favorable for symptomatic patients. In addition, patients with CAD amenable to percutaneous coronary intervention should undergo such intervention, followed by treatment of the carotid stenosis. In addition, patients should be considered for CEA with regional anesthesia before CABG, if possible.[139-141]

Recommendation 5.1. For patients with symptomatic carotid stenosis of 50% to 99%, who require both CEA and CABG, we suggest CEA before, or concomitant with, CABG to potentially reduce the risk of stroke and stroke/death. The sequencing of the intervention depends on the clinical presentation and institutional experience (grade 2C).

5.2. For patients with severe (70%-99%) bilateral asymptomatic carotid stenosis or severe asymptomatic stenosis and contralateral occlusion, we suggest CEA before or concomitant with CABG (grade 2C).

5.3. For patients requiring carotid intervention, staged or synchronous with coronary intervention, we suggest that the decision between CEA and CAS be determined by the timing of the procedure, the need for anticoagulation or antiplatelet therapy, patient anatomy, and patient characteristics (grade 2B).

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