SOCIETY FOR VASCULAR SURGERY CLINICAL PRACTICE GUIDELINES FOR MANAGEMENT OF EXTRACRANIAL CEREBROVASCULAR DISEASE

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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 treatment of carotid artery disease. At the time, several randomized trials, comparing carotid endarterectomy (CEA) and carotid artery stenting (CAS), were published. Since that publication, several studies and a few systematic reviews comparing CEA and CAS have been published, and the role of medical management has been re-emphasized. The current publication updates and expands the 2011 guidelines with specific emphasis on five areas: is carotid endarterectomy recommended over maximal medical therapy in low risk patients; is carotid endarterectomy recommended over trans-femoral carotid artery stenting in low surgical risk patients with symptomatic carotid artery stenosis of >50%; timing of carotid Intervention in patients presenting with acute stroke; screening for carotid artery stenosis in asymptomatic patients; and optimal sequence for intervention in 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 has been done with 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 0-2), carotid revascularization is considered appropriate in symptomatic patients with greater than 50% stenosis and is recommended and performed as soon as the patient is neurologically stable after 48 hours but definitely before 14 days of onset of symptoms. 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 who are at increased risk for 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. In patients with symptomatic carotid stenosis 50-99%, 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 clinical presentation and institutional experience

SUMMARY OF RECOMMENDATIONS

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

1.1. In low surgical risk patients with asymptomatic carotid bifurcation atherosclerosis and a stenosis of >70% **(documented by validated duplex ultrasound or CTA/angiography)**, we recommend carotid endarterectomy with best medical therapy over 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 carotid endarterectomy recommended over trans-femoral carotid artery stenting in low surgical risk patients with symptomatic carotid artery stenosis of >50%?

2.1 We recommend carotid endarterectomy over trans-femoral carotid artery stenting in low/standard risk patients with a >50% symptomatic carotid artery stenosis. **Grade 1 (Strong), Quality of Evidence: A (High).**

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

3.1. In patients with recent stable stroke (modified Rankin 0-2), we recommend carotid revascularization for symptomatic patients with greater than 50% stenosis to be performed as soon as the patient is neurologically stable after 48 hours but definitely before 14 days of 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 onset of symptoms, we recommend carotid endarterectomy 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 in patients who suffered a disabling stroke, have a modified Rankin score ≥3 whose area of infarction exceeds 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 re-evaluated for revascularization later if neurologic recovery is satisfactory. Level of Recommendation: Grade 1 (Strong), Quality of Evidence: C (Low)**

4. Screening for carotid artery stenosis in asymptomatic patients

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

4.1 We recommend against the 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).**

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

4.2. In selected asymptomatic patients who are at increased risk for carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis particularly if patients are willing to consider carotid intervention if significant stenosis is discovered. **Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).**

4 C. 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 over 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 and coronary artery disease?

5.1 In patients with symptomatic carotid stenosis 50-99%, 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 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 carotid endarterectomy and carotid stent be based on timing of procedure, need for anticoagulation or antiplatelet therapy, patient anatomy and patient characteristics. **Level of recommendation: Grade 2 (Weak), Quality of Evidence: B (Moderate).**

INTRODUCTION

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 prevention and treatment of stroke more than several decades. Initial hopes that CEA could reverse the clinical course of stroke were proven 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] This 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 had a role in the treatment of established stroke, with limited role of vertebral reconstruction in the treatment of cerebrovascular insufficiency. However, over the following decades, surgical refinement of CEA and the increasing detection of asymptomatic carotid stenosis identified by noninvasive vascular studies, CEA assumed a primarily prophylactic role for prevention of major stroke in asymptomatic patients or those with evidence of transient cerebral or ocular ischemia. Large prospective randomized trials [2-6] have established the role and efficacy of CEA in stroke prevention.

Over 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 being performed annually in the

United States. Of which, 90% in patients without neurological symptoms and 11% are catheter based by a variety of specialists including vascular surgeons, general surgeons, neurosurgeons, cardiologists, thoracic surgeons, interventional radiologists, and interventional neurologists.[7] However, others feel that the best data we have regarding symptom status come from VQI and NSQIP where the number is closer to 60-70%, and while they may not be generalizable to the entire U.S. they are far better than NIS data.[8]

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

In 2011, the Society for Vascular Surgery 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 the

2011 Guidelines, since vascular surgeons play a major role, if not predominant role, in the management of patients with carotid bifurcation disease.

METHODOLOGY

Guideline framework

The writing committee met several times, both in person and on several conference calls, to select the most important issues/questions which are of major interest to the clinician to be addressed in the Clinical Practice Guidelines. A systematic review/meta-analysis was conducted by the Mayo Clinic Evidence Practice Center to address these questions which will be published separately in the *Journal of Vascular Surgery*. These five issues/questions include:

I. **Is carotid endarterectomy recommended over maximal medical therapy for asymptomatic carotid stenosis in low surgical risk patients?**
II. **Is carotid endarterectomy recommended over trans-femoral carotid artery stenting in low surgical risk patients with symptomatic carotid artery stenosis of >50%?**
III. **What is the optimal timing of carotid intervention in patients presenting with acute stroke?**
IV. **Screening for carotid artery stenosis in asymptomatic patients**
V. **What is the optimal sequence for intervention in patients with combined carotid and coronary artery disease?**

However, since several other important topics could not be covered in the Clinical Practice Guidelines e.g., optimal modern medical therapy and risk factor modification,

transcarotid artery reconstruction (TCAR) etc., these topics were addressed in separate Comprehensive Implementation Document, which will be used as a reference for further details to the readers in regard to Management 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 in 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 approach to rate the certainty of evidence (confidence in the estimates) and to grade the strength of recommendations.[18] This system, adopted by more than 100 other organizations, is adapted by SVS to express the level of certainty as A, B and C; consistent with high, moderate and low certainty; respectively. GRADE categorizes recommendations as strong (GRADE 1) or weak (also called conditional, GRADE 2) on the basis of the certainty of evidence, the balance between desirable and undesirable effects, the patient's values and preferences, and other decisional factors. GRADE 1 recommendations are meant to identify practices for which benefit clearly outweighs risk that 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. Detailed explanation of the GRADE approach has been presented to the vascular surgery community.[19, 20] The Committee reached consensus about all the recommendations and the level of supporting evidence.

Evidence synthesis

The Committee commissioned several systematic reviews that are published separately in a document titled as the technical review supporting guidelines.[14] The protocols and inclusion criteria for the reviews were determined a priori through collaboration between the committee and Mayo Clinic evidence-based Practice Center. The questions selected for the guideline were specified using the PICO framework (population, intervention, comparison, outcomes) and chosen based on daily clinical dilemmas faced by patients and surgeons in practice. Patient-important outcomes[21] were chosen for decision making. Meta-analyses were conducted when appropriate.

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

Evidence to decision framework:

The guideline committee considered patient values and preferences, and feasibility and acceptability of the recommended interventions. Availability of surgical expertise and institutional experience were also factors that were considered when making recommendations. Stroke prevention was considered the most critical outcome across all guideline questions and the overall certainty of evidence was dependent on the certainty in this outcome. The guideline committee made strong recommendations about the third question (timing of revascularization) despite variable certainty of the direct evidence and based on additional indirect evidence and by placing higher value on avoiding the possibility of any worsening of neurological deficits. The

strong recommendation against routine screening in average risk patients was based on the lack of comparative studies showing improvement in outcomes with screening.

Q1. Is carotid endarterectomy recommended over maximal medical therapy in low surgical risk patients?

Patients	Intervention	Comparison	Outcomes	Study Design
Asymptomatic low risk patients with > 70% internal carotid artery stenosis	Carotid endarterectomy (CEA)	Maximal medical therapy	Stroke and death at 1 and 5 years	RCT

Evidence and rationale

There have been several controlled randomized trials that have compared CEA with best medical therapy. The results of ACAS[2] and ACST[5] favored CEA in the management of low surgical risk patients with severe asymptomatic carotid artery stenosis. ACAS which randomized 1662 patients to immediate CEA versus 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 of 53% [95% confidence interval, 22% to 72%).[2] This trial recommended CEA for patients (aged <80 years) as long as the expected combined stroke and mortality rate for the individual surgeon was not >3%. This trial's conclusions were supported by a subsequent larger randomized controlled trial that randomized 3120 patients to immediate CEA versus medical therapy.[5] This trial also

showed an advantage in limiting stroke and death at 5 years for CEA compared to maximal medical therapy (4.1% vs 10.0%, 95% CI; 4.0-7.8). The long-term effectiveness of CEA in asymptomatic patients was confirmed by the long-term results of ACST, as reported by Halliday et al. This randomized trial compared CEA to medical arm, where patients primarily received antithrombotic and antihypertensive therapy, showed that in the CEA arm (aged <75 years) experienced significantly lower perioperative and 10-year stroke rates (13.3% vs 17.9%).[23] The strength of these conclusions have been questioned, based on 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 patients receiving lipid lowering medication in the ACST trial were analyzed, patients undergoing CEA on lipid lowering medication had a lower stroke incidence compared to medical therapy but the effect of CEA was not as great (0·7 *vs* 1·3% per year [p<0·0001] for those on lipid-lowering therapy, and 1·8 *vs* 3·3% per year [p<0·0001] for those not on lipid lowering therapy.[23]

More recently, Howard et al 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 also conducted a. 2,354 consecutive patients (2,178 patients had carotid imaging) were enrolled that included 207 with 50%-99% asymptomatic carotid stenosis. The ipsilateral stroke rate at 5 years in patients with 70%-99% carotid stenosis was 14.6% (6/53) in contrast to none in 154 patients with 50%-<70% stenosis

(*P*<.0001). For patients with 80%-99% carotid stenosis, the ipsilateral stroke rate was significantly greater than those with 50%-<80% stenosis: 5/34 (18.3%) in contrast to one out of 173 (1%) (*P*<.0001). During their systematic review of 56 reports consisting of 13,717 patients, 23 studies provided data on ipsilateral stroke and the degree of asymptomatic carotid stenosis in 8,419 patients. Ipsilateral stroke was also linearly associated with the degree of ipsilateral carotid stenosis (*P*<.0001). Patients with 70%-99% carotid stenosis (386/3,778 patients) had higher risk of ipsilateral stroke than those with 50%-<70% stenosis (181/3,806 patients) (OR 2.1, *P*<.0001). They concluded that the benefit of carotid endarterectomy might be underestimated in patients with severe stenosis (>70%). Meanwhile, the 5 year stroke risk was relatively low in patients with <70% stenosis on contemporary best medical therapy.[26]

Concerns have also been raised about whether the results of the previously described controlled trials could be attained in vascular surgical practice outside of clinical trial. Critics pointed out that these trials were performed in centers of excellence and that the patients were highly selected. However, subsequent reports on patients who would have been excluded from these trials suggest that the exclusion criterion did not falsely lower complication rates. Combined stroke and death rates after CEA in patients defined as high risk or eligible for high-risk carotid registries varied between 1.4% and 3.6%, well within the AHA guidelines.[27-29] Similarly, studies of large National Surgical Quality Improvement Program, state, and Medicare databases of between 4,000 and 35,000 patients[7, 30, 31] demonstrated stroke and death rates as low as 2.2% with a maximum of 6.9% (symptomatic patients only), suggesting that results that conform to national guidelines are achievable across large patient populations. The role of trans-femoral carotid artery stenting (TF-CAS) or trans-cervical carotid artery revascularization

(TCAR) is even less clear since there have been no completed studies comparing these treatments in patients with asymptomatic carotid stenosis to best medical therapy.

There are now several upcoming multicenter randomized trials designed to answer the role of modern pharmacologic therapy in the management of asymptomatic carotid stenosis. These trials include the Stent- Protected Angioplasty in Asymptomatic Carotid Artery Stenosis (SPACE-II) study [25] and CREST-2.[32]

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

Q2. Is carotid endarterectomy recommended over trans-femoral carotid artery stenting in 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	Carotid endarterectomy (CEA)	Trans-femoral carotid artery stenting (TF-CAS)	Stroke, death, and myocardial infarction	RCT	30 day, >30 day, 5 years or more

Evidence and rationale

Once a patient with a clinically significant symptomatic carotid stenosis is identified, appropriate treatment must be selected. Treatment is primarily directed at the reduction of stroke risk. In general, rates of stroke, MI, and death have been used when comparing CAS with CEA. In most clinical trials comparing CAS with CEA, stroke, MI, and death have been given equal weight in determining a composite end point to test overall efficacy. Data from CREST,[9] however, indicate that stroke has a more significant effect on quality of life at one year than nonfatal MI. Because the primary goal of intervention in carotid stenosis is stroke prevention, in developing its recommendations, the committee placed more emphasis on the prevention of stroke and procedurally related death than the occurrence of periprocedural MI. This may result

in committee recommendations that differ from the published results of some trials where these three end points were given equal weight in analysis.

The threat of stroke in symptomatic patients with <50% stenosis is generally considered to be small and typically does not warrant intervention. ECST and NASCET 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 to maximal medical treatment in neurologically symptomatic patients with carotid stenosis that reduced diameter >50%.[6, 33-35] NASCET demonstrated a relative risk reduction of 65% and an absolute risk reduction in stroke of 17% at 2 years (26% in medical arm vs 9% in 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 to the surgical group of 14.9%, an absolute reduction of 11.6%. In both studies, the risk of stroke in the medical arm, and therefore the benefit of CEA, increased with the 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 in stenosis of 50% to 69% was more moderate— 15.7% stroke after CEA vs 22.2% stroke with medical therapy at 5 years—but still statistically significant.[4]

Carotid endarterectomy versus trans-femoral 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, in 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 subgroup analysis.[36] Two large prospective randomized European trials, EVA-3S[11] and SPACE1,[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% confidence interval [CI], 2.0 to 7.2) and 9.6% after TF-CAS (95% CI, 6.4 to 14.0); the relative risk of any stroke or death after stenting as compared with endarterectomy was 2.5 (95% CI, 1.2 to 5.1). The 30-day incidence of disabling stroke or death was 1.5% after endarterectomy (95% CI, 0.5 to 4.2) and 3.4% after stenting (95% CI, 1.7 to 6.7); the relative risk was 2.2 (95% CI, 0.7 to 7.2). This 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 Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was designed to test "equivalence" between CEA and CAS in patients with neurologic symptoms. This trial stopped after recruitment of 1200 patients due 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 1183 randomized patients. However, the study was not powered appropriately and failed to show non-inferiority of CAS compared with CEA ($P< .09$). More recently two large randomized trials comparing CEA to TF-CAS in symptomatic patients have been completed. The International Carotid Stenting Study Trial (ICST),[10] enrolled 1713 patients and demonstrated an increased peri-procedural stroke risk for CAS (7.7%) compared with CEA (4.1%) in neurologically symptomatic patients. This observed difference was significant ($P< .002$). The rate of any stroke or death within 30 days of treatment in the stenting group was more than twice the rate recorded in the endarterectomy group (7.4% vs 3.4%, $P<$

.0004). In addition, the composite end-point of stroke, death, and MI significantly favored CEA (5.2%) vs CAS (8.5%; *P*<.006). These findings are similar to those of the symptomatic patients enrolled in the CREST Trial.[9] In CREST the peri-procedural rate of stroke and death was significantly higher in trans-femoral CAS versus CEA for symptomatic patients (6.0%±0.9% versus 3.2%±0.7%; HR, 1.89; 95% CI, 1.11 to 3.21; *P*<0.02). The rate of MI was lower after CAS versus CEA for symptomatic patients (1.0%±0.4% versus 2.3%±0.6%; HR, 0.45; 95% CI, 0.18 to 1.11; *P*<0.08) however, the differences were not significant. The Carotid Stenosis Trialists' Collaboration (CSTC) performed a meta-analysis of 4754 patients from the four randomized trials comparing CEA to TF-CAS. These investigators demonstrated a CEA-versus TF-CAS periprocedural HR of 1.61 (95% CI 0.90–2.88) favoring CEA for patients aged 65–69 years and an HR of 2.09 (1.32–3.32) for patients aged 70–74 years.[37] If octogenarians (>80 years) are removed from the data to allow CREST to be compared to other trials in which these patients were not enrolled, the results demonstrated that the 30-day stroke and death rate was significantly lower for the patients undergoing CEA (2.6%± 0.7% for CEA and 5.6%±1.0% for CAS; p=.006).[37] As shown in Figure 1 pooled analysis of 30-day outcomes of stroke and death are lower in symptomatic patients treated with CEA versus TF-CAS.[14]

The long-term outcomes of CAS versus CEA in symptomatic patients has been examined using a preplanned pooled analysis of individual patient data from the above described EVA-3S, SPACE, ICSS, and CREST Trials.[38] These four trials randomized a total of 4754 symptomatic patients with >50% ICA stenosis. Median length of follow-up was 2-6.9 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]). Beyond the peri-procedural period of 120 days there was no difference in annual rate of late ipsilateral stroke (annual event rate 0.60% CEA versus 0.64%

CAS). This lends support that both procedures have similar durability however long-term outcomes continue to favor CEA due to the lower peri-procedural stroke and death rate (Figure 2 and 3).

Perhaps concern exists whether data from randomized controlled trials of carotid endarterectomy and carotid artery stenting can be extrapolated to real world experience. In general, carotid stenting operators in these trials were highly experienced and rigorously adjudicated before being allowed to enroll patients. For example in a review of physicians treating Medicare beneficiaries with CAS less than 10% of physicians would meet the criteria to participate in CREST based on a lack of volume or high complication rate.[39] It is unclear if results similar to randomized trials will be obtained for CAS in operators who may be less experienced or patients that would not be recruitable for clinical trials. Nolan and co-workers have reviewed data from the Vascular Study Group of New England and have shown a higher rate of stroke and death in symptomatic patients treated with CAS compared to CEA (5.1% CAS vs 1.6% CEA, p=.001).[40] Similarly, in a study by Hicks and coworkers looking at almost 52,000 carotid procedures in the VQI found that in symptomatic high risk patients (as determined using MEDICARE criteria) the risk of stroke and death following CEA was 2.3% versus 3.6% for CAS (p<.001). The difference in stroke was two fold higher for CAS both in the general population as well as propensity matched patient cohorts (HR2.23; 1.58-3.15, p<.001).[41] The lower stroke and death rates observed in registries includes only in-hospital events and as such may be lower than that observed in clinical trials that use 30-day event rates and mandatory post-procedure evaluation by an independent neurologist.

Timing of CEA

There is increasing evidence 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%-8% at 48 hours, 4%-17% at 72 hours, 8%-22% at 7 days and 11%-25% at 14 days.[17]

Transcarotid artery revascularization (TCAR)

Early data suggests that TCAR may have a role in the treatment of patients with symptomatic carotid occlusive disease. Studies have shown that TCAR has a similar rate of diffusion-weighted infarcts (DWI) on post-procedure MRI compared to CEA while trans-femoral CAS is associated with a 2-3 fold higher rate of DWI.[42] Up to 50% of the DWI and strokes that occur following trans-femoral CAS are contralateral suggesting arch pathology as the etiology.[43] Two recent trials ROADSTER-1 and ROADSTER-2 have been completed.[44-46] The incidence of 30-day stroke in the symptomatic per protocol patients in both of these trials was 0.6% in each trial. There were no deaths 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 that examined 3286 propensity matched patients from the Vascular Quality Initiative demonstrated a significantly lower incidence of in-hospital stroke and death in patients treated with TCAR versus TF-CAS 1.6% vs 3.1% (RR 0.51, 95% CI 0.37-.72).[47] There was no difference in myocardial infarction between the groups. Lastly, Malas and coworkers examined a more recent cohort of patient from the VQI Trans-carotid Revascularization Project.[48] These investigators propensity score matched 6,384 pairs of patients who had undergone either TCAR or CEA. In this cohort there were 3,333 symptomatic patients that were compared. There was no difference in in-hospital stroke and death between symptomatic patients undergoing TCAR versus CEA (2.2% vs 2.6%, p=.46) and TCAR was associated with a lower incidence of cranial nerve injury and shorter hospital stay.

The impact of developing a TCAR program on overall carotid revascularization outcomes was examined by Columbo and coworkers. These investigators compared the risk of MACE defined as stroke, death and MI in centers who performed only CEA vs those centers that performed both CEA and TCAR. At one year the incidence of MACE was 10% lower at centers that performed both TCAR and CEA vs CEA alone (OR 0.9, .81-.99, p=.04).[49] While 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 there is currently inadequate data to make a recommendation on the role of TCAR in low surgical risk patients with symptomatic carotid stenosis. In summary, TCAR is superior/preferable over TF-CAS or CEA in high surgical risk patients (anatomically and physiologically). (See Implementation Document)

Recommendation: 2.1 We recommend carotid endarterectomy over trans-femoral carotid artery stenting in low/standard risk patients with a >50% symptomatic carotid artery stenosis.

GRADE I, A.

Figure 1. 30 day death and stroke

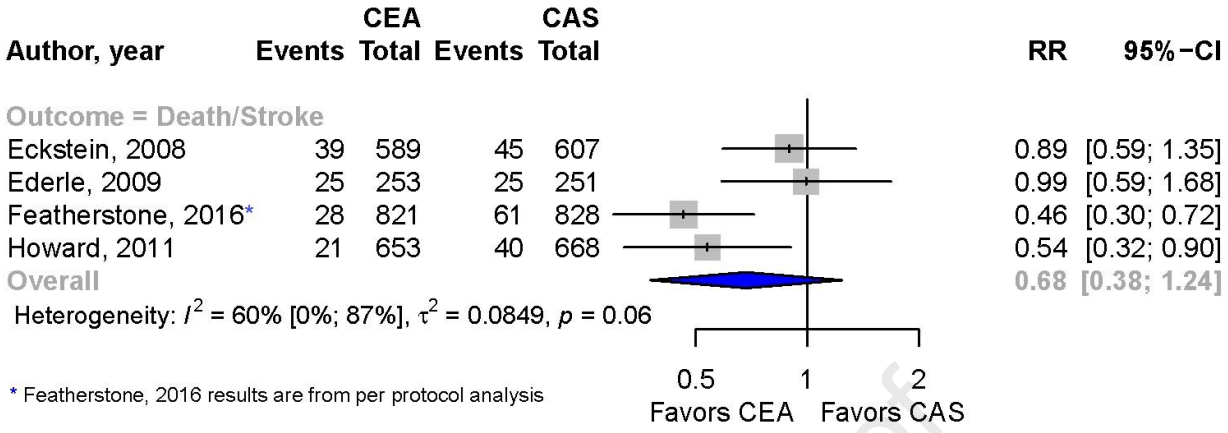


Figure 2. Five year risk of death

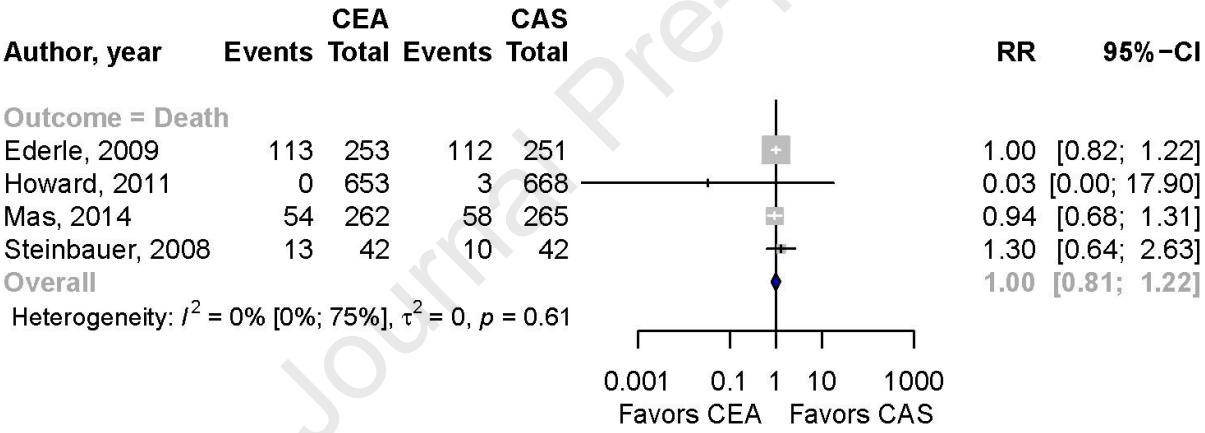
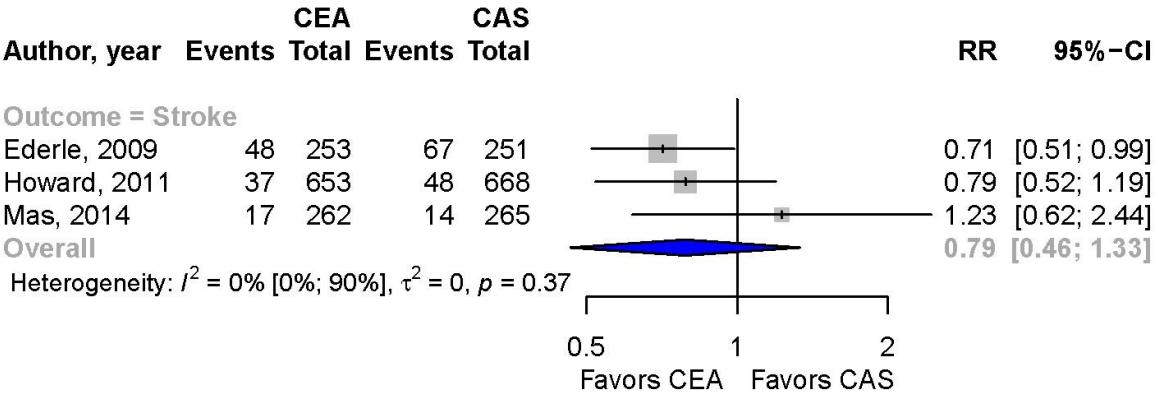


Figure 3. Five year risk of any stroke



Q3. What is the optimal timing of carotid Intervention in patients presenting with acute stroke?

Patients	Intervention	Comparison	Outcomes	Study Design	Subgroups
Patients who present with a stroke who have greater than 50% ipsilateral carotid stenosis	Urgent Carotid Endarterectomy or Carotid Stenting	Early vs delayed Intervention	Patients with Rankin score 2 or less benefit from early intervention	retrospective	CEA within 48 hours, one week, fourteen days and six weeks of index event

Evidence and rationale

Patients

Acute stroke is often associated with intracranial thrombosis or embolization. As a consequence, a major management goal is to identify those patients with intracranial occlusions and to re-perfuse the ischemic brain as rapidly as possible. Primarily, therapy is directed at the intracranial occlusion that affects a significant amount of the vasculature and resultant brain at risk. Only about 15% of acute stroke patients present within the 6-hour time window for acute

intervention. However, as techniques and diagnosis improved, neurointerventionalists have expanded this therapeutic window.

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

However, in acute stroke patients who present obtunded or severely neurologically debilitated, it is often necessary to delay the CEA as they may face a higher risk of hemorrhagic transformation of an infarct or intracerebral hemorrhage (ICH). Patients with a significant neurologic deficit (modified Rankin >2), with an area of infarction exceeding 30% of the middle cerebral artery (MCA) 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, time to the initiation of therapy, time to perfusion, 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 re-perfusion, and age.[51-53]

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

Numerous series have documented the safety of early CEA (from 0-14 days after index event). In a single center series from Sharpe and Naylor et al, 30-day death/ stroke rate of 2.4% when patients had a CEA performed within 48 hours of symptom onset.[55] Other registry data from Germany, Sweden, the United States, and single series reports from the US have shown equally good results with CEA performed in the first week, but not within the first 48 hours.[56-59]

In an analysis of the Vascular Quality Initiative (VQI) of 8,408 patients, results were comparable among patients who underwent surgery after 48 hours but less than 14 days post-stroke to those performed later than 14 days after index event. When cohorts were analyzed to 3-8 days and 8-14 days, multivariate analysis demonstrated that performing CEA between 3-7 days post-stroke was protective for postoperative stroke/death (p=0.003) and any postoperative complication (p=0.028). The authors concluded that surgery should be delayed for at least 48 hours after an acute stroke and should be performed within 14 days post-stroke.[59] Avgerinos et al corroborated this data suggesting CEA's performed 2-5 days after index neurological event have similar outcomes to CEA's performed later.[60]

These findings confirmed the results of an analysis of the Swedish Vascular Registry, including 2,596 patients who underwent CEA for symptomatic carotid stenosis, including stroke. The combined stroke/death rate was 11.5% among those undergoing surgery within the first 2 days of the neurologic event, as opposed to 3.6%, 4.0%, and 5.4% among those undergoing CEA between 3-7, 8-14, and 15-180 days following the acute neurologic event, respectively. A multivariate analysis demonstrated that patients who underwent CEA within the first 2 days following an acute neurologic event experienced a relative OR of 4.24 (CI, 2.07-8.70, p< 0.001) for perioperative complications compared to those undergoing surgery within 3-7 days.[58] These data were corroborated by Hasan et al[14] in their meta-analysis concerning timing of intervention after index stroke. Averginos et al demonstrated an increased risk of complications if the CEA was performed within 48 hours of index event (RR = 2.3053) for stroke but no difference between 2- 14 days.[60] This short delay may allow more complete patient evaluation and let the symptoms stabilize and plateau.

The preponderance of evidence indicates that CEA performed early (< 2 weeks) after an acute stroke is preferable to delayed 4-6 weeks' intervention.[61-67] The data on carotid stenting in the setting of acute stroke are scant, even in recent meta-analysis conducted by Hasan et. al. [14] Most papers were based on anecdotal studies and thus we cannot draw any significant conclusions as to the benefits of CAS in acute strokes with carotid based lesions at this time. Currently, CEA is the procedure of choice in patients with stable strokes and greater than 50% carotid bifurcation stenosis.

Recommendations for management of acute neurologic syndrome:

3.1 In patients with recent stable stroke (modified Rankin 0-2), we recommend carotid revascularization for symptomatic patients with greater than 50% stenosis to be performed as soon as the patient is neurologically stable after 48 hours but definitely before 14 days of onset of symptoms. (Grade I, B)

3.2 In patients undergoing revascularization within the first 14 days after onset of symptoms, we recommend carotid endarterectomy rather than carotid stenting. (Grade I, Level B)

3.3 We recommend against revascularization regardless of the extent of stenosis in patients who suffered a disabling stroke, have a modified Rankin score ≥3 whose area of infarction exceeds 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 re-evaluated for revascularization later if neurologic recovery is satisfactory. (Grade I, C)

Q4.

A. 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, incidence of stroke or death related to carotid disease	Any

Evidence and rationale

There is no consensus on which patient populations should undergo carotid screening for the detection of asymptomatic carotid disease, and there is unfortunately no direct evidence on the benefits of screening with regard to the actual outcomes of future stroke. The rationale behind screening for asymptomatic disease is based upon 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] With a prevalence of <5% in the general population[68, 69], screening does not appear to reduce stroke risk, and may in fact be harmful if it leads to inappropriately performed invasive procedures. The rate of false positive carotid Duplex ultrasound tests may additionally 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 United States Preventive Services Task Force (USPSTF).[70]

Recommendation: 4.1 We recommend against the routine screening for clinically asymptomatic carotid artery stenosis in individuals without cerebrovascular symptoms or significant risk factors for carotid artery disease. (Grade I, B)

B. 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, incidence of stroke or death related to carotid disease	Any	Patients with: atherosclerotic risk factors, peripheral arterial disease, AAA, coronary artery disease, audible neck bruit, prior radiotherapy to the neck, findings of cerebral infarction on brain imaging studies

Evidence and rationale

Atherosclerotic risk factors / medical comorbidities predisposing towards 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] 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 who have a carotid bruit on physical examination, and for those in whom coronary artery bypass grafting is planned.[74] The Society for Vascular Surgery has advocated for consideration of carotid artery screening in high-risk patients 55 years or older with cardiovascular risk factors.[75]

Several groups have attempted to further refine and identify population subsets where the prevalence of carotid stenosis is ≥ 20%, possibly justifying screening in asymptomatic cases. In a report of a single-institution screening program, a model identifying patients at high-risk for ≥ 50% asymptomatic stenosis was proposed. Patients screened were older than 60 years of age and had one or more of the following risk factors: hypertension, coronary artery disease, 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 ≥ 50% of 22.1%.[77]

Similarly, a report from the Western New York stroke screening program identified the following variables to be associated with ≥ 60% carotid stenosis: age ≥ 65 (Odds Ratio, 4.1), current smoking (Odds Ratio, 2), coronary artery disease (Odds Ratio, 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 note that screening before coronary artery bypass grafting is probably indicated in the following subset of patients: age ≥ 65, presence of left main coronary artery stenosis, history of smoking, history of transient ischemic attack, stroke or carotid bruit, and known peripheral arterial disease.[78] Based upon these and other reports, the Society for Vascular Surgery does advocate carotid artery screening in high-risk patients 55 years or older with appropriate cardiovascular risk factors.[75, 79]

Other investigators have noted that the prevalence of occult carotid stenosis is increased in diabetics as compared to non-diabetics (8.7 vs 2.8%, $p<0.01$),[80] and in hemodialysis patients 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%. 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 has recommended screening of asymptomatic patients is appropriate if they are ≥ 60 years of age and have three or more traditional atherosclerotic risk factors.[83]

Unfortunately, few direct comparative studies evaluate the efficacy of screening with respect to the actual clinical outcomes of stroke or death. Most studies in the literature use the prevalence of significant carotid stenosis in the studied populations as the actual outcome measure. In a report by Berens, et al, more than 1000 patients 65 years or older who were undergoing cardiac surgery were screened with carotid duplex scans prior to surgery. The prevalence of disease was 17% for ≥ 50% stenosis, and 5.9% for ≥ 80% stenosis. Using multivariate analysis, five variables were found to be significant independent predictors of ≥ 80% stenosis: female sex, peripheral vascular disease, history of transient ischemic attack or stroke, smoking history and left main coronary disease. If all patients with at least one of those

risk factors were screened, the mathematical model predicted that 95% of patients with ≥ 80% stenosis would be identified prior to their cardiac operation.[84]

In Lin, et al, the outcome of 3233 patients who underwent cardiac surgery was studied, and comparisons performed between those who underwent a preoperative carotid duplex scan (N=515) and those who did not (N=2718). There was no difference between risk factors or a history of prior transient ischemic attack between the two cohorts. Among patients who had screening with ultrasonography prior to isolated coronary artery bypass grafting (n=306), the incidence of significant disease was relatively low: 25 (8.2%) had unilateral moderate (50-69%) stenosis, 10 (3.3%) had bilateral moderate stenosis, 9 (2.9%) had unilateral severe (70-99%) stenosis, 2 (0.7%) had bilateral severe stenosis, 5 (1.6%) had unilateral total occlusion, and 1 (0.3%) had bilateral total occlusion. The outcomes with regard to perioperative mortality and stroke did not differ between those who had a Duplex and those who did not. Operative intervention of severe carotid stenosis prior to CABG occurred in two of 17 (11.8%) of patients identified.[85]

When the results of these two studies were combined in a systematic review / meta-analysis, screening in these defined populations did reveal a benefit with regard to the mortality outcome, and less so for the stroke outcome. (Figure 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 (Figure 5)[14]:

- Patients with current cigarette smoking
- Patients with hypertension and coronary artery disease
- Patients with renal failure and diabetes, hypertension, or coronary artery disease

- Patients with hypertension, hypercholesterolemia and coronary artery disease

Subgroups

Patients with peripheral arterial disease

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

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

Patients undergoing coronary artery bypass surgery

Multiple reports in the literature document a markedly increased prevalence of occult carotid artery stenosis in patients with coronary artery disease, particularly in those undergoing coronary artery bypass surgery.[84, 85, 98-107] Two direct comparative studies regarding screening of CABG patients utilizing the actual outcomes of stroke and death have been previously discussed in detail.[84, 85, 98-107] Increase prevalence of carotid stenosis has been documented in patients

undergoing coronary angioplasty as well.[108] Among patients undergoing coronary artery bypass, a carotid bruit and diabetes mellitus increased the predictive value.[104] Additionally, carotid stenosis in coronary bypass patients is noted to be a risk factor for perioperative stroke.[104] Considering the prevalence of occult carotid disease, carotid screening in patients who are undergoing coronary artery bypass is felt to be appropriate. The evidence in favor of screening in patients who have documented coronary artery disease 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 felt 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 bruits and carotid stenosis, 28 prospective cohort articles involving more than 17,000 patients were analyzed.[109] Stroke rates were 1.6 per 100 patient-years for those with bruits compared with 1.3 per 100 patient-years for those without carotid bruits. Clearly, the presence of a carotid bruit likely increases the risk of cerebrovascular disease, and therefore may justify screening in 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%. Sensitivity was 56%, specificity was 98%, and overall accuracy was 97.5%. However, in another observational study of more than 1500 patients who underwent carotid ultrasonography specifically because of the presence of an audible bruit, 31% of subjects had a significant (≥

50%) stenosis.[111] However, in patients with 50-99% carotid stenosis, carotid bruits had an accuracy of 75%, a sensitivity of 71%, a specificity of 81%, and a positive likelihood ratio of 3.65. Therefore, although carotid bruits are not necessarily accurate enough to confirm or to exclude significant carotid stenoses, these signs are felt to be an appropriate indication for further directed screening with carotid duplex ultrasonography, particularly if the carotid bruit is noted in a patient with other atherosclerotic risk factors.

Asymptomatic patients with prior neck irradiation

With an increased use and success of radiotherapy to treat head and neck malignancies, survival of these diseases has gained remarkable progress.[112] Vascular injury and carotid stenosis has received increased attention. Patients who have had neck irradiation more than five years prior have an eight times higher risk of developing carotid stenosis compared to those with a post-radiotherapy time interval of less than 60 months. Severe post-radiotherapy carotid stenosis is additionally associated with age, smoking and heart disease. Patient who have undergone prior radiotherapy of the head and neck may have a prevalence of significant carotid stenosis that may justify screening in asymptomatic cases.[113] The highest incidence of carotid stenosis is noted approximately 15 years following 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 may involve the proximal common carotid arteries as well; 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 prior radiotherapy undergo screening Duplex evaluation even in the absence of clinical cerebrovascular symptoms.[114] However, the optimal timing and frequency of screening are undefined, and this concept is not universally

accepted. There does not appear to be sufficient evidence to recommend routine screening in asymptomatic patients with prior neck radiotherapy in the absence of other defined risk factors.

Patients with abdominal aortic aneurysm (AAA)

While patients with peripheral arterial disease and severe coronary artery disease are clearly at greatly increased risk for having occult carotid artery stenosis, the correlation in patients with abdominal aortic aneurysm is not as robust. The prevalence of carotid stenosis of ≥ 70% was noted to be 8.8% in a population of AAA patients as compared with 12.5% in a cohort of PAD patients.[115] In a prospective study of patients with AAA, the prevalence of asymptomatic carotid stenosis ≥ 70% was found to be 10.8%.[116] No correlation was noted between the size of the AAA and the degree or presence of carotid stenosis. In an additional report of 332 patients with AAA who underwent carotid duplex scans, a higher prevalence of carotid stenosis was noted; 30.4% were found to have ≥ 50% stenosis in at least one or both carotid arteries.[117] However, several additional studies have revealed a prevalence of carotid stenosis in patients with abdominal aortic aneurysms as less than 20%.[118] Clearly, the correlation of carotid atherosclerosis with isolated abdominal aneurysmal disease is not felt to be as significant as the relationship with coronary and lower extremity atherosclerotic occlusive disease, and therefore the routine screening for carotid stenosis in asymptomatic patients with AAA 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 neurological symptoms represent a population that may benefit from imaging of the carotid artery. An increased subsequent stroke rate of 4.4% in patients with 60-79% initially asymptomatic stenosis has been reported if a silent

infarct was identified on brain imaging studies.[120] Therefore, screening is generally recommended in patients with asymptomatic cerebral infarctions.[120] The detection of cerebral emboli using Transcranial Doppler (TCD) studies also has a high positive predictive value to identify asymptomatic patients at high risk of stroke; patients with ≥2 microemboli / hour on TCD 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<0.0001).[121] However, at the current time 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 increased risk for carotid stenosis, we suggest screening for clinically asymptomatic carotid artery stenosis particularly if patients are willing to consider carotid intervention if significant stenosis is discovered. (GRADE 2, B)

These high-risk groups include:

- **patients with lower extremity peripheral arterial disease**
- **patients undergoing coronary artery bypass surgery**
- **patients age ≥ 55 and with at least two traditional atherosclerotic risk factors**
- **patients age ≥ 55 and active cigarette smoking**
- **patients with diabetes, hypertension *or* coronary artery disease**
- **patients with clinically occult cerebral infarction noted on brain imaging studies**

Other remarks:

1. **In these patient cohorts, the presence of a carotid bruit additionally increases the likelihood of detecting a significant stenosis.**

2. **Asymptomatic individuals with an abdominal aortic aneurysm or prior radiotherapy to the neck who do not fall into any of the-high risk groups noted above do not require screening.**

C. 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 ultrasonography or other imaging (CTA, MRA)	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 higher degree of stenosis is generally thought to represent a progressively increased risk of future stroke.[6, 33] However, plaque morphology clearly plays a significant role as well.[122] Morphological 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 70-99% 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 varying degrees of carotid artery stenosis have been extensively developed, widely utilized and validated.[125] Duplex ultrasound also has the ability to evaluate features of plaque morphology that may indicate patients at high risk of stroke.[122]

Determination of the degree of carotid stenosis is based upon analysis of hemodynamic parameters obtained from Doppler analysis, including the peak systolic and end diastolic velocities. Ultrasound criteria for the degree of carotid stenosis should be defined based on angiographic / 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 / sec to denote an angiographic stenosis of ≥ 50%. A combination of peak systolic velocity of 230 cm / sec and an end diastolic velocity of ≥ 100 cm / sec, or 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 in predicting 50-69% or ≥ 70% stenosis are 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 imaging, including severe vascular calcification and arterial tortuosity.[15]

Current contrast enhanced magnetic resonance angiography can provide three dimensional images which may rival those of formal arteriography.[75] Its main advantages include the absence of radiation, and avoidance of iodinated based contrast materials. Additionally, MRA can be combined with MR brain imaging, delineating clinically silent cerebral infarction. It can also evaluate plaque morphology, particularly 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, due to its considerable expense.

Multi-dimensional computed tomographic angiography (CTA) can rapidly and accurately evaluate soft tissue, bone and vascular structures simultaneously. It is additionally able to evaluate the extent of vessel calcification, particularly in the aortic arch. CTA is less likely to overestimate the severity of carotid stenosis as compared to MRA.[15, 75] Radiation and the use of contrast remain its most significant limitations. CTA is not appropriate for screening purposes, due to its significant cost and the degree of radiation exposure.[75]

Catheter arteriography was previously considered the "gold standard" in the evaluation of carotid artery stenosis, particularly preoperatively prior to CEA.[75] Due to its invasive nature and small but present risk of complications, it has no role in screening for extracranial cerebrovascular disease.

Recommendation: 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 over CTA, MRA, or other imaging modalities. (GRADE 1, B)

Figure 4.

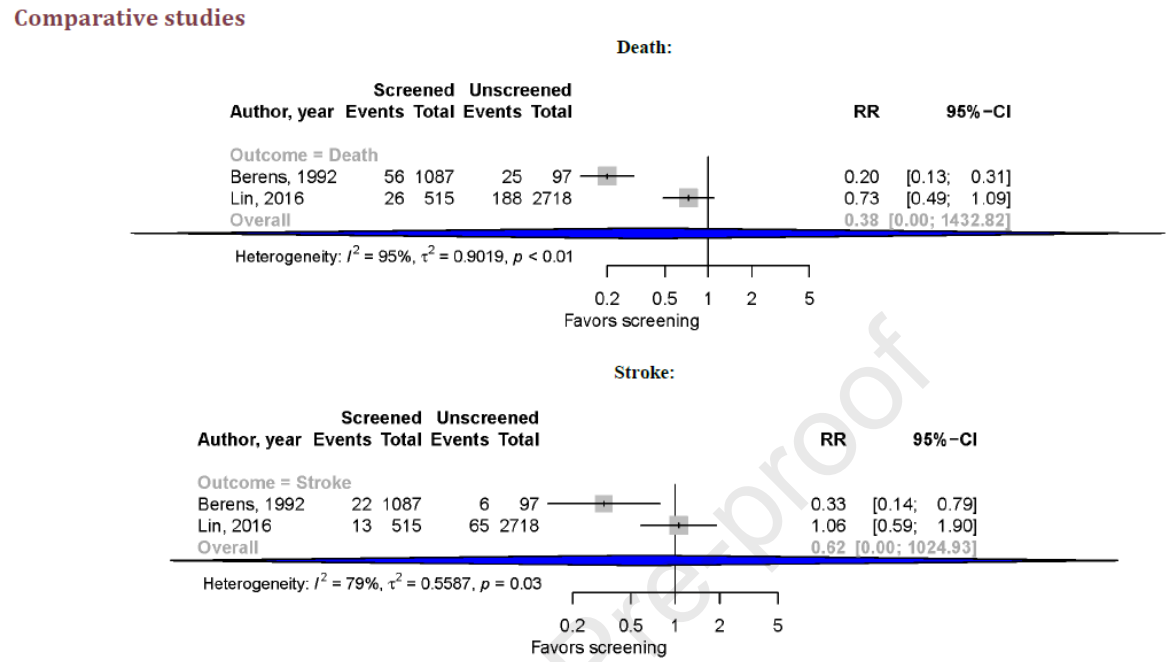
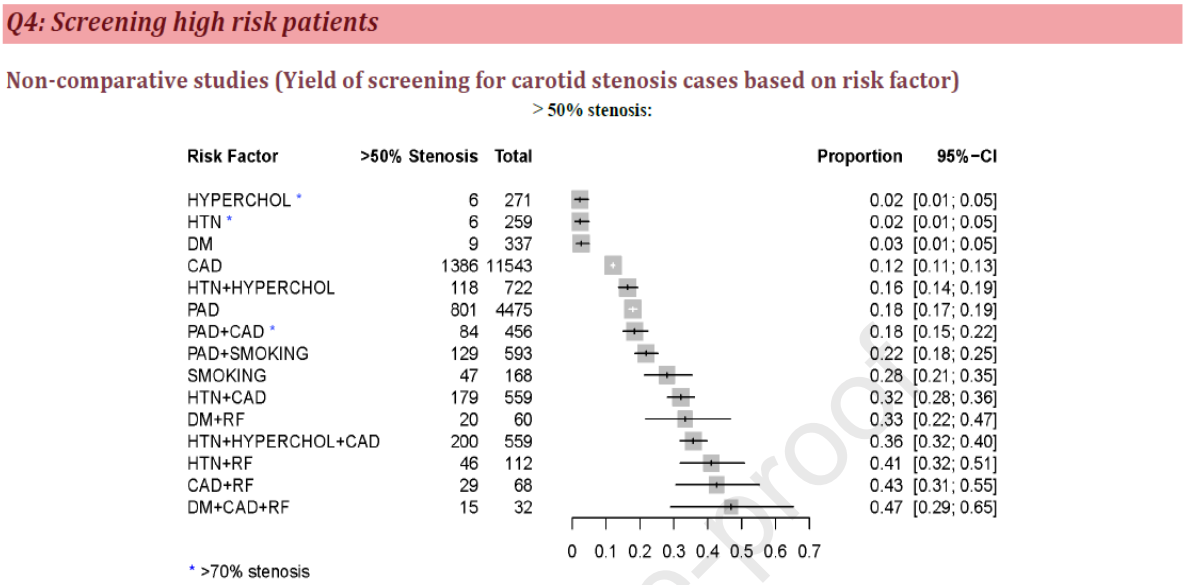


Figure 5.



Hyperchol – Hypercholesterolemia

HTN – Hypertension

DM – Diabetes mellitus

CAD – Coronary artery disease

PAD – Peripheral artery disease

RF – Renal failure

Q5. What is the optimal sequence for intervention in patients with combined carotid and coronary disease?

Carotid endarterectomy (CEA)

Patients	Intervention	Comparison	Outcomes	Study Design	Subgroups
Patients with both carotid stenosis > 70% and coronary artery disease (CAD) requiring coronary artery bypass graft (CABG)	Carotid Endarterectomy (CEA) or stent (CAS) and CABG	Combined CEA /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 50-99% stenosis and a history of stroke or TIA in the preceding 6 months who require CABG is supported by the literature.[128-133] However, the optimal timing for these interventions is unclear. In patients with severe (>70%) stenosis and symptomatic disease, there is minimal literature to address the timing of intervention.[134] In an analysis of multiple observational studies, patients undergoing combined CABG and CEA compared to CABG first had a similar risk of death (RR 0.58 [0.32; 1.05]), stroke (RR 0.87 [0.34; 2.22]), and MI (RR 0.64 [0.09; 4.34]).[14] When comparing CABG first to CEA first, the groups had a similar risk of death (RR 0.94 [0.44;2.01]), stroke (RR 1.4 [0.64; 3.06]), and MI (RR 0.51 [0.22; 1.18]). Finally, if the group of CABG first is compared to the group with CEA first, the risks of death, stroke, and MI are also similar. As expected, there is a small trend toward higher risk of MI if the CEA is performed first, and an increased trend toward risk of stroke if the CABG is done first, but these differences are not significant.

One of the most controversial issues is the role of prophylactic CEA/CAS in CABG patients with unilateral 70-99% asymptomatic stenosis, where the stroke risk may be less than 2%..[135, 136] There are two randomized controlled trials[137, 138] comparing combined CEA/CABG with a strategy of CABG first and delayed CEA in patients with unilateral asymptomatic carotid stenosis, and several observational series. In the Illuminati et al series,[137] the risk of stroke with CABG first was higher than the combined series, yet in the Weimar series[138] the contrary was true. Due to small numbers in both series these differences were not significant and therefore one must assess larger series to obtain a meaningful interpretation.

For patients undergoing CAS, there is a trend for decreased mortality for CAS first, but the number of patients assessed is small.[14] If the option of carotid intervention is considered as

either CEA or CAS, when comparing combined carotid intervention to carotid intervention first for asymptomatic patients, the endpoints of stroke and stroke/death are slightly favored in the carotid intervention group.[14] Because this data is based primarily on observational data, the certainty of the conclusions remains low.

Patient's values and preferences

Patients undergoing CABG are already at 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 for either coronary disease or carotid disease, they may 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 coronary disease amenable to percutaneous coronary intervention should be treated in that manner, followed by treatment of the carotid stenosis. In addition, patients should be considered for CEA with regional anesthesia prior to CABG if possible.[139-141]

Recommendations:

5.1 In patients with symptomatic carotid stenosis 50-99%, 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 clinical presentation and institutional experience (*GRADE 2, C*)

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 (Grade 2, C)

5.3 In patients requiring carotid intervention staged or synchronous with coronary intervention, we suggest that the decision between carotid endarterectomy and carotid

stent be based on timing of procedure, need for anticoagulation or antiplatelet therapy, patient anatomy and patient characteristics. (*Grade 2, B*)

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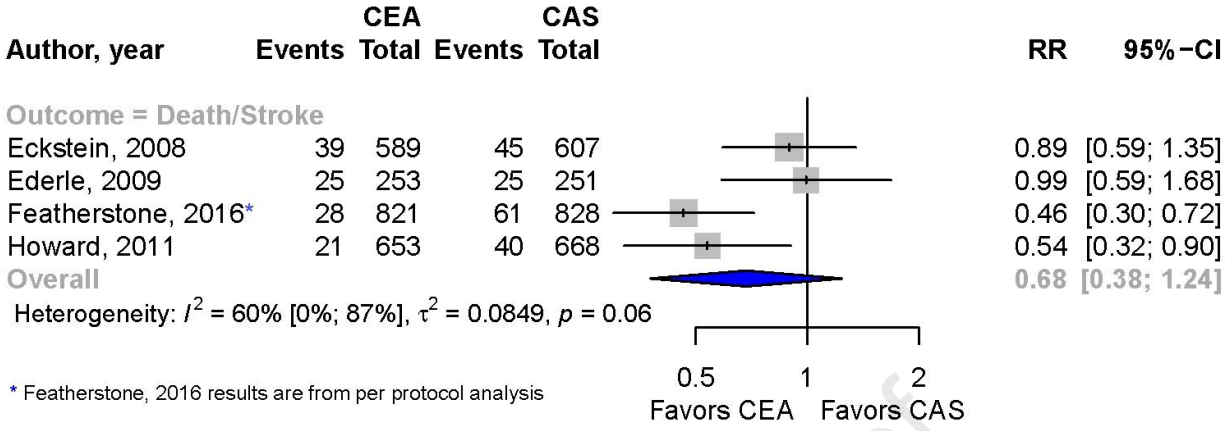
Figure 1. 30 day death and stroke



* Featherstone, 2016 results are from per protocol analysis

Figure 2. Five year risk of death

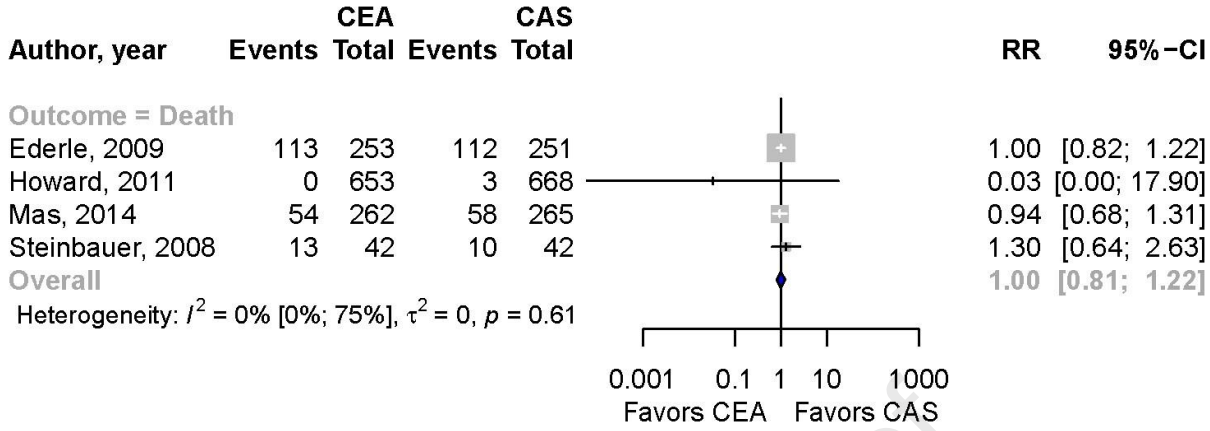


Figure 3. Five year risk of any stroke

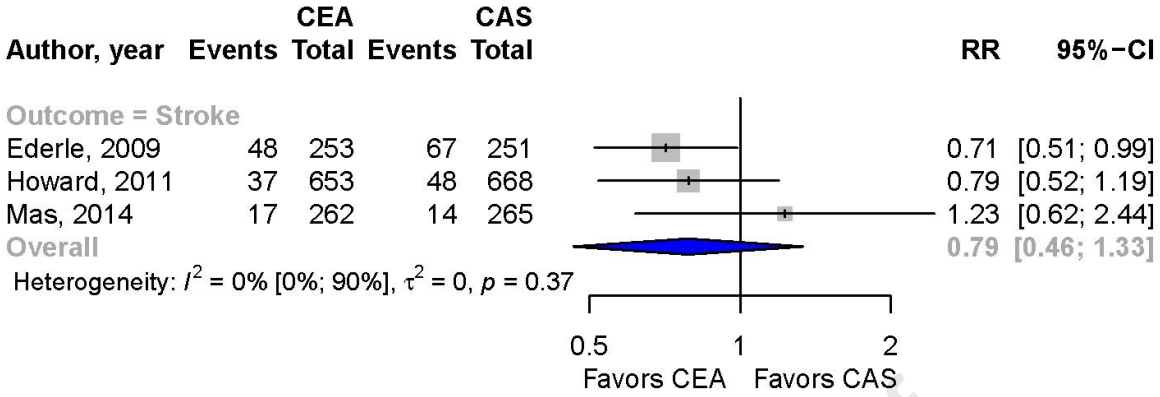


Figure 4.

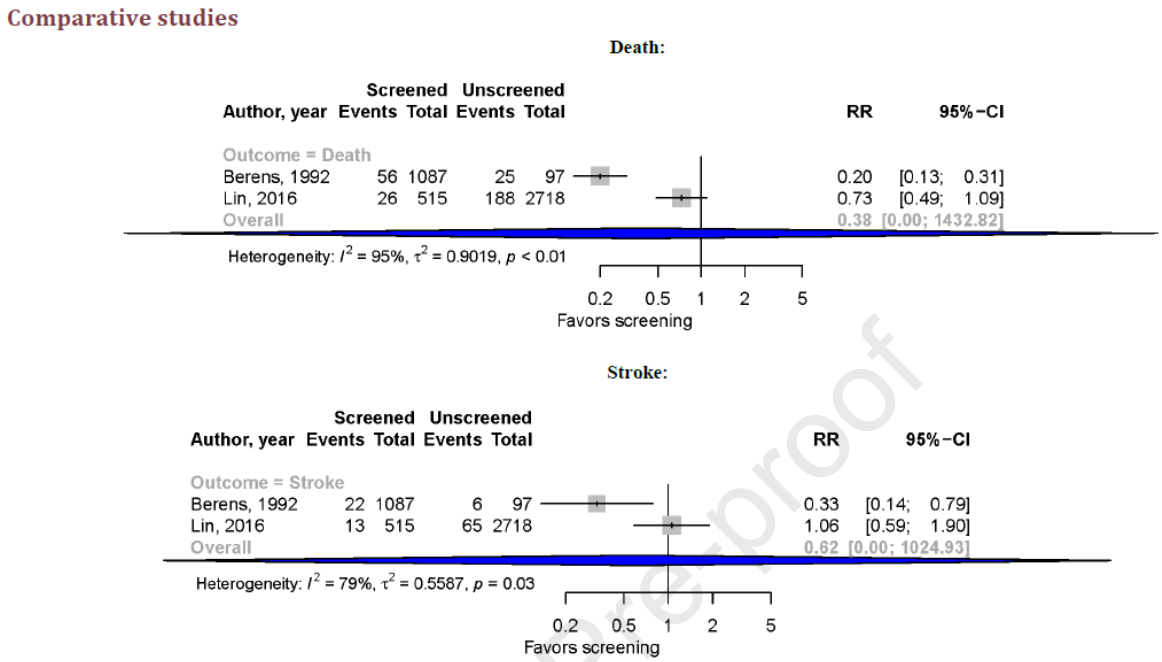
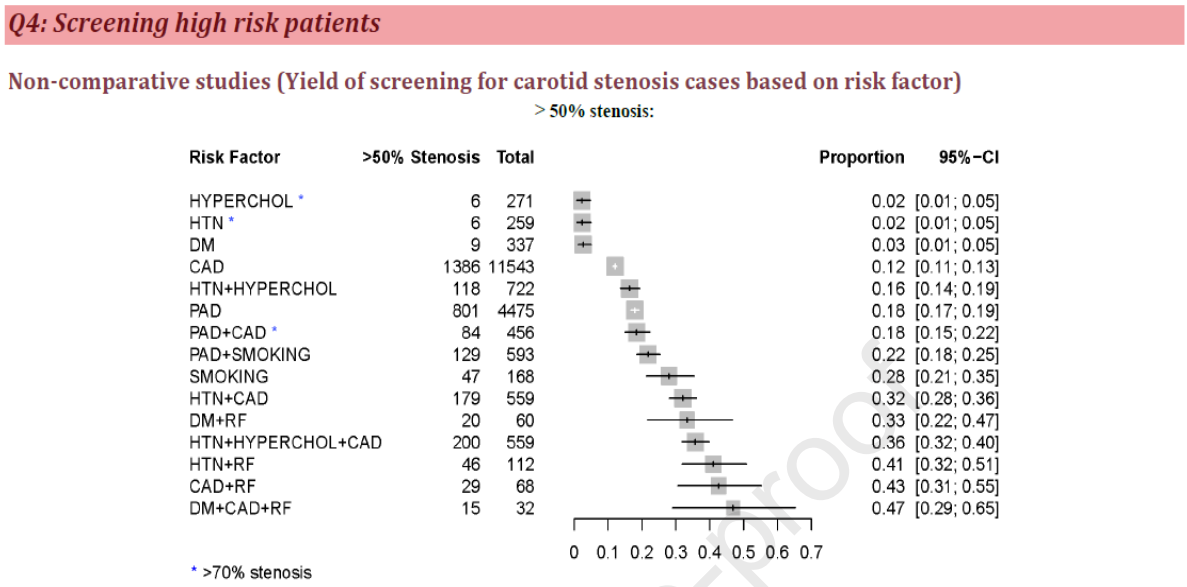


Figure 5.



Hyperchol – Hypercholesterolemia
HTN – Hypertension
DM – Diabetes mellitus
CAD – Coronary artery disease
PAD – Peripheral artery disease
RF – Renal failure